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Early Diagnosis in Gastric Cancer: Pilot Project

Mide Kanserinde Erken Tanı: Pilot Proje

Hikmet AKGÜL,[a]
Salim DEMİRCİ,[a]
Hilmi Ender KOCAOĞLU,[a]
Sancar BAYAR,[a]
Ali Ekrem ÜNAL,[a]
Marlen SÜLEYMAN,[f]
Serkan AKBULUT,[g]
Berna SAVAŞ,[b]
Arzu ENSARİ,[b]
Necati ÖRMECİ,[c]
Recep AKDUR,[d]
Atilla Halil ELHAN,[e]
Mine Esin OCAKTAN[d]

Departments of
[a]Surgical Oncology,
[b]Pathology,
[c]Gastroenterology,
[d]Public Health,
[e]Biostatistics,
Ankara University Faculty of Medicine,
[f]Clinic of General Surgery,
Surgical Oncology,
Ankara Training and Research Hospital,
Ankara
[g]Clinic of General Surgery,
Surgical Oncology,
Adana Numune Training and
Research Hospital,
Adana

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Yazışma Adresi/*Correspondence:*
Serkan AKBULUT
Adana Numune Training and
Research Hospital,
Clinic of General Surgery, Adana,
TURKEY/TÜRKİYE
sarkhany@gmail.com

ABSTRACT Objective: Gastric cancer, fourth most common cancer type around the world is the second leading cause of cancer related deaths. Nevertheless when appropriately treated at early stage 5 year survival rates are higher than 90%. In eastern countries extensive endoscopic screening increased early gastric cancer (EGC) diagnosis rate up to 70%. In Turkey EGC diagnosis rate is low, a pilot screening project therefore is planned by Department of Surgical Oncology, Ankara University School of Medicine. **Material and Methods:** 7316 subjects were included in the study to whom upper gastrointestinal endoscopy was applied. From 1120 of these participants 1139 biopsy samples were taken. **Results:** In gastric cancer patients (n:21) 4 had a diagnosis at the early stage. Also 14 (1.41%) mild dysplasia and 2 (0.2%) severe dysplasia were detected. In addition, 54.8% of volunteers with endoscopic biopsies were *Helicobacter pylori* positive and a rate of 41.23% and 22.47% for atrophic gastritis and intestinal metaplasia was detected, respectively. Previously EGC detection rate was 6.3% among the subjects admitted to a hospital with gastric cancer in Turkey. By this screening programme we found an almost 4 fold increase in EGC rate. **Conclusion:** We therefore recommend that endoscopic screeening for gastric cancer is a requirement for Turkey. This preliminary study should be followed by a more extensive project evaluating the cost effectiveness of screening and its effect on mortality rates.

Keywords: Stomach neoplasms; endoscopy; early detection of cancer; gastritis, atrophic; metaplasia; *helicobacter pylori*

ÖZET Amaç: Dünyada en sık görülen 4. kanser tipi olan mide kanseri, kansere bağlı ölüm sıralamasında da 2. sıradadır. Erken evrede yakalanıp uygun bir şekilde tedavi edilebilirse 5 yıllık sağkalım oranı %90'dan yüksektir. Uzak doğu ülkelerinde yaygın endoskopik taramalarla erken mide kanseri saptama oranı %70'lerin üzerine çıkmıştır. Ülkemizde erken mide kanseri saptama oranı çok düşüktür, bu yüzden Ankara Üniversitesi Tıp Fakültesi Cerrahi Onkoloji Bilim Dalı tarafından pilot tarama projesi planlanmıştır. **Gereç ve Yöntemler:** Bu projeye katılan 7316 kişiye üst gastrointestinal sistem endoskopisi yapılmış ve bu kişilerden 1120'sinden toplam 1139 endoskopik biyopsi örneği alınmıştır. **Bulgular:** Saptanan 21 mide kanserli olgunun 4'ü erken evrede yakalanabilmiştir. Ayrıca 14 (%1.41) olguda hafif displazi, 2 (%0.2) olguda ağır displazi saptanmıştır. Ek olarak gönüllülerin %54.8'inde *Helicobacter pylori* pozitifliği, helikobakter pilori pozitifliği olanların %41.23'ünde atrofik gastrit ve %22.47'sinde intestinal metaplazi saptanmıştır. Türkiye'den daha önceden yayınlanmış çalışmalarda mide kanseri şikayeti ile hastaneye başvuran hastaların %6.3'ü erken evrede iken, bu tarama programında erken mide kanseri saptama oranı 4 kat daha yüksektir. **Sonuç:** Türkiye' de mide kanseri için endoskopik taramanın gerekli olduğunu düşünmekteyiz. Bu çalışma, tarama yapmanın maliyet etkinliğini ve mortalite oranları üzerindeki etkisini değerlendirmek için daha geniş projeler ile takip edilmelidir.

