Table 5 Risk factors influencing severe complications after pancreaticoduodenectomy by univariate analysis

	Severe complications*		
	− (n = 89) (%)	+ (n = 38) (%)	*P* value
Age (y)			
≤75	64 (71.9)	26 (68.4)	
>75	25 (28.1)	12 (31.6)	.692
Gender			
Male	46 (51.7)	25 (65.8)	
Female	43 (48.3)	13 (34.2)	.143
Total bilirubin level (mg/dL)			
≤10	58 (65.2)	29 (76.3)	
>10	31 (34.8)	9 (23.7)	.216
Type of biliary drainage			
Internal drainage	41 (46.1)	26 (68.4)	
External drainage	48 (53.9)	12 (31.6)	.021
Preoperative cholangitis†			
Yes	6 (6.7)	10 (26.3)	
No	83 (93.3)	28 (73.7)	.002
Waiting periods for operation from drainage			
≤4 wk	65 (73.0)	22 (57.9)	
>4 wk	24 (27.0)	16 (42.1)	.093
Histology			
Pancreatic cancer	47 (52.8)	8 (21.1)	
Other disease	42 (47.2)	30 (78.9)	.001
Operative procedure			
PpPD	64 (71.9)	27 (71.1)	
PD/PrPD	25 (28.1)	11 (28.9)	.922
Operative time (min)			
≤420	66 (74.1)	26 (68.4)	
>420	23 (25.9)	12 (31.6)	.508
Intraoperative bleeding (mL)			
≤1000	64 (71.9)	25 (65.8)	
>1000	25 (28.1)	13 (34.2)	.490
Red blood cell transfusion			
Yes	31 (34.8)	10 (26.3)	
No	58 (65.2)	28 (73.7)	.347
Pancreatic texture			
Soft	38 (42.7)	28 (73.7)	
Hard	51 (57.3)	10 (26.3)	.001

PD = pancreaticoduodenectomy; PpPD = pylorus-preserving pancreaticoduodenectomy; PrPD = pylorus-resecting pancreaticoduodenectomy.
*"Severe complications" was defined in this study as a condition that was grade III or more based to the Clavien classification.
†Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013.

All postoperative complications were significantly higher in the internal drainage group (41.8%) than in the external drainage group (23.3%; $P = .027$). Moreover, severe complications (grade III or more) were significantly higher in the internal drainage group (38.8%) than in the external drainage group (20.0%; $P = .021$). The overall incidence of pancreatic fistula was significantly higher in the internal drainage group (38.8% vs 21.7% in external drainage group; $P = .037$). Pancreatic fistula was classified into 3 categories by the International Study Group on Pancreatic Fistula (12). The proposed clinical grading of the 26 patients with pancreatic fistula in the internal drainage group were grade A, n = 12; grade B, n = 9; and grade C, n = 5. The 13 patients with pancreatic fistula in the external drainage group were grade A, n = 6; grade B, n = 7; and grade C, n = 0. Twenty-five of 127 patients with preoperative biliary drainage had infectious complications. There was no significant difference between internal drainage and external drainage (15% in external drainage group vs 23.9% in internal drainage group). There were no significant differences between the 2 groups concerning the incidence of other postoperative complications, such as DGE, bile leakage, intra-abdominal abscess, and intra-abdominal hemorrhage.

The mortality rate in this study was 3.1% (4 of 127 patients). Two patients died because of pancreatic fistula, 1 patient because of intra-abdominal hemorrhage, and 1 patient because of nonocclusive mesenteric ischemia.

Table 6 Risk factors influencing severe complications* after pancreaticoduodenectomy by multivariate analysis

Risk factor	*P* value	Odds ratio	95% CI
Internal drainage	.125	2.01	.8–4.9
Preoperative cholangitis†	.019	4.61	1.3–16.5
Soft pancreas	.846	1.79	.1–5.1
Other disease except pancreatic cancer	.141	4.22	.6–28.8

CI = confidence interval.
*"Severe complications" was defined in this study as a condition that was grade III or more based to the Clavien classification.
†Preoperative cholangitis was defined by the new diagnostic criteria of acute cholecystitis referred to as the Tokyo Guidelines 2013 (TG13).

The association between preoperative cholangitis and postoperative complications

Table 4 shows the association between preoperative cholangitis and postoperative complications. The incidence of preoperative cholangitis in this study was 12.6% (16 of 127 patients). Ten of 16 patients (62.5%) with preoperative cholangitis were given plastic stent exchange or change to ENBD and the administration of antibiotics.

All postoperative complications were significantly higher in patients with cholangitis (62.5%) than patients without it (22.8%; $P = .007$). Severe complications (grade III or more) were significantly higher in patients with cholangitis (62.5%) than patients without it (25.2%; $P = .002$). Likewise, the overall incidence of DGE was significantly higher in patients with cholangitis (31.2% vs 5.4% in patients without cholangitis; $P = .001$). DGE was classified into 3 categories by ISGPS.[13] The proposed clinical grading of 5 patients with DGE among those with cholangitis were grade A, n = 1; grade B, n = 3; and grade C, n = 1. The 6 patients with DGE among the 111 without cholangitis were grade A, n = 4; grade B, n = 1; and grade C, n = 1. The incidence of wound infection was significantly higher in patients with cholangitis (25%) than patients without it (4.5%; $P = .003$). There was no significant difference between patients with and without preoperative cholangitis (31.3% in patients with preoperative cholangitis vs 18.0% in patients without preoperative cholangitis). There were no significant differences between the 2 groups concerning the incidence of other postoperative complications, such as pancreatic fistula, bile leakage, intra-abdominal abscess, and intra-abdominal hemorrhage.

Risk factors influencing severe complications after PD

Univariate and multivariate analyses were used to reveal risk factors influencing severe complications (grade III or more) after PD. Table 5 shows the results of 12 parameters univariately examined as potential risk factors for 38 patients with severe complications (grade III or more) vs 89 patients without severe complications after PD. Four factors were extracted as being useful for discriminating between patients with and without severe complications after PD: internal drainage ($P = .021$), preoperative cholangitis ($P = .002$), soft pancreas ($P = .001$), and other disease except pancreatic cancer ($P = .001$) were identified. A multivariate logistic regression analysis revealed that preoperative cholangitis (odds ratio 4.61, 95% confidence interval 1.3 to 16.5; $P = .019$) was the significant risk factor for morbidity after PD (Table 6).

