その配分の適切性も加味される必要がある．

近年，ガイドライン導入による診療に対する効果を評価する目的で quality indicator を設定し，ガイドライン導入前後での変化を捉えてガイドラインを評価しようとの試みもなされている．ただし，胆道癌においては何をもって quality indicator とするかは非常に複雑な問題であり，今後，これらについて広く討議する必要があるものと思われる．

本ガイドラインの対象読者は医師を中心とした医療関係者である．この点に関して，AGREE による評価においても指摘されたように，治療を受ける側，すなわち患者サイドに立った表記がなされていないという問題点がある．しかし，1つのガイドラインで医療サイドと患者サイドの両方に立った表記をすることはかなり困難である．特に，専門用語の使用などの点で大きな制約を受けかねない．このような背景から，いくつかの他癌腫では患者や一般的な読者を想定したガイドラインが医療従事者向けのものとは別に作成されている．この点に関しては，本ガイドラインでも医療情報サービス「Minds」の協力を得て，現在，患者用のガイドラインの制作を試みているところである．

本ガイドラインには依然として上記のような多くの問題点もあり，今後の改訂ではこのような点に関して改善策を打ち立てていく必要がある．

■ おわりに ■

本稿では「胆道癌診療ガイドライン」[2]について，その作成の目的，経緯，評価，今後の課題を中心にまとめた．

最後に，本ガイドラインは，あくまでも作成段階における最も標準的な診療指針を胆道癌診療にかかわる医療者の目安となるようにまとめたものであることを強調したい．すなわち，本ガイドラインは実際の診療行為を強制するものではなく，個々の診療に対しては各施設の状況や個々の患者の個別性を加味して担当する医師が最終的に対処法を決定すべきである．昨今，法廷などでガイドラインが100%守らねばならない regulation として取り扱われることもあるが，前述のようなガイドライン本来の目的を鑑みれば，このような目的にガイドラインの内容が問われることは適切でないことは明らかである．

今後，このガイドラインが臨床医に適切な情報を提供し，患者に対して最適な医療が行われることに役立つことを期待する．

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別添３

厚生労働科学研究費補助金
（総括・分担）研究報告書

がん診療ガイドラインの作成（新規・更新）と公開の維持および その在り方に関する研究

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研究要旨
現在、膵癌診療ガイドラインは2009年度改訂版（第2版）が最新版として平成21年9月に発刊されている。すでに初版（2006年度版）はWeb公開されているが、2009年度版のWeb化を想定した資料整備が急務である。第3版発刊へ向けた改訂委員会が平成22年7月11日に発足され、最新情報の提供と公開の維持のための更新作業を進める。

A．研究目的
膵癌診療ガイドラインの改訂にともなう最新情報の提供と公開の維持を目的とする。

B．研究方法
初版（2006年度版）についてのアンケート集計なども反映してよりよいガイドライン作成を目指す。今年度は2009年度改訂版のWeb化を想定した資料作成を中心に作業を進めた。また、本ガイドライン作成担当母体である日本膵臓学会膵癌診療ガイドライン改訂委員会を2回開催し、第3版発刊作業について検討した。
（倫理面への配慮）
膵癌治療は非常に成績が悪いために一般人の方が読んでも期待を持たせるように今後につながりそうな試みなどを「明日への提言」に記載した。

C．研究結果
1．2009年度改訂版Web化を想定した資料作成、データ整理を行った。

2．第3版の平成24年度発刊に向けた膵癌診療ガイドライン改訂委員会が発足した。平成22年7月11日に第1回、平成22年10月15日に第2回改訂委員会が開かれた。

3．改訂に向けての検討事項は、CQの表現方法、CQの追加事項、ステージ分類をJPSかUICC分類のどちらを採用するかである。現行ガイドラインは日本膵臓学会編集の膵癌取扱い規約によるステージ分類に従って記載されているが、切除できない場合は、UICC分類の方が非常に理解しやすい点からUICC分類に従って変更することを検討した。

D．考察
科学的根拠に基づいてガイドラインを維持するには、最新データベースの構築、新薬などの最新情報の収集を絶えず図る必要がある。しかし、人的労力の過剰な負担などガイドライン改訂委員のvolunteerによって作成されていることが問題と思われる。また、膵癌取扱い規約の第6版が平成21年7月に発刊されており、2009年度改訂版はその前の第5版をもとに作成されていることから最新ガイドラインの作成は急務である。

