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Morphological changes in human gastric tumours after eradication therapy of Helicobacter pylori *in a short-term follow-up*

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SUMMARY

Background: It is controversial as to whether the development of gastric cancer is influenced by *Helicobacter pylori* eradication. If eradication itself influences the tumour morphology, this may affect the tumour discovery rate.

Aim: To investigate the morphological changes in the gastric neoplasm after *H. pylori* eradication.

Methods: We studied 37 patients with eradication therapy. After a 1-month follow-up, endoscopic re-evaluation was performed and the appearance was compared with first image. All lesions were resected endoscopically, and were subjected to histological assessment and to immunohistochemistry. Serum gastrin levels were determined before and after eradication.

Results: Twenty-nine of 37 patients underwent successful eradication. The appearance of 11 lesions (33% of 33 lesions) became indistinct after successful eradication. All lesions were of the superficial-elevated type and the height of the lesions decreased. We detected normal columnar epithelium over the neoplasm in eight of the lesions. Higher expression of single-stranded deoxyribonucleic acid in the deep area was characteristic in tumours with an indistinct appearance. These changes did not correlate with the serum gastrin levels.

Conclusions: The morphology of the gastric neoplasm change after eradication in the short-term. This may contribute to the decreased tumour discovery rate.

INTRODUCTION

Helicobacter pylori plays an important role in the promotion of atrophic gastritis.[1] Long-term infection of *H. pylori* results in glandular atrophy and intestinal metaplasia. It has been accepted that there is a strong association between *H. pylori*-associated gastritis and gastric cancer.[2–4] Uemura *et al.* clearly demonstrated that gastric cancer developed only in patients with *H. pylori* infection by prospective study.[5] *Helicobacter pylori* eradication therapy is widely accepted as a prevention of peptic ulcer. We have previously demonstrated that the extent of gastric atrophy and intestinal metaplasia improved in some cases after successful eradication therapy.[6] Severe gastric atrophy induced by *H. pylori* is thought to be an important risk factor in the development of gastric carcinoma; therefore, it is speculated that control of histological gastritis is linked to the control of gastric cancer developments. Indeed, Uemura *et al.* had reported that eradication therapy of *H. pylori* decreased the occurrence of second gastric cancer in patients with pre-treated gastric cancer by

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endoscopic mucosal resection.[7] We also found a low Ki-67 labelling index in gastric cancer cells in *H. pylori*-negative gastric cancer tissue compared with *H. pylori*-positive tissue, suggesting that *H. pylori* has a growth promoting role on gastric cancer cells.[8] However, it is still controversial as to whether eradication therapy of *H. pylori* diminishes the incidence of gastric cancer.

One of the difficulties of this field seems to be based on the methodology used to evaluate the gastric carcinogenesis. Researchers can evaluate the degree of carcinogenesis only by the discovery rate of gastric cancer by endoscopic examination. Due emphasis must be placed on the differences in diagnostic ability of each examination. Moreover, endoscopic morphology might be influenced directly by eradication therapy, this affecting the discovery rate of gastric cancer.

In the present study, we focused on the morphological changes in gastric neoplasms after the eradication therapy with a short-term follow-up study. We then examined the histological and molecular biological changes induced by eradication therapy, and discussed the clinical implication.

METHODS

Patients

Thirty-eight patients with gastric neoplasm (27 men, mean age: 69.1 year old) were included in this study, and 45 lesions (28 gastric carcinomas and 17 gastric adenoma) were studied. All patients received an endoscopic examination and the endoscopic features were recorded in a database. No patients who had undergone gastrectomy were included in the study. All patients had histological gastritis in both corpus and antrum and were confirmed as being *H. pylori*-positive by rapid urease test (PyloriTek, Serim Research, Elkhart, IN, USA), Giemsa staining, ^{13}C-urea breath test (UBT; Otsuka UBiT-IR200, Tokushima, Japan) or the presence of serum IgG antibodies against *H. pylori* (E-plate, Eiken, Tokyo, Japan). Patients were considered as *H. pylori*-positive if at least two of them were positive. After diagnosis of the *H. pylori* infection, all patients received eradication therapy by the use of a proton-pump inhibitor (lansoprazole 60 mg, twice daily), amoxicillin (1500 mg, twice daily) and clarithromycin (400 mg, twice daily) for 1 week. The successful clearance of *H. pylori* was judged more than 4 weeks later by UBT or the *H. pylori* stool antigen test (Meridian Diagnostics, Cincinnati, OH, USA). A second endoscopic observation was performed prior to endoscopic mucosal resection (average 33.9 days) of the gastric tumour. From the patients we received written informed consent and the Ethical Committee of Hiroshima University approved our protocol.

Evaluation of endoscopic findings

First, endoscopic pictures were saved in the database. Secondly, endoscopic observations were performed using the same endoscopic system and saved in the same manner. Later, the pictures were printed out and three specialists judged the alterations of endoscopic appearance independently, unaware of the clinical information including the evaluation of the eradication therapy. They evaluated the endoscopic changes concerning: (i) difficulties to point out the tumour itself or its margin (whether tumour became indistinct or not), (ii) tumour height or depth, (iii) tumour surface and (iv) the degree of redness in background mucosa. If more than two specialists recognized the finding, we regarded it as being significant.

Determination of serum pepsinogen and gastrin levels

Fasting serum was collected from all patients. The samples were centrifuged immediately at 4 °C and stored at −20 °C until use. Serum concentrations of pepsinogens (PGs) and gastrin were determined by enzyme-linked immunosorbent assay and modified radioimmunoassay.[9]

Immunohistochemistry

About 4-μm sections of formalin-fixed paraffin-embedded tissues were used for immunohistochemical staining. After deparaffinization and hydration, internal peroxidase was blocked by incubating with 0.3% H_2O_2 in methanol for 15 min. After incubation with 5% skim milk/phosphate-buffered saline (PBS) for 20 min, the sections were reacted with the primary antibody (diluted with PBS) for 2 h at room temperature. The primary antibodies used were anti-single-stranded DNA (ssDNA) polyclonal antibody (dilution of 1:300; Dako, Kyoto, Japan),[10] and antihuman Ki-67 antigen (MIB-1, dilution of 1:100; Dako).[8] We performed the immunostaining using an LSAB2 kit (Dako). Antigen retrieval was carried out with microwave

treatment before reacting with anti-Ki-67. Strong signals in the nuclei of the epithelial cells were taken to be positive result.

Statistics

Results are reported as mean ± s.d. Statistical analysis was performed by chi-square test with STATVIEW software (SAS Institute Inc., Cary, NC, USA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Clinical features of patients and changes in endoscopic findings

Following initial enrolment of 38 patients, one patient dropped out of this protocol because of a suspicious tumour invasion into the submucosal layer, which was followed by an operation. Therefore, 37 patients with 44 lesions (27 carcinomas and 17 adenomas) were finally enrolled. *Helicobacter pylori* eradication therapy succeeded in 29 patients (78%) with 33 lesions. The clinical features are summarized in Table 1. In 11 of the lesions, we found that the presence of the lesion came to be indistinct compared with the primary image (Table 1). All of these lesions were found in patients who underwent successful eradication therapy and no lesions in the cases of failed eradication showed this alteration.

