Original

Clinicopathological and Histological Characteristics of Cancer of the Remnant Stomach After Pylorus-preserving Pancreaticoduodenectomy

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Objectives: Gastric cancer may follow pylorus-preserving pancreaticoduodenectomy (PPPD) for diseases of the pancreas head owing to the occurrence of duodenogastric reflux (DGR) after this procedure. In practice, however, these cancers are found in sites distant from the gastric anastomosis. We histopathologically examined the gastric mucosa for the presence of *Helicobacter pylori* (*H. pylori*) infection and DGR by using surgical specimens obtained from patients who developed gastric cancer after PPPD. **Methods:** We examined 4 specimens of gastric cancer occurring after PPPD for mucosal atrophy, *H. pylori* infection, trefoil factor family 2 (TFF2) expression, *p53* protein expression, DGR, and gastritis cystica polyposa (GCP), which is frequently associated with DGR. **Results:** Mild-to-moderate mucosal atrophy (Sydney classification) and *H. pylori* infection of the atrophic mucosa were found in all specimens. TFF2 expression, which like *H. pylori* infection is carcinogenic, was detected in the deep or intercellular layers of the gastric fundal mucosa in all specimens. Expression of the *p53* protein, but not GCP, was found in the atrophic mucosa. **Conclusions:** *H. pylori* infection in combination with chronic atrophic gastritis promotes the development of cancer in the remaining stomach after PPPD. Further, *p53* and TFF2 expression, which confers cells with enhanced proliferative capacity, may induce a highly pro-neoplastic state.

Key Words: pylorus-preserving pancreaticoduodenectomy (PPPD), gastric cancer, *Helicobacter pylori* (*H. pylori*), trefoil factor family2 (TFF2), *p53*

Introduction

Gastric cancer may occur after pylorus-preserving pancreaticoduodenectomy (PPPD) for diseases of the pancreas head. We searched Igaku-Chuo-Zasshi (in Japanese) databases for articles containing the keyword "PPPD, gastric cancer" and found that thus far, 27 cases of gastric cancer occurring after PPPD have been reported in Japan. Our institution is the only one to have encountered 5 such cases (gastrectomy, 4; endoscopic mucosal resection, 1). This unusually high incidence may be explained on the basis of the large number of long-term survivors as well as the considerable number of PPPDs conducted at our institution. A number of factors may be implicated in the pathogenesis of gastric cancer after PPPD: *Helicobater pylori* (*H. py-lori*) infection, duodenogastric reflux (DGR), proliferation of the gastric mucosa at the site of the pancreaticogastrostomy, and nuclear DNA ploidy pattern. However, since few such cases have been reported, the mechanism of development of these cancers remains to be elucidated.

According to the Japanese Classification of Gastric Carcinomas (13th edition)[1], cancers of the remnant stomach are defined as "any gastric cancer occurring after gastrectomy, including recurrent gastric cancer, regardless of the presence of a lesion at the primary operation, the extent of resection, and the type of gastric reconstruction surgery performed". However in practice, tumors within the anastomosis are termed "remnant gastric cancers" and those in sites distant from the stomach side of

the anastomosis are called "cancers of the remaining stomach". The cancers discussed in this study are of the latter type. The clinicopathological characteristics of these cancers are identical to those of conventional gastric cancer; the background lesion is chronic atrophic gastritis that eventually differentiates into adenocarcinoma. Differentiated adenocarcinomas and undifferentiated gastric cancers are the common types of cancers of the remaining stomach. Therefore, we consider that as in the case of conventional gastric cancer, DGR, including cytotoxic antibodies and bile, contributes to the development of cancers of the remaining stomach by inducing gastritis[2].

