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Review Article

Status of Endoscopic Screening Strategies for Upper Gastrointestinal Tract Cancer

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Abstract

Upper gastrointestinal tract cancer (UGIC), which includes both gastric and esophageal cancer, is a major threat to human health. Patients in the early stage have a significant chance to obtain a better prognosis, when compared to patients in the advanced stage. Improving the detection rate of early UGIC is important to improve the survival rate and prognosis. The endoscopic screening of UGIC includes opportunistic and population-based screening, and this has been carried out in a few regions. Compared to these two gastroscopy screening strategies, the early detection ability of opportunistic screening is no less than that for population-based screening, and the compliance of population-based participation is better. Considering economic factors, bundled opportunistic gastroscopy screening is cost-effective. Overall, the screening strategy for UGIC is limited by economic, medical and geographical factors, and the prospect of opportunistic screening is considerable.

Introduction

Upper gastrointestinal cancer (UGIC) mainly includes gastric cancer and esophageal cancer. In the 2018 global cancer statistics, the incidence of gastric cancer (7.2%) and esophageal cancer (4.2%) accounted for 11.4% of globally new cancer cases, with a mortality rate of 16.1% (9.5% for gastric cancer and 6.6% for esophageal cancer).[1] The epidemiology of gastric cancer suggests that East Asia accounts for more than 60% of worldwide new cases,[2] while another phenomenon is that the age-standardized morbidity and mortality of gastric cancer are declining worldwide. This may be correlated to the reduction in *Helicobacter pylori* (*Hp*) infection.[3,4] However, the incidence and burden of cases of gastric cancer continue to rise due to the aging population.[5] Therefore, an effective screening strategy for UGIC is urgently needed.

Keywords: Cancer screening; Gastroscopy; Upper Gastrointestinal tract cancer.

Abbreviations: AFE, auto-fluorescence endoscopy; aOR, adjusted odds ratio; ASR, age-standardized rate; BLI-bright, blue laser imaging-bright; CAG, chronic atrophic gastritis; CI, confidence interval; EGC, early gastric cancer; ESCC, esophageal squamous cell carcinomas; GC, gastric cancer; GIM, gastric intestinal metaplasia; H&N, head and neck; HGIN, high-grade intraepithelial neoplasia; *Hp*, *Helicobacter pylori*; HR, hazard ratio; ICER, cost-effectiveness ratios; NBI, narrow-band imaging; NCSP, national cancer screening program; OR, odds ratio; QALY, quality-adjusted life-year; RR, relative risk; UGIC, upper gastrointestinal tract cancer; UGIS, upper gastrointestinal series; WLI, white light imaging.

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The development of gastric and esophageal cancer may take decades before the emergence of clinical symptoms.[6,7] This window makes it possible for the detection and treatment of early UGIC. Screening is an important method to improve its early diagnosis. For example, upper gastrointestinal barium radiography, which is an anti-cancer screening item, is acceptable and simple. Furthermore, serological screening, such as the ABCD serum screening strategy, can identify a part of the high-risk population of gastric cancer.[8–10] At the same time, it is also necessary to understand that the serum antibody of *Helicobacter pylori* (*Hp*) cannot reflect the damage to the gastric mucosa caused by *Hp*, even if the result is negative. Moreover, various screening strategies, such as swallow-pull balloon cytological examination,[11] cytology combined with biomarker screening,[12] and expiratory markers,[13] have been used in clinic to detect early esophageal cancer, since these improves the method of screening. At present, gastroscopy is the most important part of the screening and treatment of early UGIC. The present study reviews the present strategies for gastroscopy screening.

Development of gastroscopy screening strategies

Gastroscopy screening for UGIC was derived from the cancer screening program of high-risk regions, which aims to identify high-risk populations through different screening methods, including radiography and serological testing, in order to increase the detection rate, and improve the curative dissection of UGIC.

Past screening strategies

In the 1960s, a population-based gastric cancer screening program was initiated in Japan, and barium radiography was initially used as the main method. Then, gastroscopy was used in 1983, and the participation increased annually. This became the primary screening item in 2016, with a participation rate of nearly 90%.[8] In South Korea, X-ray and gastroscopy examinations have been performed in the National Cancer Screening Program (NCSP) for the population-based screening of UGIC biennially, since 1999.[14] The 10 years of screening data revealed that the number of people who underwent gastroscopy screening increased, accounting for 84.5% in 2016.[15] From 2005 to 2014, China successively carried out gastric cancer population-based screening programs in rural areas (263 project sites), the Huaihe River Basin (32 project sites), and cities (66 cities).[16] Opportunistic gastroscopy screening is a supplementary part of the population-based gastroscopy screening program, and this works in regions where population-based screening is not available.