Table 1. Clinical features of patients and alterations of tumour findings

	Eradicated ($n = 29$)	Non-eradicated ($n = 8$)	*P*-value
Clinical features			
Mean age (range)	69.8 (48–84)	69.3 (54–78)	N.S.
Gender (male/female)	19/10	8/0	N.S.
Period (days)	33.3	36.0	N.S.
Lesions			
Number	33	11	
Elevated/depressed	20/13	3/8	N.S.
Tumour diameter (mm, mean ± s.d.)	15.9 ± 5.6	13.1 ± 10.7	N.S.
Carcinoma/adenoma	21/12	6/5	N.S.
Endoscopic change			
Indistinct	11 (33%)	0 (0%)	**0.03**[1]

[1] Chi-square test.

Table 2. Clinicopathological features of 33 gastric tumours with successful eradication; comparison between adenoma and carcinoma

	Adenoma ($n = 12$)	Carcinoma ($n = 21$)	*P*-value
Tumour features			
Elevated/depressed	11/0	9/13	
Mucosal/submucosal	12/0	21/0	
Diameter (average; mm)	11.5	18.5	
Endoscopic alterations			
Indistinct	6 (50%)	5 (24%)	0.12[1]

[1] Chi-square test.

Comparison between adenoma and carcinoma

We compared the endoscopic alteration in patients with gastric adenoma and in those with adenocarcinoma. The clinicopathological features of patients with the adenomas and carcinomas were summarized in Table 2. All adenocarcinoma tissues were confirmed histologically to be limited in the mucosal layer. We could find the endoscopic alteration not only in six adenomas but also in five carcinomas (Table 2). The representative endoscopic features were demonstrated in Figures 1 and 2. After eradication, the tumours became flattened and indistinct, and it was difficult to point out the tumour itself or to set the clear horizontal margin of the tumours. Although this alteration was frequently detected in adenoma tissue, we could not find the statistical difference in the endoscopic change of tumours between two groups.

Characteristics of the lesions that became unclear after eradication

We tried to clarify the characteristics of the lesions that became indistinct after successful eradication therapy. As shown in Table 3, this phenomenon was characteristically found in elevated lesions. Moreover, a flattened appearance had a close association with the incidence of unclear change. Although it is well-known that the redness of the background mucosa often diminishes after eradication therapy, it was not associated with the indistinct appearance.

Changes in histological findings by eradication

We then examined the histological features using sections taken from the endoscopic resection stained

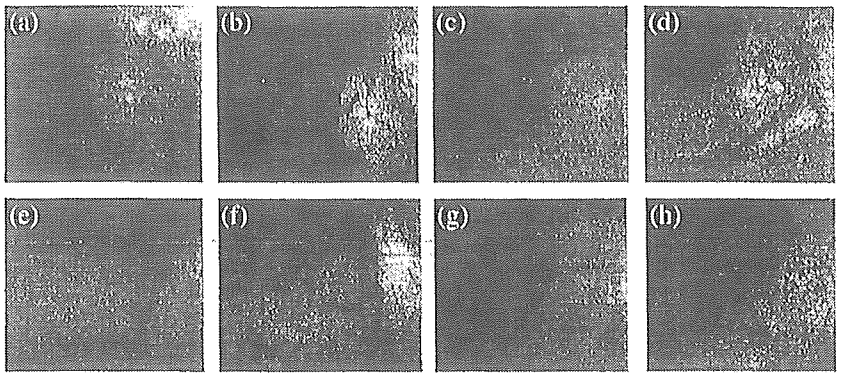

Figure 1. Endoscopic features of the gastric adenoma at pre- (a–d) and post-eradication therapy (e–h). Patients were 71 years female (a, b, e, f) and 67 years male (c, d, g, h). Ordinary (a, c, e, g) and dye-endoscopic (b, d, f, h) observation. Tumours became flattened and indistinct after eradication therapy.

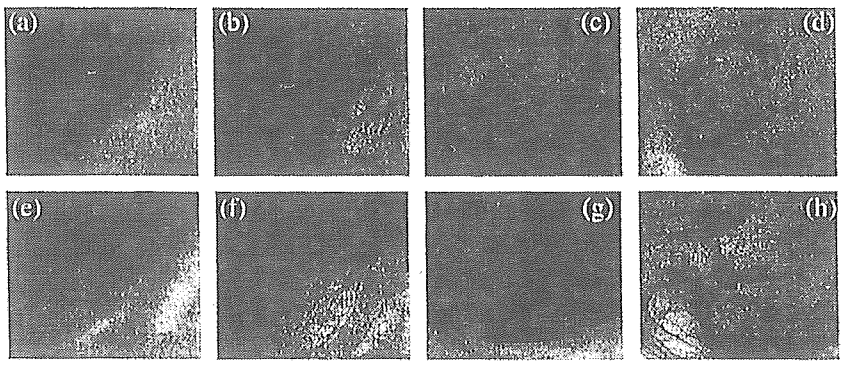

Figure 2. Endoscopic features of the gastric adenocarcinoma at pre- (a–d) and post-eradication therapy (e–h). Patients were 64 years male (a, b, e, f) and 75 years male (c, d, g, h). Ordinary (a, c, e, g) and dye-endoscopic (b, d, f, h) observation. Tumours became flattened and indistinct after eradication therapy as seen in cases with adenoma.

Table 3. Characteristics of the lesions, which became indistinct after successful eradication therapy

	Indistinct (n = 11)	No change (n = 22)	P-value
Tumour features			
Elevated/depressed	11/0	9/13	<0.01[1]
Carcinoma/adenoma	5/6	16/6	0.12[1]
Endoscopic alterations			
Flattened	11 (100%)	2 (9%)	<0.01[1]
Diminished redness	6 (55%)	6 (27%)	0.12[1]
Histological alterations			
Normal columnar			
Epithelium over the tumour	8 (73%)	3 (14%)	<0.01[1]
Serum pepsinogens (pre-eradication)			
PG I (ng/mL, mean ± s.d.)	33.0 ± 23.9	30.0 ± 25.5	N.S.
PG II (ng/mL, mean ± s.d.)	18.2 ± 7.9	19.2 ± 11.9	N.S.
PG I/II (mean ± s.d.)	1.73 ± 0.97	1.49 ± 0.87	N.S.

[1] Chi-square test.

with haematoxylin and eosin. We could detect the appearance of normal columnar epithelium to various degrees over the tumour tissue (Figure 3) in 12 lesions. Of 12, 11 were found in patients who underwent successful eradication therapy. Especially, in three cases, the atypical epithelium covers the bulk of the tumour tissue. This change was found not only in adenoma (nine lesions) but also in carcinoma tissue (three lesions) and showed a close association with the endoscopic finding of unclear margin (Table 3).