Kuipers et al[3] conducted a prospective study in which they found that *H. pylori* infection contributed to the occurrence of atrophic gastritis and the subsequent progression from catarrhal gastritis to intestinal metaplasia. *H. pylori* infection acts as a promoter of carcinogenesis; the risk of developing gastric cancer significantly increases in the presence of persistent *H. pylori* infection[4][5]. Furthermore, in a stomach carcinogenic model of *H. pylori* infection, trefoil factor family 2 (TFF2)-positive cells were found in the deep gastric fundal mucosa; this was accompanied by a decrease in the number of parietal cells. TFF2-positive cells, being highly proliferative, multiply ectopically and induce a highly pro-neoplastic state[6]. Spasmolytic polypeptide expressing metaplasia (SPEM) is metaplasia which stained in TFF2 (Spasmolytic Polypeptide) and resembles the shape of Brunner's glands tumor of the gastric fundal gland base. Because a large number of myeloid cells are involved in SPEM, and TFF2-positive cells show differential multiplication in SPEM, TFF2 peptides can be visualized by immunostaining for proliferating cell nuclear antigen (PCNA)[7]~[9]. Moreover, it has been suggested that SPEM develops from chief cells because PCNA immunostaining, which is the marker of cell proliferation, was not observed in the original cells present in the hypertrophy in the gastric fundal gland base; moreover SPEM was observed in the second-cell zone of hypertrophy and showed double-staining with the gastric intrinsic factor which was the marker of chief cells[10][11]. Furthermore, intestinal metaplasia of the gastric mucosa was considered a precursor of gastric cancer, particularly, intestinal and differentiation type cancer, long before the development of Correa's multistep multifactorial process of human gastric carcinogenesis[12]. Abnormalities of the *p53* gene are frequently found in areas of intestinal metaplasia, and in an experiment involving a mouse model of intestinal metaplasia, cells showing intestinal metaplasia and *p53* abnormalities were found to eventually differentiate into cancer cells[13]. *H. pylori* infection reportedly leads to abnormalities of the *p53* gene[14]. The *p53* gene is an important cancer-suppressing gene; however, the clinical significance of intranuclear *p53* accumulation in areas of intestinal metaplasia is unclear[15]. Monoclonal antibody DO-7, which we used this time recognizes both variant and wild-type proteins; however, we analyzed mutation of the *p53* gene on the basis of abnormal accumulation of the variant *p53* protein, because the expression of wild-type *p53* protein cannot be determined from immunostaining. The presence of the *p53* protein in the gastric mucosa has been suggested to indicate a highly pro-neoplastic state.

With regard to the contribution of DGR, gastritis, specifically stomal gastritis, is found in gastric anastomoses; gastric cystica polyposa (GCP) are found in the deep mucosa and indicate stomal gastritis. These specific mucosal changes have been found to be associated with the development of remnant gastric cancer in rats[16].

In the present study, we discuss the clinicopathological characteristics of 4 specimens obtained via gastric resection for gastric cancer occurring after PPPD, and review relevant literature.

Patients and Methods

Tissue material

Of 437 patients who underwent PPPD between 1984 and 2003 at our institution, surgical specimens were obtained from 4 patients who developed gastric cancer more than 1 year after the PPPD (Table 1). Gastrectomy was performed in all 4 patients (Table 1). The specimens were fixed in 10% formaldehyde and embedded in paraffin. Slides of 4-μm-

Table 1 Primary disease and histopathological findings of cancer of the remaining stomach after PPPD in the present study

Case	a	b	c	d
Age	64	63	66	74
Sex	F	M	M	M
Primary disease	Pv-Ca	Bi-Ca	Bi-Ca	Bi-Ca
Histology	tub2	tub2	tub2	pap
Stage	II	II	I	I
Antacid internal use period (year)	2	(−)	1	(−)
Time to gastric cancer development (month)	155	167	87	39
Location of CRS	Pylous-ring	Cardia	Corpus	Antrum
Marco of CRS	0-IIc	0-IIc	0-IIc	Borr2
Histology of CRS	tub1	por2	tub1	tub1
Depth	sm	mp	m	se
Stage of gastric cancer	IA	IB	IA	II
Treatment	Distal gastrectomy	Proximal gastrectomy	Total gastrectomy	Distal gastrectomy
Reconstruction of PPPD	III	II	II	II
Gastric atrophy	Mild	Mild	Mild	Moderate
H.pylori infection	Moderate	Mild	Mild	Mild
Inflammatory cells infiltration	Mild	Mild	Mild	Mild
Intestinal Metaplasia	Mild	Normal	Moderate	Mild
TFF2 (PCNA index)	+ + +	+ + +	+ + +	+ + +
p53	+ +	+ +	+ +	+ +
GCP	(−)	(−)	(−)	(−)

PPPD: pylorus-preserving pancreaticoduodenectomy, Pv-Ca: carcinoma of the ampulla of Vater, Bi-Ca: lower bile duct cancer, CRS: cancer of the remaining stomach, TFF2: trefoil factor family 2, PCNA: proliferating cell nuclear antigen, GCP: gastritis cystica polyposa.

thick serial sections of the gastric mucosa in and surrounding the cancer of the remaining stomach were stained with hematoxylin and eosin (HE) and Giemsa, and subject to immunohistochemistry.

