います．そこをどうエビデンスを形にしていくかというのはすごく難しいと問題だと思います．

宮崎　ご理解いただきありがとうございます．胆道癌の化学療法では新しい薬がでてきてpromisingなことがいえそうだということで，さらには分子標的．例えば膵癌などもそうですし，neuroendocrine tumorなどでもラパマイシンがでてきています．胆道癌に対する分子標的治療．現在はしっかりしたデータはないと思いますが，可能性としてどうでしょうか．

森実　今のところは，さまざまな作用機序の薬剤が開発中ですが，中でもEGFRやVGFRをターゲットとした薬剤への関心が高いようです．ただ，今のところエビデンスとしてちゃんと結果をだしたものはなくて，あれが良さそう，これが良さそうと，良さそうだから大規模な治験に着手したという，ところですね．ABC-02試験でちゃんとデータがでたということからグローバルの製薬会社も胆道癌の領域に少しずつ注目し始めているのは確かです．日本は胆道癌が多い国ですからリーダーシップをとっていかなくてはいけないと考えています．

宮崎　先生がその中心として是非国内で臨床試験をやっていただきたいと思います．山雄先生は分子標的についていかがでしょうか．

山雄　分子標的治療，あるいは癌ワクチンなど臨床試験は森実先生を中心にやっていただいていて，私どもの施設も参加させていただいています．胆道癌といいますと膵癌と違って非常に難しい面がありますね．特に胆管炎のコントロール．登録できる症例が限られてくるわけです．イギリスに比べて圧倒的に胆管癌が多いので，是非この分野でもいろいろな薬がでてくるのを期待しますが，その辺のところもクリアしないといけないと思います．

宮崎　分子標的というのは可能性はあるけれど今後の展開を期待したいというところでしょうか．

森実　臨床試験がやりづらいジャンルであって，一番ネックにあるのは胆管炎のコントロールのinterventionalなアプローチ，日本人は器用だという話を先ほどしましたが，山雄先生が中心になってされているinterventionalなものに関して日本人はかなり得意な分野に入ると思います．ここが進歩しないと逆に抗がん剤の進歩もあり得ないと思います．

宮崎　しっかりしたドレナージをして患者さんの状態を良くしなくては抗がん剤も投与できないということですね．分子標的の今後の可能性ということに触れていただきました．太田先生．外科領域で今後の可能性という意味では肝移植がMayo Clinicからだされていると思います．その辺はどうですか．

太田　私自身は肝移植にあまりタッチしていませんが，論文で読むところではMayo Clinicで肝門部胆管癌に対してケモラディエーションを先行させてその後肝移植した結果が1年生存で確か90％ぐらい，5年生存でも80％と非常に良い成績ですね．前提としてかなり患者さんをセレクトして．遠隔転移がないのは当然のこととして，リンパ節転移がある症例もカットしているという形ですから，conventionalなsurgeryといいますか，肝移植以外のsurgeryでもそれに近いデータがだせると思いますが，80％という数字はすごいと思います．

宮崎　そうですね．局所進展で広範囲胆管癌で深達度が進んでいないというような症例には非常にいいですね．下部まで及んでいると今度はPDが必要になってきますから．ドイツのベルリンのピーター・ノイハウスのグルー

プがだしていますが，あまり成績は良くないですね．彼らは手術侵襲も大きいし，合併症率，死亡率も高いので最近の論文でも否定的に書いています．肝門部のところで広範囲で右からも左からもとれなくて，深達度もたいしたことなくてリンパ節転移がないというような症例にはいいですね．

太田　そうですね．症例をセレクトすれば非常にいい治療のオプションになる可能性があります．

宮崎　ひとつの治療オプションとしてわれわれが持ち得るということですね．incidentalにPSCの患者さんで肝移植手術をしたら肝内胆管癌があった，いわゆる「incidental cholangiocarcinomaについて」の症例が欧米でだされていますが，それくらいでみつけられた肝内胆管癌の肝移植データにおいても意外と予後が良くないですね．本当にがんが局限していかないと，「進んだものには大変難しい」，Mayo もPreliminaryとしてやっている，と，今後の問題だと常にディスカッションで書かれています．症例を選べば今後の可能性はあると思いますが，注意深く適応としていかないといけないだろうという感じがします．

今日は胆道癌治療の新展開ということで，診断から外科切除，化学療法，interventionといろいろなお話を先生方からいただきました．最後にお一人ずつ今後の胆道癌診療を大きく展開する，特に治療成績を向上させるため，患者さんのQOLを良くするためにここを是非やって展開したいという夢といいますか，そういう点を一言ずつお話しいただきたいと思います．太田先生からお願いします．

太田　論文を読むと移植というのは大きな希望があるのではないかと思っています．もうひとつは抗がん剤との併用ですね．今まで切除不能とされていた，あるいは切除してもすぐ再発するような腫瘍．胆管癌は比較的きちんと切除できれば予後はいいですが，胆嚢癌は肉眼的には取りきれたつもりでも，すぐ再発することが多いですね．そういうものにneoadjuvantを行って，その後に切除を行うことで成績が向上できないかということを考えています．