Benefits of gastroscopy screening

Endoscopy has become the first choice for UGIC screening in Japan and South Korea. The UGIC screening program has achieved remarkable results in high-risk areas, leading to a 40% decrease in mortality.[17,18] A meta-analysis of 342,013 subjects revealed a reduction in gastric cancer mortality in Asia.[19] For the screening process in Korea, gastroscopy exhibited a stronger ability to identify (adjusted odds ratio [aOR] = 2.10, 95% confidence interval [CI] = 1.90–2.33) local gastric cancer, when compared to the indirect upper gastrointestinal series (UGIS),[20] and this reduced the mortality for esophageal cancer (hazard ratio [HR] = 0.497, 95% CI = 0.464–0.531)[21] and gastric cancer (OR = 0.53, 95% CI = 0.51–0.56, in South Korea; OR = 0.695, 95% CI = 0.489–0.986, in Japan).[22,23] The regional screening results in China also revealed that endoscopic screening reduced the mortality for esophageal cancer by 37%, and gastric cancer by 33%.[24] In addition, compared to upper gastrointestinal barium radiography, endoscopy has no ray exposure, and the cost-effectiveness of gastroscopy is seven times higher.[25]

Accuracy of gastroscopy screening

Gastroscopy allows for the direct observation of the esophagus and gastric mucosa, as well as the morphology of vessels, and this can also make depression lesions more prominent using simple staining and biopsy techniques, which are conducive for detecting early cancer. A study reported that the sensitivity of gastroscopy to upper gastrointestinal malignancies ranges within 69.0–95.4%, and that the specificity for endoscopy screening and UGIS was 96.0% and 96.1%, respectively.[26] In China, the strategy of spraying Lugo iodine under gastroscopy to identify the unstained areas of precancerous lesions can reduce the morbidity, and increase the detection rate of early esophageal cancer.[27] In another study, the sensitivity of endoscopic screening for localized gastric cancer was 65.7%, which was significantly higher than that for UGIS.[28] Therefore, both opportunistic and population-based gastric cancer screening should include esophageal cancer screening, in order to provide additional benefits.

Developed techniques based on gastroscopy, such as narrow-band imaging (NBI), have led to new progress in the detection of early UGIC.[29] For the detection of esophageal squamous cell carcinomas (ESCCs) in the head and neck (H&N) region, NBI has a sensitivity of 100% and 97.2%, respectively, and an accuracy was 86.7% and 88.9%, respectively. These results were significantly better, when compared to white light imaging (WLI) ($p <$ 0.001).[30] For the detection of early gastric cancer, previous studies and meta-analyses have revealed that NBI is superior to WLI, and that the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for diagnosing early gastric cancer was 87.2%, 98.6%, 82.1%, 99.0% and 97.8%, respectively,[31] with a diagnostic odds ratio of 102.75 (95% CI = 48.14–219.32).[32]

For auto-fluorescence endoscopy (AFE) and blue laser imaging-bright (BLI-bright). Prospective double-blinded studies have revealed that the clinical value of AFE remains limited. Furthermore, although this has an advantage in detecting elevated gastric musical neoplasias, the sensitivity (74% *vs.* 64%, $p > 0.05$) and specificity (83% *vs.* 40%, $p = 0.0003$) are inferior to those for WLI.[33] Furthermore, for blue laser imaging-bright (BLI-bright) is superior to WLI, in terms of the real-time detection of gastric cancer (93.1% *vs.* 50.0%, $p = 0.001$), especially for lesions in the lower third of the stomach, depressed-type lesions, and small lesions of <10 mm.[34]

Other gastroscopy screening methods

Magnetic-controlled capsule endoscopy screening is an emerging endoscopic technology, which can be used as a supplement to the intolerance of traditional endoscopy. Its accuracy has been verified in some studies, but the examination cost is high, and its promotion value needs further economic research.[35,36]

Comparison of population-based and opportunistic screening

The purpose of the screening is to expand the population-accepted screening and improve the detection rate of early UGIC. However, a full-coverage gastroscopy screening would bring huge medical pressure. Hamashima *et al*. estimated the potential of endoscopic screening in Japan, and indicated that when 30% of the radiograph screening population was replaced with gastroscopy, the amount of gastroscopy increased by 8.6% of the current.[37] Furthermore, recent economic assessments have revealed that population-based endoscopic screening in high-risk areas is cost-effective.[38] However, this remains difficult to apply in low- and medium-risk areas, because the incremental cost-effectiveness ratio of screening remains high.[39]

The population-based gastroscopy screening system has not been estimated in most regions in the world. Thus, opportunistic screening occupies the main position. The present study compared the object, effect, compliance and cost-effectiveness of two screening methods.

