Endoscopic Gastric Cancer Screening and Surveillance in High-Risk Groups

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Gastric cancer remains a major cancer problem world-wide and future incidence will likely increase due to rapidly aging population demographics. Population-based screening is being undertaken in Korea and Japan, where gastric cancer incidence rates are high, and seems to be effective in reducing mortality from gastric cancer. However, such strategies are difficult to implement in countries with a low incidence or limited resources. Thus, screening strategies should be directed towards high-risk population subgroups. Gastric cancer has a relatively long mean sojourn time, and prognosis of early-stage disease is excellent. In general population, screening at 2-year interval in Korea seems to be effective for early-stage diagnosis. In subjects with atrophic gastritis or intestinal metaplasia, surveillance is recommended at 1 to 3 years intervals according to European and Japanese recommendation. Screening intervals for family members with sporadic gastric cancer has not yet been adequately evaluated, but 1-year interval is recommended for hereditary diffuse gastric cancer family-members. Gastric cancer patients treated by endoscopic resection are the highest-risk group, and 1-year interval surveillance can detect most metachronous gastric cancers at an early stage. Future gastric cancer surveillance strategies using endoscopy should be guided by risk-stratification assessment, and further refinement of optimal surveillance intervals is needed.

Key Words: Stomach neoplasms; Endoscopy; Screening; Surveillance

INTRODUCTION

Gastric cancer (GC) remains a major global cancer problem. Although the proportion of GC among the major cancers is decreasing from the top place in 1975, when the International Agency for Research on Cancer first published global cancer statistics, to fifth place (6.8% of total cancers) in 2012.[1] However, approximately 1 million GC cases are still diagnosed per year, which is expected to increase in number as populations age worldwide. This GC increase is particularly relevant in Eastern Asian counties where approximately half of global GC cases develop. GC was the third most common cause of cancer-related death in 2012. The high GC mortality ranking relative to GC incidence reflects its ominous outcome if detected at late stages. Age-standardized GC incidence in Korea (63.3

for male and 25.1 for female per 100,000 in 2011) is the highest in the world.[2] In contrast to global statistics, however, in Korea GC is the second most common cancer but ranks third in cause of cancer mortality. In Korea, GC mortality rate has been continuously decreasing during the last three decades, to one-third the incidence level, i.e., 19.3 for male and 7.1 for female per 100,000 in 2011.[2] This is a remarkable reduction from when mortality rates and incidence rates were similar in the early 1980's, before screening was introduced.[2]

Usually GC symptoms are absent or nonspecific in early disease stages, and existence of symptoms, especially alarm symptoms, suggests that the GC is of very advanced stage, for which curative surgical resection is often impossible. Preventing GC can involve primary prevention and secondary prevention approaches. As a primary preventative strategy, *Helicobacter pylori* treatment is theoretically promising, acting by reducing gastric inflammation and subsequent mucosal changes such as atrophy or intestinal metaplasia (IM).[3] Regional guidelines recommend *H. pylori* treatment for the purpose of GC prevention in countries with high-risk populations.[4,5] However, evidence for the effectiveness of this approach remains limited and requires confirmation in the large studies that are current-

ly ongoing.[6]

Secondary prevention is the policy of detecting GC in the early stages so that it can be cured by appropriate treatment. Currently, Korea uses this strategy for GC control.[7] Japan also has long implemented this approach using X-ray screening,[8] but recently added the primary prevention strategy of screening and treating *H. pylori* infection in persons with gastritis.[9] Although GC screening using endoscopy seems to provide good protective opportunity to the population, the screening effect on mortality reduction and its cost-effectiveness remains uncertain. The cost of endoscopy in Korea is quite low and allows systematic population-based screening. However, endoscopy is an expensive procedure in most other countries, so screening cost-effectiveness needs to be evaluated by correlating GC incidence with associated testing costs in different countries.[10] In this context, GC screening should also be stratified in populations at the individual level, according to the risk of the subjects. Moreover, risk stratification should be applied according to the result of initial evaluation, and subsequent surveillance schedules need to be standardized, similar to the policies that have been adopted for colorectal cancer screening.[11] Even in a low- to intermediate-risk population such as Singapore, endoscopic surveillance for high-risk subjects with precancerous lesions seems to be a cost-effective approach for GC prevention.[12]

In this paper, current recommendations from the literature and guidelines for GC screening and surveillance strategies for GC-high-risk groups are discussed.