Serum pepsinogen levels and endoscopic alteration

Sera from patients were collected before eradication therapy and the serum level of PGs was estimated. We examined the relationship between serum levels of PGs

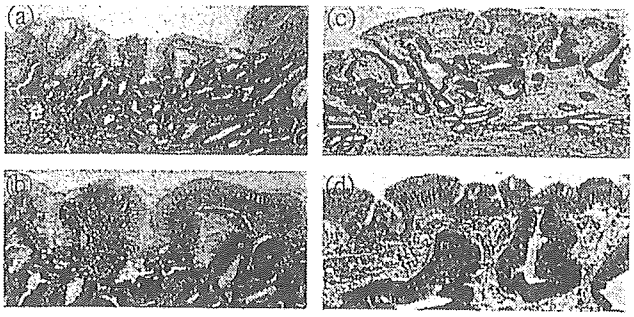

Figure 3. Histological features of gastric neoplasm at posteradication. Cases of gastric adenoma (a, b) and adenocarcinoma (c, d) with successful eradication therapy. (a, c) Low magnification of gastric tumour specimen, (b, d) high magnification of surface epithelium. Patients were 71 years female (a, b) and 82 years male (c, d).

and the endoscopic findings. As shown in Table 3, relative high levels of PG I and a high I/II ratio were found in patients with endoscopic changes compared to those in the patients with no-changes; however, this is not statistically significant.

Relationship between serum gastrin level and endoscopic changes

Further to this, we studied the alteration of serum gastrin levels. Fasting sera were collected before and after eradication therapy. As shown in Table 4, a decrease of the serum gastrin level was not so obvious after 1 month of eradication therapy. We could not find a difference in the level of gastrin between patients with indistinct tumour appearance and those with no change.

Expressions of Ki-67 and ssDNA in tumour cells

We examined the cell kinetics in these lesions using immunohistochemical staining with the use of tumour specimens at posteradication. We could not detect any

Table 4. Changes in serum gastrin levels after eradication therapy

		Gastrin level (pg/mL, mean ± s.d.)	
	Number	Before eradication	After eradication
Successful eradication			
Indistinct	10	322.1 ± 356.0	296.1 ± 314.3
No change	16	309.9 ± 271.1	211.0 ± 173.1
Failed eradication	7	176.8 ± 162.5	245.6 ± 279.5

Table 5. Expressions of Ki-67 and ssDNA in gastric tumour cells

	Number	Ki-67 LI (%)	ssDNA LI (%) (deep area dominant)
Successful eradication†			
Indistinct	6	17.5 ± 16.3	46.2 ± 13.2 **(3/6)***
No change	14	15.4 ± 12.9	45.9 ± 20.8 **(0/14)***
Failed eradication†	7	9.0 ± 5.5	40.3 ± 27.6 (0/7)

LI, labelling index; ssDNA, single-stranded deoxyribonucleic acid.
* $P < 0.05$, chi-square test.
†Mean ± s.d.

difference in the Ki-67 labelling index, which is a marker for cell proliferation, or the ssDNA labelling index, which is a marker for cell apoptosis (Table 5).[11] However, in cases where there were indistinct tumour appearance after eradication, ssDNA expression was more frequently detected from deeper within the tumour at posteradication (Figure 4, Table 5). In other specimens, ssDNA expression was uniformly detected, and no lesions showed luminal side-dominant pattern in ssDNA expression.

DISCUSSION

In the present study, we demonstrated the direct effect of *H. pylori* eradication therapy on the morphological appearance in gastric adenomas and carcinomas. The

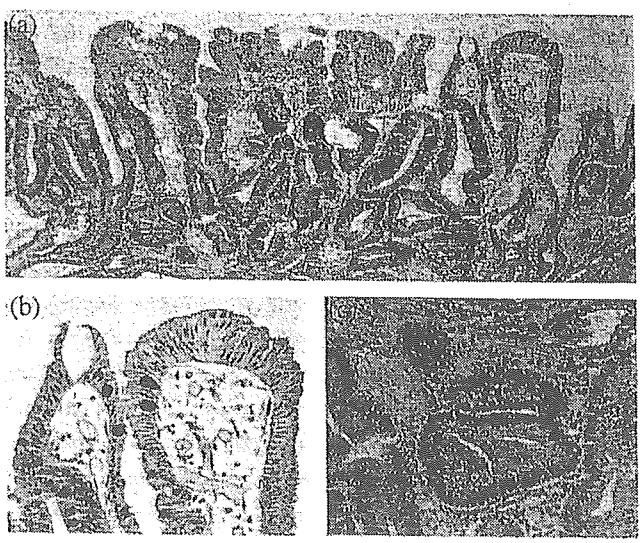

Figure 4. Expression of single-stranded DNA (ssDNA) in adenoma cells. Immunohistochemical analysis was performed as described in Methods. (a) Low magnification of gastric tumour specimen, (b) high magnification of the surface area, (c) high magnification of the deep area. Patient was 67 years male.

typical changes after eradication were (i) a flattened aspect to the elevated lesion and indistinct border of tumour lesion when viewed at endoscopy and (ii) the appearance of a normal columnar epithelium over the neoplastic lesion. Uemura *et al.* previously demonstrated the low incidence of a second cancer development by the eradication therapy in patients who underwent endoscopic mucosal resection of the gastric cancer.[7] In addition, we have published data demonstrating a low Ki-67 labelling index in those gastric cancer cells without *H. pylori* infection.[8] These results are indicative of the promoting effect of *H. pylori* on the growth of gastric cancer cells.

We found that the gastric tumour had flattened and showed indistinct feature after a short period and this result completely agrees with the previous findings. It is of interest that the main morphological change revealed by endoscopic observation was that it had flattened and this was only in the elevated lesions, regardless of the tumour's histology. No morphological change was found in the cases that had depressed features. This indicates that *H. pylori* eradication may inhibit the upward (expansive) growth of the gastric tumour. We have also found that most gastric cancers discovered after successful eradication therapy were of the flat, depressed type (under submission). This phenomenon also agrees with our hypothesis.

The mechanism of the tumour promoting effect of *H. pylori* is still unknown. In the *in vitro* studies, *H. pylori* itself was found to have the effect of modifying the expressions of several genes in gastric carcinoma cells.[12] And in the *in vivo* studies, *H. pylori* has been proved to modify directly the state of apoptosis or the cell cycle regulatory system including p27 expression.[13, 14] Recent evidence has clarified the direct mechanism of the translocation of harmful proteins (Cag A) from *H. pylori* to the host cell followed by specific intracellular signalling.[15, 16] Semino-Mora *et al.* recently demonstrated the presence of *H. pylori*-derived toxic proteins and mRNAs in gastric tumour cells *in vivo*.[17] However, their theory is still controversial, and, until now, it has been believed that *H. pylori* cannot exist on the surface of gastric carcinoma cells. Indeed, no evidence has demonstrated *H. pylori*-induced signalling, including CagA phosphorylation, in the human gastric carcinoma cells *in vivo*.

