厚生労働科学研究費補助金
がん臨床研究事業

切除可能膵胆道領域がんに対する補助療法の研究

平成21年度　総括研究報告書

研究代表者　小菅智男

平成22（2010）年4月

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別紙３

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研究代表者　小菅　智男　国立がんセンター中央病院副院長

研究要旨
切除可能膵胆道がんに対する有効な補助療法の確立を目的として多施設共同の臨床試験を計画した。本年度は「膵がん切除例に対する術後補助療法としてのゲムシタビンとS-1併用療法(GS療法)の第Ⅰ/Ⅱ相試験」の第Ⅰ・Ⅱ相試験を完了し、第Ⅲ相試験を実施するために必要な準備を整えた。

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A．研究目的

代表的な難治がんのひとつである膵胆道がんは、死亡数が年々増加しており、有効な治療法を確立することはがん対策における重要な課題である。診断法の進歩により、切除可能な段階で発見される症例は増加しつつあるが、治療成績は未だに不良である。膵胆道がんの切除例に対してはこれまで様々な集学的治療が試みられてきたのにもかかわらず、その有用性についてのエビデンスが乏しく、標準的な治療法は確立していなかった。

そこで、本研究グループでは、2001年4月にゲムシタビンが膵がんに対する化学療法剤として保険適用となったのを機会に、ゲムシタビンの補助化学療法剤としての有用性を評価するための多施設共同無作為化比較試験を開始し、平成19年度に最終解析の結果を報告した。ヨーロッパでもこの研究に類似した臨床試験が行われて同様な結果が得られた。これらの結果により、膵がんに対してはゲムシタビンを用いた補助化学療法は実質的な標準治療として取り扱われるようになった。しかしながら、補助療法による全生存期間の延長効果はわずかであり、より効果の

高い治療法が望まれている。2006年8月に膵がんに対する保険適用が承認されたS-1は膵胆道がんに有効な数少ない化学療法剤のひとつとして期待を持たれており、2007年には胆道がんに対する適応も認められた。そこで、膵胆道がんを対象に、S-1を取り入れた補助化学療法の有用性を検証するための臨床研究を計画した。

B．研究方法

切除可能膵がんに対する術後補助化学療法としてゲムシタビンとS-1の併用療法(GS療法)の有用性を検討するため、平成19年度に策定した以下の研究実施計画書に従い、症例の収集と結果の解析を行う。

試験の概要：

1)表題：膵がん切除例に対する術後補助療法としてのゲムシタビンとS-1併用療法(GS療法)の第Ⅰ/Ⅱ相試験

2)目的：

第Ⅰ相部分：膵がん切除例に対する術後補助療法としてのGS療法の毒性を評価し、投与量規制毒性（DLT）の発現頻度により第Ⅱ相試験における推奨用量を決定する。

第Ⅱ相部分：膵がん切除例に対する術後補助療法としてのGS療法の有効性と安全性を評価する。

3)評価項目

第Ⅰ相部分：

主要評価項目：DLTの発現頻度

第Ⅱ相部分：

主要評価項目：全生存期間

副次的評価項目：有害事象、無病生存期間

4)対象：浸潤性膵管がん肉眼的治癒切除例（R0、R1）

5)薬剤の投与量：

第Ⅰ相部分：

・S-1とゲムシタビンの投与量はレベル0からレベル2の３段階を設定する。
・2週を1コースとして12コース投与を継続する。
・レベル1より投与を開始して、各レベル6例を登録し、DLTの発現頻度より推奨用量を決定する。