宮崎　森実先生．お願いします．

森実　日本で使えるS-1単剤もしくはGEM+S1併用療法が現在の標準治療であるGEM+CDDPに勝てるのか，というのをひとつの研究課題として全国のグループで研究をやってきています．それ以外にも国内ではいろいろな多施設の共同研究が行われています．実際に100例ぐらいの患者さんが1年強で集まってくるような多施設研究の地盤が固まりつつあります．日本で胆道癌は患者さんが多いということと，このように予後の悪い癌の場合は抗がん剤の治療成績があがらない限りはクリアできないということ，さらには薬物治療の開発の地盤も固まってきている，ということで，今後リーダーシップをいかにとっていくか，国際的にどうアピールしていくかというのが大事なことではないかと思います．

宮崎　最後に山雄先生，お願いします．

山雄　私は診断面について話させていただきますと，胆道癌はまだまだ黄疸でみつかる症例が圧倒的多数です．無黄疸，かつ早期の胆道癌がみつかるような指標が何かみつからないか．ハイリスクグループといわれるようなものが確かに胆道癌ではありますがそれは少数ですので，合流異常，胆石以外の，何かbreakthroughがないか．血清マーカーでチェックできるようなものがあれば，今の診断技術を駆使すれば必ずみつかると思います．もうひとつは胆道のドレナージに関しては今後，新たな手技を前向き試験で確立していきたい

と思っています.

宮崎　ありがとうございました. 胆道癌の症例数は私が知っている範囲では欧米などでも肝外胆管癌はあまり変化ないですが, 肝内胆管癌は増えているというデータがあり, そのリスクグループも徐々にわかってきているようです. 今, 山雄先生がおっしゃたようにもう少し早い段階でみつけたり, さらには予防までいければ素晴らしいと思いますし外科医の役割もまだまだ多いと思います. 内科, 外科協調して胆道癌診療に取り組まなくてはならない課題はいっぱい残されていることを今日改めて認識されました. しかし, 最近5～10年では胆道癌診療も変わってきて, 適応も拡大されて患者さんもある程度の期待が持てるようになってきつつあることを感じさせていただけた今日の座談会でした. どうもありがとうございました.

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〔お知らせ〕

第65回手術手技研究会
会期延期のお知らせ

5月13日(金)夕方～14日(土)の開催を予定しておりました第65回手術手技研究会ですが, 今般の震災を受け, 以下のとおり会期と場所を変更して行います.

会　　長：塩崎　均（近畿大学　医学部長）
当番世話人：宇田川　晴司（虎の門病院　消化器外科）
会　　期：2011年9月9日（金）夕方～10日（土）
会　　場：東京ファッションタウンビル（〒135-8071　東京都江東区有明3-6-11）
主　　題：Ⅰ 各種エネルギーデバイスを用いた郭清術, その是非と手技
主　　題：Ⅱ 私の推奨する吻合手技, ここにはこれがお奨めです
ホームページ：http://www.procomu.jp/jsast2011/

第65回手術手技研究会事務局
虎の門病院　消化器外科（〒105-8470　東京都港区虎ノ門2-2-2）
事務担当：上野　正紀
TEL：03-3588-1111　FAX：03-3582-7068
E-mail：jsast65@tora.email.ne.jp

厚生労働科学研究費補助金（がん臨床研究事業）
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

平成21年度～平成23年度

（研究分担者　中尾昭公・名古屋セントラル病院・院長）

研究要旨
難治癌と言われる膵癌の診療において、膵癌に関するEBMに基づいた効果的・効率的な診断・治療法を体系化し、臨床医に実際的な診療指針を提供することを目的に、膵癌診療ガイドラインは初版(2006年)、第2版(2009年)が出版され、より一般へ向けた公開のためのweb化も果たされてきた。次年度には第3版出版を予定し改訂作業を進めている。本研究期間においてはガイドライン改訂・更新作業ならびに内容の評価、評価結果の検証を行った。

A．研究目的
膵癌診療ガイドラインの更新、公開の維持を目的とした。

B．研究方法
日本膵臓学会からガイドライン改訂委員を選出。文献は1990年以降の医中誌、MEDLINEを検索、構造化抄録は2名の連名で作成。エビデンスレベル、推奨度はMINDS2007を利用。アンケート、公聴会、web公開により外部意見を集約した。
ガイドラインの評価については作成に直接関わっていない膵癌外科系専門医2名、臨床ガイドラインに精通している非専門医1名、生物統計学専門家1名、患者代表1名の計5名から構成される外部評価委員により独立した評価を行った。評価はAGREE、Shaneyfelt、COGSによる評価法を用いた。
（倫理面への配慮）該当なし。

C．研究結果
2009年9月第2版出版。一般向けにも公開を目的とし2010年度に第1版(2006年度版)、2011年度に第2版のweb化を行った。
内容評価の結果、ガイドラインの対象や目的・作成プロセス・推奨(勧告)の明確さなどについてはいずれの評価方法でも高い評価が得られた。利害関係者の参加、適用可能性などについては評価が低かった。
2012年度の第3版出版に向け、構造化抄録、CQに対する推奨・推奨度案の作成を終了した。