Thus, it is likely that *H. pylori* indirectly influences tumour cell growth by regulating the inflammatory reaction around the tumour tissue. Several cytokines have been reported to be induced by *H. pylori* infection[18] and some of them, such as interleukin-1 and hepatocyte growth factor, may act as growth factors for tumour cells.[19] In the present cases all were confirmed to have *H. pylori*-induced chronic gastritis in the background mucosa. Ohkusa *et al.* demonstrated that, after eradication, gastric inflammation had decreased by 1–3 months.[20] We found that ssDNA expression was mainly detected in the deeper area of the gastric tumour in three lesions at posteradication, and all three showed indistinct appearance. In other specimens, ssDNA expression was uniformly detected, and no lesions showed luminal side-dominant pattern in ssDNA expression. These suggest the importance of the growth inhibitory signals from the mucosal side (as opposed to those from the luminal side). This indicates the importance of gastric inflammation in the gastric mucosa rather than *H. pylori* itself on the luminal side. In this study, ssDNA expression was examined only in lesions after eradication, this should be examined at pre- and post-eradication and should be compared in the next step.

Gastrin is known to be an important gut-related hormone and a growth factor for gastric cancer cells[21, 22] and gastric tumour cells have been shown to contain its receptor. Reports have indicated that, after eradication therapy of *H. pylori*, a decreased level of several cytokines such as interleukin (IL)-1, IL-2, tumour necrosis factor-α and interferon-γ, in the gastric mucosa as well as increased acid output results in the decreased level of serum gastrin.[23, 24] However, our results showed that the decrease of the gastrin level is not so obvious after eradication, and alteration of the tumour lesion was not correlated with the serum gastrin level. In our protocol, the observation period is short and that may be a reason for the incomplete depression of the gastrin level. It is unlikely that our new findings of the morphological changes were induced by a gastrin-related system.

It was a surprising finding that a normal columnar epithelium appeared over the tumour tissue after successful eradication therapy. The reason for the alteration is still unknown but we can suggest two possibilities. First, *H. pylori* may directly affect the differentiation of gastric epithelial cells and its eradication could modify this effect although we could find little evidence to support this possibility. Secondly, the appearance of normal epithelium was induced as a regenerative change against injured tumour tissue.

After eradication therapy, it seems likely that gastric acid output increases in patients with atrophic gastritis.[25] In the cases we examined, most patients showed atrophic changes in the corpus suggesting low acid output and recovery after eradication therapy. This may lead to surface injury of the tumour lesion and thus induce regenerative changes. Indeed, we found surface erosion on the tumour lesion in four cases after eradication therapy (data not shown). We also confirmed that the mucosal injury by gastric biopsy before endoscopic resection did not correlate with the appearance of normal foveolar epithelium.

Recently, it has been a topic of discussion as to whether eradication therapy of *H. pylori* influences the reduction of gastric carcinogenesis or not. Previously published data indicated a reduced rate of second cancer discovery in patients who received an endoscopic mucosal resection for the first cancer.[7] Recently, a Chinese group has published data that conflict with previous findings.[26] They demonstrated, with a randomized-controlled trial, that *H. pylori* eradication eliminated cancer incidence in patients with no precancerous lesions upon presentation compared with infected subjects. There was a concurrent 37% relative decrease in cancer incidence in the overall population, but this difference did not reach a level of statistical significance.[26] The only way to study the degree of gastric carcinogenensis is through endoscopic discovery. If eradication therapy itself has an influence on the morphological change of the gastric tumour, this therapy must have an influence on cancer discovery rate. In the present study, we demonstrated the flattened and indistinct appearance of the gastric tumour after eradication even after a short time. Generally, the morphological feature of elevation is the most important characteristic required to find out the gastric neoplasms. Even if the true incidence of cancer was not affected by eradication, the incidence of cancer discovery would be decreased by successful eradication therapy in cases where there is an elevated tumour feature. Moreover, the appearance of normal foveolar epithelium must make it difficult to detect the gastric cancer by endoscopic observation. This must contribute to the reduction in the rate of cancer discovery after successful eradication therapy.

Taken together, this is the first report that has described the typical morphological changes of gastric adenoma or carcinoma tissue over a short period. However, the question still remains as to why only a part of the tumour tissue showed these alterations. It should be clarified as to what is the typical appearance of a gastric tumour that has been affected by *H. pylori* eradication therapy. Moreover, it should also be discussed as to whether eradication therapy can truly diminish the occurrence of gastric cancer and reduce the gastric cancer induced mortality rate of the population.

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〔原　著〕

ヘリコバクター・ピロリ感染と胃癌発生からみた胃内視鏡検診間隔

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要　旨

内視鏡検診により効果的に胃癌診断を行うには，胃癌発生リスクに応じた検査間隔の設定が必要と考えられる。今回，(1)胃炎の状態別の胃癌リスクの検討による適当な検査間隔，(2)血清ペプシノゲン（PG）値による血液検査による適当な検診間隔の推定，の2点について検討を行った。対象は，(1)内視鏡的に経過観察が可能であった1,526名，(2)空腹時血清PG値を測定でき，内視鏡的に胃粘膜の状態が観察しえた498例である。検討（1)では，胃癌は36例発生した。胃癌発見頻度は全体では0.40%・年，胃体部優勢胃炎群では1.43%・年，pangastritis群0.75%・年，前庭部優勢胃炎群0.049%・年であった。発見効率の面からいうと，胃体部優勢胃炎群で毎年内視鏡検査を行うのと同等の効率を得るには，pangastritis群では2年に1回，前庭部優勢胃炎群ではそれ以上の間隔となった。検討（2)では，胃体部優勢胃炎群，pangastritis群，前庭部優勢胃炎群ではそれぞれ血清44.4±24.0，49.0±22.5，53.9±19.2，血清PGII値20.3±8.4，18.7±7.9，16.6±6.9，I/II比2.24±1.01，2.65±0.98，3.51±1.14であり，各群のPG値に差を認めた。以上より，胃炎の状態により胃癌発見頻度が異なり，胃癌のリスクが低い*Hp*陰性群および前庭部優勢胃炎群は検診間隔を5年に1回程度以上に延ばすことは可能と考えられた。また，血清PG値で，胃癌のリスクが高い体部優勢胃炎群およびpangastritis群と，リスクが低い*Hp*陰性群および前庭部優勢胃炎群とを区別することは可能であった。

キーワード　内視鏡，検診間隔，ヘリコバクター・ピロリ，ペプシノゲン

I　はじめに

内視鏡検診により効果的に胃癌診断を行うには，胃癌発生リスクに応じた検査頻度を設定することが必要と考えられる。これに関連して，Uemuraらは，内視鏡検査による経過観察から，ヘリコバクター・ピロリ菌（以下，*Hp*）による持続的炎症を基盤として胃癌が発生し，胃炎の状態によってそのリスクが異なることを報告している[1]。（図1）に*Hp*関連慢性胃炎の自然史のシェーマを示す。胃炎は，前庭部優勢胃炎，pangastritis，体部優勢胃炎と進展し，それに一致して胃癌発生のリスクは高くなる[2]。しかし，Uemuraら[1]の報告でも，望ましい検診間隔等についてまでは言及されていない。

そこで，今回われわれは，(1)胃炎の状態別の胃癌リスクの検討による適当な検査間隔，(2)血清ペプシノゲン（PG）値による血液検査による適当な検診間隔の推定，の2点について検討を行ったので，報告する。