Comments

Routine preoperative biliary drainage for jaundiced patients with PD remains still controversial for occurrence of biliary drainage–related complications. However, preoperative biliary drainage for jaundiced patients is generally accepted in Japan. Because period for the expected waiting time until surgery in Japan generally requires a few weeks. All 127 jaundiced patients with PD in the present study underwent preoperative biliary drainage. Therefore, the present study focused on the advantage or disadvantage by various types of preoperative biliary drainage. This is the first study to compare whether internal drainage or external drainage is better for preoperative biliary drainage in patients with PD. Moreover, it remains controversial how biliary drainage–related complications affect the incidence of postoperative complications after PD. In the present study, we evaluated the associations between biliary drainage–related complications and postoperative complications after PD between internal drainage and external drainage.

The occurrence of preoperative cholangitis during biliary drainage was clarified to be the independent risk factor of severe complications after PD. Two previous studies reported that occurrence of preoperative cholangitis significantly increased postoperative complications including pancreatic fistula or DGE.[16,17] Preoperative cholangitis significantly increased DGE and wound infection in the present study. Many pancreatic surgeons believe that DGE after PD is secondary caused by pancreatic fistula or intra-abdominal abscess. However, in the present study, there was no significant difference between patients with and without intra-abdominal abscess according to the incidence of DGE (18.7% in patients with intra-abdominal abscess vs 7.2% in patients without

intra-abdominal abscess, $P = .144$). This study demonstrates that there was no significant association between intra-abdominal abscess and DGE.

Stent occlusion was reported to cause more than half the incidence of preoperative cholangitis, and cholangitis occurred in 26% of patients who underwent internal drainage.[6] The cause of cholangitis because of internal drainage may be stent occlusion or ascent of microorganisms from the open passage to the duodenum and subsequent reflux of duodenal contents.[18,19] In this study, patients undergoing internal drainage had significantly higher incidence of cholangitis because of biliary drainage (22.4% vs 1.7% in external drainage group). As a result, internal drainage, which was associated with more preoperative cholangitis, significantly increased the incidence of morbidity compared with external drainage (41.8% vs 22.3%). Biliary drainage was shown to increase infectious complications such as wound infection after PD.[20] On the other hand, Jagannath et al[21] reported that a positive intraoperative bile culture was associated with higher morbidity rates after PD, and biliary drainage was not associated with increased morbidity. In addition, biliary drainage with complications such as cholangitis was reported to increase significantly the incidence of positive bile culture.[21] Therefore, clinicians have to take special care not to initiate preoperative cholangitis because of biliary drainage.

Preoperative internal biliary drainage may increase postoperative complications after PD compared with external drainage. However, there are some disadvantages in external drainage such as PTBD or ENBD. Drains for external drainage may be dislodged or pulled out by patients at the unconscious level. Other drawbacks of PTBD are the invasiveness of the technique or seeding risk. Other drawbacks of ENBD are patient discomfort or cosmetic problems because of the presence of the tube through nasopharynx. In contrast, compared with external drainage, internal drainage allows normal bile flow, which is important from the viewpoint of intestinal immunity and the prevention of bacterial translocation.[22–24] One problem with internal drainage is cholangitis because of stent occlusion. In this study, plastic stents in all cases were used as internal drainage. Metallic stents in patients with unresectable pancreatic cancer were reported to provide large caliber, longer patency, and lower incidence of acute cholangitis compared with plastic stents.[25] A few studies reported that metallic stents have more advantages compared with plastic stents as preoperative internal biliary drainage in patients awaiting PD, such as those undergoing neoadjuvant therapy for pancreatic cancer.[26–28] Moreover, covered metallic stents may be possible not only to protect against tumor ingrowth but also to minimize bacterial adherence and sludge formation that cause biliary infections.[29,30] Additional studies are required to evaluate how the use of metallic stents as preoperative biliary drainage affects surgical technique or perioperative course.

There are several limitations to this study for the retrospective study. First, external drainage by PTBD was performed by choice in the early period. One might consider that there is a bias because of the increasing experience between the early period in this study and the latter period concerning the operative time, intraoperative bleeding, and red blood cell transfusion. Second, in our institution, we have performed pylorus PrPD instead of PpPD by the result of clinical trial since February 2009.[9] A bias for the period affects a significant difference between drainage type and operative procedure. However, we checked that there was no significant difference between patients with and without severe complications concerning operative procedures.

In conclusion, preoperative cholangitis during biliary drainage significantly increases the incidence of postoperative complications after PD. In particular, plastic stents as internal biliary drainage may increase preoperative cholangitis related to stent occlusion during the waiting period for PD. Therefore, management of biliary drainage to prevent preoperative cholangitis should be standardized for patients who require preoperative biliary drainage for PD.

References

1. Kimmings AN, van Deveter SJ, Obertop H, et al. Endotoxin, cytolines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage. Gut 2000;46:725–31.
2. Coates JM, Beal SH, Russo JE, et al. Negligible effect of selective preoperative biliary drainage on perioperative resuscitation, morbidity, and mortality in patients undergoing pancreaticoduodenectomy. Arch Surg 2009;144:841–7.
3. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001;234:47–55.
4. Hodul P, Creech S, Pickleman J, et al. The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. Am J Surg 2003;186:420–5.
5. Povoski SP, Karpeh MS, Conlon KC, et al. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg 1999;230:131–42.
6. van der Gaag NA, Rauws EAJ, van Eijck CHJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med 2010;362:129–37.
7. Iacono C, Ruzzenente A, Campagnaro T, et al. Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. Ann Surg 2013;257:191–204.
8. Nagino M, Takada T, Miyazaki M, et al. Preoeprative biliary drainage for biliary tract and ampullary carcinomas. J Hepatobiliary Pancreat Surg 2008;15:25–30.
9. Kawai M, Tani M, Hirono S, et al. Pylorus ring resection reduces delayed gastric emptying in patients undergoing pancreatoduodenectomy: a prospective randomized controlled trial of pylorus-resecting versus pylorus-preserving pancreatoduodenectomy. Ann Surg 2011; 253:495–501.
10. Tani M, Terasawa H, Kawai M, et al. Improvement of delayed gastric emptying in pylorus-preserving pancreaticoduodenectomy: results of a prospective, randomized, controlled trial. Ann Surg 2006;243:316–20.
11. Kawai M, Tani M, Terasawa H, et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for consecutive 104 patients. Ann Surg 2006;244:1–7.

