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Role of Endoscopy in Screening and Treatment of Gastrointestinal Cancer

René Lambert*

Screening Group, IARC, Lyon, France

Abstract

Gastrointestinal cancer includes tumors of the proximal and distal stomach which are explored by upper GI endoscopy, using a flexible endoscope. It includes also tumors of the large bowel (colon and rectum), explored with flexible endoscopes by a complete colonoscopy or by a simple sigmoidoscopy. In 2008 the number of incident cases occurring in the World is estimated at 988 602 for gastric cancer and at 1 235 108 for colorectal cancer. A trigger role is played by Helicobacter pylori infection in gastric cancer, and by Diet, Nutrition and physical activity, in colorectal cancer. Gastric cancer is more frequent in developing countries of Asia and Latin America; colorectal cancer is more frequent in more developed countries of North America and Europe. For both tumors, endoscopic diagnosis is based on a 2 steps analysis, with detection followed by charaterization and prediction of histology, before decision of endoscopic resection. Techniques of endoscopic resection include polypectomy with a ligating snare, and modalities of resection called EMR and ESD. Endoscopic diagnosis with eventual treatment is the final step of all screening strategies, either in organized mass screening under the control of Health Authorities, or in Opportunistic screening in individual cases. In mass screening, endoscopy is performed only in persons with a positive filter test. In opportunistic screening endoscopy is a primary procedure. In secondary prevention of cancer, the early treatment of the tumor has a positive impact on survival and mortality. In the colorectum the treatment of premalignant adenomatous polyps has an impact on the reduction of incidence and could be considered as a primary prevention.

Keywords: Sigmoidoscopy; Polypectomy; Tumors; Premalignant adenomatous polyps

Terminology and Definition of Screening

In clinical practice gastrointestinal cancer concerns tumors located in the stomach and in the large bowel, with colon and rectum. The occurrence of tumors in the long segment of the small intestine is relatively rare, and as a rule, these are considered separately. Gastric cancer is located in the distal stomach and antrum, or in the proximal stomach or cardia. The cardia includes the esophago-gastric junction, where tumors develop either from the squamous epithelium of the distal esophagus or from the gastric epithelium of the cardia. In synthesis for clinical practice, the term gastrointestinal cancer includes tumors of the distal esophagus and of the stomach, explored by upper GI endoscopy and tumors of the large bowel, explored by colonoscopy.

In clinical practice persons complaining from appealing digestive symptoms consult their doctor; then an advanced cancer can be detected by radiology or endoscopy. On the other hand, at each tumor site, and in usually asymptomatic persons, screening corresponds to early detection of cancer at a completely curable stage, and will increase the overall 5 years survival from the disease, with a reduction in the mortality rate. In addition, the detection and treatment of premalignant neoplastic precursors will decrease the incidence rate of cancer. The impact on cancer incidence is a major consequence of endoscopic screening, with detection and treatment of precursors.

In countries showing a significant burden of cancer, the National Health Authorities may institute, and support, a policy of Mass screening in all the population aged at least 50 years; in the age range where the risk increases significantly. Cost effectiveness requires a two steps procedure of screening with a "filter test" in all persons and an endoscopic screening in these with a positive test. Screening can be developed in a basis, of individual relationship between an asymptomatic person and a doctor. This "opportunistic "screening", a complement to Mass screening, also concerns asymptomatic persons.

The Burden of Gastrointestinal Cancer

The burden of cancer in the global population of a country is estimated at each tumor site in the IARC database GLOBOCAN [1], of which the last edition is for the year 2008. In this database the number of incident cases of cancer, both sexes, occurring in 2008 is estimated in the World, at 988 602 for stomach, 1 235 108 for colo-rectum, without taking in account the esophagus. Observed, and therefore precise, annual data on incidence and mortality are also found in Population based Cancer Registries, which concern only a fraction of the population.

Incidence, the annual number of cases occurring, at each cancer site, in the population is expressed as an Age Standardized Rate (ASR) of incidence for 100 000 persons, allowing a comparison of the risk between countries having different proportions of age classes in their population. The figures are displayed in the IARC database "Cancer incidence in Five Continents [2], of which the last edition is in 2008. In the same way, the annual number of deaths, at each cancer site, occurring in a country, is expressed as an Age Standardized Rate (ASR) of Mortality for 100 000 persons. Mortality is, at each tumor site, the yearly number of deaths in the corresponding population of 100 000 persons. In the GLOBOCAN database [1], cancer mortality in 2008 is estimated in the world for both sexes at 737 419 for stomach and 609 051 for colo-rectum.