第Ⅱ相部分

・第I相部分において推奨用量と決定された投与量レベルを用いる。

6)予定参加者数：

第I相部分：各投与量レベル6例

第Ⅱ相部分：55例（第Ⅰ相部分の同レベルの患者も含む）

胆道がんについては膵がんよりもエビデンスの乏しい現状を鑑み、臨床試験に関する情報を収集し、実行可能で意味のある臨床試験の検討を進める。

（倫理面への配慮）

介入研究であるため、臨床研究に関する倫理指針に則り、研究を計画・実行する。臨床試験の内容については参加施設毎に倫理審査委員会の承認を得ている。

C．研究結果

平成20年4月から第Ⅰ相試験を開始し、平成21年2月までに完了した。これにより、第Ⅱ相部分での投与量をレベル0と決定し、平成21年2月24日から第Ⅱ相部分の症例登録を開始した。症例集積は順調に進み、平成21年9月24日に症例登録を締め切った。全登録症例数は61例で、このうち第Ⅱ相部分は55例となった。レベル0での安全性は許容範囲内であることが確認された。

胆道がんの補助療法については、世界の状況も含めて検討した結果、他の

研究組織との協力が必須であるという結論に至った。

D．考察

切除可能膵がんに対する術後補助療法については、ゲムシタビン単剤による化学療法が実質的な標準治療として扱われるようになった。しかしながら、補助療法による全生存期間の延長効果はわずかであり、より効果の高い治療法が望まれている。2006年8月に膵がんに対する保険適応が認可されたS-1は数少ない化学療法剤のひとつとして期待を持たれており、非切除膵がん症例での臨床試験が進められている。そこで、ゲムシタビン単剤の化学療法よりも高い効果を期待して、ゲムシタビンとS-1の併用化学療法（GS療法）について臨床試験を計画した。当初は第Ⅲ相試験としてゲムシタビン単剤による補助化学療法との比較試験を検討した。しかし、非切除症例に対する臨床試験の結果、GS療法はゲムシタビン単剤に比べて、効果は高いものの有害事象の程度や頻度も高いことが示唆された。補助化学療法では通常の化学療法に比べて安全性が特に重要であるため、これを考慮して第Ⅰ相試験から行うことに計画を変更した。実際、第Ⅰ相部分ではレベル1で規定数のDLTが発生し、レベル0が第Ⅱ相部分での用量と決定された。第Ⅱ相部分は順調に実施され、最終的にこの用量での安全性が確認された。これにより、本レジメンを用いた第Ⅲ相試験を行うための基盤が整った。

胆道がんの補助療法については、本研究班の参加施設で実施可能であり、しかも意義のある研究計画について検討を続けてきた。しかし、胆道がんに関しては症例集積の困難さが最大の問題点であり、他の研究組織と協力して試験を計画する必要があるとの結論に達した。

膵胆道外科の領域では、化学療法の臨床試験に精通した施設は限られているため、こうした取り組みを全国規模の多施設共同研究として行なうことは、がん医療の均てん化にも資するものと考えている。

E．結論

膵がんの補助療法に関しては、GS療法に関する第Ⅰ・Ⅱ相試験を完了し、第Ⅲ相試験を実施するために必要な準備を整えた。胆道がんの補助療法について有用な臨床試験を行うためには、大規模な研究組織を構築する必要がある。

F．健康危険情報

本研究で行った臨床試験における有害事象の発生は許容範囲内であった。

G．研究発表

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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

研究成果の刊行に関する一覧表

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Pancreaticojejunostomy with Invagination of the Punched Pancreatic Remnant After Medial Pancreatectomy and Enucleation for Multiple Metastases of Renal Cell Carcinoma: Report of a Case

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Abstract
We report the successful resection of multiple pancreatic metastases of renal cell carcinoma (RCC), achieved by performing medial pancreatectomy and enucleation, preserving as much of the pancreatic parenchyma as possible. Most of the distal remnant pancreas was placed into the jejunal lumen and all three cut surfaces were covered to prevent pancreatic leakage. The postoperative course was uneventful, without any sign of pancreatic fistula. The patient is well without any evidence of recurrence or impairment of exocrine or endocrine pancreatic functions 1 year after surgery. Considering the unusual behavior of RCC metastasis and the difficulty in predicting the pattern of recurrence, we should devise the optimal surgical strategy to provide cancer-free surgical margins and preserve as much of the pancreatic parenchyma as possible.