E．結論
今年度の作業により、最新情報の提供・公開へ向けた資料を整備できたことになる。今後はそれをもとに日本膵臓学会のホームページ上などでの公開を進めていきたい。また、膵癌治療におけるRCTの結果など最新データを基に更新作業を進め、膵癌診療ガイドラインを3年ごとに最新化・改訂する必要性を改訂委員会で検討した。

F．健康危険情報
○○○○○○○○○○○○○○○○○○○
（分担研究報告書には記入せずに、総括研究報告書にまとめて記入）

G．研究発表
1．　論文発表
該当なし
2．　学会発表
該当なし
（発表誌名巻号・頁・発行年等も記入）

H．知的財産権の出願・登録状況
（予定を含む。）
1．特許取得
該当なし
2．実用新案登録
該当なし
3.その他

がん診療ガイドラインの作成（新規・更新）と公開の維持および その在り方に関する研究

分担研究者　今村正之　関西電力病院・学術顧問

研究要旨

膵・消化管神経内分泌腫瘍（NET）は上皮性のがんに比し比較的緩徐に悪性化していくが、転移傾向の強い腫瘍も多く、肝転移を来たすと予後は制限される。外科的切除の限界を超えると種々の治療がなされる。最近分子標的薬の開発も進み、種々の治療法がなされている。　近年、発生数が急速に増加しており、診断と治療法の標準化が国際的に課題となっている。米国や EU でいくつかののガイドラインが作成されているが、本邦で私たちが行った統計的調査では、欧米と異なった腫瘍分布が見られ、独自の診療ガイドラインの作成が求められている。今回、各分野の医師が集まり、本邦の患者に適したガイドラインを作成すべく。研究を進めている。

A. 研究目的

本邦での膵・消化管 NET の研究と臨床は国際的に高い水準にあり、早期発見と早期治療も専門施設では実施されている。分子標的薬の有効性も示されてきた今日、広く患者の健康維持に益する診療ガイドラインを作成し、多くの患者の早期診断と早期治療、肝転移患者の延命向上に益するのが目的である。

B. 研究方法

本邦の NET 診療と研究を専門とする臨床医師と病理医予防医学医、遺伝医学医、コンサルタント医などが集まり委員会を形成り、患者本位の診療ガイドライン作成に向けて、国際的論文と研究発表の成果を検討し集積し、本邦に即したガイドライン作りをして、倫理的に問題のないものとするために、日本内分泌外科学会と日本膵臓学会、日本癌治療学会それに、患者代表にも評価を受けることとしている。

C. 研究結果

現在、委員会委員が、国際的に評価しうる論文を収集し検討し、調査している。診療現場から生まれた本邦患者診療からの成果は、発表している。それらの経験と論文調査の成果を本 12 月 11 日に持ち寄り、討論し Clinical Question を作成する予定である。

D. 考察

本邦での NET 研究と診療の水準は比較的高く、国際学会での評価も高い。欧米では診療上の制限のために、治療法や検査法の制限を受けるが、本邦では比較的医師の自由裁量が生かされた診療がなされている。一方、我が国で認められていない診断法や治療薬があり、本邦の患者がその恩恵を受けられていないことも明らかとなっている。

それらをまとめて、NET 患者の十分な治療体制を作れるようにガイドラインでも訴えていきたい。

E. 結論

1年半以内に完成させて、本邦患者の診療に益するものとしたい。その内容では、各診療の意義と手順を明らかにして、分子標的薬と国際的に用いられいるが本邦で認められていない検査法、診断薬、治療薬の有用性についても盛り込み、NET 深慮言うが国際的に最前線であるように益したい。

F. 健康危険情報

特になし

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H. 知的財産権の出願・登録状況

1．特許取得

なし。

2．実用新案登録

なし。

3．その他

なし。

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TOPIC HIGHLIGHT

Kazuhiro Hanazaki, MD, Professor and Chairman, *Series Editor*

Recent standardization of treatment strategy for pancreatic neuroendocrine tumors