Survival is estimated from the annual follow-up of cases included in registries, and expressed as a 5 year Relative Survival (5y-RS) which takes in account the life expectancy of persons of same sex and age, not suffering from this cancer. The 5 y-RS of stomach cancer is high in Japan where the respective figures in men and women were 61.2% et 60.4% in 11 cancer registries in 1993-96 [3] and much lower in the European registries in period 1995-99 in the Eurocare 4 study [4]. In these registries the figures for both sexes, vary with countries, in the range 15% to 25%. Concerning colorectal cancer the respective figures of the 5y-RS in men and women, in Concord Study [5] are 58.6% and

***Corresponding author:** Rene Lambert, Screening Group, IARC, Lyon, France, E-mail: lambert@iarc.fr

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60.0% in period 1990-94 in the USA registries, 61.1% and 57.3% in Japan and 45.3 and 48.1% in Europe.

Role of Environmental Factors and Country Development

In a large majority of cases (95%), cancer is a sporadic disease and the risk is influenced by an abnormal exposure to environmental factors which should be controlled in the primary prevention of cancer.

Infectious agents play a role in gastric cancer, through a sequence of atrophic gastritis [6] and in 2008, 660 000 stomach cancer in the World were attributed to *H. pylori* infection [7].

Diet and nutrition are causal factors of colorectal cancer, because of the excessive amount of ingested meat and fat .In association to diet there is a decrease in physical activity. As an example In the UK, it is estimated that in 2010, 54% of colorectal cancer are attributable to these factors [8]. Alcohol and tobacco are additional promoting factors at all sites of digestive cancer.

Factors linked to lifestyle and environment explains the large variations in the risk of cancer observed between different regions of the world, mostly in relation to development and resources of the countries.

Stomach cancer is more frequent in less developed countries of Asia and South America and the incidence is much lower in the more developed countries. This cancer is associated to the role of an infectious agent, the bacteria H pylori, classified as a carcinogen by the WHO-IARC agency in Lyon. Carcinogenesis is linked to atrophic gastritis with intra-luminal growth of anaerobic bacteria and formation of carcinogenic nitrosamines [6]. In the analysis of the global burden of infection-associated cancers in 2002 [9] 61.4% of cases of gastric cancer were attributable to H pylori, in developed countries and 64.4% in developing countries.

Colorectal cancer has a much higher incidence in developed countries of Europe and North America; this difference relates to factors linked to nutrition (more calories ingested daily) and to physical activity (less walking) . In the other part of the world fewer calories are ingested and there is more daily physical activity. A specific primary prevention of colorectal cancer occurs in India because of the vegetarian diet and practice of enough physical activity; in 1998-2002, the respective figures of the ASR incidence/ 100000 in men and women were fairly low, 5.9 and 4.4 in the urban registry of Mumbai [2], and mass screening interventions are not justified [10,11].

The link between country development and environmental factors, also explains the temporal trends in incidence of gastrointestinal cancer: In Japan the risk of stomach cancer decreased recently, while the risk of colorectal cancer increased. The rapid development of all “emerging” countries of the world is associated to an increased incidence of colorectal cancer.

Diagnosis of Superficial Lesions in Screening Endoscopy

Strategy of endoscopic diagnosis

Non-polypoid, neoplastic and non neoplastic lesions are preponderant in the stomach and almost as frequent as polypoid lesions in the colon and rectum. There are two successive steps in endoscopic diagnostic as underlined by the Japanese School of endoscopy: detection and then characterization.

Detection of a suspect area requires a complete cleanliness of the mucosal surface and fist in standard vision. Noteworthy, in the proximal colon may flat lesions are missed because they are not washed of the covering mucus. The criteria of suspicion are as follows:

i. An elevation or depression as compared to the surrounding mucosa.

ii. A change in the color of the mucosa, more clear and pale or more red.

iii. An abrupt change or interruption in the course of sub-epithelial capillaries.

Detection is then completed by chromoscopy using a blue dye like the indigocarmine solution at 0.2% to 0.5%; then the morphology of the non-polypoid lesions is classified in the categories elevated (0-II a), flat (0-II b), or depressed (0-II c), of the Paris classification [11]; in addition ulcerated lesions are classified in the category (0-III). The size of the lesion is also determined by comparison with the diameter of a forceps biopsy. There are diminutive lesions (up to 5mm), small lesions (5 to 9 mm) and large lesions (over 10 mm).