Gastric mucosal atrophy

Gastric mucosal atrophy was evaluated by performing HE staining, using the Sydney classification[17].

***H. pylori* infection**

Because preoperative examination for *H. pylori* infection had been performed in only 2 of the 4 patients, Giemsa staining of the specimens followed by evaluation according to the Sydney classification were performed to confirm *H. pylori* infection.

Expression of TFF2-positive cells

Sections were incubated for 3 min at room temperature with anti-PCNA antibody (PC 10, DAKO) diluted 1 : 400 for immunostaining using the labelled streptavidin biotin (LSAB) method. We selected 1 area of the deep region of the gastric fundal gland mucosa with high immunostaining intensity and counted 500-1,000 cells, which constituted a gastric fundal gland, with a microscope (magnification, $\times 100$), and calculated the positive rate for PCNA positive crypt cell nuclei (PCNA index).

Expression of the *p53* protein

Sections were incubated for 3 min at room temperature with anti-*p53* polyclonal antibody (clone DO-7, DAKO) diluted to 1 : 200 as the primary antibody; for *p53* protein expression, cells were immunostained with the LSAB method. Cells showing nuclear staining were considered as *p53*-positive cells. The staining intensity was classified into 3 grades: 0, 1 and 2 (negative, positive by observation with a $\times 200$ or $\times 400$ microscope, and clearly positive by observation with a $\times 40$ microscope, respectively); only cells showing grade 3 staining were counted. On the basis of the immunostaining intensity 2, we selected 1 region of the gastric fundal gland (magnification, $\times 50$) for which we calculated the positive rate similar to PCNA index.
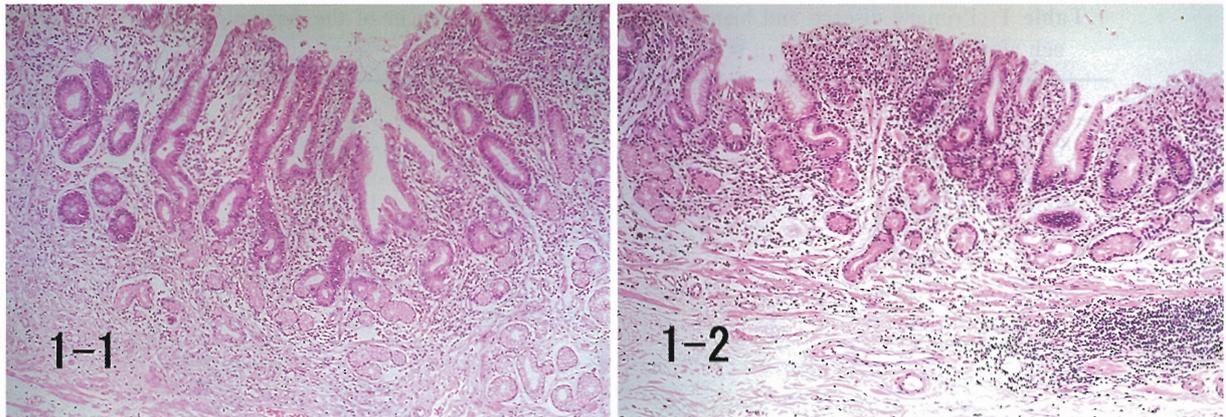
Fig. 1 Gastric mucosal atrophy (HE staining: ×50)
Specimen (a) of differentiated-type cancer showed mild gastric atrophy with mild intestinal metaplasia (as per the Sydney classification) (Fig. 1-1). Specimen (b) of poorly-differentiated-type cancer showed mild gastric atrophy without intestinal metaplasia (Fig. 1-2).
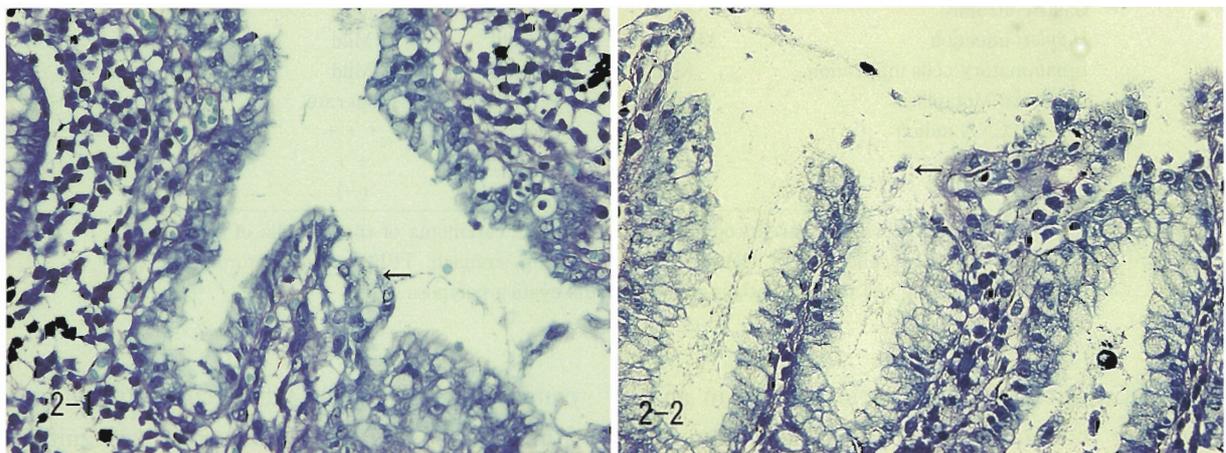