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Abstract

Recent advances in localization techniques, such as the selective arterial secretagogue injection test (SASI test) and somatostatin receptor scintigraphy have promoted curative resection surgery for patients with pancreatic neuroendocrine tumors (PNET). For patients with sporadic functioning PNET, curative resection surgery has been established by localization with the SASI test using secretin or calcium. For curative resection of functioning PNET associated with multiple endocrine neoplasia type 1 (MEN 1) which are usually multiple and sometimes numerous, resection surgery of the pancreas and/or the duodenum has to be performed based on localization by the SASI test. As resection surgery of PNET has increased, several important pathological features of PNET have been revealed. For example, in patients with Zollinger-Ellison syndrome (ZES), duodenal gastrinoma has been detected more frequently than pancreatic gastrinoma, and in patients with MEN 1 and ZES, gastrinomas have been located mostly in the duodenum, and pancreatic gastrinoma has been found to co-exist in 13% of patients. Nonfunctioning PNET in patients with MEN 1 becomes metastatic to the liver when it is more than 1 cm in diameter and should be resected after careful observation. The most important prognostic factor in patients with PNET is the development of hepatic metastases. The treatment strategy for hepatic metastases of PNET has not been established and aggressive resection with chemotherapy and trans-arterial chemoembolization have been performed with significant benefit. The usefulness of octreotide treatment and other molecular targeting agents are currently being assessed.

Key words: Gastrinoma; Glucagonoma; Insulinoma; Multiple endocrine neoplasia type 1; Octreotide; Pancreas preserving total duodenectomy; Pancreatic neuroendocrine tumors; Selective arterial secretagogue injection test; Somatostatin receptor scintigraphy

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INTRODUCTION

As pancreatic neuroendocrine tumors (PNET) are rarely encountered in hospitals, standardization of diagnosis and/or the treatment strategy have not progressed until recently. However, recent advances in localization techniques, such as the selective arterial secretagogue injection test (SASI test) and somatostatin receptor scintigraphy (SRS) have promoted curative resection surgery of PNET[1-3]. As the number of resections has rapidly

increased, a few important characteristic pathological features of PNET have been revealed year by year. The World Health Organization pathological classification of PNET was evolutionally simplified in 2003 at the Lion Meeting, and the term carcinoid was declared a misnomer[3] (Table 1). Recently, a study group in the EU published a few guidelines on gastroenteropancreatic neuroendocrine tumors (GEPNET)[5-7]. In this work I will review important progress in the standardization of both surgical and medical treatment strategies for PNET.

EPIDEMIOLOGY OF PNET

In Western countries, PNET is found in about 1 per 100000 population and represents 1%-2% of all pancreatic neoplasms[5-7]. In the USA, it is suggested that the incidence and prevalence of PNET has substantially increased over the last 30 years probably due to the rapid progress of innovative diagnostic techniques[8]. On the other hand, there have been a few epidemiological studies on NET in Japan[9,10]. In 2006, the Japanese NET study group (NET Work Japan) performed a nationwide survey to examine the epidemiology of GEPNET in Japan, using a stratified random sampling method to select departments of medical facilities where GEPNET were treated in 2005[9,10]. The first survey revealed that the overall prevalence was 2.23 patients per 100000 population [95% confidence interval (CI): 1.93-2.76] per year. The total number of patients treated for functioning PNET was estimated to be 1627 (95% CI: 1.10-1.57), and the overall prevalence of insulinoma and gastrinoma was 0.84 and 0.23 per 100000 population per year, respectively. Furthermore, the results in the second survey showed that the incidence of PNET in 2005 was estimated to be 1.01 per 100000 population per year (95% CI: 0.88-1.25). Accordingly, the incidence of functioning PNET and non-functioning PNET was 0.50 and 0.51 per 100000 population per year, respectively[9,10]. As the incidence of PNET in the USA has been reported to be about 0.32 per year per 100000 population by Yao *et al*[11], PNET seems to develop about three times more frequently in Japan compared to that in the USA.