CURRENT GUIDELINE RECOMMENDATIONS FOR GASTRIC CANCER SCREENING

The Korean National Cancer Screening Program (NCSP) provides regular 2-year interval GC screening by upper gastrointestinal X-ray or upper endoscopy for citizens aged ≥40-year-old.[7] The Korean NCSP started GC screening in 1999 as a Medicaid program, but has since expanded to all nationals aged ≥40 years since 2005. Although this recommendation is not based on sound published scientific evidence, the current trend of GC mortality reduction in Korea despite a stable age-standardized GC incidence during last decade supports a mortality-reducing effect of the current screening program.[2] The current Korean NCSP does not; however, provide different recommendation for screening intervals according to GC risk-stratification assessment.

Japan also has a high incidence of GC, and the Japanese guidelines for GC screening recommended photofluorography (indirect X-ray using small films) for population-based and opportunistic screening.[8] The Japanese guidelines, however, do not recommend endoscopy as a screening tool in the general population due to the lack of sufficient evidence of mortality reduction from GC. However, endoscopy can be considered as an opportunistic screening method at the individual level.[8] The first randomized controlled trial (RCT) comparing annual upper gastrointestinal series (GI X-ray) and upper endoscopy with different follow-up schedules according to serological test results are currently underway in Japan.[13]

The Asia Pacific 2008 consensus guidelines on GC prevention recommended *H. pylori* screening and treatment to reduce GC development in high-risk populations.[4] The guidelines endorse the existing practices for GC surveillance in high-risk populations including Korea and Japan. The screening program is limited for high-risk populations in Singapore and Taiwan, whereas there is no GC screening program in China, even though this country is the main contributor of East Asian GC cases and accounts for the half of the global GC burden.[1,14]

The European Society of Gastrointestinal Endoscopy, a group of European gastrological societies, recently published management for precancerous conditions and lesions in the stomach (MAPS) guidelines.[15] These guidelines focus on surveillance of precancerous lesions including atrophy, IM, and dysplasia, but do not address general-population screening.

SCREENING INTERVAL OF GASTRIC CANCER

Adequately understanding GC natural history is essential to develop effective screening-interval guidelines for the general population or high-risk subgroups. RCTs of different follow-up periods can provide high-level evidence for establishing optimal GC screening intervals. Although GC screening is provided to Koreans aged ≥40 years every 2 years, no RCT has yet been performed regarding GC screening intervals using endoscopy. Thus, as of October 2014, detailed studies on Korean or global populations to justify 2-year screening intervals for GC remain rare.[16]

The sojourn time of a cancer is the asymptomatic period during which a cancer can be detected through screening tests before typical diagnostic symptoms develop. The sojourn time is a theoretical concept that is actually impossible to measure. Thus, the mean sojourn time (MST) is used as a statistical parameter for establishing cancer screening intervals in a general population.[16] Recently, the MST of GC was calculated in a study using a male cohort of more than 61,000 participants that voluntarily attended a cancer-screening program and were re-screened by endoscopy.[17] A total of 91 incident cases were found during 19,598,598 person-years of follow-up. The MST of GC was 2.37 years (95% confidence interval [CI], 1.92 to 2.96).

This 2.37-year MST supports the 2-year GC screening interval currently suggested by the Korean NCSP.