Characterization is after the detection of the suspect mucosal area. It aims to predict the histopathology of the lesion before a biopsy of before treatment decision. In supplement to standard vision, one may use the zoom , the technique of surface enhancement, and with recent models of video-endoscopes the techniques of image processing like Narrow Band Imaging in the Olympus instruments [12], FICE in the Fujinon instruments and i-Scan in the Pentax instruments. With help of some magnification, the surface pattern of epithelial crypts and crests is classified in the gastric and in the colonic mucosa in order to predict histopathology of hyperplastic serrated polyps and of neoplastic premalignant lesions. The neoplastic lesions are classified in categories of low, mid and high grade dysplasia and of carcinoma with estimation of the depth of invasion in the mucosa or extension in the submucosa. Characterization is based on analysis of the micro-architecture with the pit pattern of the mucosa and on the vascular pattern of sub-epithelial capillaries, visible in endoscopy [13-15]. After characterization, the treatment decision is taken between abstention with a simple diagnostic biopsy, resection by endoscopy, or direct surgery.

Endoscopic diagnosis of gastric lesions

At endoscopy the squamo-columnar epithelial junction, or Z line, offers a demarcation between esophagus and stomach and is located above the pinch of the diaphragm. Proximal to this junction, in the squamous epithelium, there are small islands of ectopic cardiac mucosa, some of which show scattered goblet cells, suggesting intestinal metaplasia. The upper pole of the gastric folds is distal to the Z line mark. At this level the gastric mucosa of the cardia with mucous neck cells and pyloric gland cells offers a short transition to the fundic type of epithelium with oxyntic cells. In this area superficial neoplastic lesions show slight elevations (type 0-II a) or depressions (type 0-IIc), which correspond to the categories listed in the Paris Classification; and some of them are ulcerated (type 0-III). Any doubt about the type of lesion located in this area should be resolved by histopathology: neoplasia develops as well from the squamous epithelium or from columnar cells in the epithelium of the cardia.

In the fundus and antrum, most polypoid lesions are non-neoplastic and the usual morphology of neoplasia is flat or depressed (types 0-II a, 0-II b and 0-II c). When observed in magnification, the normal regular surface pattern of pits in the surface of these lesions is changed to irregular epithelial crests or to an amorphous surface suggesting a carcinoma with sub-mucosal invasion. The network of sub-epithelial

capillaries around the neck of gastric pits is replaced by irregular and large vessels.

Endoscopic diagnosis of colonic and rectal lesions

In the colon and rectum, near to 50% of the lesions detected are adenomatous, and adenomas larger than 10 mm are called "advanced". The upward growth of hyperplastic non-neoplastic polyps and of neoplastic adenomas results in polypoid, pediculated (type 0-I p) or sessile (type 0-I s) lesions.

Non polypoid lesions with a slightly elevated (type 0-II a) or flat (type 0-II b) morphology, are either neoplastic or non neoplastic. Those with a depressed morphology (type 0-II c) are less frequent, but are always evolutive and a carcinoma with invasion of the sub-mucosa is frequent. The Laterally Spreading Tumors (LST) [16] are large neoplastic lesions which often associate granular sectors (type 0-I s) and non granular sectors, often depressed (type 0-II a and 0-II c). Among non-neoplastic lesions, the Sessile serrated lesions, are also large, over 10 mm in diameter; with a predominant pattern of lateral growth (0-II a or 0-II a + I s) and have a significant risk of progression to serrated adenomas.

After detection, the classification of the microarchitecture of non-polypoid lesions, or characterization, plays a major role in treatment decision. The pit pattern of the colonic mucosa is then described in multiple categories [13-15]: In type I, the normal columnar epithelium shows small and regular pit openings surrounded by sub-epithelial capillaries. The type II corresponds to non-neoplastic, hyperplastic lesions with regular and large pit openings which are less contrasted. The types IIIs, IIIL, IV and VI, VN, correspond to neoplastic lesions with a progressive irregularity of the epithelial crests, from low to high risk of malignancy. The type VN is suggestive of sub-mucosal massive invasion by a carcinoma. The micro-architecture of the sub-epithelial vascular pattern is also classified in the categories: faint, network; dense, irregular and sparse, which point to the progression from low to high risk of malignancy.