図1：*Hp*関連慢性胃炎の自然史のシェーマ

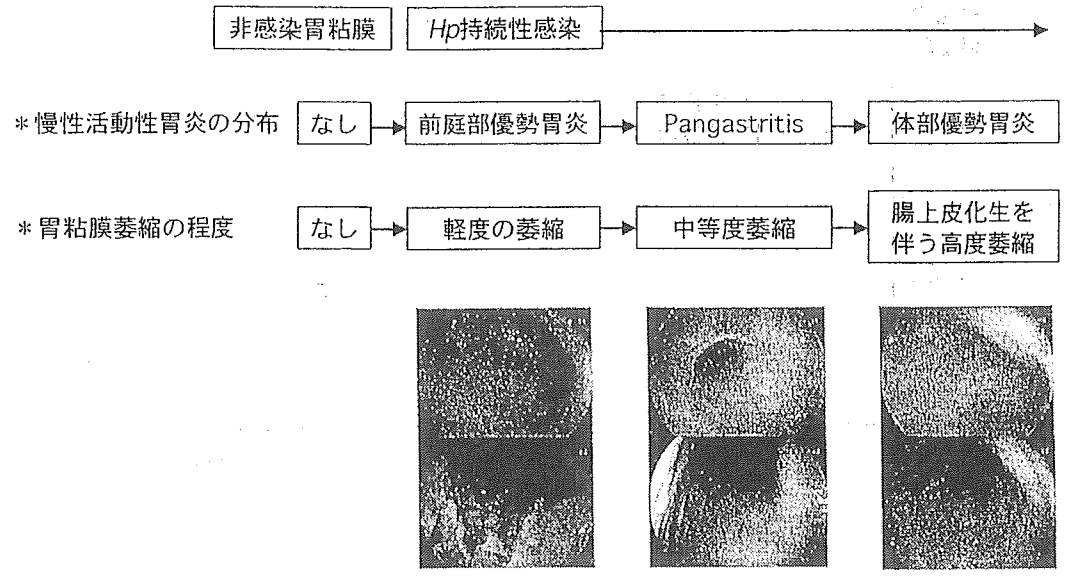


表1：発見胃癌の特徴

胃癌	:36人に発生
平均年齢	:59.7歳
男女比	:23/13
Hp	:全例陽性
深達度(早期/進行)	33/3
組織型(分化型/未分化型)	:23/13
部位(U/M/L)	:10/10/16
肉眼型(IIc/IIa/2/4)	:30/4/1/1
進行癌	:5.9(4型)，7.0(2型)，7.1年目(IIc類似)に診断(いずれも毎年内視鏡施行)

II．(1)胃炎の状態別の胃癌リスクの検討による適当な検査間隔

A．対象および方法

対象は内視鏡的に経過観察が可能であった，年齢が20～76歳（平均52.4歳）の1,526人である[1]。これら患者の*Hp*感染状況，除菌状況，胃粘膜の状態をチェックし，胃炎に関しては，前庭部優勢胃炎，pangastritis，胃体部優勢胃炎の3型に分類した。そして，内視鏡検査により，1年から10.6年（平均7.8年）の経過観察を行った。

B．結果

観察期間中，36人に胃癌が発見された。発見時の平均年齢は59.7歳，男女比は23：13，*Hp*は全員陽性であった。発見胃癌の深達度，組織型，部位に関して，（表1）に示す。進行癌が3人に発見されたが，1人が分化型，2人が未分化型だった。いずれも，毎年内視鏡を受けていた人からであった。

（図2）に*Hp*感染の有無による累積胃癌発生率

図2：*Hp*感染の有無による累積胃癌発生率

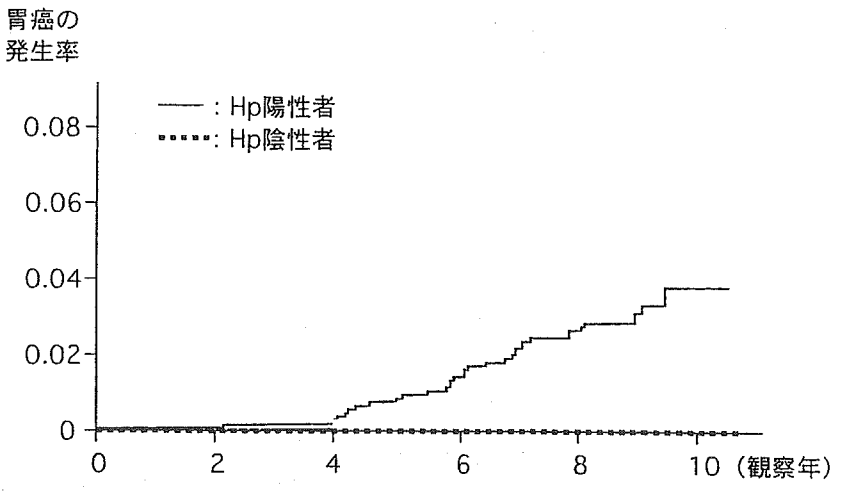
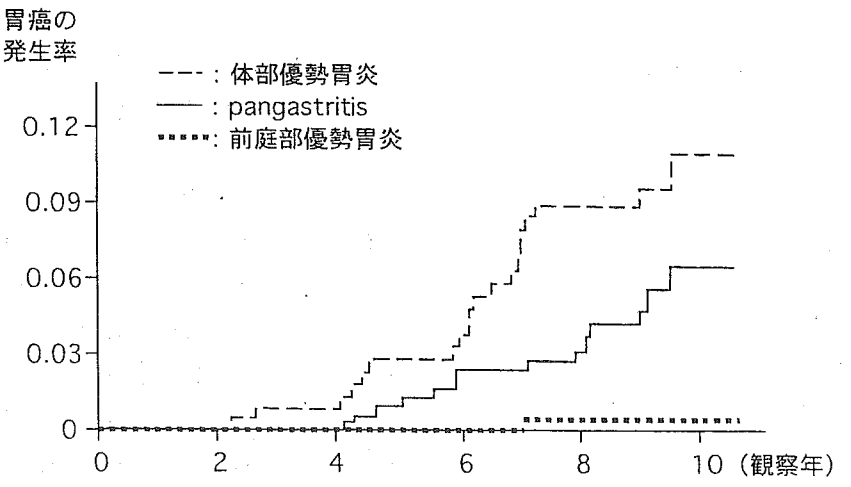


図3：胃炎の型別の累積胃癌発生率



の違いを示す[31]。*Hp*陰性群からは1例も胃癌の発生はみられなかった。一方，*Hp*陽性群に関しては，0.40%・年で胃癌の発生をみた。

（図3）に胃炎の型別の累積胃癌発生率を示す[31]。胃炎の型が異なれば，胃癌の発生率は大きく異なっており，体部優勢胃炎群は1.43%・年，pangastritis群は0.75%・年，前庭部優勢胃炎群は0.049%・年であった。前庭部優勢胃炎は胃癌のリスクが低く，体部優勢胃炎およびpangastritisは胃癌のリスクが高いことが示された。発見効率の面からいうと，体部優勢胃炎群を毎年内視鏡検査を行うのと同等の効率を得るためには，pangastritis群は2年に1回，前庭部優勢胃炎群はそれ以上の間隔，5年に1回程度以上でもよいということになる。