The MST in persons aged between 40 to 49 years was 1.25 years (95% CI, 0.95 to 1.68), which is significantly shorter than the 3.18 year MST in people aged 50 to 59 years, or 3.74 years in those aged between 60 to 69 years.[17] This finding is interesting when compared to MST observations with colorectal cancer, in which the MSTs were remarkably similar irrespective of sex and age subgroups. In colorectal cancer, MSTs ranged from 4.5 (95% CI, 4.1 to 4.8) to 5.8 years (95% CI, 5.3 to 6.3) for both sexes and all age subgroups of 5-year interval from the age of 55.[18]

The finding that the MST for GC was shorter in persons aged 40 to 49 years suggests that theoretically a shorter interval of GC screening in younger subpopulations is necessary. Histological GC subtypes include diffuse- and intestinal-types, with the former having more aggressive features including faster growth and more frequent metastasis, typically leading to poorer prognosis. Intestinal-type GC develops according to the Correa pathogenesis pathway, which is mediated by *H. pylori* infection-induced atrophy and IM.[3] Diffuse-type GC is more frequent in younger populations, whereas intestinal-type GC is the prevalent form in older patients.[19] The MST exceeds 3 years in persons in their fifties and sixties, suggesting that a less-frequent screening interval might be adequate rather than the currently employed 2-year interval.

Several retrospective Korean studies suggested that adequate screening interval might be widened to 3-year rather the 2-year interval that the current NCSP recommends. Park et al.[20] showed that the proportion of gastric neoplasms that could be treated by endoscopic submucosal dissection (ESD) was 54.5%, 51.5%, and 50.0% in the respective groups with screening intervals of <12, 12 to 24, and 24 to 36 years. The advanced gastric cancer (AGC) proportions were 16.7%, 16.2%, and 25.0% in these respective groups. Thus, those authors recommended biennial screening interval after considering both of these parameters, and suggested that these results reflect the long natural history of gastric adenoma and early gastric cancer (EGC).

In another Korean observational study, Nam et al.[21] reported GC stage distribution according to screening interval. The risk of detecting AGC did not increase in the 2- or 3-year interval endoscopy screening groups compared with the annual screening group (odds ratio [OR], 1.11 and 1.21, respectively; comparison with both, *p*>0.05), whereas it significantly increased in the 4- or 5-year interval screening groups.[21] The authors suggested that EGD intervals of 3 years can be considered for GC screening rather than the current 2-year interval provided by the Korean NCSP. A Japanese case-control study in 2012 indicated a 30% reduced GC mortality with endoscopic screened within 36 months before GC diagnosis compared to no screening.[22]

Cancer development is a relatively rare outcome and large scale RCTs might be sometimes unrealistic and may be considered unethical if a screening policy is already implemented such as the Korean NCSP for GC. Thus, elaborate population-based observational studies using data from large cohorts is an appropriate alternative way to find the most effective and acceptable screening strategy for a given population.

FAMILY MEMBERS OF GASTRIC CANCER PATIENTS

Family history of GC was shown to be associated with the increased risk of GC, having OR ranging between 2 to 10 according to the ethnic groups studied.[23] An estimated 20% of GC patients have a family history of GC.[24] Most of the GC patients with a family history in Eastern Asian countries are sporadic cases rather than having a GC attributable to inherited syndromes that predispose GC development. A recent report suggested that among 1,273 GC patients, family history of GC in a first-degree member was associated with a higher proportion of differentiated-type histology and was also associated with better prognosis, even in advanced stages (International Union Against Cancer [UICC] stage III or IV).[24] Previous studies suggested that microsatellite instability was more frequent in GCs of patients having family history, and is associated with better prognosis.[25,26] These finding suggest that persons who have GC patient(s) as family members does not necessarily indicate more frequently needed GC screening than the generally recommended 2-year interval in Korea. GCs in the family members are disproportionately of the intestinal type, which has better outcome compared to diffuse-type GC. More precise characterization of GCs in the family members should be defined using a classification system suggested by recent cancer genome studies.[27,28] Before concrete evidence is generated that characterizes GC in family members, there appears to be no basis to recommend a more frequent screening interval compared to individuals without family history of GC.