Treatment of Superficial Lesions in Screening Endoscopy

In upper GI endoscopy as well as in colonoscopy and sigmoidoscopy the detection of a lesion with a superficial morphology in digestive lumen is followed by a step of characterization on which is based the treatment decision between 2 options:

i. No treatment: This applies at first to small hyperplastic polyps with a serrated morphology; when there is no suspicion of neoplasia; it applies particulary to small polyps, less than 10 mm in diameter, located in the distal colon. Abstention is also proposed when the lesion is not estimated curable by endoscopic resection and when surgery is the selected option. This occurs for a carcinoma with deep invasion in the colonic wall or when complementary staging confirms the presence of positive lymph nodes. The applied techniques are endoscopic ultrasound (EUS), computed tomography scan (CT-Scan), or magnetic resonance imaging (MRI).

ii. Endoscopic resection: This applies to non-neoplastic hyperplastic polyps, when their diameter is up to 10 mm and to neoplastic lesions classified as premalignant adenomas or as carcinomas classified T1-N0, when the extension is limited to the mucosa or to less than 1000 µ in depth in the submucosa. Endoscopic resection is proposed for premalignant adenomas and for T1-N0 carcinomas. In this situation, before treatment decision, complementary techniques of loco-regional staging are often proposed to control the status of the lymph nodes. For resection, polypectomy with a ligating snare is adapted to treat neoplastic and non-neoplastic polypoid lesions: the diathermic snare, lifted across the top of the lesion till its foot, is then strictured. Endoscopic resection of non protruding and relatively flat lesions is performed after the sub-mucosal injection of a solution to rise the area of resection, by a simple endoscopic mucosal resection (EMR) or by a resection with sub-mucosal dissection (ESD) Depending on the size of the lesion the resection is called "*en bloc*" when there is a single fragment or "*piece meal*" when there are multiple fragments.

The Sub-mucosal Injection before Endoscopic Resection

The volume of fluid injected with a needle catheter in the sub-mucosa to form a cushion, varies from 5 to 50 ml. Various solutions are used: Normal saline solutions (0.9%) are easily available and not expensive; a dye like indigo-carmine is often added in complement to improve the contrast. The cushion with a saline solution is short-lasting; long-lasting cushions are obtained with solutions of hyaluronic acid or of hydroxypropyl methylcellulose which are more expensive agents. The endoscopic resection of a lesion in the colorectal mucosa is legitimate only if there is a rising of the sub-mucosal cushion because the absence of rising suggest deep tumoral invasion of the colonic wall or tissue sclerosis in depth.

The Technique of Endoscopic Mucosal Resection (EMR)

The EMR technique is adapted to the resection of flat or sessile neoplastic lesions in the colorectal mucosa and instrumentation is passed by the accessory channel of the endoscope. In addition, a soft and transparent cap can be fixed to the tip of the colonoscope, to flatten the folds and improve visualization of the exposed mucosa. At first, the limits of the lesion are marked with an electrocautery by a circumferential series of white superficial coagulation marks. Then a safety cushion is created under the lesion by the sub-mucosal injection of saline or hyaluronic acid. EMR is safer in the distal, than in the proximal colon, where the colonic wall is thinner with a significant risk of perforation, because the resection by an electrocautery snare of the protruding zone bearing the flat lesion requires some traction. After resection, a simple oozing of blood is cauterized with the heater probe. On the other hand, if a large amount of blood comes from the opened vessel, a hemostatic. Endo-clip is closed on the vessel. Lesions less than 2 cm in diameter are removed "*en bloc*", in a single fragment. Larger lesions can be removed in multiple, but contiguous, fragments by the "*piece meal*" method. Several options are available for collection of the tissue after resection; if there was a cap at the tip of the endoscope, the fragments are collected into the cap. Specially designed retrieval devices can also be used.

The Technique of Endoscopic Submucosal Resection (ESD)

Endoscopic sub-mucosal dissection (ESD) is another modality of endoscopic treatment in which ligating snares are replaced by electrocautery knifes. This technique is less frequently used in the colon than in the stomach, because the wall of the large bowel is thinner, particularly in the proximal colon. ESD is a time consuming procedure, performed under sedation or general anaesthesia. The first step of ESD is a deep circumferential incision of the mucosa around the lesion. There are different models of electrocautery knifes, either unprotected at the tip (needle-knife), or with a more or less protected extremity (hook-knife, flex-knife, Insulation-Tipped IT-knife). Therefore the lesion is dissected "en bloc" in a single piece even if it is larger than 20 mm. The second step of ESD is sub-mucosal dissection conducted with the help of a transparent cap. Then the extremity of the endoscope

is introduced in the interval between the muscular and the mucosal layers, allowing dissection of the sub-mucosa with the electrocautery knife, under control of the eye. If there is a point of significant bleeding an endo-clip can also be used. At the end of the procedure the resected lesion is collected in a retrieval basket or seized with a grasping forceps passed through the accessory channel. Resection of large lesion is more complete after ESD with an "en bloc" resection than after EMR and the risk of recurrence is less.