RECENT STANDARD OF DIFFERENTIAL DIAGNOSIS OF FUNCTIONING PNET

Characteristic clinical symptoms of functioning PNET

Recurrent peptic ulcers in gastrinoma, necrolytic migratory erythema in glucagonoma, and watery diarrhea in VIPoma are characteristic symptoms due to an excessive increase of the responsible hormone in blood. These symptoms easily lead to the correct diagnosis when the measurement of blood hormone levels is promptly followed. However, the symptoms due to hypoglycemia do not easily lead to the diagnosis of insulinoma[12]. This may sound strange, but it is true. The diagnosis of insulinoma is the most difficult among the functioning PNET. Patients with insulinoma are often misdiagnosed for long periods. The patient eats much food and looks healthy but somewhat strange without any organic illness. We should be very careful in diagnosing insulinoma as there are a number of diseases that cause hypoglycemia, and a variety of special tests are required for insulinoma diagnosis, which will be described below.

Recently, the differential diagnosis of gastrinoma has also become difficult. This is due to both the easy and long-term use of proton pump inhibitors for recurrent peptic ulcers or regurgitation esophagitis without a precise assessment of both serum gastrin levels and gastric hyperacidity status[13-15].

Measurement of serum hormone levels

The measurement of serum hormone levels is very useful for the differential diagnosis of PNET other than insulinoma. The normal range of serum gastrin levels in patients with gastrinoma is quite different in patients with and without a history of gastrectomy[12]. When a patient undergoes a distal gastrectomy, normal serum gastrin levels are usually lower than 90 pg/mL[1]. Jensen's group in NIH performed an aggressive study on both the fasting serum gastrin levels and the gastrin provocative testing of both patients with gastrinoma and normal volunteers[14,15]. They revealed that various physiological conditions were correlated with basal serum gastrin levels, and have recommended that an increase of 120 pg/mL or more as the positive range for the intravenous secretin test[14,15].

Inhibition test and stimulation test for diagnosis of symptomatic GEPNET

C-peptide inhibition test with hog insulin: This test is not 100% reliable for the diagnosis of insulinoma[12], but it can be completed in only 2 h and can serve as a valuable screening tool. Although this test might not be popular currently, we have favored this test for a long time similar to the group at the Mayo Clinic[15].

Intravenous secretin test for insulinoma: When 2 U/kg • body weight of secretin is intravenously administered, plasma insulin level rises more than 200% within 4 min in normal volunteers, but does not rise more than 100% in patients with insulinoma[16,17]. We have developed this test and used it for patients in whom other tests were non-diagnostic in the differential diagnosis of insulinoma.

Intravenous secretin test for gastrinoma: A bolus injection of 2 U/kg • body weight of secretin into the peripheral vein increases the serum level of gastrin by more than 100 pg/mL in patients with gastrinoma, but does not increase the serum level of gastrin in those without gastrinoma. This well known test has been successfully used for the differential diagnosis of gastrinoma since 1972[18]. Although this test has been proved to be useful for years, we have to be careful as this test is also positive in patients with hypergastrinemia due to atrophic gastritis. It has been shown that antral G-cells also have secretin receptors and release gastrin when stimulated with pharmacological doses of secretin[19].

Table 1 World Health Organization classification of pancreatic neuroendocrine tumors

WHO classification	Well-differentiated neuroendocrine tumor	Well-differentiated neuroendocrine carcinoma	Poorly-differentiated neuroendocrine carcinoma
Biological behavior	Benign/uncertain behavior	Low malignancy	High malignancy
Metastases	-	+	+
Ki-67/MIB-1 index (%)	< 2	2-20	> 20
Pathological differentiation	Well-differentiated	Well-differentiated	Poorly-differentiated
Vascular invasion	-/+	+	+
Size (diameter)	≤ 2 cm	> 2 cm	Any size

Alteration of the original Table by Klöppel[4]. WHO: World Health Organization.