図4：胃炎の型別の血清PGI値

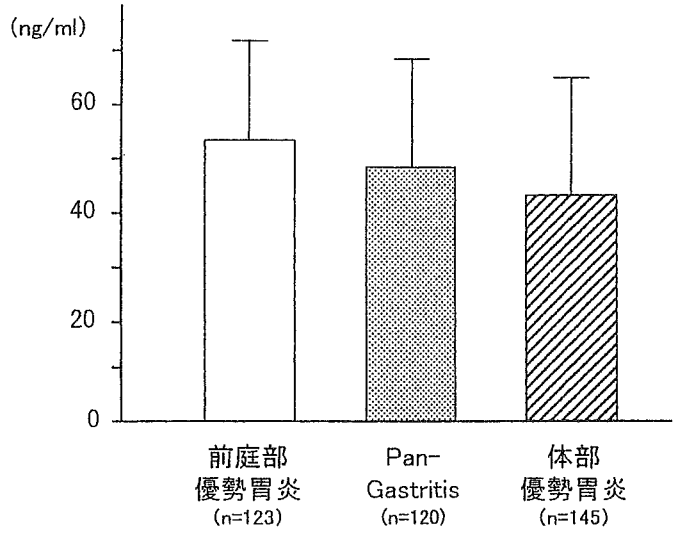
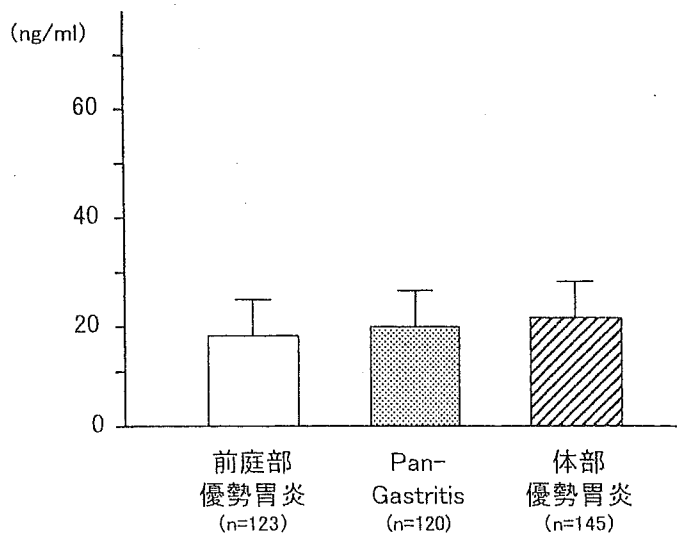


図5：胃炎の型別の血清PGII値



Ⅲ　(2)血清ペプシノゲン(PG)値による血液検査による適当な検診間隔の推定

A．対象および方法

対象は空腹時血清PG値を測定でき，内視鏡的に胃粘膜の状態が観察しえた年齢が17～85歳（平均年齢50.0歳）の498人である。*Hp*感染状態および胃粘膜の組織学的胃炎の状態別に血清PG値を検討した。

B．結果

血清PGI値は，前庭部優勢胃炎群では53.9±19.2ng/ml，pangastritis群では49.0±22.5ng/ml，体部優勢胃炎群では44.4±24.0ng/mlと，前庭部優勢胃炎群，pangastritis群，体部優勢胃炎群の順で，PGI値は低下していた（図4）。

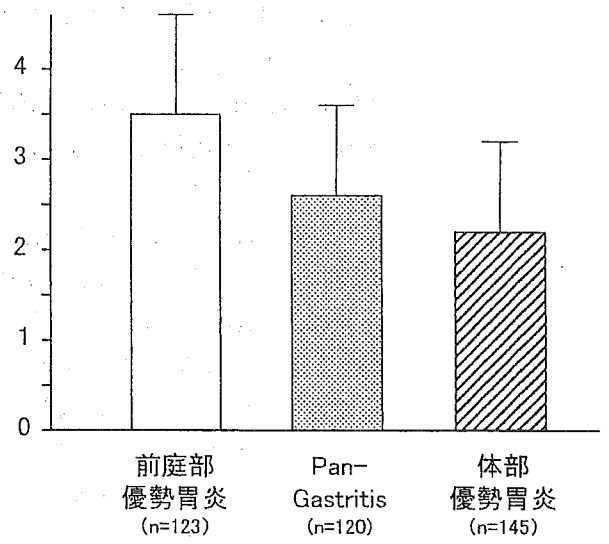
血清PGII値は，前庭部優勢胃炎群では16.6±6.9ng/ml，pangastritis群では18.7±7.9ng/ml，体部優勢胃炎群では20.3±8.4ng/mlと，PGII値は各群で大きな差はなかった（図5）。

PGI/II比は，前庭部優勢胃炎群では3.51±1.14，pangastritis群では2.65±0.98，体部優勢胃炎群では2.24±1.01であり，PGI/II比は前庭部優勢胃炎群，pangastritis群，体部優勢胃炎群の順で，低下していた。つまり，前庭部優勢胃炎群に比し，pangastritis群，体部優勢胃炎群は，この順で強い胃粘膜萎縮を伴っていることを示している（図6）。

PG値による判定を，血清PGI値が70ng/ml以下かつPGI/II比3以下を（+），血清PGI値が50ng/ml以下かつPGI/II比3以下を（2+），血清PGI値が30ng/ml以下かつPGI/II比2以下を（3+）とする亜分類[11]を用いて，各胃炎別にPG値による判定をみた結果を（図7）に示す。体部優勢胃炎群の79%，

pangastritis群の57%がPG値による判定が陽性なのに対して，前庭部優勢胃炎群では28%，*Hp*陰性群では2%のみが陽性であった。つまり，PG値による判定が（3+）であれば体部優勢胃炎もしくはpangastiritisである可能性が92%，（2+）であれば76%，（+）であれば82%，陽性者全体では83%であった（表2）。つまり，PG値により，胃癌のリスクが高い体部優勢胃炎群およびpangastritis群と，リスクが高くない前庭部優勢胃炎群および*Hp*陰性群とを，簡便に区別することが可能であった。

図6：胃炎の型別のPGI/II比



Ⅳ　考察

内視鏡検査による一次スクリーニングは，集団検診ではなく，個別検診，施設検診，人間ドックにおけるがん検診の中で行われることが多い。また，近年，受診者もはじめから内視鏡検査を希望することが増えてきている。その理由は，内視鏡検診の診断能が高いことにある。平成14年度の全国集計[5]でも，内視鏡による胃がん発見率は0.24%（うち早期がん割合は67.4%）で，これは同年度の間接X線検査による発見率0.11%（同60.9%）に比較し，高率である。その他の胃疾患に関しても胃潰瘍が3.77%，胃ポリープが