12. Yokoe M, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholecystitis in revised Tokyo Guidelines. J Hepatobiliary Pancreat Sci 2012;19:578–85.
13. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005; 138:8–13.
14. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142: 761–8.
15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
16. Park YC, Kim SW, Jang JY, et al. Factors influencing delayed gastric emptying after pylorus-preserving pancreatoduodenectomy. J Am Coll Surg 2003;196:859–65.
17. Sohn TA, Yeo CJ, Cameron JL, et al. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg 2000;4:258–67; discussion 267–8.
18. Hochwald SN, Burke EC, Jarnagin WR, et al. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. Arch Surg 1999;134: 261–6.
19. Lermite E, Pessaux P, Teyssedou C, et al. Effect of preoperative endoscopic biliary drainage on infectious morbidity after pancreatoduodenectomy: a case-control study. Am J Surg 2008;195: 442–6.
20. Povoski SP, Karpeh Jr MS, Conlon KC, et al. Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg 1999; 3:496–505.
21. Jagannath P, Dhir V, Shrikhande I S, et al. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. Br J Surg 2005;92:356–61.
22. Clements WD, Diamond T, McCrory DC, et al. Biliary drainage in obstructive jaundice: experimental and clinical aspects. Br J Surg 1993;80:834–42.
23. Parks RW, Clements WD, Smye MG, et al. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. Br J Surg 1996;83:1345–9.
24. Kamiya S, Nagino M, Kanazawa H, et al. The value of bile replacement during external biliary drainage: an analysis of intestinal permeability, integrity, and microflora. Ann Surg 2004;239:510–7.
25. Moss AC, Morris E, Leyden J, et al. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev 2007;33:213–21.
26. Adam AA, Evans DB, Khan A, et al. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. Gastrointest Endosc 2012;76:67–75.
27. Decker C, Christein JD, Phadnis MA, et al. Biliary metal stents are superior to plastic stents for preoperative biliary decompression in pancreatic cancer. Surg Endosc 2011;25:2364–7.
28. Cavell LK, Allen PJ, Vinoya C, et al. Biliary self-expandable metal stents do not adversely affect pancreaticoduodenectomy. Am J Gastroenterol 2013;108:1168–73.
29. Kahaleh M, Tokar J, Conaway MR, et al. Efficacy and complications of covered Wallstents in malignant distal biliary obstruction. Gastrointest Endosc 2005;61:528–33.
30. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63:986–95.

治療における新展開—切除不能例への治療戦略

ペプチドワクチンを用いた膵癌治療

Strategy by vaccine-immunotherapy for the patients with pancreatic cancer

和歌山県立医科大学第２外科
谷　眞至　　山上裕機

【ポイント】

◆ペプチドワクチンは直接癌細胞を傷害しないが，リンパ球などの効果細胞を介して標的とする部位が明らかになっていることから，理論的根拠に基づいたペプチドワクチン療法の開発が可能である．

◆自然発癌において，腫瘍細胞は宿主免疫監視機構をすり抜けて発育していることから，様々な免疫逃避機構の存在に関する推測ができる．

◆今後，新しいペプチドの同定ならびにワクチンアジュバントの開発など，解決しなければならない問題が山積しており，さらなる治験などの臨床試験の推進が必要である．

臨外　69(1)：64～69，2014

はじめに

膵癌は切除が治癒の可能性を有する唯一の治療法であるが，いまだに切除不能症例が切除可能症例を上回り，その予後は不良である[1]．また，切除可能例においても高率に再発をきたし，術後の治療が重要となっている．

ゲムシタビン塩酸塩は5-FUとの比較試験において膵癌化学療法における標準治療となった[2]．さらなる治療成績の向上を探索する目的で多くの薬剤との比較試験ならびにゲムシタビン塩酸塩との併用が試みられたが，上皮成長因子受容体（epidermal growth factor receptor：EGFR）に対する分子標的治療薬であるエルロチニブが唯一，ゲムシタビン塩酸塩単剤と比較して生存において優越性を示した薬剤である[3]．しかし，その生存期間中央値は併用群6.2か月，ゲムシタビン塩酸塩単独群5.9か月[3]とわずかであり，副作用や費用対効果を考えると新たな標準治療との結論には至らないのが現状である．また，遠隔転移症例を対象に，FOLFIRINOX療法が無作為化比較試験でゲムシタビン塩酸塩に対し有意に生存期間を延長することが報告され[4]，アブラキサンも今後の併用療法の有望な候補薬剤となってくると考えられる．FOLFIRINOX療法はゲムシタビン塩酸塩を含まないレジメンであり，臨床の現場ではその効果に期待がもたれているが，日本人に対するfeasibilityの検証結果，特に好中球減少などの有害事象の検討が待たれるところである．

一方，免疫療法は，抗癌剤や癌細胞に特有あるいは過剰に発現している特定の分子の機能を抑える分子標的治療薬とは異なり，副作用の点から開発が望まれている治療法である．ペプチドワクチンは直接癌細胞を傷害するのではなく，リンパ球などの効果細胞を介してはいるものの標的とする部位が明らかになっていることから，理論的根拠に基づいたペプチドワクチン療法の開発が可能となり，治験を含む臨床試験が行われている．