D．考察
推奨度C1やC2が多いためか選ぶべき選択肢が明確でないとの意見もあったが膵癌では前向き臨床試験が少なく現状では致し方ないと考えられる。膵癌治療の現状は未だ厳しく、エビデンスレベルの高い論文は少ないため、エビデンスは現在ないが将来に繋がりそうな試みなどを委員会の判断で加えた。
EBMに基づくガイドライン作成の維持には最新情報の収集と解析を絶えず図り定期的な改訂が必要と考えるが、人的労力の委員への過剰な負担などが懸念される。公開用にweb化を進めてきたが、今後の改訂作業へも有効活用できるよう整備することも必要と思われる。

E．結論
本ガイドラインの更新・公開にあたり課題は残るものの総じて高評価を得てきたと考えられる。
ガイドラインを実際の臨床現場で用いられることを目的としているので、より多くの医師、コメディカル、患者などからの評価を受け、意見を求めることが重要である。またどのような評価方法を用いるのかについても今後検討が必要である。

F．健康危険情報

G．研究発表
1．論文発表
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3)膵癌取扱い規約第6版：日本膵臓学会編．金原出版株式会社，東京，2009.
4) Yamaguchi K, et al: EBM-based Clinical Guidelines for Pancreatic Cancer 2009 From the Japan Pancreas Society: A Synopsis. Jpn J Clin Oncol 2011;41:836-840, 2011
2．学会発表　該当なし

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

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(7)836–840
doi:10.1093/jjco/hyr077

Review Article

EBM-based Clinical Guidelines for Pancreatic Cancer 2009 From the Japan Pancreas Society: A Synopsis

Koji Yamaguchi[1,*], Masao Tanaka[2] and Committee for Revision of Clinical Guidelines for Pancreatic Cancer of Japan Pancreas Society

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Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine, 2006, were published by the Japan Pancreas Society (Committee for Revision of Clinical Guidelines for Pancreatic Cancer) in March 2009 in Japanese[1] and were revised to Clinical Practice Guidelines for Pancreatic Cancer Based on Evidence-based Medicine 2009 in July 2009 in Japanese.[2] These guidelines were established according to Evidence-Based Medicine. A total of 443 papers were collected from 2544 reports concerning pancreatic cancer that were listed on PubMed and Igakuchuo Zasshi from July 2004 to April 2007. This new guidelines were written by members of the Committee for Revision of Clinical Practice Guidelines for Pancreatic Cancer in the Japan Pancreas Society. The guidelines show algorithm for the diagnosis (Fig. 1) and treatment (Fig. 2) of pancreatic cancer, address five subjects: diagnosis, chemotherapy, radiation therapy, surgical therapy and adjuvant therapy, and include 25 clinical questions (CQs) and 39 recommendations. The corresponding CQ numbers are inserted in the algorithms. There are five degrees of recommendation:

A Strongly recommended because there is strong scientific evidence.
B Recommended because there is scientific evidence.
C1 Recommended although there is no scientific evidence.
C2 Not recommended because there is no scientific evidence.
D Not recommended because there is evidence showing that it is ineffective or harmful.

This article presents a synopsis of the guidelines in English.

Diagnosis

CQ1-1 What are risk factors for pancreatic cancer?

The below-mentioned risk factors have been reported to have evidences supporting the relationship between the factors and pancreatic cancer:

(i) Family history: pancreatic cancer and hereditary pancreatic cancer syndrome.
(ii) Accompanying diseases: diabetes mellitus, obesity, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm (IPMN).
(iii) Habits: tobacco.

RECOMMENDATION 1-1

(i) Patients with more than one risk factor are recommended to undergo further examination to detect pancreatic cancer (Grade B).
(ii) IPMN progresses to invasive cancer and accompanies pancreatic cancer. IPMN should be adequately assessed and carefully followed up (Grade B).

CQ1-2 What are the clinical symptoms of pancreatic cancer?
The below-mentioned clinical symptoms have been reported as those of pancreatic cancer:

(i) Abdominal pain is the most frequent symptom, followed by jaundice, back pain and body weight loss.
(ii) Clinically silent pancreatic cancer.
(iii) Fifty percent of pancreatic cancer patients show early-onset diabetes mellitus (glycogen metabolism disturbance) within 3 years.

RECOMMENDATION 1-2

(i) Patients with unexplainable abdominal pain, back pain, jaundice and/or body weight loss should undergo further examination for pancreatic cancer. However, the clinical outcome of symptomatic pancreatic cancer is poor (Grade B).

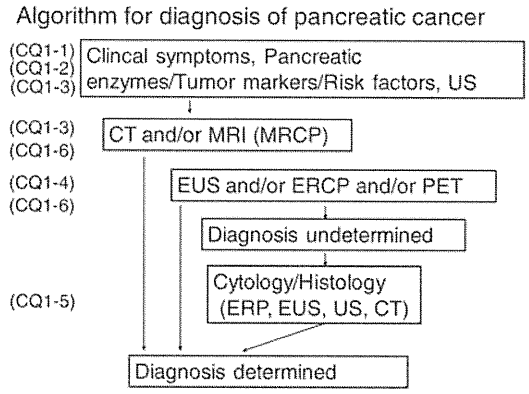

Figure 1. Algorithm for diagnosis of pancreatic cancer.