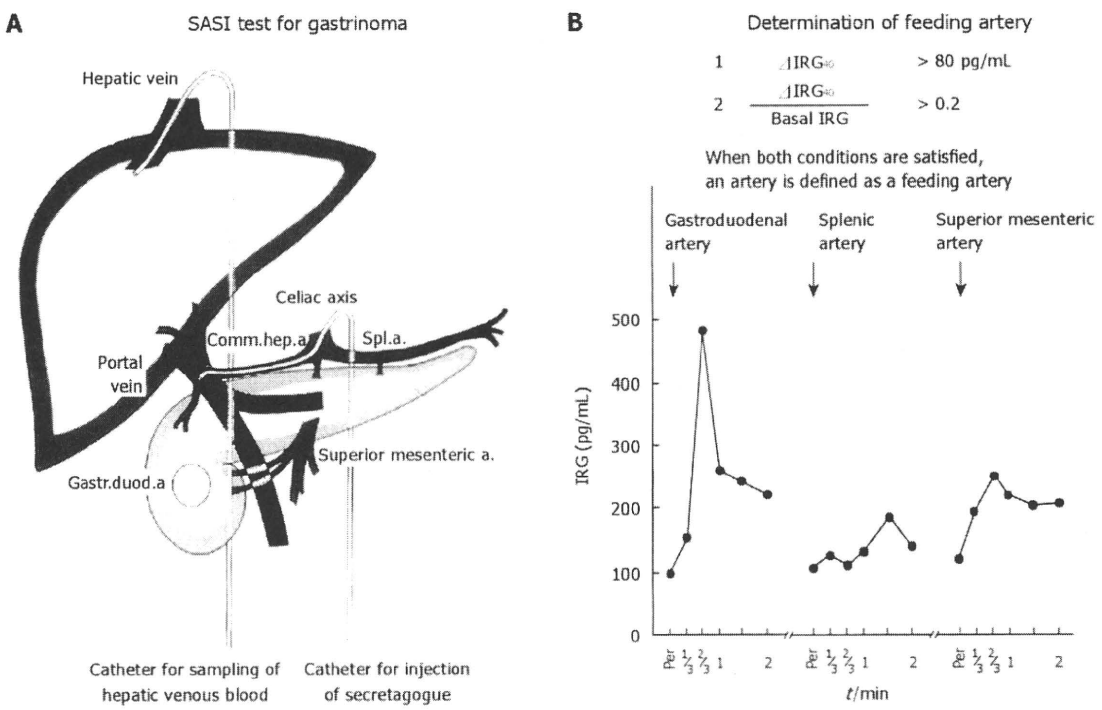

Figure 1 Schema of the selective arterial secretagogue injection test. Results of the selective arterial secretagogue injection (SASI) test in a patient with Zollinger-Ellison syndrome. In this patient, serum immunoreactive gastrin (IRG) at 40 s after the injection of 30 units of secretin rose only after injection into the gastroduodenal artery. Thus, it was diagnosed that the gastrinoma(s) was located in the upper part of the pancreas and/or the duodenum. Gastr.duod.a: Gastroduodenal artery; Spl.a.: Splenic artery; Superior mesenteric a.: Superior mesenteric artery.

RECENT PROGRESS IN LOCALIZATION OF BOTH FUNCTIONING AND NONFUNCTIONING PNET

Imaging techniques such as computed tomography, ultrasonography (US), endoscopic US (EUS), or intraoperative US (IOUS) have been useful for the localization of most PNET greater than 2 cm in diameter[20-23]. However, imaging techniques have difficulty in visualizing PNET less than 5 mm, and cannot identify a functioning PNET among various types of PNET including nonfunctioning PNET[20-23]. As the functioning PNET shows characteristic symptoms even when less than 5 mm, the SASI test is useful for preoperative localization of functioning PNET leading to curative resection surgery[1,20-22].

SRS is indispensable for localization of ectopic NET and the distribution of NET throughout the body[24].

SASI test with secretin or calcium

The SASI test was first described for localization of gastrinoma, and has gradually proved useful for the localization of other symptomatic PNET[1,20-22,25]. At the time of abdominal arteriography, secretagogue (30 U of secretin for gastrinoma and 1 mL of 8.5% calcium gluconate for insulinoma and glucagonoma) is injected into the splenic artery, the gastroduodenal artery and the superior mesenteric artery. Then, 2 mL blood samples are drawn from the hepatic vein through a catheter inserted *via* the femoral vein, before and 20, 40 and 60 s after the injection of secretagogue to detect the change in hormone levels in hepatic venous blood. When the rise in hormone levels 40 s after injection is significantly higher than measurement errors, the artery is diagnosed as a feeding artery of PNET. Functioning PNET is then located in the feeding area of the identified feeding artery. More precise localization is possible by injecting secretagogue into a branch of

the identified artery. When the splenic artery is identified as a feeding artery of insulinoma, more precise localization is possible by injecting calcium solution into the distal, middle and proximal portion of the splenic artery[2,3]. Both the sensitivity and specificity of the SASI test for both gastrinoma and insulinoma has been shown to be more than 90% , respectively[2,3,10,11,15] (Figure 1).