Key words Multiple pancreatic metastases · Renal cell carcinoma · Medial pancreatectomy · Pancreatic fistula

Introduction

Pancreatic metastases are often associated with diffuse systemic disease at the time of diagnosis, so pancreatic surgery is rarely indicated. However, solitary and multiple isolated pancreatic metastases from renal cell carcinoma (RCC) are potentially manageable by radical surgery, because of their slow growth pattern and potentially positive outcome.[1–3] The effectiveness or palliation of pancreatic resection for metastatic RCC in selected patients has been reported,[1–3] but the appropriate procedures for pancreatic resection are poorly documented, especially for multiple metastatic lesions.[3–6] Not only the indications for pancreatectomy but also the types of surgical procedure are a major clinical concern. The precise detection of tiny hypervascular pancreatic metastatic lesions, using multidetector-row computed tomography,[7] and improved postoperative morbidity after procedures such as medial pancreatectomy[8,9] have made atypical resections possible in patients with multiple pancreatic metastases from RCC.[2]

We report a case of multiple pancreatic metastases from RCC, treated successfully by medial pancreatectomy and enucleation of two metastatic lesions, instead of a radical pancreatectomy. A pancreaticojejunostomy was performed with invagination of the punched remaining pancreas to prevent a postoperative pancreatic fistula after this atypical pancreatectomy.

Case Report

The patient was a 54-year-old man who had undergone a right nephrectomy for RCC 10 years earlier. He was referred to us after a follow-up abdominal computed tomography (CT) revealed a pancreatic tumor in the pancreatic neck without any specific symptoms. Multidetector-row CT demonstrated three hypervascular tumors in the neck (T1: 30 mm in diameter) and tail (T2: 7 mm in diameter and T3: 10 mm in diameter) of the pancreas (Fig. 1A–C). Ultrasonography showed slight dilation of the distal part of the main pancreatic duct (MPD; Fig. 1D). There was no evidence of local recurrence of the RCC or extrapancreatic metastatic spread. Laboratory findings were all within normal limits, including the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels. Glucose tolerance was also normal and the hemoglobin A_{1c} (HbA_{1c}) percentage was 4.7% (normal range <5.6%). We performed medial pancreatectomy with enucleation

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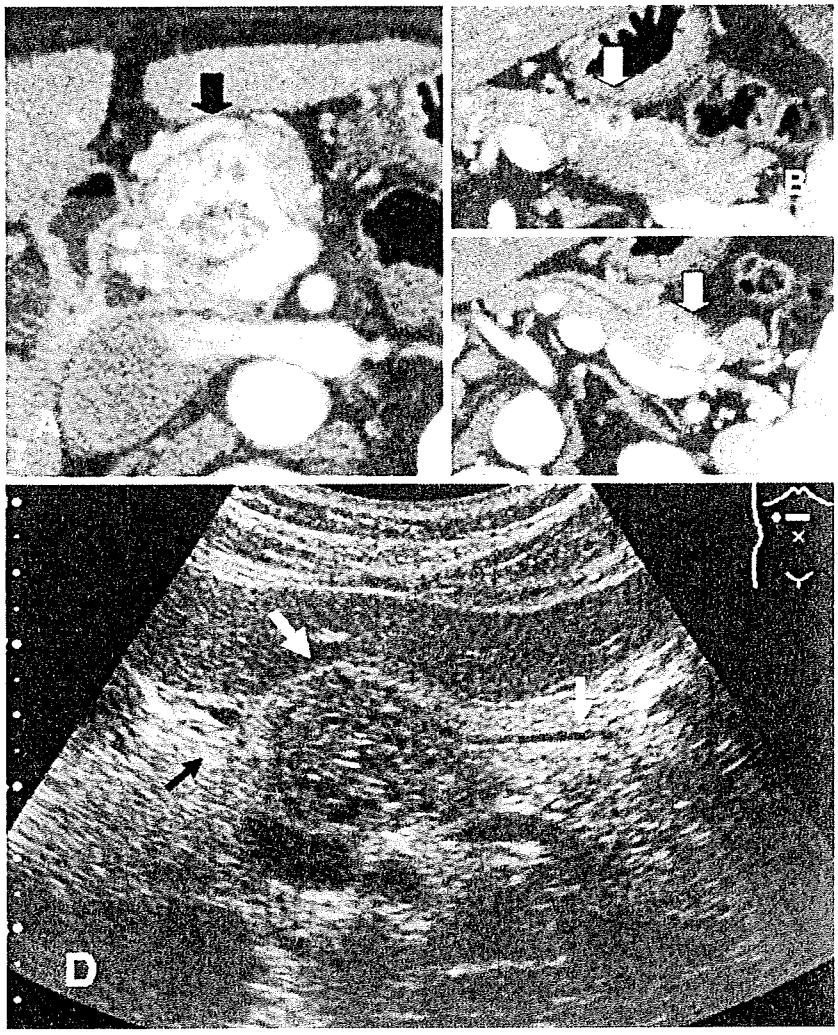