癌免疫療法の歴史とT細胞の癌細胞識別

免疫療法は，OK-432やレンチナンなどの内因性サイトカイン誘導効果による非特異的免疫療法薬に始ま

り，IL-2などの大量のサイトカイン投与が行われた．悪性黒色腫など一部の疾患には効果が認められ，担癌宿主が自己の癌細胞に対する免疫能を有することが明らかとなったが，消化器癌には効果を認めなかった[5~7]．これらの治療においては非特異的に活性化されたNK細胞やリンパ球が抗腫瘍効果を担っていたと考えることができる．さらに，リンパ球を大量増殖させて生体内に移入する養子免疫療法が試みられたが，その治療効果は限定的なものであった[8,9]．

T細胞は異物となる抗原を特異的に認識して排除するが，抗原受容体であるT細胞受容体は直接抗原を認識しないことが抗体とは異なるところである．抗原の分解物質であるペプチドが，主要組織適合性複合体（major histocompatibility complex：MHC）に結合し，免疫応答を誘導する．腫瘍関連抗原においては，細胞傷害性T細胞（cytotoxic T lymphocyte：CTL）が認識できる腫瘍抗原ペプチドが報告され[10]，それまでは漠然としていた腫瘍抗原が明らかとなり，理論的根拠に立脚した腫瘍抗原を標的とした癌ワクチン療法が考案されることになった．

標的となる腫瘍細胞に特異的に発現している内因性抗原である腫瘍関連抗原は，樹状細胞に取り込まれ，プロテアソームによるプロセシング作用を受けてペプチド断片となり，MHC（ヒトではHLA）class I分子のα_1，α_2ドメインに結合する．そしてゴルジ体を介して細胞表面へ表出し，MHC（HLA）−ペプチド複合体によりペプチドがCD8陽性T細胞に提示され，CD8陽性T細胞を活性化することにより抗原特異的なCTLが誘導される．ペプチドワクチン療法では腫瘍特異的CTLを誘導しうるペプチドを同定し，それを癌患者に投与することで，樹状細胞に取り込まれ，上述の作用機序により腫瘍特異的CTLが誘導される．腫瘍抗原の同定に伴って特異的T細胞の頻度やサブセットなどが生命予後と関連する[11]ことからも，T細胞が癌細胞の消去を担っていることが推測される．

CTLによる細胞傷害活性を基盤とした癌免疫療法は，その作用機序が化学療法とはまったく異なることから，有害事象の軽減や有効性が期待される．しかし，膵癌には期待されたような臨床効果はみられなかった[12]．その原因として癌細胞の免疫逃避機構の存在が示唆される．

免疫逃避機構

化学発癌モデルやウイルス発癌モデルとは異なり，自然発癌において腫瘍細胞は宿主免疫監視機構をすり抜け発育している．一定以上の腫瘍細胞量にまで成長した腫瘍細胞はヘテロな集団であり，様々な免疫逃避機構が推測される[13,14]．腫瘍細胞は遺伝子変異を起こしやすく，腫瘍関連抗原の発現も不安定であり，CTLが認識できない細胞が存在する．腫瘍抗原だけでなくHLA class Iの発現が低下するため，HLA−ペプチド複合体が形成されず，CTLが腫瘍細胞を認識できない．このHLA class Iの発現が低下する現象は多くの癌腫で報告されており[15~17]，膵癌でも同様の報告がされている[14]．また，HLA class I発現の低下・消失は患者生存率の低下と相関し，再発も多いことが他の癌腫で報告されている[18,19]．

さらに癌微小環境における免疫抑制因子の存在が危惧される．腫瘍細胞や周囲の間質細胞から産生されるIL-10に代表される免疫抑制性サイトカインやTGF-β[20]，制御性T細胞により[21]，CTLは免疫抑制状態となる．

腫瘍新生血管を標的とした癌ワクチン療法

VEGF-Aはほとんどの腫瘍で発現が上昇しており，VEGFR-1およびVEGFR-2の2つのレセプター型チロシンキナーゼと結合する[22]．VEGFR-1およびVEGFR-2を介したシグナル伝達を遮断することで，血管新生の阻害や癌細胞の増殖・転移を抑制することが期待できる[23]．また，VEGFR-2はVEGFR-1よりVEGF-Aによる血管内皮細胞の増殖や血管透過性などの主要なシグナル伝達を強く担うレセプターであり，VEGFR-2のシグナル伝達を遮断することは，腫瘍新生血管の阻害ならびに腫瘍細胞の浸潤・転移を抑制できる可能性を示唆している．

当科で施行した医師主導型第I相臨床試験で用いたペプチドはVEGFR-2由来エピトープペプチド（VEGFR2-169，Elpamotide；エルパモチド）であり，VEGFR-2を特異的に認識し，最も強い腫瘍新生血管を傷害するCTLを誘導することができる[24]．また，担癌患者からも特異的CTLが誘導できることが明らかになっている．VEGFR-1由来ペプチドも同定されており，ペプチドをパルスした細胞に対し細胞傷害活

表1 VEGFR-2-169投与による免疫応答と臨床効果

	ペプチド投与量（mg）		
	0.5 (n=6)	1.0 (n=6)	2.0 (n=6)
免疫応答			
局所皮膚反応（＋）	5	4	6
CTL反応（＋）	3	4	4
臨床効果			
PR/SD/PD	0/4/2	0/4/2	1/3/2
全生存期間（日）	233	207	344

（文献28から改変）

表2 VEGFR-2-169投与による局所皮膚反応と臨床効果

	局所皮膚反応	
	陽性	陰性
PR＋SD	12	0
PD	3	3

（文献28から改変）

性を有することが確認され，VEGFR-1を内因性に発現した細胞においても特異的活性化CTLの誘導が確認できている[25]．免疫逃避機構を克服するには，癌細胞自体を標的にするのではなく，膵癌細胞の増殖や転移に必須で[26,27]，かつHLA class I発現が安定している腫瘍新生血管を標的とする新しい発想での免疫療法を施行することとした．