Fig. 2 *H. pylori* (Giemsa staining: ×150)
Specimen (a) showed moderete *H. pylori* infection (as per the Sydney classification) (Fig. 2-1). Specimens (b) showed mild *H. pylori* infection (WFig. 2-2). Mild inflammatory invasion was observed. Neutrophils, which were identified by their lobed nuclei and purple color, were observed in the peripheral mucosa.

Scoring of immunoreactivity

Immunoreactivity was scored according to the presence of immunoreactive cells: −, none or ＜5% positive cells; +, 5-25% positive cells; + +, 25-75% positive cells; + + +, ＞75% positive cells.

Effect of DGR

We tested the specimens for the precancerous lesion GCP[16] by HE staining.

Results

Gastric mucosal atrophy

Specimens obtained from case (a), (b) and (d) showed mild gastric atrophy (as per the Sydney classification); specimen (c) showed intestinal meta-plasia along with numerous goblet cells, indicating moderate gastric atrophy. Specimen (a), which was a differentiated-type cancer, showed mild gastric atrophy with mild intestinal metaplasia (as per the Sydney classification) (Fig. 1-1). Specimen (b), which was a poorly-differentiated-type cancer, showed mild gastric atrophy without intestinal metaplasia (Fig. 1-2). Overall, atrophic gastritis of the entire mucosa was found in all 4 specimens (Table 1).

H. pylori infection

Although *H. pylori* infection was not found in the areas of intestinal metaplasia, it was detected in the atrophic gastric mucosa in all 4 specimens. Speci-

men (a) cancer showed moderate *H. pylori* infection (as per the Sydney classification) (Fig. 2-1). Specimen (b) showed mild *H. pylori* infection (Fig. 2-2). Moreover, inflammatory cell invasion was noted in the *H. pylori* infected areas (Table 1). Because neutrophils in particular were observed in the same areas, it seemed to be inflammation due to the *H. pylori* infection.

TFF2 expression

Cells appearing densely brown after PCNA immunostaining are considered positive for TFF2. These cells were identified using a loupe, and in the case of all specimens, they were seen in the deep or intercellular layers of the gastric fundal gland mucosa surrounding the cancer (Fig. 3-1, 3-2). As compared with HE specimens (Fig. 3-5, 3-6), TFF2 was detected in the chief cells of the gastric fundal gland base by immunohistochemistry (Fig. 3-3, 3-4). The expression of TFF2 was 85, 87, 88 and 90% in specimens (a), (b), (c) and (d), respectively. There was no clear difference in the expression of TFF2 between differentiated-type cancer and poorly-differentiated-type cancer.

Expression of the *p53* protein

TFF2 was widely distributed in the specimens, but expression of *p53* was mainly found deep in the atrophic mucosa of the gastric fundus in all 4 specimens. As compared with an HE specimen (Fig. 4-3, 4-4), *p53* was detected in the chief cells of the gastric fundal gland by immunohistochemistry, and *p53*-positive cells were stained brown-yellow (Fig. 4-1, 4-2). *p53* expression was 39, 37, 30 and 38% in specimens (a),(b), (c) and (d), respectively. There was no clear difference in *p53* expression between differentiated-type cancer and poorly-differentiated-type cancer.

Contribution of DGR

The gastric gland fossa epithelium and deep layers of the gastric fundal mucosa were subject to HE staining. Duct distension due to mucous effusion was observed, but hyperplasia of the gastric epithelium and GCP were not observed (Table 1).