Anahtar Kelimeler: Mide neoplazileri; endoskopi; kanserin erken tespiti; gastrit, atrofik; metaplazi; *helicobacter pylori*

Gastric cancer, fourth most common cancer type around the world is the second leading cause of cancer related deaths. Approximately a million new gastric cancer cases are expected to occur every year.[1]

The main treatment for gastric cancer is surgery and at early stages results are often very good. Therapeutic approach for early gastric cancer (EGC)

differs depending on the pattern of tumor growth, infiltration depth, lymph node metastasis and differentiation degree. When appropriately treated 5 years survival rates are higher than 90%.[2-5]

In endemic regions screening programmes in order to catch the EGC cases are reported to be beneficial. Countries with high rates of gastric cancer like Japan and South Korea have also increased EGC rates due to the implementation of extensive screening programmes.[6,7] EGC diagnosis rate increased up to 70% in these countries whereas in western countries this rate remains at only 15%. It was reported that mortality rates decreased with screening by photofluorography in Japan.[8] But in a recent study endoscopy was suggested to more likely detect localised gastric cancer comparing with upper gastrointestinal series (UGIS) and diagnosis rates increased 2.7 to 4.6 fold via endoscopic screening.[9,10]

According to Globocan 2012 data, in Turkey age standardised gastric cancer incidence was expressed to lie between the frequencies seen in east Asia and western countries. According to a previous report EGC diagnosis rate was 6.3% in Turkey.[11] Due to the lack of screening programmes, most patients admit to hospitals at advanced stages and this adversely affects the disease outcome. In this study we therefore planned a pilot screeening programme in order to assess the EGC rate and find out whether endoscopic screening for gastric cancer is required in Turkey or not.

MATERIAL AND METHODS

STUDY DESIGN

In Turkey, eastern regions are known to have higher gastric cancer rate than western regions.[12] In order to represent gastric cancer distribution accurately Ankara was selected as the pilot region because of its heterogeneous population content related with migrations occured from both western and eastern localisations.

A pilot study covering 6 different districts of Ankara was planned and conducted by Surgical Oncology Department of Ankara University Medical School. The study was supported by State Planning Organization of Turkey.

The study protocol was approved by ethics committee of Ankara University. Thereafter with the help of health care departments belonging to 6 districts of Ankara, Public Health Department of Ankara University and local governers, education regions for volunteers were constituted. Volunteers who gave informed consent at the education meetings were included in the study.

A total of 8300 volunteers admitted to the screeening programme all of whom took a questionnaire designed to assess the presence of risk factors related with gastric cancer. Totally 984 volunteers did not have an endoscopic evaluation and were excluded from the study (872 volunteers did not attend the appointment, 112 volunteers could not tolerate gastroscopy or did not fast properly before the procedure). All the endoscopic evaluations were performed by 3 different experienced gastroenterologists. Biopsies were taken in case of malignancy suspicion. Histopathological examinations of the biopsy specimens were done by 2 experienced pathologist.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences 19.0 (SPSS, Inc., Chicago, IL, USA). Demographic variables were presented as the mean ± SD (standard deviation). The Pearson Chi square test was performed to test the significance of relationship between two categorical variables. $p<0.05$ was considered statistically significant.

RESULTS

ENDOSCOPIC FINDINGS

The study included 7316 subjects of whom 67.8% was female (n=4957) and 32.2% was male (n=2359). The mean age of the subjects was 47.8. ± 11.2 years.

Esophageal, gastric and duodenal endoscopic screening results were evaluated separately. In 88.1% of the participants, esophageal and esophagogastric junctional mucosa seemed normal whereas 11.7% of the subjects had esophagitis at different grades according to Los Angeles Classification.[13] Suspicious appearance for Barrett esopha-

gus was detected in 9 patients. One subject was determined to have malignancy in the proximal part of esophagus (Table 1). At cardioesophageal junction minimal laxity, moderate laxity and hiatal hernia was observed in 30%, 6.3%, and 5.6% of the volunteers, respectively.