■当科で行った第I相臨床試験

HLA-A*2402を有する切除不能膵癌患者を対象に，医師主導型第I相臨床試験「切除不能進行再発膵癌に対する腫瘍新生血管を標的としたHLA-A*2402拘束性エピトープペプチドとgemcitabine併用による第I相臨床試験」（ClinicalTrials. gov ID：NCT00622622）を施行した．種々の理由からdrop outした3名を除き，評価対象患者は18名で，主要評価項目は安全性とした．注射部位反応やCTL反応解析などの免疫反応，臨床的反応を副次的評価項目とし，推奨投与量を決定することとした．VEGFR2-169を0.5 mg，1.0 mg，2.0 mgの各コホート6名とし，週1回の投与とした．ゲムシタビン塩酸塩は1,000 mg/m^{2}とし，通常投与と同じ3週投薬・1週休薬とした．

免疫学的解析ではVEGFR2-169特異的CTLが11例（61%）で誘導され，注射部位反応も15例（83%）に認められた（表1）．副作用は許容範囲内であり，投与量を規定する毒性は認めなかった．臨床的効果は，ペプチド投与部位の局所皮膚反応が陽性であった15例のうち12例（80%）がpartial response（PR）またはstable disease（SD）であったが，陰性であった3例すべてがprogress disease（PD）であった（表2）．さらに2 mg投与群の生存期間が最も長かった（表1）．以上の結果から，推奨投与量は2 mg/bodyとした[28]．

■第II/III相臨床治験の意義—PEGASUS-PC試験

この医師主導型第I相臨床試験の結果から，pivotal studyとなる第II/III相臨床治験（PEGASUS-PC試験）へと発展し，153例が登録された．主要評価項目である全生存期間では，実薬群とプラセボ群で統計学的有意差は認められなかった．しかし，注射部位反応によるサブグループ解析を行ったところ，強い皮膚反応が認められた患者については生存期間が延長している傾向があり，注射部位の潰瘍は実薬群においてのみ認められた事象であることから，エルパモチドにより誘導されたVEGFR-2特異的CTLにより引き起こされた特異的な事象と考えられた．以上より，エルパモチド単剤は一部の患者に対して生存期間を延長できる可能性があることが明らかとなった[29]．今後の詳細な解析結果からVEGFR2-169の有効なsubsetが具体的になるが，引き続き臨床応用可能な有望なペプチドが開発されることに期待する．

PEGASUS-PC試験では生存期間の有意な延長は認めなかったものの，日本で初めてのペプチドワクチンによる膵癌に対する質の高い治験であるだけでなく，従来の抗腫瘍薬とはまったく異なった新しい解析方法で行われた点が，今後の免疫療法の発展の礎になると考えられる[29]．すなわち，通常，有効性は主にKaplan-Meier法により生存割合を算出し，log-rank検定あるいはWillcoxon検定によって治療群間の比較検定を行うことで，主要評価項目である生存期間あるいは無病生存期間の差により評価される．しかし，癌ペプチドワクチンにおいては，抗原特異的免疫応答を介した薬理薬効から遅発性の効果発現が想定されている（図1）．このことを考慮し，観察期間後期に重み付けを置くHarrington-Fleming法[30]による解析が行われ，独立行政法人医薬品医療機器総合機構（PMDA）がこれを許可したことは免疫療法の新時代を感じさせるものである．

ペプチドワクチンの効果発現の特性

ペプチドワクチンは生体の免疫反応を介した効果であるため，従来の抗腫瘍薬とは違った観点から評価をしなければならない．米国FDAではすでにガイダンスが発行されているが，日本には癌ワクチン療法のガイダンスはなく，日本バイオセラピィ学会が2012年12月に「がん治療用ペプチドワクチンガイダンス」を発行した（http://jsbt.org/guidance）．統計検定においても，Harrington-Fleming法[30]のような薬剤の特性に応じたハザード比の変化に対応した検定が必要である．また，腫瘍縮小効果はRECIST（Response Evaluation Criteria in Solid Tumours）での評価が一般的であるが，病勢進行（PD）の場合，遅延性の効果については評価ができない．そこでPD基準を修飾したirRC（immune-related response criteria）が提唱された[31,32]．irRCが生存期間延長効果と相関するかについては，今後のさらなる臨床研究が必要である．

複数のペプチドワクチンによる治療

StageⅢ大腸癌では，RNF43とTOMM34由来のHLA-A24拘束性ペプチドと経口抗癌剤であるUFT/LVを投与したところ，RNF43とTOMM34の双方に対するCTL反応陽性群の生存期間中央値が36.1か月であるのに対し，CTL反応陰性群の生存期間中央値は9.5か月と短かった（$p=0.0079$）[30]．標準治療不応進行食道癌ではTTK，LY6K，IMP3由来のHLA-A24拘束性ペプチドを投与したところ，3つの抗原に対するCTL陰性群に比較して，陽性抗原数が増えるにつれ生存期間が延長し，TTK，LY6K，IMP3の3抗原すべてに反応を示した群のみに1年以上の長期生存例がみられた[33]．今後は，複数のペプチドワクチン投与の方向にある．

おわりに

有効なペプチドワクチンの同定だけでなく，免疫モニタリングとしてELISPOT assayなどが広く行われているが，今後もquality assessmentやquality controlが必要である．また，T細胞反応，Treg・myeloid-derived suppressor細胞・NK細胞・樹状細胞の解析，腫瘍関連抗原に対する抗体などが検討されているが[34,35]，免疫療法において有効性を示唆するバイオマーカーのさらなる開発が必要である．

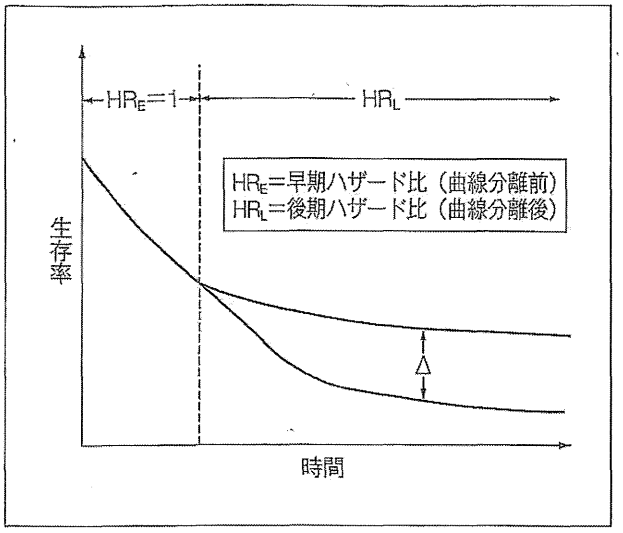


図1　癌ワクチン療法における生存曲線分離の効果遅延
癌ワクチン療法では，生存曲線がある一定の期間をおいてから分離するseparation of curveの現象がみられる．