Fig. 1. Multidetector-row computed tomography (MDCT) showed **A** a 30-mm hypervascular tumor in the pancreatic neck (T1; *black arrow*); **B** a 7-mm tumor in the pancreatic tail (T2; *white arrow*); and **C** a 10-mm hypervascular tumor in the pancreatic tail (T3; *white arrow*). **D** Abdominal ultrasonography showed a round and heterogeneous echoic mass, 30 mm in diameter, with slight dilation of the main pancreatic duct (*white arrows*); the *black arrow* indicates the gastroduodenal artery

of two metastatic lesions, to preserve as much pancreatic exocrine and endocrine function as possible.

Surgical Procedure

Intraoperative ultrasonography was performed to identify all the nodules, to define the relationships between the nodule and MPD, and to establish the appropriate resection line. A T1 tumor was located about 5 mm distal from the gastroduodenal artery, adjacent to the MPD. A T2 tumor and a T3 tumor were located about 50 mm and 30 mm proximal from the splenic hilum, respectively. Both tumors were near the MPD. After dissecting and mobilizing the pancreatic neck, body, and tail from the surrounding tissue, we performed a medial pancreatectomy for the T1 tumor. The pancreatic parenchyma was transected using a Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) with sufficient proximal and distal margins from the T1 tumor. The proximal side of the MPD was ligated and cut, and the proximal stump of the pancreas was sewn in a fish-mouth shape. We then enucleated the T2 and T3 tumors using the Harmonic scalpel. Enucleation was done to excise the affected parenchyma with a minimal resection margin. A 4-F stent tube (Suikan tube, Sumitomo Bakelite, Tokyo, Japan) was inserted into the MPD of the distal remnant pancreas (Fig. 2A). We divided the jejunum with a linear stapler and then made a jejunal loop. A small incision was made in the lateral wall of the jejunal loop and the distal remnant pancreas was put into the jejunal lumen (Fig. 2B). The three cut surfaces of the pancreatic parenchyma were all covered within the jejunal lumen. Once the pancreas was in place, a row of interrupted 4-0 absorbable sutures was applied circumferentially to secure the edge of the jejunal cuff to the pancreas, and an end-to-side pancreaticojejunostomy was made. The pancreatic tube was connected to a drainage bottle in a closed fashion.