Evaluation of gastric endoscopic findings revealed that 4.6% of the volunteers had normal gastric mucosa. In 91.8% of the subjects inflammation at different localisations was detected (Table 2). Some of the volunteers had prior gastric operations (stomach with prior partial resection; n:45 (0.6%), stomach with gastroenterostomy operation; n:16 (0.2%)).

When duodenal endoscopic findings were evaluated, normal duodenal mucosa, active ulcer and chronic ulcer or healed ulcer scars were detected in 77.8%, 7.7%, 1.4% of volunteers respectively and in 1 of the volunteers polypoid neuroendocrine tumor was detected (Table 2). In 45 (0.6%) volunteers duodenum could not be evaluated because of prior partial gastric resections.

TABLE 1: Distribution of mucosal appearance patterns in the endoscopic evaluation of esophagus.

Esophagus		n (%)
Normal mucosa		6449 (88.1)
Esophagitis	Grade A	646(8.8)
	Grade B	168(2.3)
	Grade C	22(0.3)
	Grade D	21(0.3)
Suspicion of Barret esophagus		9(0.1)
Malignancy		1(0.013)

HISTOPATHOLOGICAL FINDINGS

From 1120 of 7316 volunteers, a total of 1139 biopsies were taken from different localisations during endoscopy. Histopathological evaluation of 85 esophageal biopsy specimens identified 1 patient with malignancy and 4 patients with Barrett esophagus (Table 3).

In 409 of 992 (41.23 %) biopsies taken from stomach chronic atrophic gastritis (CAG) were detected and 209 of volunteers with CAG had concomitant premalignant lesions such as intestinal metaplasia (n:193), mild dysplasia (n:14) and severe dysplasia (n:2). Thirty of 298 specimens with chronic non atrophic gastritis (CNAG) was detected to have accompanying premalignant lesion in the form of intestinal metaplasia. A total of 223 (22.47%) diagnosis of intestinal metaplasia per 992 gastric biopsy specimens was detected. Also 1.41% mild dysplasia and 0.2% severe dysplasia were detected in gastric biopsies (Table 4).

One neuroendocrine tumor in bulbus was detected according to duodenal biopsy results (Table 5).

TABLE 2: Distribution of mucosal appearance patterns in the endoscopic evaluation of stomach and duodenum.

Stomach		n (%)	Duodenum	n (%)
Normal mucosa		340 (4.6)	Normal mucosa	5693(77.8)
Gastritis	superficial gastritis	364 (5.0)		
	antral gastritis	1237(16.9)	Bulbitis	893 (12.2)
	proximal gastritis	206 (2.8)		
	pangastritis	4906 (67.1)	Inflammation in the second part of duodenum	8 (0.1)
Gastric ulcer	Type I	68 (0.9)	active	562 (7.7)
	Type II	33 (0.5)		
	Type III	68 (0.9)	Duodenal ulcer	100 (1.4)
	Type IV	2 (0.027)	chronic	
Gastric polyp (1-2 polyps)		3 (0.041)	Duodenal polyp	3 (0.041)
Gastric polyposis (multiple polyps)		2 (0.027)	Diverticule	7 (0.1)
Suspicious lesions for malignancy		25 (0.34)	Suspicious lesions for malignancy	1 (0.013)
Suspicious lesions for dysplasia		1 (0.013)	Submucosal lesion	4 (0.054)

By histological examination of tissue biopsy samples 54.8% of the volunteers was *Helicobacter pylori* (HP) positive while 45.2% was HP negative. Intestinal metaplasia was detected in 25.3% of subjects positive for HP infection. The association between HP infection and intestinal metaplasia was statistically significant ($p<0.05$). In 2.5% of volunteers different grades of dysplasia was detected but the relation between dysplasia and HP infection was not statistically significant ($p>0.05$). Also there was no statistical significant relation between atrophic gastritis, non atrophic gastritis, benign lesions like gastric ulcer and HP infection. In volunteers without HP infection, rates of normal mucosa, active ulcer, non atrophic gastritis (31% accompanying intestinal metaplasia), chronic atrophic gastritis (62.2% accompanying intestinal metaplasia), minimal inflammation detected were 3.5%, 3%, 12.9%, 34.6%, 45.6% respectively.

In 27 volunteers malignant lesions were detected by endoscopic screening (Figure 1-6 are views of some of these malignant lesions). Diag-

TABLE 3: Results of the histopathological evaluation of esophageal biopsy specimens.