Discussion

PPPD was developed for the treatment of chronic pancreatitis and cystic diseases of the pancreas head, while preserving as much organ function as possible. Currently, PPPD is performed for the treatment of both benign and malignant diseases of the pancreas head. In Japan, 27 cases of gastric cancer occurring after PPPD have thus far been reported, and the incidence of this type of cancer is approximately 0.1% at our institution. According to Tanikawa et al[18], this type of cancer accounts for approximately 0.2% of all gastric cancers occurring after operations on the stomach. The rate of detection of gastric cancer by radiographic screening of the upper digestive tract is 0.12%. No statistically significant difference was found between these incidences, and no effect of the previous malignant tumors was considered to be present.

Cancer of the remaining stomach is more common after distal gastrectomy than after PPPD. Cancer of the remaining stomach after PPPD is more common among men (sex ratio, 3 : 1) and in individuals aged around 60 years. Matsukura et al[19] examined 33 cancers of the remaining stomach and found that gastric cancer after peptic ulcer surgery was more likely to occur after Billroth II reconstruction (B-II) (11/17, 65%), whereas gastric cancer after gastric cancer surgery was more likely to occur after Billroth I reconstruction (B-I) (13/16, 81%). Therefore, they concluded that DGR is more likely to occur after surgery for gastric ulcer