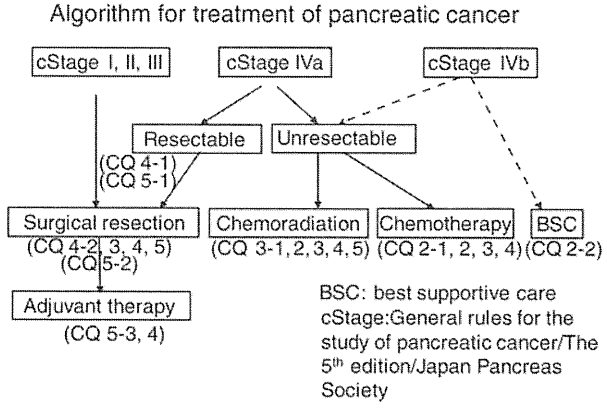

Figure 2. Algorithm for treatment of pancreatic cancer.

(ii) Early-onset diabetes mellitus (poor glycogen metabolism) and deterioration of diabetes mellitus suggest the presence of pancreatic cancer and necessitate further examination for pancreatic cancer (Grade B). Early-onset diabetes mellitus (within less than 3 years) may indicate pancreatic cancer.

CQ1-3 What is the first step when pancreatic cancer is suspected?

The below-mentioned examinations are the first-step diagnostic procedures of pancreatic cancer:

(i) Serum pancreatic enzyme
(ii) Tumor markers
(iii) Ultrasound (US)
(iv) Computed tomography (CT).

RECOMMENDATION 1-3

(i) The serum pancreatic enzyme level is important, but is not specific for pancreatic cancer (Grade C1).
(ii) Serum tumor makers including CA19-9 are recommended for the diagnosis of pancreatic cancer and follow-up of pancreatic cancer (Grade B), but they are not useful for the diagnosis of early pancreatic cancer.
(iii) US is recommended for the first screening for pancreatic cancer (Grade B) but has a low rate of detecting pancreatic cancer (Grade C1). Dilatation of the main pancreatic duct or a pancreatic cyst is an important indirect sign of pancreatic cancer (Grade B). Further examination, including CT, is therefore strongly recommended if such signs are evident (Grade A).
(iv) Patients the abnormal findings listed above should be periodically examined and careful follow-up is recommended if no diagnosis of pancreatic cancer obtained (Grade B).

CQ1-4 What is the second step when pancreatic cancer is suspected?

RECOMMENDATION 1-4

(i) Qualitative diagnosis is important and is strongly recommended to determine the treatment of pancreatic cancer (Grade A).
(ii) US and CT (enhancing) should be performed and additional examination by magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), ERP or positron emission tomography is strongly recommended when necessary (Grade A).

CQ1–5 What is the significance and indications for cytology and biopsy of pancreatic cancer?

RECOMMENDATION 1-5

(i) Either a histological or cytological diagnosis is recommended before treatment started if no qualitative diagnosis of pancreatic mass obtained. Aspiration cytology or histology with US guidance, cytology or histology under endoscopic ultrasonography, pancreatic juice cytology under endoscopic retrograde cholangiopancreatography (ERCP) or histology under ERCP should be obtained to achieve a definite diagnosis, depending on the patients or institution (Grade B).
(ii) Aspiration cytology under endoscopic ultrasonography is useful when the lesion is not detected by ultrasonography or CT (Grade C1).
(iii) A genetic analysis is important to confirm the cytology or histology (Grade C1).

CQ1-6 How do you determine clinical staging of pancreatic cancer?

RECOMMENDATION 1-6

Multidetector CT or EUS is recommended for staging diagnosis (TNM) of pancreatic cancer (Grade B).

Chemotherapy

CQ2-1 Is chemotherapy alone recommended for locally advanced unresectable pancreatic cancer?

Recommendation 2-1

Chemotherapy alone is recommended as one of options for the treatment of locally advanced unresectable pancreatic cancer (Grade B).

CQ2–2 What is the first-line chemotherapy for metastatic pancreatic cancer?

Recommendation 2-2

Gemcitabine (GEM) is recommended as the first-line treatment for metastatic pancreatic cancer (Grade A).

CQ2-3 How long is GEM continued for unresectable pancreatic cancer?

Recommendation 2-3

GEM is continuously administered for unresectable pancreatic cancer until clear progression becomes evident if there are no adverse effects causing interruption of the administration of GEM (Grade B).

CQ2-4 Is second-line chemotherapy recommended for unresectable pancreatic cancer?

Recommendation 2-4

There is no scientific evidence of effective second-line chemotherapy within the insurance allowance in this country, but some reports suggest effectiveness. Some recent randomized clinical trials in other countries have reported effective second-line chemotherapy. Second-line chemotherapy can be considered in patients whose physical status is good and are fully informed after a detailed explanation (Grade C1).

Radiotherapy

CQ3-1 Is chemoradiation effective for locally advanced unresectable pancreatic cancer?

Recommendation 3-1

Chemoradiation is effective for locally advanced unresectable pancreatic cancer and is recommended as one of the options for treatment (Grade B).

CQ3-2 What is the standard combined chemotherapy for chemoradiation for locally advanced unresectable pancreatic cancer?

Recommendation 3-2

5-fluorouracil (5-FU) (Grade B) is the standard chemotherapy for chemoradiation for locally advanced pancreatic cancer.