Screening object

Population-based screening is primarily differentiated from opportunistic screening, in which invitations to target populations are issued from population registers. In population-based gastroscopy screening, the objects are included in national or local cancer screening programs. The policymaker decides the screening intervals and target population, constructs the re-examination system, and provides the budget, such as South Korea's National Cancer Screening Program (NCSP).

Meanwhile, the objects for the opportunistic gastroscopy screening were individuals who were advised to undergo gastroscopy in the course of other medical services, and those who underwent an endoscopy that was paid by themselves, excluding populations supported by national programs. The screening interval was inconstant, and was based on the awareness of cancer prevention of patients, and the whole examination cost was shouldered by themselves. According to the budget, there are two types of opportunistic screening: individual and collective opportunistic screening. These are applied in Japan.

Table 1. Detection ability of gastric cancer between the two strategies

	Risk level	Strategy	GC / Total	EGC / GC
Kim B[43]	High-risk	Population-based gastroscopy screening	100/34,416 (0.3%)	74/100 (74%)
		Opportunistic screening	26/11,238 (0.2%)	14/26 (53.8%)
Lau J[44]	Middle-risk	Opportunistic screening	5/1,414 (0.35%)	3/5 (60%)
Zhou Q[45]	High-risk	Opportunistic screening	190/6,701 (2.84%)	88/190 (46.3%)

EGC: Early Gastric Cancer, GC, Gastric Cancer.

Screening effect

There is uncertainty in the ability to prevent and decrease the mortality of UGIC between these two different endoscopic screening strategies. The effect of the population-based gastroscopy screening strategy for detecting UGIC has been verified in various countries. At present, the detection rate by gastroscopy for early gastric cancer in Japan is 75.1%, and the 5-year survival rate of gastric cancer is 64.6%.[40] Furthermore, the gastroscopy detection rate for early gastric cancer in Korea is 63.9%, and the 5-year survival rate is 74.6%.[41] The population-based gastroscopy strategy aims to improve the early diagnosis and treatment of UGIC, which has been carried out in 194 high-risk areas for gastric cancer in China since 2005. According to a 10-year statistical analysis of six high-risk areas, it was found that compared to areas without gastroscopy screening, the incidence and mortality of UGIC decreased by 23% (relative risk [RR] = 0.77, 95% CI = 0.74–0.81) and 57% (RR = 0.43, 95% CI = 0.40–0.47) in the gastroscopy screening group, and decreased by 14% (RR = 0.86, 95% CI = 0.84–0.89) and 31% (RR = 0.69, 95% CI = 0.66–0.72) for all participants.[24,42]

Kim *et al*.[43] compared the population-based endoscopic screening group (n = 34,416) and opportunistic screening group (n = 11,238), and revealed that the detection rate for gastric cancer using these two screening strategies was 0.3% and 0.2%, respectively, but there was no significant difference (p = 0.299). Another study revealed that in middle-risk areas for gastric cancer, the detection rate for UGIC in asymptomatic patients by opportunistic endoscopy is 0.35%.[44] However, the proportion for early gastric cancer was significantly higher when the population-based gastroscopy screening strategy was applied, when compared to opportunistic gastroscopy screening (74.5% *vs.* 53.8%, p = 0.046).[43] This means that population-based endoscopy screening is superior to opportunistic screening, in terms of detecting early gastric cancer. The detection rate of cancer in some of the reviewed studies are presented in Table 1.[43–45]

Screening compliance

Compliance is the basis of screening surveillance. The NCSP data revealed that 67% of participants chose gastroscopy for screening in the future two years, and 47.8% of participants who accepted UGIS chose gastroscopy in the future. Furthermore, participants with a family history of gastric cancer had better compliance with gastroscopy (aOR = 2.05, 95% CI = 1.17–3.60).[46] A latest research in China revealed that the compliance rate for gastroscopy screening in urban and rural areas is 45.2% and 48.4%, respectively, and the demographic characteristics differed, or even reversed, in urban and rural populations with good compliance.[47]

Among these two different screening strategies, people who underwent opportunistic gastroscopy screening had better compliance. A large sample study conducted in South Korea revealed that under the definition of regular gastroscopy for at least once every two years, people who underwent opportunistic gastroscopy had better compliance (27.1% *vs.* 19.1%, p < 0.001). The study also suggested that compared to screening methods, the compliance of the screening population is more important.[43] Combined with the study conducted by Jun,[22] it was found that the death toll for gastric cancer obviously decreased with the increase in frequency of gastroscopy. Furthermore, it was observed that opportunistic gastroscopy has more advantages in screening populations that require multiple gastroscopy examinations, such as patients with chronic gastric mucosal atrophy or post-endoscopic treatment of early UGIC.