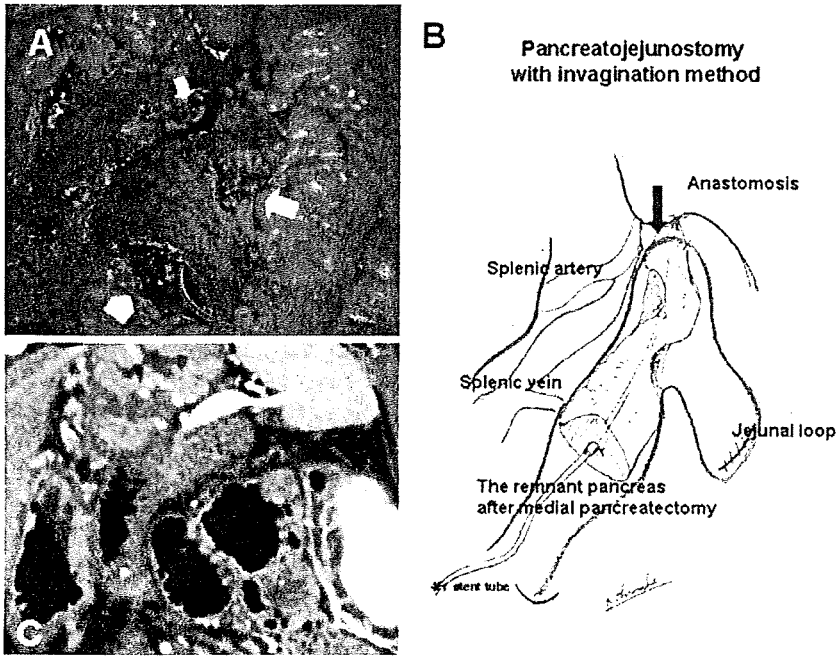

Fig. 2. **A** The *arrowhead* indicates the cut surface after the medial pancreatectomy with a 4-F stent tube. The *white arrows* indicate the row surfaces after enucleation of the two metastatic lesions. **B** Schematic illustration of the invagination method. The *black arrow* indicates the anastomosis. **C** MDCT showed the invaginated remnant pancreas, 2 months after the operation

Pancreatic juice was drained continuously through the tube for 2 weeks. We measured the amylase concentration of the collected fluid from a peripancreatic drain inserted near the anastomosis.

The intraoperative blood loss was 170 ml and the operative time was 284 min. Histologically, all of the tumors were surrounded by a fibrous capsule separating them distinctly from the normal pancreas. This tumor consisted of cells arranged in trabecular structures with clear granular cytoplasm; these findings were compatible with metastatic RCC. All surgical margins were negative for cancer cells, and no metastases were found in the dissected peripancreatic lymph nodes.

The patient had an uneventful postoperative course, without any sign of pancreatic leakage, and he was discharged on day 18. Multidetector-row CT done 2 months later showed the invaginated remnant pancreas (Fig. 2C). The patient was well without any evidence of recurrence 1 year after surgery. His body weight was the same as before surgery, he did not complain of any symptoms of pancreatic exocrine insufficiency such as diarrhea, and the HbA_{1c} level was 5.0%. Normal glycemia has also been maintained without medication and he has not needed oral enzyme supplements.

Discussion

Even in the presence of multiple pancreatic metastases or extrapancreatic metastatic sites, the resection of pancreatic metastases from RCC has been advocated in selected patients because of the unusually positive outcome.[2,3] Table 1 shows the clinical characteristics of 12 consecutive patients with pancreatic metastases from RCC, surgically treated at the National Cancer Center Hospital between January 1988 and December 2007, including the subject of this case report. Six (50%) patients had multiple metastases; four (33%) had undergone previous surgery for extrapancreatic metastases before the pancreatectomy; and seven (58%) had extrapancreatic metastases after the pancreatectomy. None of the patients in this series, including the 3 who had multiple pancreatic metastases and did not undergo a total pancreatectomy, have suffered local or pancreatic recurrence in the remnant pancreas. Three patients (25%) died of disease, two (16%) are alive with recurrent disease, and eight (75%) are alive with no evidence of disease. This suggests that aggressive or prophylactic resection might be unnecessary, because the behavior of metastatic RCC is difficult to predict and pancreatic metastases have been mistaken as localized disease due to their slow-growing and indolent nature. According to Zerbi et al.,[3] the choice of a standard or an atypical surgical procedure is probably less important than an accurate search for multiple pancreatic lesions. We performed a medial pancreatectomy with enucleation of two lesions instead of a total or distal pancreatectomy for multiple pancreatic metastases from RCC, to preserve the endocrine and exocrine pancreatic function.