ペプチド投与において，より有効に強力なCTLが誘導できるワクチンアジュバントの開発も必要である．例えば，CpG-ODNはTLR-9 agonistであるが，CpGは樹状細胞の活性化を介して大量のⅠ型インターフェロン産生を誘導し，自然免疫とともに獲得免疫を活性化することでペプチドワクチンの効果増強が得られる可能性が報告された[32]．さらに，LY6KおよびTTK由来のペプチドワクチン療法にCpG-Bを併用する第Ⅰ相臨床試験において，CpG-ODNは癌ワクチンにおけるアジュバントとして有用であった[36]．癌ワクチン療法を推進するためには，多くの解決しなければならないことがあり，いかにトランスレーショナルリサーチへと発展できるかがカギとなるものと考える．

2010年に免疫療法治療薬としてはsipuleucel-T（Provenge®）が，世界初の前立腺癌に有効な癌ワクチン療法としてFDAに認可されたが[37]，膵癌に対するペプチドワクチンの分野では承認されたものはいまだないのが現状であり，ペプチドワクチン療法剤が開発されるよう治験などの臨床試験の推進が必要である．

文献

1) 日本膵臓学会：膵癌登録報告2007．膵臓22：e1-e429, 2007
2) Burris HA 3rd, Moore MJ, Andersen J, et al：Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer：a randomized trial. J Clin Oncol 15：2403-2413, 1997
3) Moore MJ, Goldstein D, Hamm J, et al：Erlotinib plus gem-

citabine compared with gemcitabine alone in patients with advanced pancreatic cancer : a phase Ⅲ trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 25 : 1960–1966, 2007
4) Vaccaro V, Sperduti I, Milella M : Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 365 : 768–769, 2011
5) Rosenberg SA, Lotze MT, Yang JC, et al : Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. J Natl Cancer Inst 85 : 622–632, 1993
6) Tani M, Tanimura H, Yamaue H, et al : In vitro generation of activated natural killer cells and cytotoxic macrophages with lentinan. Eur J Clin Pharmacol 42 : 623–627, 1992
7) Yamaue H, Tanimura H, Iwahashi M, et al : Role of interleukin-2 and interferon-gamma in induction of activated natural killer cells from mice primed in vivo and subsequently challenged in vitro with the streptococcal preparation OK432. Cancer Immunol Immunother 29 : 79–86, 1989
8) Tani M, Tanimura H, Yamaue H, et al : Generation of $CD4^+$ cytotoxic T lymphocytes stimulated by immobilized anti-CD3 monoclonal antibody and interleukin-2 in cancer patients. Int J Cancer 60 : 802–807, 1995
9) Rosenberg SA, Spiess P, Lafreniere R : A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science 233 : 1318–1321, 1986
10) Van Der Bruggen P, Traversari C, Chomez P, et al : A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 254 : 1643–1647, 1991
11) Galon J, Costes A, Sanchez-Cabo F, et al : Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313 : 1960–1964, 2006
12) Von Hoff DD, Ervin TJ, Arena FP : Randomized phase Ⅲ study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT). J Clin Oncol 31 (suppl) : abstr LBA148, 2013
13) Khong HT, Restifo NP : Natural selection of tumor variants in the generation of "tumor escape" phenotypes. Nat Immunol 3 : 999–1005, 2002
14) Ryschich E, Notzel T, Hinz U, et al : Control of T-cell-mediated immune response by HLA class I in human pancreatic carcinoma. Clin Cancer Res 11 : 498–504, 2005
15) Marincola FM, Jaffee EM, Hicklin DJ, et al : Escape of human solid tumors from T-cell recognition : molecular mechanisms and functional significance. Adv Immunol 74 : 181–273, 2000
16) Garrido F, Algarra I, Garcia-Lora AM : The escape of cancer from T lymphocytes : immunoselection of MHC class I loss variants harboring structural-irreversible "hard" lesions. Cancer Immunol Immunother 59 : 1601–1606, 2010
17) Ishigami S, Natsugoe S, Nakajo A, et al : HLA-class I expression in gastric cancer. J Surg Oncol 97 : 605–608, 2008
18) Tsukahara T, Kawaguchi S, Torigoe T, et al : Prognostic significance of HLA class I expression in osteosarcoma defined by anti-pan HLA class I monoclonal antibody, EMR8–5. Cancer Sci 97 : 1374–1380, 2006
19) Kitamura H, Torigoe T, Asanuma H, et al : Down-regulation of HLA class I antigens in prostate cancer tissues and up-regulation by histone deacetylase inhibition. J Urol 178 : 692–696, 2007
20) Teicher BA : Transforming growth factor-beta and the immune response to malignant disease. Clin Cancer Res 13 : 6247–6251, 2007
21) Ichihara F, Kono K, Takahashi A, et al : Increased populations of regulatory T cells in peripheral blood and tumor-infiltrating lymphocytes in patients with gastric and esophageal cancers. Clin Cancer Res 9 : 4404–4408, 2003
22) Folkman J : Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1 : 27–31, 1995
23) Li Y, Wang MN, Li H, et al : Active immunization against the vascular endothelial growth factor receptor flk1 inhibits tumor angiogenesis and metastasis. J Exp Med 195 : 1575–1584, 2002
24) Wada S, Tsunoda T, Baba T, et al : Rationale for antiangiogenic cancer therapy with vaccination using epitope peptides derived from human vascular endothelial growth factor receptor 2. Cancer Res 65 : 4939–4946, 2005
25) Ishizaki H, Tsunoda T, Wada S, et al : Inhibition of tumor growth with antiangiogenic cancer vaccine using epitope peptides derived from human vascular endothelial growth factor receptor 1. Clin Cancer Res 12 : 5841–5849, 2006
26) Itakura J, Ishiwata T, Friess H, et al : Enhanced expression of vascular endothelial growth factor in human pancreatic cancer correlates with local disease progression. Clin Cancer Res 3 : 1309–1316, 1997
27) Seo Y, Baba H, Fukuda T, et al : High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. Cancer 88 : 2239–2245, 2000
28) Miyazawa M, Ohsawa R, Tsunoda T, et al : Phase I clinical trial using peptide vaccine for human vascular endothelial growth factor receptor 2 in combination with gemcitabine for patients with advanced pancreatic cancer. Cancer Sci 101 : 433–439, 2010
29) Yamaue H, Tani M, Miyazawa M, et al : Phase Ⅱ/Ⅲ clinical trial with VEGFR2-epitope peptide and gemcitabine for patients with locally advanced, metastatic, or unresectable pancreatic cancer : Pegasus-PC Study. J Clin Oncol 30 (suppl 34) : abstr 223, 2013
30) Zucker DM, Yang S : Inference for a family of survival models encompassing the proportional hazards and proportional odds models. Stat Med 25 : 995–1014, 2006
31) O'day SJ, Maio M, Chiarion-Sileni V, et al : Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma : a multicenter single-arm phase Ⅱ study. Ann Oncol 21 : 1712–1717, 2010
32) Wolchok JD, Hoos A, O'day S, et al : Guidelines for the evaluation of immune therapy activity in solid tumors : immune-related response criteria. Clin Cancer Res 15 : 7412–7420, 2009
33) Kono K, Iinuma H, Akutsu Y, et al : Multicenter, Phase Ⅱ clinical trial of cancer vaccination for advanced esophageal cancer with three peptides derived from novel cancer-testis antigens. J Transl Med 10 : 141, 2012
34) Butterfield LH, Palucka AK, Britten CM, et al : Recommendations from the iSBTc-SITC/FDA/NCI Workshop on Immunotherapy Biomarkers. Clin Cancer Res 17 : 3064–3076, 2011
35) Disis ML : Immunologic biomarkers as correlates of clinical response to cancer immunotherapy. Cancer Immunol Immu-