Screening cost-effectiveness

Zhou *et al*. investigated the cost of gastric cancer screening in high-risk populations (n = 27,970). They found that the total cost for gastric cancer in a screened population and in an unscreened group was $4,041.10 and $4,228.00, respectively. If 68.9% (20/29) of advanced gastric cancer patients are diagnosed at the early stage by screening, merely an extra of $1,020.00 per screening would needed, providing economic and social benefits.[48] Furthermore, a study conducted for opportunistic gastroscopy screening in middle-risk areas (gastric cancer age-standardized rate [ASR] of 8.2/100,000.0) revealed that the detection rate for UGIC or precancerous lesions was 12.7%, and the cost of each case was $3,960.00, and when the detection rate for UGIC was 0.35%, the cost of each case was $141,400.00.[44]

For people who underwent opportunistic gastroscopy, the bundled endoscopy strategy was found to be more cost-effective. Gupta *et al*. conducted a Markov model analysis, and the result suggested that gastroscopy bundled with colonoscopy can reduce the number of gastrointestinal cancer-related deaths by 61.1/100,000.0, which is one-third more than that for single gastroscopy or colonoscopy, and the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) was $95,559.00, which is lower than that for a single endoscopy examination ($115,664.00).[39] However, there is a prerequisite, according to the study conducted by Areia.[49] In middle-risk areas for gastric cancer (ASR = 13.1/100,000.0), the combined screening strategy for detecting UGIC would be cost-effective only when patients plan to undergo colonoscopy, and an additional gastroscopy would only cost €60.00. The study also suggested that a single gastroscopy would cost €137.00, and that it would be cost-effective to conduct independent gastroscopy screenings every five years, in which only the ASR for gastric cancer would be over 25/100,000. In summary, the average detection cost of UGIC is the lowest in opportunistic gastroscopy bundled with a planned colonoscopy, and performing an opportunistic gastroscopy every five years in high-risk areas would be cost-effective.

The endoscopic surveillance of the esophageal adenocarcinoma precancerous status, Barrett's esophagus, is cost-effective.[50] However, its large-scale endoscopic screening would not be cost-effective.[51] In high-risk regions, performing a gastroscopy every

Table 2. Cost-effectiveness details of lectures referred to screening

	Strategy	Country	Risk level	Object and aim disease	Threshold to pay	Advise
Gupta N[39]	Opportunistic gastroscopy bundled with colonoscopy	Various	Various	50 years old, UGIC	$50,000.00	For GC/ESCC/EAC, not cost-effective
Inadomi J[50]	Review	Various	Various	50 years old, BE	$100,000.00	Cost-effective
Xia R[38]	Program screening	China	High-risk area	40–69 years old, UGIC	$30,828.00	Gastroscopy every two years is cost-effective
Wu B[52]	Program screening	China	High-risk area	Over 40 years old, ESCC	$1,151.00	Gastroscopy every 1–3 years is cost-effective
Shah SC[54]	Strategy 1: Opportunistic gastroscopy bundled with colonoscopy every three years, when GIM is identified; Strategy 2: Biennial opportunistic gastroscopy bundled with colonoscopy; Strategy 3: No gastroscopy	United States	Low-risk (Asian-American)	50 years old, GC	$100,000.00	Strategy 1 is cost-effective ($75,959.00–74,329.00/QALY)
Saumoy M[55]	Strategy 1: Opportunistic gastroscopy bundled with colonoscopy every three years, when GIM is identified; Strategy 2: Biennial opportunistic gastroscopy bundled with colonoscopy; Strategy 3: No gastroscopy	United States	Low-risk area	50 years old, GC	$100,000.00	Strategy 1 is cost-effective for non-Hispanic black ($80,278.00/QALY), Hispanic ($76,070.00/QALY), and Asians ($71,451.00/QALY), but not for non-Hispanic white ($122,428.00/QALY)
Kowada A[53]	Biennial screening for mild-moderate CAG, annual for severe CAG	Japan	High-risk area	GC after *Hp* eradication	$100,000.00	Cost-effective
Lau J[44]	Opportunistic screening	Singapore	Middle-risk area	UGIC+HGIN	Not available	$3,950.00/lesion
Areia M[49]	Strategy 1: Upper endoscopy only every five years; Strategy 2: Opportunistic gastroscopy bundled with colonoscopy every 5–10 years; Strategy 3: Gastroscopy after biennial serology screening positive.	Portugal	Middle-risk area	GC	€37,000.00	Strategy 1 is cost-effective when the risk is over 25/100,000; Strategy 2 is cost-effective when the risk is over 10/100,000