Among the GCs in patients having family members, a small portion of GCs arises in hereditary syndromes such as hereditary diffuse gastric cancer (HDGC).[29] Currently, modified criteria for clinically diagnosing HDGC includes: (1) two or more cases of documented diffuse GC in first- or second-degree relatives, with at least one case diagnosed at age of 50 years, or (2) three or more cases of confirmed diffuse GC in first- or second-degree relatives, independent of age of onset. Among 25% to 30% of families meeting the HDGC criteria have germ-line mutations in the E-cadherin (*CDH1*) gene.[29] The *CDH1*

germline mutation incidence was high in GC patients from low-risk geographic areas versus high-incidence areas such as Korea and Japan.[26] Prophylactic gastrectomy is recommended to those having a *CDH1* mutation from the age of 20 years, but annual endoscopic surveillance using a high-definition endoscope should be offered for those who do not have a gastrectomy.[30,31]

Familial intestinal GCs having the intestinal-type histology meet the familial GC definition.[29,32] In contrast to HDGC, underlying genetic or molecular changes in this syndrome have not been well-characterized and a distinct screening policy has also not been established. In this familial syndrome, GCs usually occur in aged persons, so surveillance screening can be offered at a starting age that is older than with HDGC. Considering the frequency of disease occurrence in the family members and the uncertainty of MST in familial GC, it might be prudent to follow all family members with intensive endoscopic surveillance.[32]

H. pylori treatment is recommended by European and Chinese guidelines for the first-degree family members of GC patients.[5,33] Although infection with this organism was high in those family members, a GC-preventive effect after bacterial eradication has not yet been confirmed. Current Korean guidelines also recommend treating *H. pylori*, but the evidence level is not concrete and the recommendation is weak.[34] The Korean Health Insurance system, which covers almost of all Korean people, currently does not reimburse the fee for *H. pylori* diagnosis or costs for antibiotics in family members. The 2008 version of the Japanese guidelines also did not recommend treatment due to lack of direct evidence its GC prevention in family members.[35] The GC preventive effect by primary prevention through *H. pylori* treatment and by secondary prevention by endoscopic surveillance should be confirmed in future studies in this high-risk group.

ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA

Atrophic gastritis is common endpoint of mucosal inflammation in the *H. pylori*-infected stomach, and is a well-established precancerous change for GC. This condition is characterized by loss of appropriate gastric glands that are replaced either by connective tissue (nonmetaplastic atrophy) or by inappropriate-type glands (metaplastic atrophy).[36] Many regional guidelines recommend *H. pylori* treatment for this condition without high level of evidences from well-designed RCTs.[4,5,35] Although, reversibility of gastric atrophy after *H. pylori* eradication was suggested in a meta-analysis, reversibility of IM or a GC-preventive effect of treatment have not yet been confirmed.[37]

Presence and severity grading of atrophic gastritis is required for risk stratification, but there is no uniform standard. Endoscopic severity grading is a simple and traditional way of grading.[38] Organized gastric mucosal biopsy and histological evaluation using a visual-analogue scale suggested by the updated Sydney system has been a standard method of biopsy-based atrophy evaluation.[39] For better risk stratification, operative link for gastritis assessment (OLGA) staging system was suggested that report gastritis in terms of stages by combining histological atrophy distribution and severity.[40] Histological evaluation of atrophy is subject to poor interobserver or intraobserver agreement.[15] Thus, the operative link for gastric intestinal metaplasia (OLGIM) system using IM instead of atrophy was suggested for better predicting GC risk with a higher interobserver agreement rate.[41] Although the OLGA system was revealed to be useful for risk stratification in retrospective studies,[42,43] further prospective validation in discriminating high-risk populations is needed.