plus B-II, whereas *H. pylori* infection is more likely to follow surgery for gastric cancer plus B-I. It is significantly different in time to detection of gastric cancer after gastrectomy (p < 0.01) and sites of carcinogenesis in the remaining stomach (p < 0.05); gastric cancer after B-I tended to be associated with *H. pylori* infection, Stage I and II cancer, and well-differentiated adenocarcinoma, whereas gastric cancer after B-II was associated with absence of *H. pylori* infection, Stage III and IV cancer, and poorly differentiated adenocarcinoma (p < 0.2). In this study, the clinical characteristics of cancers of the remaining stomach after PPPD, namely, male predominance, history of malignant disease, and occurrence after 39-167 months (average 120 months), indicate that this type of cancer resembles gastric cancer occurring after surgery for gastric cancer
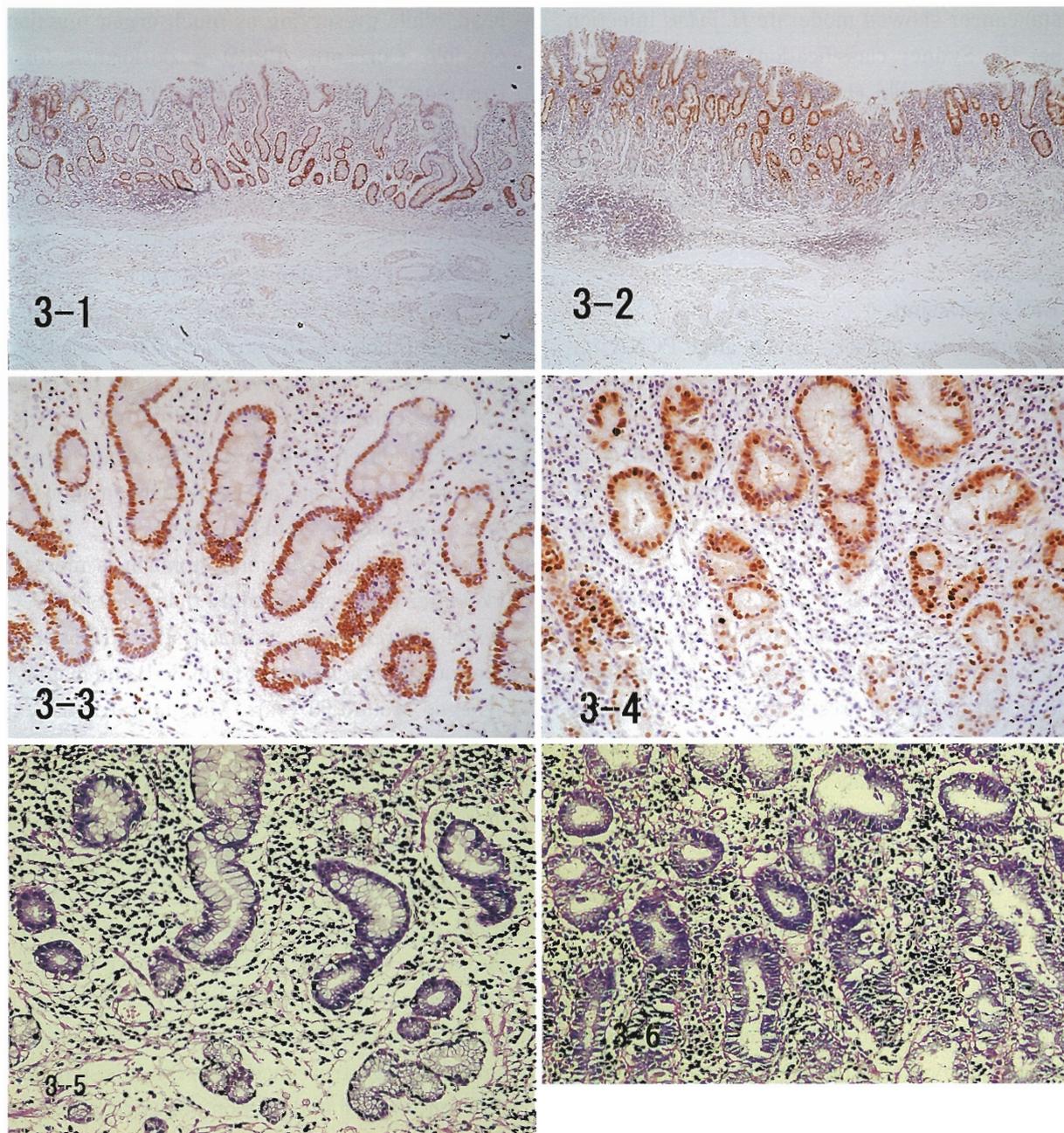
Fig. 3 TFF2 expression (PCNA immunostaining: loupe examination and ×100, HE: ×100)
Cells stained dense brown are positive for TFF2 and were widely observed in the deep or intercellular layers of the gastric fundal gland mucosa surrounding the cancer. These cells were identified using a loupe (Fig. 3-1, 3-2). As compared with HE specimen (Fig. 3-5, 3-6), TFF2 was detected in the chief cells of the gastric fundal gland base by immunohistochemistry (Fig. 3-3, 3-4). Specimen (a) (Fig. 3-1, 3-3 and 3-5) and specimen (b) (Fig. 3-2, 3-4 and 3-6) showed high TFF2-positive rate.