	Upper, middle sections of esophagus	Squamocolumnar junction
Normal mucosa	1	4
Esophagitis	4	35
Ulcer	1	6
Squamous papilloma	11	5
Leiomyoma	1	-
Melanosis	2	-
Foveolar metaplasia or columnar metaplasia	-	10
Barrett esophagus	-	4
Malignancy	1	-
Total biopsy	21	64

TABLE 4: Results of the histopathological evaluation of gastric biopsy specimens.

			Antrum	Corpus	Cardia	Fundus	Anastomosis line
Normal mucosa (n:24)			18	6	-		
Mild inflammatory changes (erosion, foveolar hyperplasia, regeneration, minimal gastritis) (n:175)			124	32	5	8	6
Chronic non atrophic gastritis	All CNAG (n:298)		190	89	12	6	1
(CNAG) (n:298)	CNAG + premalignant lesions(n:30)	Intestinal metaplasia (n:30)	24	6			
Chronic atrophic gastritis	All CAG (n:409)		312	91	2	4	
(CAG) (n:409)	CAG + premalignant lesions(n:179)	Intestinal metaplasia (n:163)	157	35	1		
		Mild dysplasia (n:14)	12	1	1		
		Severe dysplasia (n:2)		2			
Ulcer (n:30)			20	5			5
Polyps (n:31)	Hamartomatous		2	2	2		
	Hyperplastic		5	3	4		
	Inflammatory		1				
	Fundic gland polyp		-	10		2	
Malignancy (n:25)	Adenocarcinoma		11	5	5		
	Non Hogdkin lymphoma		1	-			
	Neuroendocrine tumor -		2				
	Gastrointestinal stromal tumors			-	-	1	
Total Biopsy (n:992)			684	245	31	20	12

TABLE 5: Results of the histopathological evaluation of duodenal biopsy specimens.

	Bulbus	Second part of the duodenum
Normal mucosa	-	4
Minimal inflammation	4	6
Active peptic duodenitis	20	10
Ulcer	1	-
Gastric heterotopia	2	-
Lymphoid hyperplasia	2	5
Adenomatous polyp	-	1
Lipoma	-	1
Gluten enteropathy	-	5
Neuroendocrine tumor	1	-
Total biopsy	30	32

noses of these lesions were proximal esophagus adenocarcinoma (n:1), gastric adenocarcinoma (n: 21), gastric neuroendocrine tumor (n: 2), gastric non Hodgkin lymphoma (n: 1), gastric GIST (n: 1), duodenal neuroendocrine tumor (n: 1).

In gastric adenocarcinoma cases woman to man ratio was 1.1: 1. Median age was 58 years (min 31, max 77). Tumor localisations were antrum (n:10), cardia (n:5), corpus (n:5) and 1 linitis plastica. Curative resections could be performed in 15 patients with gastric adenocarcinoma (10 subtotal gastrectomy, 5 total gastrectomy (in 1 combined splenectomy). The other 6 patients were consulted to medical oncology (n:2) or underwent to palliative surgical procedures (n:4).

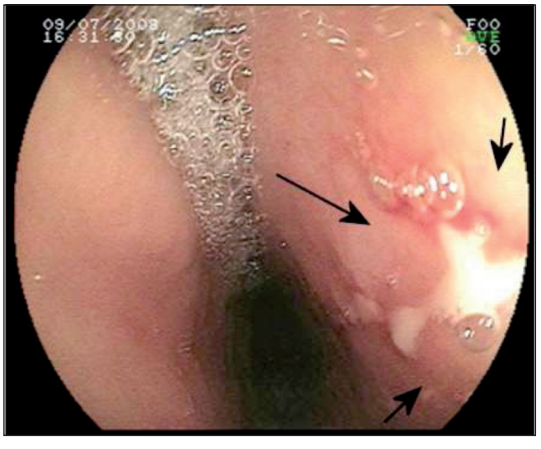

FIGURE 1: NonHodgkin Lymphoma at antrum incusura angularis.

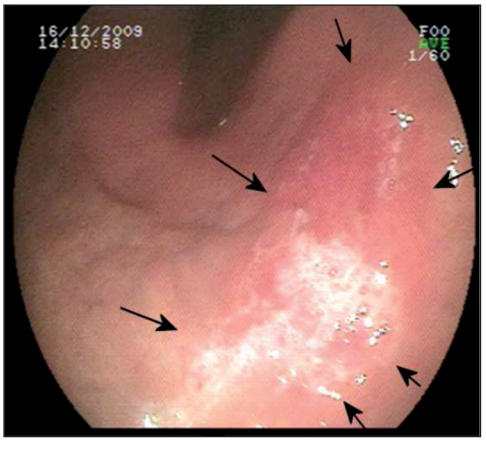

FIGURE 2: Early adenocarcinoma at cardia (Pathology T1bN0M0).