Although there is no definite evidence supporting GEM-based chemoradiation, some report its usefulness. A safe regimen of GEM-based chemoradiation can be considered as one of the options for treatment after the procedure is fully explained and the patient provides informed consent (Grade C1).

CQ3-3 Is the lymph node included in the clinical standard field of external radiation therapy for locally advanced unresectable pancreatic cancer?

Recommendation 3-3

There have been no prospective randomized clinical trials concerning this CQ. Radiation including the tumor and the positive lymph nodes in the radiation field is recommended prophylactically, although there is no supportive scientific evidence (Grade C1).

CQ3-4 Is intraoperative radiation effective for locally advanced pancreatic cancer?

Recommendation 3-4

There are reports of the efficacy of intraoperative radiation for locally advanced unresectable pancreatic cancer. However, there is no scientific evidence that intraoperative radiation improves the clinical course of locally advanced unresectable pancreatic cancer (Grade C1).

CQ3-5 Does chemoradiation improve the quality of life of patients with unresectable pancreatic cancer?

Recommendation 3-5

Cancer radiation therapy (Grade C1) and chemotherapy (Grade B) are therefore recommended to improve the quality of patients with unresectable pancreatic cancer.

Surgical therapy

CQ4–1 Is surgical resection useful for Stage IVa pancreatic cancer?

Recommendation 4-1

Surgical resection with an intended curative resection is recommended for pancreatic cancer up to Stage IVa* (Grade B).

Stage IVa*: Stage IVa indicates (S2 or R2 or PV2) and (N0 or N1) by Japan Pancreas Society Classification of pancreatic cancer, 4th Edition.

CQ4–2 Is preservation of the stomach useful in pancreatoduodenectomy for pancreatic head cancer?

Recommendation 4-2

It is not clear whether preservation of the stomach improves the rate of post-operative complications, quality of life, post-operative pancreatic function and nutrition status of patients with pancreatic cancer or not (Grade C1).

Preservation of the stomach decreases the operation time and blood loss in pancreatoduodenectomy but does not decrease the survival rate after a surgical resection (Grade C1).

CQ4-3 Does combined portal vein resection improve the clinical outcome of patients with pancreatic head cancer?

RECOMMENDATION 4-3

The effect of prophylactic portal vein resection intended to increase the curability on the clinical course of patients with pancreatic cancer is unclear. A portal vein resection is indicated when surgical and dissection margins can be free from cancer cells by portal vein resection (Grade C1).

CQ4-4 Is a radical resection with extended lymph node dissection useful for pancreatic cancer?

RECOMMENDATION 4-4

The contribution of extended lymph node and nerve plexus dissection to the improvement of clinical course of patients with pancreatic cancer is unclear and there is no evidence to support the performance of such an extended radical resection (Grade C2).

CQ4-5 Is the incidence of complications after pancreas resection low in a high volume center?

RECOMMENDATION 4-5

The incidence of complications tends to be low in pancreatic surgery including pancreatoduodenectomy and the management of complications tends to be superior in institutions with a high volume of pancreatic surgery (Grade B).

CQ4-6 Is surgical bypass or biliary stent significant in unresectable pancreatic cancer?

RECOMMENDATION 4-6

Hepaticojejunostomy for the obstructive jaundice and prophylactic gastrojejunostomy is recommended in patients with unresectable obstructive jaundice after laparotomy (Grade B).

Adjuvant therapy

CQ5-1 Does pre-operative therapy improve the clinical outcome of patients with pancreatic cancer?

RECOMMENDATION 5-1

There is increasing evidence supporting the efficacy of pre-operative treatment [(i) chemoradiation and (ii) chemotherapy]. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-2 Is intraoperative radiation therapy recommended at the time of resection of pancreatic cancer?

RECOMMENDATION 5-2

There has been no definite evidence supporting the usefulness of intraoperative radiotherapy. However, clinical trials or analyses of the long term are required to determine whether such therapy improves the clinical outcome (Grade C1).

CQ5-3 Is post-operative chemoradiation recommended for pancreatic cancer?

RECOMMENDATION 5-3

Meta-analysis of 5-FU-based post-operative chemoradiation revealed no supportive evidence. However, clinical trials or analyses of the long term are required to determine whether GEM-based post-operative chemoradiation improves the clinical outcome (Grade C1).

CQ5-4 Is post-operative adjuvant therapy recommended for pancreatic cancer?

RECOMMENDATION 5-4

There is no definite international consensus on post-operative adjuvant therapy. Post-operative GEM is safe and effective and is recommended as post-operative chemotherapy (Grade B).

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(Nagoya University). *Adjuvant therapy*: O. Ishikawa (Osaka Medical Center for Cancer and Cardiovascular Diseases), T. Okusaka (National Cancer Center) and T. Shimosegawa (Tohoku University).

Conflict of interest statement

None declared.