The mechanism of metastasis of RCC to the pancreas is still unclear. While hematogenous systemic spread is possible, peripancreatic lymph node involvement with pancreatic metastases is considered to be rare.[1,2] Sellner

Table 1. Operative procedures and outcome of 12 patients with pancreatic metastases from renal cell carcinoma surgically treated at the National Cancer Center Hospital between 1988 and 2007

Case no.	Age (years)/Sex	Site (RCC)	Interval (months)	Metastases before pancreatectomy	Tumor number	Operation	Recurrence after pancreatectomy	Management of recurrence	Follow-up time (months)	Outcome
1	60/M	Right	41	—	4	TP	—	—	240	NED
2	47/F	Left	55	—	7	TP	Thyroid	Resection	169	NED
3	66/M	Right	209	Lung/Lymph nodes	1	DP	Lung/Lymph node	No treatment	89	AWD
4	81/F	Right	363	—	5	PPPD	Liver	No treatment	12	DOD
5	58/M	Right	142	Lung	2	TP	Lung/Bone/Liver	No treatment	63	DOD
6	61/F	Right	136	—	1	PPPD	—	—	66	NED
7	62/M	Right	81	—	1	DP	Lung	No treatment	56	AWD
8	50/M	Left	21[a]	Lung	1	Completion TP	Right kidney/Lung	Partial nephrectomy/ Pneumonectomy	51	NED
9	70/F	Right	90	—	1	DP	—	—	41	NED
10	73/F	Left	243	Lung/Pituitary	1	PPPD	Liver/Pituitary	No treatment	17	DOD
11	64/F	Left	19[b]	—	4	DP	—	—	15	NED
12	54/M	Right	122	—	3	MP/Partial resections	—	—	12	NED

RCC, renal cell carcinoma; TP, total pancreatectomy; DP, distal pancreatectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; MP, medial pancreatectomy; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease

[a] Pancreatic lesions were detected synchronously at the time of nephrectomy. Distal pancreatectomy with left nephrectomy was performed; pancreatic head lesion was not resected, but treated with interferon-α chemotherapy

[b] Pancreatic lesions were detected synchronously at the time of nephrectomy. Interferon-α chemotherapy was performed

et al.[2] hypothesized that RCC has a high affinity for the parenchyma of the pancreas, and that only this location provides the conditions it needs to mature and manifest metastases. However, this explanation of the behavior of metastatic RCC might not justify prophylactic radical resections in all patients. Total pancreatectomy used to be generally accepted for multiple scattered metastases, but taking metastatic mechanisms into consideration, the parenchyma should be preserved if complete extirpation with a free margin is possible. Oncologically, hematogenous systemic metastases might develop in any extrapancreatic organs, and there are no clear data supporting completion pancreatectomy or radical pancreatectomy including regional lymph node dissection.

A pancreatic fistula might form from the cut surface after partial resection of two metastatic lesions on the distal side of the pancreatic remnant following such an atypical resection. To prevent pancreatic leakage from the three cut surfaces, we inserted almost all of the distal remnant pancreatic parenchyma into the jejunal lumen and covered all the cut surfaces. A pancreaticojejunostomy using the invagination method is thus recommended, especially for patients with a normal pancreas, to prevent stenosis of the pancreatic duct opening.[10] After conventional pancreaticojejunostomy with a duct-to-mucosa anastomosis, there is a possibility of stricture of the anastomosis, which would lead to exocrine and endocrine insufficiency. However, anastomotic stricture does not tend to occur with the invagination technique because there is no pancreaticojejunal anastomosis, although it is still necessary to survey the long-term efficiency of this procedure. Although the distal remnant pancreas was mobilized from its surrounding attachments and splenic vessels, an enhanced CT scan done 2 months after the operation showed sufficient blood flow of the pancreatic parenchyma.