Japanese studies reported the usefulness of risk stratification of glandular atrophy using pepsinogen (PG) tests.[44] A PG I level <70 ng/mL or a PG I/II ratio <3.0 seems to be associated with high GC risk. Japanese literature recommends risk stratification using PG in combination with *H. pylori* serology tests. If the PG test is negative, then there is no atrophy, and no surveillance is needed except for *H. pylori* eradication in infected subjects. Endoscopic surveillance is recommended regardless of *H. pylori* infection status in PG test-positive cases because there is a significant risk of developing GC. But the suggested surveillance interval differs according to *H. pylori* status. In *H. pylori*-negative and PG-positive cases, the surveillance interval is as frequent as once per year because this group has such severe atrophy that *H. pylori* is spontaneously eliminated from the unfavorable inhabitancy. Asaka et al.[9,45] suggested surveillance intervals of less frequent, 3 to 5 years in cases with both PG- and *H. pylori*-positive testing because of less severe atrophy in this group, but recently more frequent 1 to 2 years interval was suggested if there's atrophy.

European guidelines about the MAPS suggest a different GC surveillance strategy from the Japanese approach.[15] For histological assessment for premalignant conditions, at least four biopsies of the proximal and distal stomach, on the lesser and greater curvature, were recommended and OLGA and OLGIM systems were suggested to be useful in determining the subgroups with higher risk of GC. The consensus was that: (1) extensive atrophy and/or extensive IM should be endoscopically surveilled at a 3-year interval, and (2) mild-to-moderate atrophy/IM that is limited to the gastric antrum need not surveillance after *H. pylori* eradication.[15]

The current Korean NCSP does not recommend risk stratification using endoscopic- or biopsy-confirmed atrophy or

IM, and subsequently a different surveillance schedule is not suggested. The policy of screening endoscopy at 2-year intervals for all populations aged ≥40 years might be sufficient for Korean adults because they have high prevalence (≥60%) of *H. pylori* infection and consequently have a high chance of unrevealed glandular atrophy or IM.[46] Whether screening for GC is necessary for lifelong *H. pylori* naive persons or for those who had eradicated *H. pylori* before atrophy develops should be evaluated urgently to save the enormous associated costs in the current strategy.

Chung et al.[47] reported that annual screening of the Korean population improved detection of early-stage and endoscopically treatable GC, suggesting that intensive screening and surveillance may be useful for high-risk subpopulations with epidemiologic risk factors or premalignant lesions such as IM. However, another Korean study suggested that an annual endoscopy interval did not have benefit in terms of GC stage or proportion of endoscopically treatable GCs identified.[20,21] Moreover, atrophy or IM are mainly associated with intestinal-type GC in more aged populations, and these cancers usually grow slowly and have less aggressive feature compared to diffuse-type GC.[19,43]

METACHRONOUS GASTRIC CANCER SURVEILLANCE AFTER ENDOSCOPIC RESECTION

The proportion of GC diagnosed in an EGC stage is increasing in Korea due to routine screening endoscopy and easy availability of endoscopy as a nonulcer dyspepsia workup tool. If the lesion meets the absolute or expanded indication it is usually treated by endoscopic resection (ER).[48] ER is an excellent minimally invasive treatment modality that can preserve the entire stomach and consequently provide an excellent quality-of-life. This treatment, however, renders the patients in a high-risk state for developing metachronous GC because most of the remaining gastric mucosa has persistent inflammation or end-stage sequelae such as atrophy. The reported glandular atrophy rate following ER is more than 90%.[49]

Previous studies after ER reported incidence of metachronous GC as high as 3.0% to 4.0 % per year.[50-52] Cumulative metachronous GC rates were reported to be 5.9% at postoperative 3 years,[53] and up to 15% to 16% after 5 years, by Kaplan-Meier plots.[52,54] These figures categorize this group of patients as the highest-risk group for subsequent cancer development. A remarkable finding is that the most of the metachronous EGCs are also detected at the early stage within ESD indications. Thus, repeated ESDs provided cure for more than 90% of metachronous EGC cases, and surgery also provides definitive cure for the remaining small portion of disease.[53,55]