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（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

（研究分担者　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）は希少腫瘍ではあるが、最近、国際的に患者数の増加が明らかにされていて、本邦でも報告数の増加が推測されている。本腫瘍に対する、診療ガイドラインは国際的にいくつかあるが、本邦では作成されていない。機能性腫瘍は、診断の遅れのために患者は苦しい生活を余儀なくされていることが多く、非機能性腫瘍は転移を伴って診断されることが多い現状である。本腫瘍の知識の普及が火急の課題であり、また診断法と治療法が国際水準に到達していないことも早急な是正が求められている。厚生労働省の支援の下に、治療薬の承認が進んでいるが、ソマトスタチンシンチグラフィーの承認が望まれる。ガイドライン作成委員会は４２名から構成されていて、文献検索に基づき、臨床質問（CQ）とそれに対する推奨文作成をほぼ完成させている。２月末にガイドライン案が完成予定である。その後、癌治療学会、消化器外科学会、内分泌外科学会、膵臓学会での公聴会を予定していて、最終的完成予定は、平成24年末である。既に、教科書として本邦初の膵・消化管神経内分泌腫瘍（NET）診断治療実線マニュアルを昨年夏に本委員会のメンバーを中心に作成し、総合医学社から発行した。

A．研究目的

膵・消化管神経内分泌腫瘍診療の標準化と普及のために診療ガイドラインを作成することを目的とする。同時に、本邦における本疾患の診療が遅れている現状を打開して、国際的水準での診療に到達に向けて努力することを目的としている。

B．研究方法

多方面の臨床医と基礎医学者、患者さんからなる作成委員と評価委員を集めて、国際的文献を主に、本邦での診療活動とその報告を公正に評価しつつ、専門医の意見に対しては、多数の委員の立会いの下で多数決を取りながら、診療ガイドラインを作成する。多発性内分泌腫瘍症に関しては、信州大学櫻井晃洋が委員長を務める多発性内分泌腫瘍症診療ガイドライン作成委員会と連携して、作成する。討論はインターネットを通じての討論と、集合しての委員会開催を通じて作成が進められている。

（倫理面への配慮）

患者さんの個人情報は公表されることは無く、利益相関に関しても公表しつつ作成が進み、倫理メンに常に配慮している。

C．研究結果

機能性腫瘍は、診断の遅れのために患者は苦しい生活を余儀なくされていることが多く、非機能性腫瘍は転移を伴って診断されることが多い現状である。本腫瘍は人口10万人当たり、毎年約3人の新規患者発生がある。本疾患の知名度は低く、医師と患者双方への知識の普及が火急の課題である。一方、検査法と治療法の承認が国際水準に到達していないことも、早急な是正が求められている。厚生労働省の支援の下に、分子標的薬などの治療薬の承認が早急に進んでいるが、ソマトスタチンシンチグラフィーの承認が望まれる。ガイドライン作成委員会は４２名から構成されていて、文献検索に基づき、臨床質問（CQ）とそれに対する推奨文作成をほぼ完成させている。２月末にガイドライン案が完成予定である。その後、癌治療学会、消化器外科学会、内分泌外科学会、膵臓学会での公聴会を予定していて、最終的完成予定は、平成24年末である。既に、教科書として本邦初の膵・消化管神経内分泌腫瘍（NET）診断治療実線マニュアルを昨年夏に本委員会のメンバーを中心に作成し、総合医学社から発行した。

D．考察

本疾患の患者登録事業が進んでおらず、正確な経年的疾患統計が得られていないので、近い将来に登録事業を全国的に展開できるように、公的な研究会を立ち上げて、国と会員などの支援を得て、永続的な登録事業による治療法検査法の有効性の判定を経た診療ガイドライン改定を行っていくことの重要視枝を認識している。

E．結論

厚生労働省と癌治療学会の補助金のおかげで、ガイドライン作成が完成予定となった。今後の改定作業のためには、疾患登録事業の立ち上げが火急の課題である。

F．健康危険情報

とくになし

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H. 知的財産権の出願・登録状況
(予定を含む。)
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[1,2]. 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)[5,6]. 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 100 000 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 100 000 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 100 000 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 100 000 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 100 000 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 100 000 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[13,14].

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[1]. 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.