In summary, we describe how we resected multiple pancreatic metastases from RCC, by performing a medial pancreatectomy and enucleation, preserving as much of the pancreatic parenchyma as possible. Although it is difficult to predict the pattern of recurrence after such an atypical pancreatectomy, Bassi et al.[5] reported 29% pancreatic recurrence after a distal pancreatectomy in two patients and after an atypical resection in three. Thus, we must take care not to overlook recurrence in the remnant parenchyma, although should a recurrent lesion appear in either the proximal or distal remnant pancreas, it would still be possible to avoid total pancreatectomy.

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Clinical Significance of Frozen Section Analysis During Resection of Intraductal Papillary Mucinous Neoplasm: Should a Positive Pancreatic Margin for Adenoma or Borderline Lesion Be Resected Additionally?

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BACKGROUND: The clinical significance of a positive intraoperative frozen section analysis of the pancreatic margin, especially for adenoma or borderline lesion, is not well understood during operations for intraductal papillary mucinous neoplasm of the pancreas.

STUDY DESIGN: Data from 130 consecutive patients who underwent intraductal papillary mucinous neoplasm resection in a single institution were retrospectively analyzed.

RESULTS: In the first intraoperative frozen section analysis, 26 patients were positive for adenoma or borderline lesion, 10 for carcinoma in situ, 2 for cancer cells floating in the duct, and 6 for invasive cancer. Twenty-nine patients underwent additional resection, and 105 patients finally achieved a negative pancreatic margin. Among 18 patients with a positive pancreatic margin for adenoma or borderline lesion, only 1 had a recurrence. All 20 patients who suffered a recurrence harbored invasive intraductal papillary mucinous carcinoma in resected specimens. In multivariate analysis, predictive factors of recurrence after intraductal papillary mucinous carcinoma resection were the presence of lymph node metastasis, serosal invasion, and a high level of serum carbohydrate antigen 19-9.

CONCLUSIONS: The presence of adenoma or borderline lesion at the pancreatic margin does not always warrant further resection because of the low recurrence rate in the remnant pancreas. Recurrence after intraductal papillary mucinous neoplasm resection is influenced primarily by the presence and extent of invasive cancer rather than the status of the pancreatic margin. (J Am Coll Surg 2009; 209:614–621. © 2009 by the American College of Surgeons)

The reported incidence of intraductal papillary mucinous neoplasm (IPMN) has been increasing in recent years, and its biologic behavior has been progressively elucidated.[1-6] IPMN is characteristic of papillary proliferation and prominent mucin production, resulting in marked dilatation of branch or main pancreatic ducts (MPD), or both. Those features are reflected in the radiologic appearance of IPMN, making the diagnosis easy in typical cases. But the margin of IPMN is not always associated with such characteristic findings and often shows gradual transmission from low-grade atypia to normal epithelium without marked ductal dilatation or papillary projections detectable on imaging examinations. So, pre- or intraoperative assessment of tumor spread is often difficult and incorrect. To secure a tumor-free margin, intraoperative frozen section analysis (IOFSA) of the pancreatic cut margin is indispensable, at the same time preserving the largest possible pancreas remnant during resection of IPMN.[7-9] International consensus guidelines for management of IPMN also advocate the importance of IOFSA.[10] But the relative risk and biologic significance of various grades of IPMN at the pancreatic margin are not fully established, especially for those

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Abbreviations and Acronyms

HD = high-grade dysplasia
IC-IPMC = invasive cancer originating in IPMC
IOFSA = intraoperative frozen section analysis
IPMC = intraductal papillary mucinous carcinoma
IPMN = intraductal papillary mucinous neoplasm
LD = low-grade dysplasia
MD = moderate dysplasia
MI-IPMC = minimally invasive intraductal papillary mucinous carcinoma
MP = middle pancreatectomy
MPD = main pancreatic duct
TP = total pancreatectomy

with adenoma or borderline lesions. In this retrospective study, we analyzed the result of IOFSA and the incidence and loci of recurrence after IPMN resection. We also investigated the rational criteria for additional pancreatic resection during surgery for IPMN.