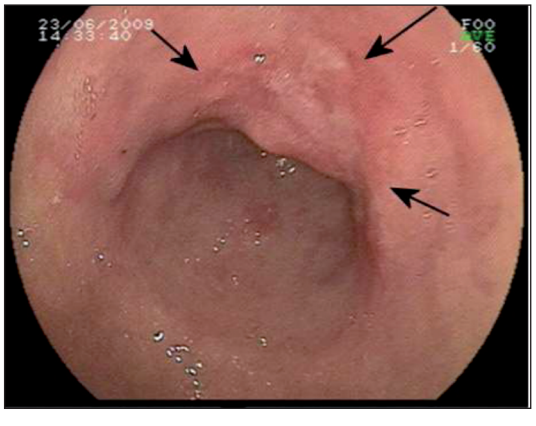

FIGURE 3: Early adenocarcinoma at antrum (Pathology T1bN1M0).

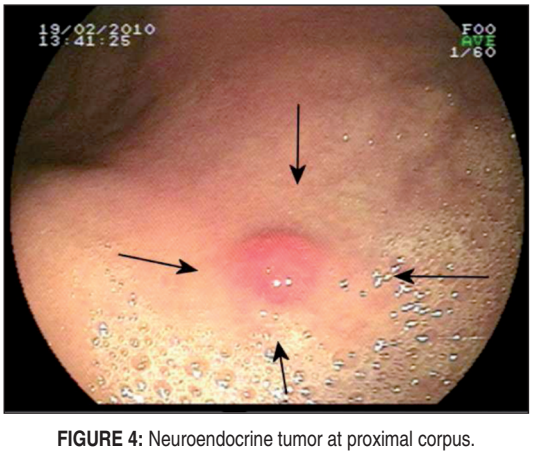

FIGURE 4: Neuroendocrine tumor at proximal corpus.

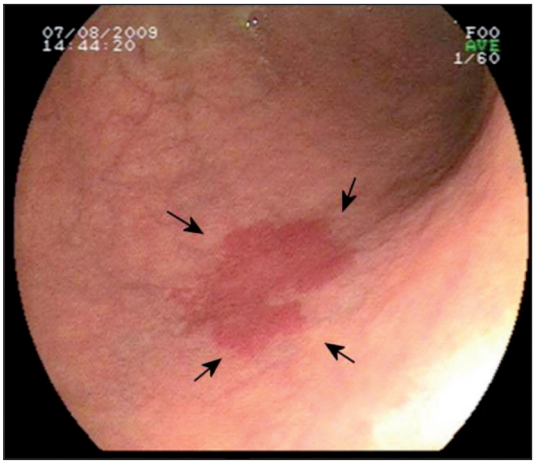

FIGURE 5: Severe dysplasia region at distal corpus.

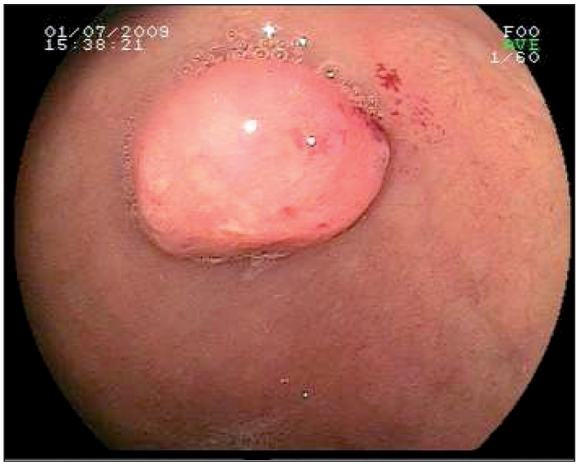

FIGURE 6: Neuroendocrine tumor at bulbus.

TABLE 6: TNM staging of the cases with gastric cancer detected by endoscopic screening.

Stage	n
IA - IB (EGC)	4
IIA	1
IIB	6
IIIA	2
IIIC	7
IV	1
Total	21

Distribution of gastric cancer according to stages were presented in (Table 6).