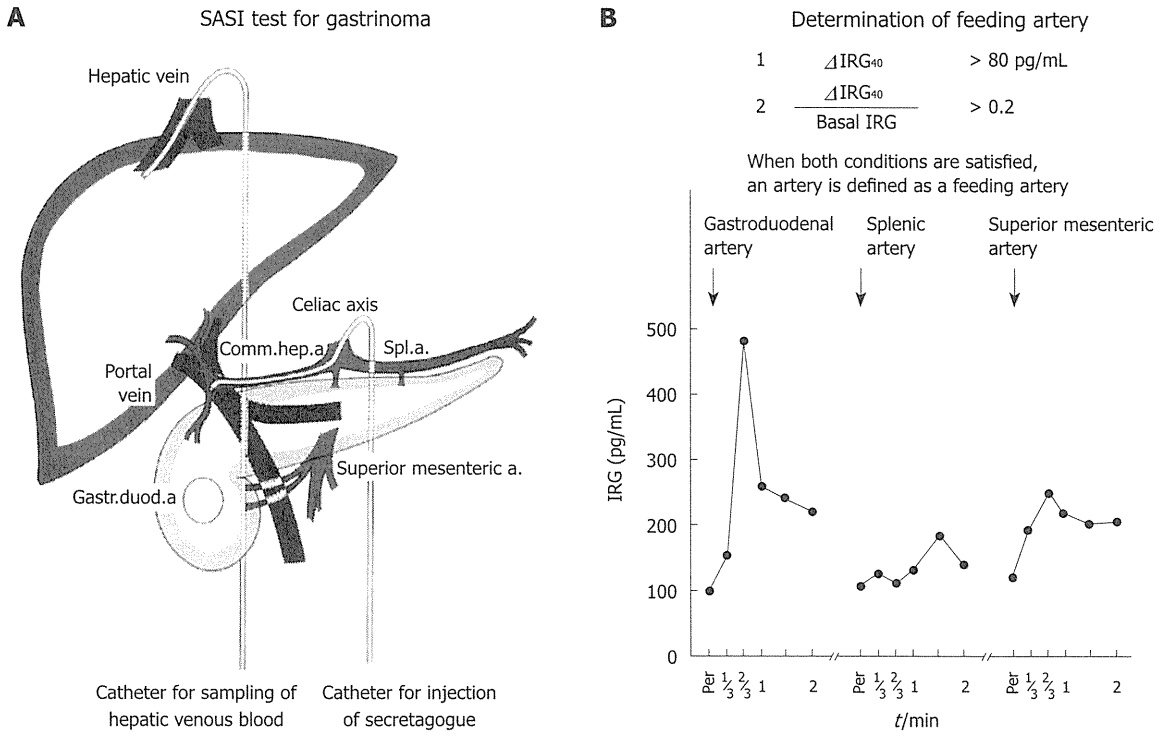

Figure 1 Schema of the selective arterial secretagogue injection test. Results of the selective arterial secretagogue injection (SASI) test in a patient with Zollinger-Ellison syndrome. In this patient, serum immunoreactive gastrin (IRG) at 40 s after the injection of 30 units of secretin rose only after 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[20]. Both the sensitivity and specificity of the SASI test for both gastrinoma and insulinoma has been shown to be more than 90%, respectively[20,21,25] (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[26-28]. 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[24].

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[30].

RECENT STANDARD OF SURGICAL TREATMENT OF PNET

The best treatment for PNET is curative surgical resection[5-8,31,32]. 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[1,31].

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[20,30-32].

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*[36] 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[40-43]. 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[20,43,44]. 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-

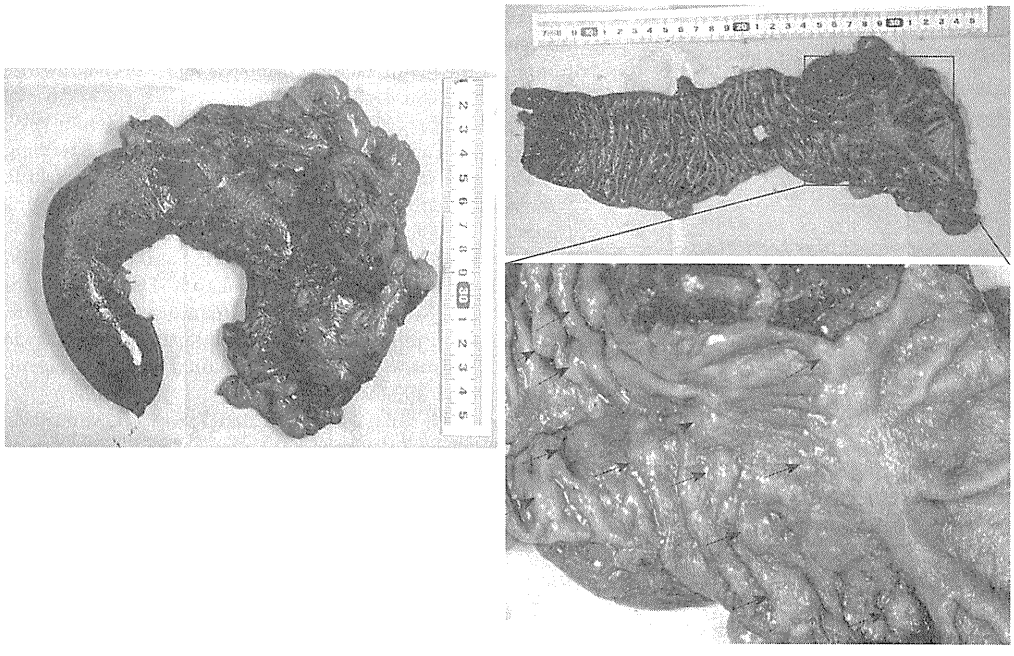

Figure 2 Numerous mucosal gastrinomas in the duodenum. Mucosal tumors with depression (arrows).

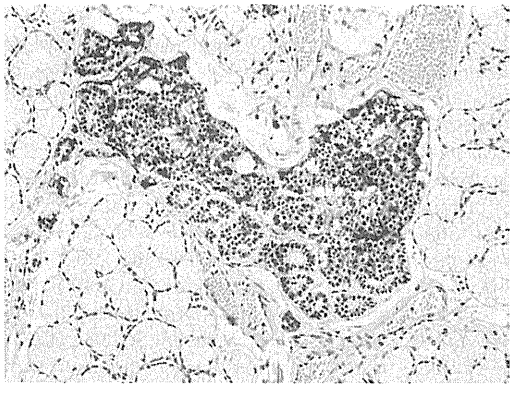

Figure 3 A cluster of G cells in hyperplasia of duodenal Brunner's glands in a patient with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome.