METHODS

From 1986 to 2007, 130 cases of IPMN were resected at the National Cancer Center Hospital in Tokyo. Except for 3 patients who underwent 1-step total pancreatectomy for IPMNs diffusely involving the entire pancreas, 127 patients underwent IOFSA of the pancreatic margin. We have been performing IOFSA routinely and making it a rule to manage pancreatic margins as follows: (1) negative (normal epithelium) or hyperplasia, no further resection; (2) positive for adenoma (low-grade dysplasia [LD]) or borderline lesion (moderate dysplasia [MD]), no more resection or additional resection in some cases, but total pancreatectomy is avoided; and (3) positive for carcinoma in situ (CIS or high-grade dysplasia, [HD]) or invasive cancer, additional resection including total pancreatectomy if necessary. In cases of LD or MD, the decision to do additional resection was made by the individual surgeon, depending on the site of the first pancreatic transection and the patient's general condition, including age, comorbidity, and compliance. Generally, to secure the safety of the pancreatoenteric anastomosis and postoperative glucose tolerance, the limit of additional pancreatic resection was considered to be just beneath the gastroduodenal artery in a left-sided pancreatectomy and 3 to 5 cm to the left side of the superior mesenteric artery in a right-sided pancreatectomy. The amount and extent of the lesions on the frozen section were also taken into consideration. According to information from pathologists, surgeons tended to perform additional resections, when feasible, for frozen sections with massive papillary proliferation or with widespreading lesions both into small branch ducts and the MPD, even if the cellular atypia in the lesion was LD or MD.

In the first IOFSA, the pancreatic margin was cut by a pathologist immediately after the specimen was retrieved from the operative field. The margin tissue was embedded in optimal cutting temperature compound (Sakura Finetek) and frozen in acetone cooled with dry ice. The 5-μm thick tissue sections cut by a cryostat (OTF5000; Bright Instrument Co Ltd) were fixed in 18% formalin with 50% ethanol, stained with hematoxylin and eosin, and immediately analyzed by more than 2 pathologists. Substantial care was taken not to touch a pancreatic stump directly in order to avoid epithelial abrasion. To ensure a freshly cut surface, the pancreas was sometimes transected at the final step of the operative procedure, or, in other cases, the pancreatic stump was secured by a surgeon immediately after the pancreas transection in the operative field. If there was difficulty in making a diagnosis, another deeper section was cut to help with the diagnosis. In an additional resection, the pancreatic stump was dissected from the surrounding retroperitoneal tissues or vessels, and 1 to 2 cm of pancreas was resected by surgical scalpel. Again, the greatest possible effort was exerted not to damage the stump.

After the IOFSA, all the margin tissues were fixed in 10% formalin and embedded in paraffin. Sections 3 μm in thickness were cut from the block, stained with hematoxylin and eosin, and analyzed for the definitive diagnosis on a subsequent day.

Patients were followed up on an outpatient basis every 3 to 6 months after operation. Postoperative examinations included a CT scan, ultrasonography, and blood test with measurement of CEA and carbohydrate antigen 19-9 (CA 19-9). The time and site of initial tumor recurrence were recorded based on radiologic findings, even if the patient did not undergo a biopsy. CT and ultrasonography were conducted when recurrence was suspected, and both studies were used to complement each other. When progression of the disease was confirmed by repeated imaging studies, the date of recurrence was deemed to be the date of the first detection of a suspicious lesion.

Statistical analysis

Comparisons of categoric variables were performed using the chi-square test. Recurrence rates were calculated by the Kaplan-Meier method. Univariate analysis was performed for predictive factors of recurrence using the log-rank test. Factors found significant by univariate analysis were subjected to multivariate analysis using the backward elimination method of the Cox proportional hazards model. Differences at $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS 11.0J software (SPSS, Inc).