図7：PG値による判定と胃炎の型

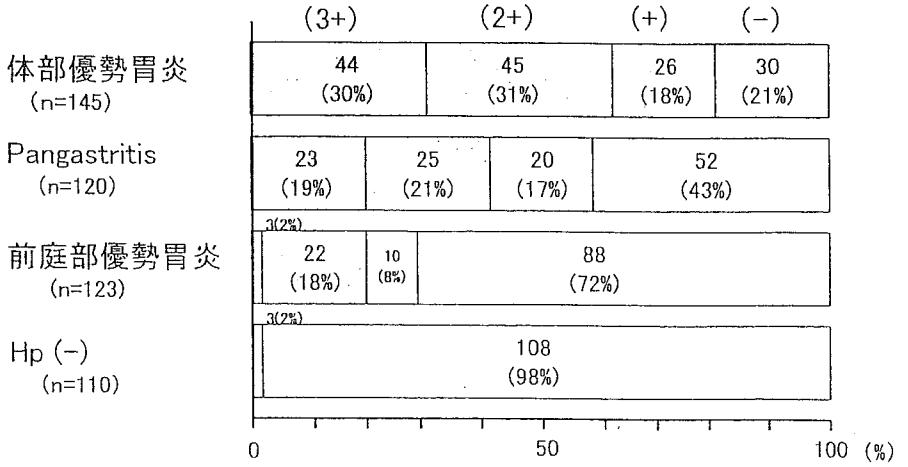


表2：体部優勢胃炎もしくはpangastritisであることの陽性率

判定	陽性率	
(3+)	67/73(92%)	183/221(83%)
(2+)	70/92(76%)	
(+)	46/56(82%)	
(−)	82/278(30%)	

7.35%に発見されており，間接X線検査のそれぞれ0.85%，1.08%を大幅に上回っている。しかしながら，内視鏡検診は，胃X線検査による検診に比べ，コストがかかること，多くのマンパワーが必要なこと，偶発症の頻度が高くなること等の問題点がある[6]。そのため，胃内視鏡による集団検診は限られた地域でしか実施されていない。内視鏡による検診の頻度に関しては，一般に1～2年に1回の間隔で行われている。しかし，内視鏡検診をより推進するためには，胃癌発生リスクに応じた検査頻度を設定して検診を効率的に行うことが必要と考えられる。しかし，これまで，この点について検討した論文は見当たらない。

胃癌の低リスク群の設定とその群の検診間隔の設定に関連して，*Hp*陰性者が胃癌のリスクがかなり低いことは，さまざまな検討で示されている。例えば日本人を対象としたケースコントロールスタディでは，Asakaら[7]がオッズ比2.56，Blaserら[8]がオッズ比2.14，Kikuchiら[9]がオッズ比4.7と，いずれも有意に*Hp*陰性者に比べ*Hp*陽性者の胃癌発生が多いことを報告している。Huangら[10]のメタ・アナリシスでも，*Hp*陽性者は*Hp*陰性者に比べ，胃癌の発生率が1.92倍（95%CI，1.32-2.78）高い。しかも，われわれの検討では*Hp*陰性者に発生する胃癌の増殖速度は遅い[11]。さらに，井上らは*Hp*抗体とPG法の結果の組み合わせで，*Hp*陰性，PG陰性の場合，胃がんの低リスクとしている[12]。これらの報告に加え，今回のわれわれの検討でも，胃炎の状態により胃癌発見頻度が異なることが明らかになり，*Hp*陰性群のみならず前庭部優勢胃炎群は検診間隔を5年に1回程度以上に延ばすことが可能と考えられた。

また，血清PG値による胃がんハイリスクのスクリーニング（ペプシノゲン法）が近年行われている。ペプシノゲン法は血清PGIおよびIIを測定し，PGI≦70ng/mlかつPGI/II比≦3をカットオフの基準値として，これに該当する者に対して上部消化管内視鏡検査による精密検査を勧告するものである[4][13]～[15]。PGIは胃底腺領域から分泌され，PGIIは胃底腺の他にも幽門腺やブルンネル腺，噴門腺からも分泌されることから，ペプシノゲン法は上記カットオフ値により，胃癌の高危険群である萎縮性胃炎を診断するものである。今回の検討で，血清PG値を用いて，胃癌のリスクが高い体部優勢胃炎群およびpangastritis群と，リスクが高くない*Hp*陰性群および前庭部優勢胃炎群とを区別することは可能であった。つまり，胃内視鏡検査を行なわなくても，胃炎の型の診断が可能であることを示している。

しかし，「はじめに」でも述べたように，胃炎は前庭部優勢胃炎，pangastritis，体部優勢胃炎と進展し，それに一致して胃粘膜萎縮は高度となる。そのため，前庭部優勢胃炎を有するものもいずれ，pangastritis，体部優勢胃炎と進展するものも出てくる。そのため，5年に1回程度PG値を測定して，胃炎の型を診断し直す方法が考えられるが，胃炎の型が変わって検診間隔に変更があったりすると現場で混乱を招く可能性が考えられる。そのため，血液検査で*Hp*抗体を測定し，*Hp*陰性者だけは検診間隔を5年に1回程度以上に延ばし，陽性者は毎年胃検診を行なうということが

現実的な方法ではないかと考える。

全員に胃X線検査を行う検診に代わって，*Hp*感染の有無により検診間隔を2つ設定した内視鏡検診を行なうことは，費用の面からも今後可能となると思われる。というのも，若年者の*Hp*感染率は年々低下しており，検診間隔を延ばせる群が増加しているためである。

ここで，検診費用を単純に試算してみる。間接X線検査1回にかかる費用を4,000円，胃内視鏡検査1回にかかる費用を14,000円，現在，間接X線検査を受けた人の10%が精密検査のため胃内視鏡検査を受けていると仮定すると，われわれの試算では，検診受診者中の*Hp*陰性者の率が約70%となると，毎年の胃X線検査による検診と*Hp*陰性者は5年に1回および*Hp*陽性者は年1回の内視鏡検診にかかる総費用がほぼ同等になる。胃癌発見率は明らかに胃内視鏡検診の方が高いことから，コストベネフィットを評価した試算ではないものの，癌患者1人を発見する費用としては，胃内視鏡検診の方が安価となることが見込める。もちろん現時点では検診対象者の中の*Hp*陰性者が比較的少ないため，現状のままで内視鏡検診に切り替えると費用面での負担が大きくなるが，現在の30歳代の*Hp*陰性者の率が約70%[16]であることから，将来*Hp*感染の有無により検診間隔を2つ設定した内視鏡検診の方が経済的にも有意になる可能性がある。

まずは，*Hp*陰性者は発癌リスクがかなり低いということを医療従事者および一般に広く周知させることが必要と思われる。

V　結語

胃炎の状態により胃癌発見頻度が異なり，胃癌のリスクが低い*Hp*陰性群および前庭部優勢胃炎群は検診間隔を5年に1回程度以上に延ばすことは可能と考えられた。また，血清PG値で，胃癌のリスクが高い体部優勢胃炎群およびpangastritis群と，リスクが高くない*Hp*陰性群および前庭部優勢胃炎群とを区別することは可能であった。ただし，*Hp*抗体測定による*Hp*陰性群のみの検診間隔を5年に1回程度以上に延ばすことが現実的な方法と思われる。

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Intervals of Endoscopic Screening of the Stomach -Relationship between Type of *Helicobacter pylori*-Associated Chronic Gastritis and Gastric Cancer Development.