nother 60：433–442, 2011
36) Iwahashi M, Katsuda M, Nakamori M, et al：Vaccination with peptides derived from cancer-testis antigens in combination with CpG-7909 elicits strong specific CD8$^+$T cell response in patients with metastatic esophageal squamous cell carcinoma. Cancer Sci 101：2510–2517, 2010
37) Kantoff PW, Higano CS, Shore ND, et al：Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363：411–422, 2010

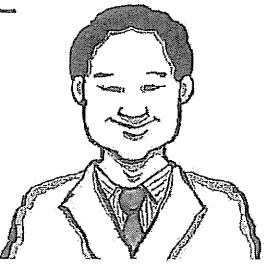
TANI Masaji, et al
和歌山県立医科大学第２外科
〒641-8510 和歌山県和歌山市紀三井寺 811-1

1200字通信

第61回

試験

板野　聡



また冬が来て，受験のシーズンとなりました．わが家では，すでに子供たちの大学受験は済んでおり，気楽といえば気楽なのですが，親として，はたまた己自身のトラウマなのか，この季節は落ち着かない気分になります．東京の友人からは，「もうすぐ，会社のある街全体が入試モードに入ります」との便りがありましたが，張りつめた空気が漂う，この季節独特の雰囲気なのだろうと想像しています．

ところで，センター試験なる制度が導入されてから久しいのですが，毎年雪によるトラブルもあり，１年で最も寒いこの時期にこうした全国規模の試験を行うことへの懸念は議論されなかったのでしょうか．それとも，学力だけでなく，寒さに耐えうる体力までが試されているのでしょうか．新しい内閣になってから見直しの話も出始めていますが，こうした観点からも検討の余地がありそうです．

さて，わが家での受験は済んだとは申しましたが，その後も大学の卒業試験や資格試験，就活といった問題があり，親としては気が休まる暇もないのが現実です．いっそ，わが身であるほうが気は楽ということで，子を持って知る親の恩の一つなのかもしれません．

「試験」といえば，私が子供の頃の父親の言葉が忘れられずにいます．それは，中学校の定期試験で，試験勉強の辛さから「大人は試験がなくていいなぁ」と言ったことへの返答でありました．「大人は毎日が試験だ」というただの一言でしたが，当時内科医として開業していた親父の言葉であり，今になって「父上殿，まったく仰せの通りでございました」と頭が下がる想いではあります．

確かに，学生の頃の試験は一定の期日があり，合格点をとることで一段落するのでしょうが，実は，それは次のステップへの始まりにすぎず，また次の試験が待っているということになります．そして，社会人になれば，毎日の一つ一つの仕事そのものが，己の能力を試されていると同時に，その責任を問われ続けていることになりますが，一方で「試験」と意識しないほどに慣らされていくものなのかもしれません．実際，われわれ外科では，手術や内視鏡処置では即座に結果が出，その場で合否を突きつけられているということになります．もちろん，内科的な診療でも，自分の経験と知識を総動員した処方の合否は，次の診察日に当の患者さんから示され，診断が正しいかどうかは時間とともに判定が下されるということでしょう．先の友人とのやり取りから，人生そのものも「試験」なのかもしれないとの想いに行き着きますが，そこまで突き詰めると興ざめと言われそうではあります．

ところで，毎月，ちょっとした出来事からこうしてエッセイを書き起こしていますが，編集室から「採用し制作に入ります」とのご返事をいただくたびに，プチ「試験」に合格したような嬉しい気分を味わうことになっています．

寺田病院外科
〒518-0441 三重県名張市夏見 3260-1

Predictors of Malignancy in Intraductal Papillary Mucinous Neoplasm of the Pancreas

Analysis of 310 Pancreatic Resection Patients at Multiple High-Volume Centers

Yasuhiro Shimizu, MD, Hiroki Yamaue, MD,† Hiroyuki Maguchi, MD,‡ Kenji Yamao, MD,§ Seiko Hirono, MD,† Manabu Osanai, MD,‡ Susumu Hijioka, MD,§ Waki Hosoda, MD,|| Yasushi Nakamura, MD,¶ Toshiya Shinohara, MD,# and Akio Yanagisawa, MD***

Objectives: The present study was a retrospective investigation of predictors of malignancy in intraductal papillary mucinous neoplasm (IPMN) of the pancreas.