CAG, Chronic Atrophic Gastritis; EAC, Esophageal adenocarcinoma; ESCC, Esophageal squamous cell carcinoma; GC, Gastric Cancer; GIM, Gastric Intestinal Metaplasia; HGIN, High-grade Intraepithelial Neoplasia.; QALY, Quality-Adjusted Life Year; UGIC, Upper Gastrointestinal Cancer.

1–3 years as a screening strategy for individuals at the age of 40 would be cost-effective.[52] In the general population of over 50 years old, the ICER for the screening and surveillance of Barrett's esophagus, combined with the screening strategy, was $95,559.00/QALY, indicating high cost.[39] For gastric mucosal atrophy after the eradication of *Hp*, biennial gastroscopy examination for patients with mild-to-moderate gastric mucosal atrophy and annual gastroscopy surveillance for patients with severe gastric mucosal atrophy are the most cost-effective, with a willingness-to-pay threshold of $100,000.00/QALY.[53] The cost-effectiveness of this strategy is also correlated to race. A study conducted in the United States revealed that gastroscopy screening and surveillance are cost-effective for Asians elder than 50 years old, non-Hispanic blacks, and Hispanics, and the ICER per QALY was $71,451.00/QALY, $80,278.00/QALY and $76,070.00/QALY, respectively (willingness-to-pay level = $100,000.00/QALY).[54,55]

The cost-effectiveness details of the lectures are presented in Table 2.[38,39,44,49,50,52-55] It should be noted that the willingness-to-pay threshold was assumed to be the per capita gross domestic product, and that the indigenization of economic effect was necessary.[56,57]

Summary

Compared to opportunistic gastroscopy, there was no significant difference in the detection rate for gastric cancer in the population-based gastroscopy screening strategy, but the proportion of early gastric cancer detected using the population-based gastroscopy screening strategy was significantly higher. The advantage of opportunistic gastroscopy is that the compliance of participants is better, and asymptomatic people would benefit more from this strategy. Opportunistic gastroscopy bundled with planned colonoscopy can lead to higher benefits in UGIC screening. Similarly, if the screening for esophageal cancer is incidentally carried out during the gastric cancer screening, additional benefits can be obtained.

Prospect of opportunistic screening

It remains difficult to carry out a broad population-based screening program for UGIC, which is limited by the number of endoscopic physicians, the risk of UGIC, and the cost-effectiveness of screening. Furthermore, the mortality rate of cancer is positively correlated with the proportion of advanced cancer.[58] Moreover, the medical cost of hospitalized patients with UGIC is rapidly increasing, and the average cost has reached ￥17,567.0 by 2016. In order to reduce the mortality for UGIC, there is a need to improve the detection rate of cancer in the early stage, regardless of the strategy used.

For areas without a population-based screening program, opportunistic gastroscopy would be an important channel for people to receive screening. Studies conducted in Japan and South Korea suggested that people over 40 years old should perform gastroscopy surveillance every two years. This is suggested for high-risk populations, such as first-degree relatives of UGIC, *Hp* infection, high salt diet, and smokers.[59,60] Opportunistic gastroscopy screening for UGIC can be performed in low- and moderate-risk areas, and this can be combined with colorectal cancer screening by colonoscopy.

Conclusions

Opportunistic gastroscopy is important for the early detection and treatment of UGIC. Based on the collected data, it was considered that opportunistic gastroscopy screening can be bundled with colonoscopy as a strategy to optimize its cost-effectiveness in low- and moderate-risk areas and populations. In high-risk areas for UGIC, population-based gastroscopy screening can be used as the main approach. However, the evaluation of monitoring intervals and cost-effectiveness ratios should be localized.

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Conflict of interest

Prof. Bin Lyu has been an editorial board member of Cancer Screening and Prevention since February 2022. The authors have no other conflict of interests related to this publication.

Author contributions

BL contributed to study concept and design, XLJ performed the acquisition of data for the references, XLJ drafted the manuscript, BL performed the critical revision of the manuscript, and BL supervised the study.

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