SRS

SRS is clearly able to visualize PNET more than 2 cm in diameter in the body, at a glance, and has contributed to the staging of PNET[2,3,25]. SRS can visualize 100% of gastrinomas larger than 3 cm in diameter, but only 20% of gastrinomas less than 5 mm, and 30% of gastrinomas less than 1 cm[27]. Thus, SRS visualized 73% of gastrinomas, 100% of glucagonomas, 88% of VIPomas, 73% of non-symptomatic GEPET, and only 46% of insulinomas, depending on both the extent of the presence and the differences in subtypes of somatostatin receptors, and the size of the tumor[27,28]. For the localization of ectopic PNET, SRS is an indispensable test[2,4].

IOUS

IOUS is useful in estimating the character of a tumor and to measure the distance between a PNET and the main pancreatic duct. In addition, the form and size of a PNET can be measured more correctly with IOUS than any other preoperative imaging technique[29].

Intraoperative rapid assay of blood hormone levels

Rapid immunoassay of insulin (IRI) and radioimmunoassay of gastrin (IRG) are useful for estimating the extent of the curability of surgery. Intraoperative measurement of both blood glucose levels and insulin using the same rate of drip infusion of glucose solution is helpful for estimating the curability of insulinoma resection[12]. The intraoperative secretin test with rapid radioimmunoassay of serum gastrin are useful for confirming the curability of gastrinoma resection surgery[5,6].

RECENT STANDARD OF SURGICAL TREATMENT OF PNET

The best treatment for PNET is curative surgical resection[5,6,31,32]. This needs to be performed before liver metastasis develops. Most PNET grow without invading the adjacent pancreatic parenchyma, and can reach a size of 1 cm[2,31].

Sporadic PNET

For a benign small PNET such as a benign sporadic insulinoma, enucleation is indicated wherever it is located in the pancreas, as long as it is 5 mm from the main pancreatic duct (MPD)[12,31]. Other sporadic functioning PNET such as gastrinomas, glucagonomas and VIPomas are thought to be potentially malignant and often multiple. Therefore, for these tumors pancreatic resection with lymph node dissection is indicated[31,33]. When the tumors are less than 5 mm in diameter, enucleation might also be indicated. R0 resection surgery for sporadic PNET has brought about complete relief of the characteristic difficult symptoms without recurrence[2,3,31,32].

PNET associated with MEN 1

In the case of multiple PNET, we must consider whether or not the patient has MEN 1. Serum calcium level and parathyroid hormone level require to be measured first, because the penetration rate of hyperparathyroidism is more than 90% in MEN 1. Genetic analysis is then performed. In patients with MEN 1, both PNET and duodenal NET are often multiple and microscopically numerous, and most are nonfunctioning[34-38].

There has been controversy regarding resection surgery for nonfunctioning PNET in MEN 1[31-33]. Recently, Goudet *et al*[35] revealed in a cohort study of 758 patients with MEN 1, that gastrinoma, nonfunctioning PNET and glucagonomas-vipomas-somatostatinomas had a high risk of death after adjustment for age, gender and diagnosis period. These PNET should be resected as early as possible before the development of hepatic metastases[31,35,36].

So far, extended distal pancreatectomy and enucleation of PNET more than 1 cm in diameter in the pancreatic head has been recommended for the prevention of liver metastases[35]. Total pancreatectomy is, so far, not indicated, because of a significant decrease in the quality of life of patients[37,38]. However, we know that some patients with PNET in MEN 1 rapidly develop liver metastases and die within a few years, therefore we will, in future, perform total pancreatectomy for selected patients based on advanced genetic analysis[38].

Pancreatic hypoglycemia in MEN 1 is often caused by multiple insulinomas which are located mostly in the body or tail of the pancreas[39]. Distal pancreatectomy is indicated for these types of insulinomas guided by the SASI test with calcium[12,39].