DISCUSSION

In Turkey like most western countries, gastric cancer patients refer to health services at advanced stages. It has been reported that 50.2-61.2% of the admissions occured at stage 4.[14-16] Gastric cancer may often be cured if it is diagnosed and treated at early stages. In order to diagnose gastric cancer at early stages screening shoud be done. According to our knowledge no extensive programme for gastric cancer screening has been done in Turkey up to now and this pilot project is the first screening programme applied in our country.

Except Japan and South Korea, no country is known to have a national programme for gastric cancer screening.[17] Screening methods include fluorography, radiological upper gastrointestinal series, HP antibody tests, serum pepsinogen tests and endoscopic procedure.[10,17,18] In Japan good results were reported related with -radiological screening-the national screening programme.[19] For cases of uncertain malignant potential endoscopic screening is alternative to radiological screening. In a study comparing the screening methods, it was suggested that screening with endoscopy performed better than photofluorography for gastric cancer diagnosis.[20] Though endoscopic screening has a high cost it was accepted as the national program in South Korea since 2000.[21] In China there is no mass screening programme for gastric cancer but only in high risk regions of the country local screening programmes are applied just as in other countries like Taiwan, Singapoor and Iran.[22-25] Nevertheless endoscopic screening is suggested to cause positive results in many studies requirement of mass screenings are still argued regarding with the high cost.[26,27] There is still an ongoing debate about the cost-effectiveness of these national screening programmes. Although it was shown to cause high costs in many countries a study from Korea reported that endoscopic screening had an acceptable cost for both genders.[28]

The cost of endoscopic screening conducted between 2007 and 2012 was 3.2 million Turkish Liras. In order to decrease screening cost, biopsies were taken only in case of malignancy suspicion.

According to our screeening results gastric cancer prevalence was 21 / 7316. Four of the 21 gastric cancer patients were at the early stage. Besides 2 patients with severe dysplasia -increased risk for gastric cancer development- were caught. Six (4 EGC, 2 severe dysplasia) of 23 patients (26%) had the opportunity of therapy at early stages. In a large scale retrospective study conducted in Turkey EGC detection rate was 6.3% among the subjects admitted to a hospital with gastric cancer, by this screening programme EGC detection rate increased almost 4 folds.[11]

Although screening costs were high, it should be considered that in advanced gastric cancer treatment, chemoradiation is also added to the therapy, and it also increases the costs and there are high survival rate differences between early and advanced gastric cancer patients and terminal stages of advanced gastric cancer patients are really heartbreaking.

Evaluation of histopathological examination results detected a rate of 41.23% and 22.47% for atrophic gastritis and intestinal metaplasia, respectively which was a remarkable finding of the study. Considering high rates of these premalignant lesions we suppose that it will not be wrong to think that Turkey is a high risk region for gastric cancer.

One of the most important results seen in this screening programme was the high incidence of HP infection which is a well-known cause of gastric cancer. According to the epidemiological data from Asia, HP infection increases the gastric cancer risk 2 folds. In our study HP infection rate was 54.8% according to pathological evaluation of the biopsies taken during endoscopic screeening which means that in our country HP positivity is as high as countries where gastric cancer is most prevalant. Seroprevalence of HP is 58.1%, 59.6%, 54.5% in China, Japan and South Korea, respectively.[29-31] Since it is known that HP eradication lowers the promotion of premalignant lesions and gastric cancer development, appropriate therapy should be given to HP positive patients according to screeening results.[31,32]

CONCLUSION

In conclusion we recommend that endoscopic screeening for gastric cancer is a requirement for Turkey. This preliminary study should be followed by a more extensive project evaluating the cost effectiveness of screening and its effect on mortality rates.

Conflict of Interest

Authors declared no conflict of interest.

Financial Support

The Project was financially supported by State Planning Organization of Turkey.

Authorship Contributions

Hikmet Akgül is manager and the chief of the Project, designed the study; Salim Demirci, E. Hilmi Kocaoğlu, Sancar Bayar, A. Ekrem Ünal interpreted the results and helped editting. Marlen Süleyman, MD collected project data and help editting. Serkan Akbulut, MD editted for publication. Berna Savaş, Arzu Ensari performed pathologic examination of biopsy specimens. Necati Örmeci coordinated and performed endoscopies. Recep Akdur, Mine Esin Ocaktan performed collection and education of the volunteers. Atilla Elhan performed statistical analyses.

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