plus B-I. *H. pylori* infection is seen in early cancer cells, and the age at onset is approximately 76 years (Table 2).

Kaminishi et al[20] have reported that DGR is an important factor in the development of remnant gastric cancer after gastrectomy, and in an experiment on rats, the rate of carcinogenesis was highest when DGR, including bile and pancreatic secretions, was present[21]~[23]. In PPPD, the preserved pyloric ring with its intact vagus nerve (pyloric branch) is expected to ensure less DGR than that seen after distal gastrectomy. In the present study, PPPD-II
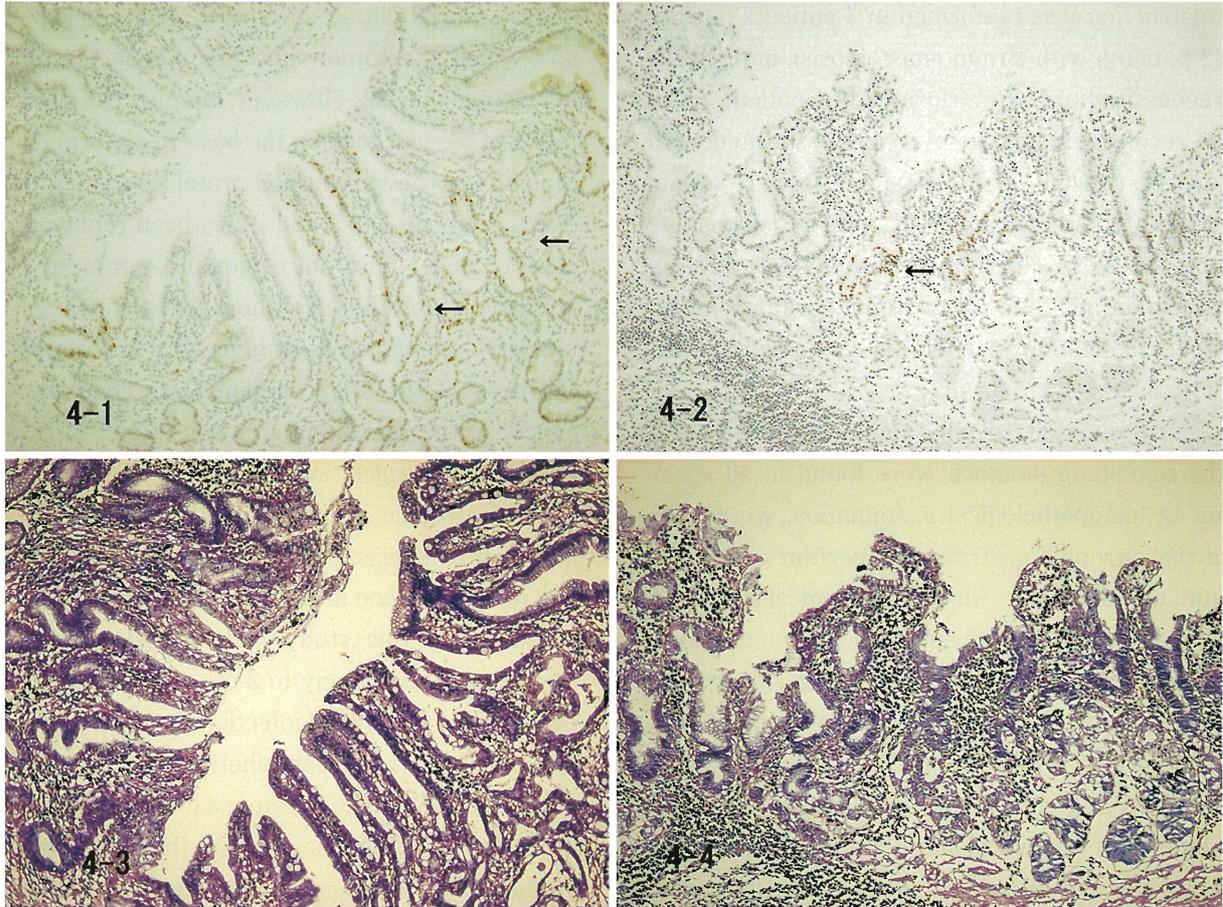
Fig. 4 Expressions of the *p53* gene (*p53* protein immunostaining and HE: ×50)
Cells in a portion of the atrophic mucosa in the gastric fundus were immunostained with
anti-*p53* antibodies and positive cells were stained brown-yellow (arrow) (Fig. 4-1, 4-2). As
compared with HE specimen (Fig. 4-3, 4-4), the *p53* gene was detected in the chief cells
of the gastric fundal gland by immunohistochemistry. These cells showed expressions of
the cancer suppressing *p53* gene. Specimen (a) (Fig. 4-1, 4-3) and specimen (b) (Fig. 4-2, 4-4)
showed the same positive rate.

Table 2 Clinicopathological characteristics of cancer of the remaining stomach

Primary disease	Peptic ulcer	Gastric cancer	Diseases of the Ph
Reconstruction	Billroth II	Billroth I	PPPD-II, III
Age (mean)	55	60	76
Time to gastric cancer development	10 year <	10 year ≥	10 year ≥
Carcinogen (hypothesis)	DGR	*H. pylori*	*H. pylori*
Background mucosa	Gastritis alkaline reflux	Chronic active gastritis	Chronic active gastritis
Cancerogenesis	Neogenesis cancer	Metachronous multiple cancer	Metachronous cancer
Location of CRS	Anastomotic region of the stump	Whole remaining stomach	Whole remaining stomach
Stage	III, IV	I, II	I, II
Histology	Por	Well	Well, Por
Gastric atorophy	(−)	(+)	(+)
H.pylori	(−)	(+)	(+)
GCP	(+)	(−)	(−)

Ph: pancreas head, CRS: cancer of the remaining stomach.

reconstruction was performed in 3 patients (including 2 patients with Braun anastomosis), and PPPD-III reconstruction was performed in 1 patient. Since these reconstructions are typically associated with little DGR, cancers in the anastomosis were attributed to GCP induced by DGR, and TFF2-positive gastric cancer was attributed to the effect of *H. pylori* infection at a site away from the anastomosis. However, our findings should be confirmed in studies with a larger sample size.