Whether *H. pylori* treatment in EGC patients can protect the remaining gastric mucosa from metachronous GC is controversial. Only two prospective RCTs have been reported to date and the results are conflicting. Fukase et al.[49] suggested that *H. pylori* eradication decreases subsequent metachronous GC risk down to an OR of 0.353 by intention to treat analysis (*p*=0.009) in study population of 544 patients followed-up to 3 years.[49] In contrast, a recently reported Korean study showed that *H. pylori* eradication did not significantly decrease metachronous GC risk (*p*=0.15) during a median 3-year follow-up in 901 patients treated with GC or dysplasia.[56] Despite their prospective RCT designs, major limitations common to both studies are a relatively short follow-up duration that precluded confirming the long-term effect of *H. pylori* eradication on GC risk, and their nonblinded study designs. Retrospective studies with longer follow-up durations also reported conflicting data. Several Korean studies showed the reduced incidence of metachronous GC after *H. pylori* treatment.[54,57] However, Japanese studies did not show significantly reduced GC incidences, especially in long-term follow-up studies.[52,58] Despite these conflicting results, most studies agree that GC still develops even after *H. pylori* treatment. This might be from severe background cancer-prone mucosal change at the time of initial GC diagnosis.

The interval of endoscopy follow-up was recommended to be annual or biannual.[48] However, in the first postoperative year frequent endoscopic follow-up is a common clinical practice because of the high prevalence of synchronous cancer, which might often be missed at initial evaluation.[52] Miss rates for synchronous GC were reported to be 14% to 20%.[52,59,60] Metachronous GC detection rate during the first year after ESD increases steeply compared to that assessed beyond 1 year.[49,56] This suggests that undetected synchronous cancers at the time of initial ESD are responsible for such discrepancy in the incidence slopes. Kato et al.[52] suggested that even massively invading cancers including AGC could be missed at initial evaluation before ESD, and accounted for four of their 21 missed cases. In most centers, the usual follow-up timing is 1 to 3 months after ESD, 6 months, and then 1 year. Endoscopy follow-up after ESD should be as early as within 3 months and additionally 6 months to detect possible missed synchronous cancer, and then with every 12-month intervals from ESD date.[52,53] The efficacy of more frequent 6-month follow-up interval compared to 12-month interval needs be evaluated, and patient subgroups who will benefit from the more frequent follow-up schedule should be defined. Routine follow-up biopsies at the ESD scar might be unnecessary if EGC lesion was resected curatively in *en bloc* with tumor-free lateral and deep margins because of little risk of local recurrence.[61]

It is unknown how long GC surveillance should continue after ESD. One study suggested that GC recurrence is self-lim-

iting after 10 years post-ESD, showing a flattened Kaplan-Meier curve.[62] However, many studies suggested that GC risk continuously increases in a linear pattern as age increases, and risk might persist so that ongoing surveillance seems to be a prudent strategy in patients once treated by ER, even after *H. pylori* treatment.[52,53] Thus, continuous surveillance beyond 5-year past the initial ESD seems to be necessary.

After surgical treatment of subtotal gastrectomy, remnant stomach GC is not a rare condition. However, because the remaining cancer-prone mucosal portion showing atrophy or IM is significantly smaller than that after ER, whether surveillance for remnant stomach is mandatory or optional remains controversial.[63,64] Several studies suggested that ESD can be applied to many remnant stomach cancers if found in early stages suitable to ER, and complete resection could be achieved in most of the cases although it is technically challenging.[65,66]

CONCLUSIONS

GC screening is an effective strategy for preventing GC mortality. GC screening program should be combined with risk stratification and surveillance strategies for high-risk groups. Such strategies can utilize limited resources effectively to improve cost-effectiveness. Currently available screening and surveillance protocols are not stringently evidence-based. Developing guidelines and recommendations for assessing GC high-risk groups is strongly needed so that acceptable strategies can be adopted, even in countries having a low GC incidence as well as in counties with high GC incidences and mortality.

Conflicts of Interest

Acknowledgments

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