Recently, increased resection surgery for gastrinoma in patients with MEN 1 revealed that gastrinomas in MEN 1 were located mostly in the duodenum and rarely in the pancreas[34,43]. We have performed curative resection of gastrinomas in 16 patients with MEN 1 using pancreaticoduodenectomy (PD) or partial duodenal resection or pancreas preserving total duodenectomy (PPTD)[44]. In all patients, duodenal gastrinomas existed; as a single tumor in 42% , multiple tumors in 50% and numerous tumors in 13% (Figure 2). In addition, it was revealed that in two of 16 patients, pancreatic gastrinomas co-existed with multiple duodenal gastrinomas. These were resected guided by localization with the SASI test. When the patient with MEN 1 has more than five duodenal gastrinomas, we would recommend PPTD instead of PD for curative surgery[2,43,44]. The purpose of PPTD is to prevent recurrence of duodenal gastrinoma by total resection of the entire duodenum and to preserve full pancreatic function without resection of the pancreatic head. PPTD can be performed without any complications and seems less invasive than PD.

We have indicated PPTD for multiple duodenal gas-

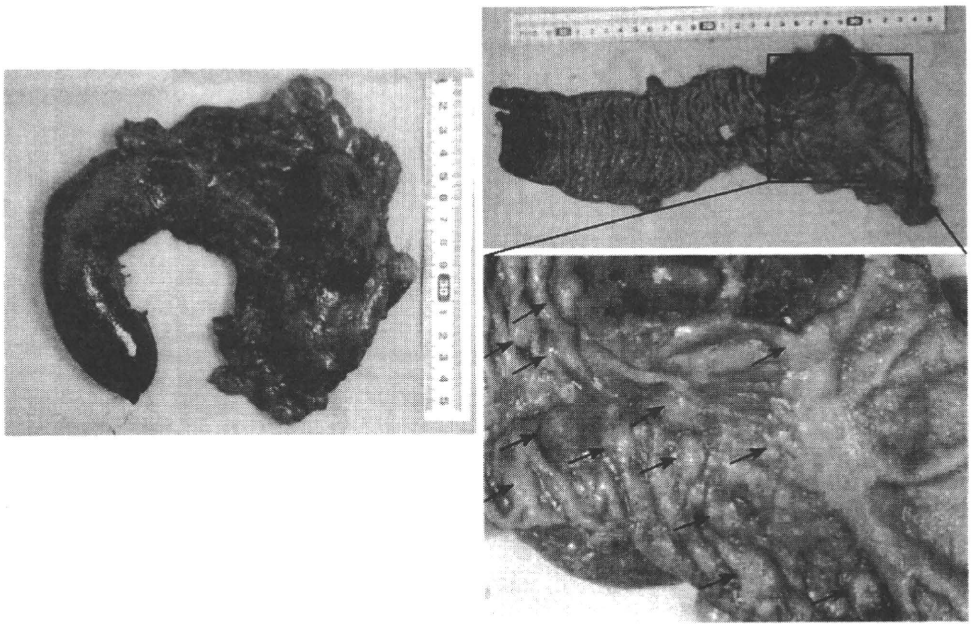

Figure 2 Numerous mucosal gastrinomas in the duodenum. Mucosal tumors with depression (arrows)

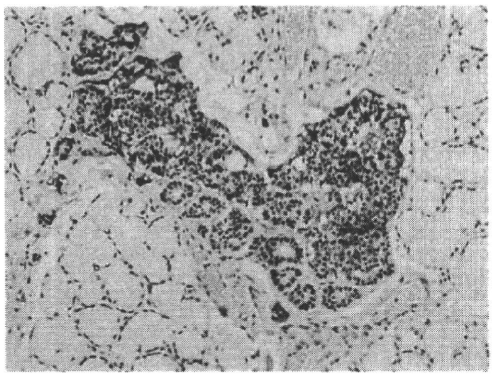

Figure 3 A cluster of G cells in hyperplasia of duodenal Brunner's glands in a patient with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome.

trinomas (more than 5 or numerous gastrinomas)[43]. In 7 patients with MEN 1, more than 5 multiple duodenal gastrinomas were suspected during surgery and PPTD was performed. However, postoperative pathological diagnosis revealed that in 3 patients, only one or two duodenal gastrinomas existed, and other submucosal tumors which were thought to be gastrinomas during surgery were diagnosed as hyperplasia of Brunner's glands in the postoperatively fixed paraffin specimen.