Because mucosal atrophy and *H. pylori* infection in the remaining stomach were found in all specimens on histopathological examination, we considered that atrophic gastritis is important as a background characteristic. An epidemiological study has reported that gastric cancer develops to a considerable extent when the degree of the atrophic gastritis is mild-to-moderate[24]. In the case of cancer of the remaining stomach after PPPD, the degree of the mucosa atrophy corresponded to the degree of development of gastric cancer. Moreover, it seems that the effect of *H. pylori* was equivalent to that of gastric cancer because gastric cancer develops in most cases of atrophic mucosa associated with *H. pylori* infection. Increased TFF2 expression is observed in the stomach of *H. felis*-infected mice, which are a model of *H. pylori* infection, and numerous myeloid cells and differentiation are observed in SPEM. TFF2-positive cells are likely to differentiate into cancer cells[25]~[28]. Because these cells were localized in the deep or intercellular layers of the gastric mucosa in all 4 specimens, we were able to confirm that a phenomenon similar to that in the carcinogenic model for *Helicobacter* infections occurred in the remaining stomach mucosa after PPPD. Generally, differentiated-type gastric cancer develops from the intestinal metaplasia mucosa, and poorly-differentiated-type cancer develops from the stomach mucosa. Abnormalities of the *p53* gene occur in 20-40% of well-differentiated gastric cancers and 20% of poorly differentiated gastric cancers[29]; these abnormal expressions are also found in areas of intestinal metaplasia[10]. In this study, expression of the *p53* protein was not detected in areas exhibiting intestinal metaplasia but were detected in atrophic gastric mucosa in all specimens. It is unclear how *p53*, which is a tumor-suppressor gene, is mutated in atrophic mucosa. However, we may estimate mutation of the *p53* gene on the basis of abnormal accumulation of the variant *p53* protein by using monoclonal antibody DO-7, and it has been reported that gastric cancer does not originate from areas of intestinal metaplasia, but rather from atrophic gastric mucosa[30]; our findings support this hypothesis. On the basis of the above findings, we conclude that cancer of the remaining stomach after PPPD is induced by *H. pylori* infection in combination with chronic atrophic gastritis, both of which lead to a highly pro-neoplastic state with TFF2 expression and *p53* expression in the atrophic mucosa.

Finally, in this study, antacids had been prescribed postoperatively to 2 of the 4 patients. However, because *H. pylori* infection was detected in all specimens, it is unclear whether the incidence of cancer of the remaining stomach can be decreased by *H. pylori* eradication. Despite this, we think that eradication of *H. pylori* infection must be considered in all cases. Moreover, atrophic gastritis is expected to pose an appreciable oncogenic risk because TFF2 expression and *p53* expression were detected in the atrophic mucosa in the non-cancerous part of the remaining stomach. Thus, TFF2 expression and *p53* expression may be used as biomarkers for a high risk of gastric cancer and may facilitate the early detection and treatment or even prevention of cancer of the remaining stomach.

Conclusion

H. pylori infection is considered to promote carcinogenesis in the remaining stomach after PPPD against a background of chronic atrophic gastritis. This infection induces a pro-neoplastic state by inducing TFF2 expression, which confers proliferative potential on cells, and by inducing *p53* expression.

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幽門輪温存膵頭十二指腸切除術（PPPD）後の残胃の癌発生に関する臨床病理組織学的検討

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<small>フルカワ ケンジ カツラガワ ヒデオ ニシカワ トシオ ヤマモト マサカズ</small>
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〔目的〕膵頭部領域疾患に対し適応される幽門輪温存膵頭十二指腸切除術（PPPD）症例では，胆汁を含む十二指腸液胃内逆流（duodenuogastric reflux：DGR）により胃に異時性に癌が発生すると考えられてきた．しかし，臨床的には，吻合部から離れた部位に癌が認められる．そこで，PPPD 後に経験した胃癌症例について，*Helicobacter pylori*（*H. pylori*）感染と DGR の 2 つの点から，PPPD 後の胃粘膜の状態について，病理組織学的に検討した．〔対象と方法〕1984〜2003 年までに経験した PPPD 後の胃癌 4 例を対象に，発生母地粘膜の萎縮，ピロリ菌の有無，TFF2 陽性細胞の有無，*p53* 蛋白の発現，DGR に関しては，DGR が原因で発癌する場合，高率に認められる gastritis cystic polyposa（GCP）の有無について検討した．〔結果〕残胃粘膜の萎縮は，全例に認められ，Sydney 分類で Mild〜Moderate，*H. pylori* も，全例で萎縮粘膜内に認められ，Mild〜Moderate であった．TFF2 陽性細胞は，全例で胃底腺粘膜の深層〜中層に発現が認められ，*H. pylori* 感染の発癌モデルと同様の現象が認められた．また，萎縮粘膜内で *p53* 蛋白の発現が認められたが，GCP は，1 例も認められなかった．〔結論〕PPPD 術後の残胃の癌の発生は，慢性萎縮性胃炎を背景に，*H. pylori* 感染がプロモーターとなり，細胞増殖能を有する TFF2 陽性細胞や *p53* が原因となり，高発癌状態を誘導していると考えられた．

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