Discussion

Endoscopic screening for stomach cancer

Screening for stomach cancer deserves a Public Health policy in countries exposed to a high risk but not in the Western world. As a rule endoscopy is not the primary test in mass screening for gastric cancer; the procedure is performed only in persons positive to a simpler imaging procedure or to a biological analysis used as a filter test. In Japan, gastro-photo-fluorography was since 1963 the filter test in mass screening for stomach cancer and is recently replaced by the less costly pepsinogen test. This strategy resulted in reduction of the risk of gastric cancer and in cancer registries of this country the proportion of localized, and curable, stomach cancer is much higher than in registries of Western countries, explaining the higher 5 year survival. The serology of *H. pylori* has also been proposed as a filter test for stomach cancer, with indicators like the Cag A antibody; it did not proved to be cost / effective. Anyhow, upper GI endoscopy is always the final diagnostic test and the early diagnostic of superficial intra mucosal gastric cancer requires an extreme attention, because there are no conspicuous precursors at a stage of pre-malignancy. In Western countries, there is no legitimacy for mass screening in gastric cancer and opportunistic screening can be proposed to individual persons using endoscopy as a primary test. In this situation the quality control in gastroscopy should be high and it deserves to be improved because of the poor quality detection of cancer at early stage.

Endoscopic screening for colorectal cancer

The legitimacy of mass screening for colorectal cancer applies to countries exposed to a high risk; this concerns Europe, North America and also the so-called "emerging countries" in Asia and in Latin America where the risk increases rapidly, in relation to the resources. As a rule colonoscopy is not the primary test in mass screening and in the concerned countries a simple filter test is proposed to the population in the age range 50-70 years and colonoscopy is performed only in persons positive to the test. On the other hand there is still a room for opportunistic screening for colorectal cancer in individual persons; then colonoscopy is the primary procedure.

Nowadays, the Fecal Occult Blood Test (FOBT), with the guaiac or the immunochemical method, is the current filter test in organized screening protocols. Screening with FOBT is proposed to persons of both sexes, from the age 50 years, and repeated in successive campaigns and persons positive to the test are submitted to colonoscopy [17]. This applies to a small percentage of the persons (2% to 5%). The final step in the strategy of organized mass screening protocols, as well as that of individual opportunistic screening, is the endoscopy of the large bowel, either by complete colonoscopy or by sigmoidoscopy which explores only the distal segment of the large bowel , but has the major advantage to be also performed by trained specialized nurses at a lesser cost. In the USA, a cohort study conducted in Health professionals has shown that screening flexible sigmoidoscopy reduces mortality from colorectal cancer by 50% and incidence by 44% [18].

The benefit of screening depends on the high quality of colonoscopy; this quality is based on the completeness of intestinal preparation and on a high standard of the 2 steps of detection by visual inspection and of characterization after detection. Secondary prevention of colorectal cancer in those countries practicing a mass screening strategy occurs through a double impact on the population. At first is the early detection of cancer at a curable stage. This has an impact on the improvement of the 5 years survival with reduction of mortality. In addition, the detection and destruction of the precursors, premalignant, adenomatous polyps have an impact on the global risk of colorectal cancer in the population. This detection requires an extreme care because the non-polypoid or flat adenoma-cancer sequence [19] is now considered to be responsible for up to 40% of advanced cancers, and the detection of those precursors requires an extreme care. The destruction of adenomatous polyps has no impact, of course, on cancer survival and mortality, but results in a reduction of the incidence of colorectal cancer. In a way this is a modality of the primary prevention of cancer. In the USA, a 19.4% decrease of the ASR incidence per 100,000 (both sexes) occurred during period 1975-2003, as shown in the SEER Registries [20]. The incidence began to decrease slightly after 1990 when opportunistic screening with colonoscopy was strongly reinforced.

Future trends in endoscopy and prevention of gastrointestinal cancer

For gastric cancer no change is expected in the near future in the role of endoscopy in mass screening in countries exposed to a high risk; on the other hand an increased efficacy of opportunistic endoscopic detection is needed in countries exposed to a low risk. For colorectal cancer, the endoscopic exploration of the colorectal mucosa by endoscopy should maintain in future trends its primacy. The question is that the priority attributed to the control of early cancer will be challenged by the eradication of adenomatous polyps which have a high prevalence (in the range of 30%) in the adult population of developed countries. Without doubt a priority should be given to the control of incidence, by the destruction of this precursor lesions; this means an increase in the role of opportunistic screening with primary endoscopy.

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