We performed immunohistochemical staining of the duodenal Brunner's glands with anti-gastrin serum, and found that there were clusters of gastrin-producing cells in the hyperplasia of duodenal Brunner's glands in all duodenal specimens after PPTD (Figure 3). Recently, Klöppel *et al*[45] reported that in patients with MEN 1, mutations in the menin gene can cause the development of clusters of gastrin-producing cells in the duodenal Brunner's glands, which are thought to be precursor lesions of gastrinoma in patients with MEN 1. This may explain the high rate of postoperative recurrence of duodenal gastrinomas in patients with MEN 1, and may theoretically support the usefulness of PPTD as a curative surgery for these patients[43,44].

TREATMENT OF HEPATIC METASTASES OF PNET

A few guidelines on the treatment of GEPNET have been published, such as the NCCN (National Comprehensive Cancer Network) guideline and Consensus guidelines by the European NET Study Group (ENETS)[5,6,8,44]. In both of these guidelines, resection surgery is first recommended for resectable hepatic metastases of GEPNET when the metastases are limited to the liver[5,6,46-49]. Now, the use of various types of cytotoxic chemotherapy for rapidly growing GEPNET and octreotide for slow growing well-differentiated GEPNET have been standardized[5,6]. These guidelines are also available for PNET.

Hepatectomy for hepatic metastases

It has been proved that resection of hepatic metastases improves the outcome of patients with PNET. Various types of resection surgery have been performed to achieve a macroscopic curative resection of hepatic metastases. Bettini *et al*[46] in Verona have reported on the usefulness of resection surgery combined with cytotoxic chemotherapy for prolongation of survival. They performed hepatic resection surgery whenever more than 90% of the hepatic metastases could be dissected, and used cytotoxic chemotherapy with CDDP, etoposide and 5-fluorouracil (5-FU) with streptozotocin as well as octreotide[49].

Radiofrequency ablation

Radiofrequency ablation (RF) has been performed in ad-

dition to surgical resection of the liver for multiple hepatic metastases, for example, for metastases located deep in the hepatic parenchyma[53]. However, a number of complications after RF have been reported, especially following percutaneous RF. Therefore RF should be performed very carefully[53].

Chemotherapy, octreotide and new molecular targeting drugs

As the few guidelines on GEPNET describe, cytotoxic chemotherapy with CDDP and etoposide, streptozotocin with or without 5-FU, *etc*., has been recommended for rapidly growing or poorly differentiated GEPNET[5,6]. For slow growing NET, octreotide with or without interferon α has been recommended[5,6].

In addition, prospective studies of mTor inhibitors with or without octreotide and tyrosine kinase inhibitors are currently underway[52,53]. New cytotoxic chemotherapy with temozolomide and capecitabine have also been reported to be effective in a small series of patients with malignant NET[54]. These drugs are also expected to be one of the new agents for PNET.

CONCLUSION

Curative resection surgery for sporadic PNET has almost been standardized using the SASI test for localization of PNET. The treatment strategy for PNET with MEN 1 has not been established, but resection surgery has been proved to contribute to the prolongation of survival in patients with MEN 1. Advances both in new chemotherapy including molecular targeting therapy and genetic analysis of PNET in patients with MEN 1 will lead us to a new treatment strategy for hereditary PNET.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan

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Abstract

Background There have been few epidemiological studies on gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in Japan.

Methods We examined the epidemiology of GEP-NETs [pancreatic endocrine tumors (PETs) and gastrointestinal neuroendocrine tumors (GI-NETs)] in Japan in 2005 using a nationwide stratified random sampling method.

Results A total of 2,845 individuals received treatment for PETs. Prevalence was estimated as 2.23/100,000 with an annual onset incidence of 1.01/100,000. Non-functioning tumor (NF)-PET constituted 47.4%, followed by insulinoma (38.2%) and gastrinoma (7.9%). Distant metastases were reported in 21% patients with NF-PETs and occurred more frequently as tumor size increased (>2 cm). Multiple endocrine neoplasia type 1 (MEN-1) was detected in 10% of

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