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*[49] 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[50]. However, a number of complications after RF have been reported, especially following percutaneous RF. Therefore RF should be performed very carefully[51].

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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Novel classification based on immunohistochemistry combined with hierarchical clustering analysis in non-functioning neuroendocrine tumor patients

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Somatostatin analogues ameliorated many symptoms caused by neuroendocrine tumors (NET), but their antitumor activities are limited especially in non-functioning cases. An overactivation of signaling pathways under receptor tyrosine-kinase (RTK) has been recently demonstrated in some NET patients, but its details have remained largely unknown. Therefore, in this study, we immunolocalized therapeutic factors and evaluated the data to study the clinical significance of the molecules in non-functioning Japanese gastrointestinal NET. Fifty-two NET cases were available for examination in this study and expression of somatostatin receptor (sstr) 1, 2A, 2B, 3 and 5, activated form of mammalian target of rapamycin (mTOR), eukaryotic initiation factor 4-binding protein 1 (4EBP1), ribosomal protein s6 (S6), extracellular signal-regulated kinase (ERK) and insulin-like growth factor 1 receptor (IGF-1R) was evaluated using immunohistochemistry. We then studied the correlation among the immunohistochemical results of the individual cases using hierarchical clustering analysis. Results of clustering analysis demonstrated that NET cases were basically classified into Cluster I and II. Cluster I was associated with higher expression of sstr1, 2B and 3 and Cluster II was characterized by an activation of the PI3K/Akt pathway and IGF-1R and higher proliferative status. Cluster II was further classified into Cluster IIa and IIb. Cluster IIa was associated with higher expression of sstr1 and 5 and higher proliferative status and Cluster IIb was characterized by ERK activation. Hierarchical clustering analysis of immunoreactivity of the therapeutic factors can classify NET cases into three distinctive groups and the medical treatment may be determined according to this novel classification method for non-functioning NET patients. (*Cancer Sci* 2010; 101: 2278–2285)

Gastroenteropancreatic endocrine tumors or neuroendocrine tumors (NET) are generally classified into two groups in terms of their localization: gastrointestinal (GI) NET or endocrine tumor and pancreatic NET.[1] Both of these tumors are considered to arise from neuroendocrine cells and are histologically characterized by positive reactions to various neuroendocrine markers, including chromogranin A, neuron specific enolase (NSE), synaptophysin, and so on. In Japan, the number of GI NET patients is far more than that of pancreatic NET[2] and the great majority of these cases are clinically non-functioning NET. A GI NET is often slow-growing and indolent, and may not become clinically apparent until the manifestation of metastatic spread,[3,4] especially those occurring in the foregut and hindgut, the most prevalent GI NET in Japanese population.[2] Therefore, it has become clinically important to manage these non-functioning advanced NET cases using medical therapy.

We previously reported that somatostatin receptor (sstr) subtypes have been recently demonstrated in the great majority of GI NET.[5] In addition, somatostatin analogues (SSA) such as octreotide that interact with sstr subtypes are the most widely used therapeutic option for NET. They are generally well tolerated and highly effective in reducing various hormone-related symptoms caused by NET, but are not necessarily so in controlling cell proliferation of tumor cells, especially in clinically non-functioning NET cases.[6] Therefore, it has become important to examine the mechanisms related to cell proliferation, especially those related to intracellular signaling pathways, other than the somatostatin pathway in individual NET patients, in order to further explore effective antitumor agents.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase working as a central regulator of many biological processes that are essential for cell proliferation, translation and cell metabolism.[7–9] It is regulated by upstream, phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathway.[10] An activation of this pathway has been commonly detected in various tumor types,[11] and may be caused by an overactivation of insulin-like growth factor 1 receptor (IGF-1R) in NET cells.[12] In addition, a previous study demonstrated an overexpression of activated (phosphorylated) extracellular signal-regulated kinase (ERK) in NET cases.[13] However, the correlation among these pathways and of those with sstr-mediated pathways has not been reported at all in NET cases.

Therefore, in our present study, we first evaluated sstr subtypes, those involved in the signaling pathway under receptor tyrosine-kinase (RTK) (PI3K/Akt/mTOR and MEK/ERK pathways) and a major therapeutic targeted RTK (IGF-1R) in 52 clinically non-functioning Japanese NET cases using immunohistochemical methods. We then examined the correlation among these factors above and that with the clinicopathological factors of individual patients using hierarchical clustering analysis, an established effective method for analyzing high-volume immunohistochemical data, which was recently applied to an analysis of leiomyosarcoma and breast carcinoma cases.[14,15] We then added the *in vitro* experiments in order to further evaluate the antitumor activities of rapamycin, one of the mTOR inhibitors.

Materials and Methods

Tumor tissues. Fifty-two Japanese cases of GI NET or endocrine tumors were retrieved from the surgical pathology files at the Department of Pathology, Tohoku University Hospital and Sendai Red Cross Hospital (both in Sendai, Miyagi, Japan). Review of the charts of individual patients showed that none of the cases examined had demonstrated any clinical evidence of

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