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Abstract

To perform the endoscopic screening of the stomach efficiently, it is necessary to settle the intervals of the examination according to the risk of gastric cancer development. Therefore, we examined acceptable intervals of endoscopic screening by analyzing the relationship between type of Helicobacter pylori (*Hp*)-associated chronic gastritis and gastric cancer development (1), and we estimated the intervals by using values of serum pepsinogens (2). We examined 1,526 people who received gastric endoscopy annually for the study 1, and 498 people who received gastric endoscopy and serum pepsinogens test for the study 2. Gastric cancer was developed in 36 patients in the study 1. The rates of gastric cancer development was 1.43%·year, 0.75%·year, 0.049%·year and 0%·year, in the patients with corpus-predominant gastritis, in the patients with pangastritis, in the patients with antrum-dominant gastritis and in the *Hp*-negative subjects, respectively. The *Hp*-negative subjects and the patients with antrum-predominant gastritis may be low-risk of gastric cancer development, and the patients with corpus-predominant gastritis and with pangastritis may be high-risk. One of each 5 year screening may be enough for the low-risk group. Values of serum pepsinogens can distinguish the low-risk group and the high-risk group.

総説

スキルス胃癌の見逃しに対する裁判所の判断について

日山 亨*, 吉原正治*, 田中信治**, 茶山一彰***

要旨：これまでのスキルス胃癌の見逃しが問題とされた民事裁判判決5例を検討した．従来はスキルス胃癌は進展が早く，予後も非常に悪いことから，仮に見逃されずにその時点で治療が開始されたとしても延命の可能性がなかったとして，病院側に対する損害賠償請求が棄却される事例が多かった．しかし，平成16年1月15日に最高裁は診断が2.7カ月遅れた事例において，病状が進行した後に治療を開始するよりも，治療の開始が早期であればあるほど良好な効果を得られた可能性があり，患者がその死亡の時点においてなお生存していた相当程度の可能性があったとして，病院側の責任を認めた．近年ティーエスワン（テガフール・ギメラシル・オテラシルカリウム配合カプセル剤）などのスキルス胃癌にも有効性を示す抗癌剤が開発・臨床応用されてきている．上記平成16年の最高裁判決は，このような医療技術の進歩を反映したものと思われ，医療技術が進歩すればそれに伴って法的に要求される医療水準も上昇することを示しているといえよう．われわれ臨床医はこのようなことを心して，日々の臨床にあたらなければならない．

Key words スキルス胃癌／見逃し／訴訟

I 緒 言

スキルス胃癌は硬癌，びまん性胃癌，linitis prastica型胃癌，Borrmann IV型胃癌などとも呼ばれ，20～30歳代の若年者にもみられる．粘膜下層以下への深部浸潤形式が他の型の胃癌とは生物学的に異なる性質を有しており，胃壁全体に広範囲な浸潤を生じ，胃壁に高度の線維増生を来す．しかも，それは急激な浸潤を生じ，他に転移しやすく，予後も極めて不良である[1]．

近年，医療過誤を巡る訴訟は増加の一途をたどっているが[2),3)]，この中にはスキルス胃癌の見逃しに関する事例も散見される．従来，スキルス胃癌は進展が早く，予後も非常に悪いことから，仮に見逃されずにその時点で治療が開始されたとしても，延命の可能性がなかったとして病院側に対する損害賠償請求が棄却される事例が多かった．しかし，平成16年1月15日に最高裁は新しい判断を示した．今回，平成16年1月の最高裁判決とそれ以前の裁判所の姿勢の違いの有無について検討したので，ここに報告する．

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II 方 法

スキルス胃癌の見逃しが問題とされた民事裁判の判決を収集し，判決文を検討した．収集には，新日本法規株式会社製CD-ROM「判例MASTER II 2004年後期版」および裁判所ホームページ[4)]の判例検索を用いた．検索のキーワードには「スキルス胃癌」，「胃癌」を用いた．

III 裁判例

スキルス胃癌の見逃しが問題とされた民事裁判は5例あった．以下，その5例の経過と判旨を紹介する．

【裁判例1】(福岡地裁小倉支部，昭和58年2月7日判決)[5]

【経過】A（昭和18年生まれ，女性）は，昭和49年4月（30歳時），疲労感，腹部不快感，背部痛等のためB医院を受診した．胃X線検査の結果，胃潰瘍と診断され治療を受けた．その後昭和51年4月17日（32歳時）に再度胃X線検査を受けたところ，再び胃潰瘍と診断された．同年6月6日の胃X線検査では，胃潰瘍は治癒したと判定された．しかし症状が持続したため，同年10月に別のCセンターで精密検査を受けたところ，スキルス胃癌（低分化型腺癌）と診断された．D病院で手術を受けたが，昭和52年3月30日(33歳時)に胃癌のため死亡した．

Aの遺族は，①B医院B医師の計3回のX線検査の読影に誤りがあった，②胃潰瘍と診断した場合にも定期的な胃X線検査による経過観察が必要であった，と主張した．一方，病院側はAに対し，昭和51年4月および6月にそれぞれ精密検査を受けるよう指示したが，Aが指示に従わなかったと反論した．

【判旨】昭和49年のX線写真では活動性潰瘍の所見であり，B医師が胃潰瘍と診断したのは，やむを得なかったとした．しかし，その後経過観察のため再検査を行うべきであったが，昭和51年までの2年間検査を行っていない点に過失があるとした．さらに，昭和51年のX線検査では，辺縁硬化像などの癌の所見が認められたにもかかわらず，胃潰瘍と診断したことにも過失があったとした．Aの死期を早めたことに対し，病院側に慰謝料（300万円）の支払いを命じた．

【裁判例2】(東京高裁，昭和58年3月15日判決)[6]

【経過】A（昭和14年生まれ，女性）は高血圧症のため，昭和50年（36歳時）頃からB医院を受診していた．昭和53年6月13日（39歳時）に上腹部痛，悪心のため胃X線検査を受けた．胃潰瘍と診断され投薬を受けたが，症状が軽快しないため同年9月12日に別のC病院で精密検査を受けたところ，スキルス胃癌および癌性腹膜炎と診断された．抗癌剤による治療を受けたが，同年11月12日に死亡した．

Aの遺族はB医院のB医師のX線の読影に誤りがあったと主張した．原審[7]ではいくばくかの延命の可能性があったと判断し，慰謝料につき請求の一部を認容した．一方，B医院側はたとえ6月に癌が発見されていたとしても，Aに延命の可能性はなかったとして控訴した．

【判旨】胃X線で胃潰瘍と診断し，投薬しながら経過観察しようとしたことには問題なしとした．またB医院側の主張を認め，たとえ6月に癌が発見されていたとしても，Aに延命の可能性はなかったとして，原判決を取り消した．