Methods: The subjects were 310 patients who underwent pancreatic resection at 3 high-volume centers. Preoperative laboratory and imaging findings were analyzed in logistic regression analyses. Endoscopic ultrasonography measurements were essential for the size of mural nodules, and a central review was conducted for pathological diagnosis.

Results: Pathological diagnosis was benign IPMN in 150 cases and malignant in 160 (noninvasive carcinoma, n = 100; invasive, n = 60). In multivariate analysis, size of mural nodules, diameter of main pancreatic duct, and cyst size of branch pancreatic duct were independent predictors of malignancy, and areas under the receiver operating characteristic curve for these 3 factors were 0.798, 0.643, and 0.601, respectively. With 7 mm taken as the cutoff value for the size of mural nodules, the diagnosis of malignant IPMN had sensitivity of 74.3% and specificity of 72.7%. Carcinoma without nodules was present in 15 patients (15/160 [9.4%]).

Conclusions: The size of mural nodules measured with endoscopic ultrasonography showed high predictive ability. However, about 10% of carcinoma patients did not have nodules, and the handling of the diagnosis in such cases is a problem for the future.

Key Words: predictor of malignant IPMN, mural nodule, diameter of MPD, cyst size of BPD, EUS, multicenter analysis

(*Pancreas* 2013;42: 883–888)

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are mucin-producing neoplasms of the pancreas that cause cystic dilation of the pancreatic duct. They were first reported by Ohashi et al[1] in 1982. These tumors are characterized by papillary proliferation by mucin-producing, atypical epithelia within the pancreatic ducts and cystic dilation of pancreatic ducts from mucus.[2] This tumor was defined as intraductal papillary mucinous tumor by the World Health Organization (WHO) in 1996 and renamed IPMN in 2000.[3] Since that time, the number of patients diagnosed with IPMN has been increasing as the disease concept spread and advances were made in diagnostic imaging.

In 2006, international consensus guidelines that set the clinical treatment approach to IPMN were published.[4] In the 2006 guidelines, resection is recommended for main pancreatic duct (MPD)–IPMN, whereas in branch pancreatic duct (BPD)–IPMN, surgery is indicated in cases with mural nodules, BPD 30 mm or greater, and MPD dilation. However, controversy exists regarding the need for surgical resection in BPD-IPMN because of the relatively lower risk of malignant IPMN.[4–8] With the 2006 guideline indications,[4] it is reported that resection is performed in many cases of adenoma.[9] In the new International Consensus Guidelines revised in 2012,[10] BPD-IPMN size of ≥30 mm is a weaker indicator of malignancy than the presence of mural nodules and positive cytology, and BPD-IPMN ≥30 mm without these signs can be observed without immediate resection.

In this study, we standardized preoperative examination modalities and used common definitions for the type of lesion in a large number of patients who underwent pancreatic resection at multiple institutions. We also conducted a central review of pathological findings and investigated predictors of malignancy using objective data. To our knowledge, this is the first detailed report of an investigation of a large number of cases in multiple institutions.

MATERIALS AND METHODS

Study Population

The study population was 372 patients with IPMN who underwent pancreatic resection at Wakayama Medical University (WMU), Aichi Cancer Center Hospital (ACC), or Teine-Keijinkai Hospital (TKH) between 1996 and March 2011. Fifty-nine cases in which endoscopic ultrasonography (EUS) was not performed preoperatively and 3 cases with missing tumor marker data were excluded. A retrospective investigation of preoperative examination findings and pathological findings was done with 310 patients as subjects. Indications for surgery were not consistent in the 3 hospitals.

Patient background factors investigated were age at time of operation, sex, presence or absence of symptoms, complication with cancer of other organs, preoperative laboratory values (serum amylase, carcinoembryonic antigen [CEA], and carbohydrate antigen 19-9 [CA-19-9 level]), imaging findings (tumor location, size of mural nodules, diameter of MPD, cyst size of BPD, type of lesion), operative procedure, and pathological findings.

In preoperative examination, EUS and computed tomography (CT) were considered to be essential. As for size of mural

From the *Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya; †The Second Department of Surgery, Wakayama Medical University, School of Medicine, Wakayama; ‡Center for Gastroenterology, Teine-Keijinkai Hospital, Sapporo; Departments of §Gastroenterology and ||Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya; ¶Department of Clinical Laboratory Medicine, Wakayama Medical University, School of Medicine, Wakayama; #Department of Pathology, Teine-Keijinkai Hospital, Sapporo; and **Department of Pathology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

Received for publication August 15, 2012; accepted October 22, 2012.

Reprints: Yasuhiro Shimizu, MD, Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Kanokoden 1-1, Chikusa-ku, Nagoya 464-8681, Japan (e-mail: yshimizu@aichi-cc.jp).

The authors declare no conflict of interest.

nodules, height of nodules from EUS observation was used in all 310 cases. For diameter of MPD and cyst size of BPD, the CT measurement values were used in all cases.

In this study, type of lesion was classified as MPD-IPMN, mix-IPMN, and BPD-IPMN. With MPD-IPMN, the lesions exist in the MPD, and there is no cystic formation of 10 mm or greater of the surrounding branches. Cases with cystic dilation of BPD are taken to be mix-IPMN or BPD-IPMN. Mix-IPMN is defined as when the diameter of MPD is 10 mm or greater, and BPD-IPMN as when the diameter of MPD is less than 10 mm. The 310 subjects were classified as MPD-IPMN, mix-IPMN, or BPD-IPMN subsets, and predictors of malignancy were investigated for each group.

According to the WHO (2000) histological classification of IPMN,[3] pathological diagnosis is classified as intraductal papillary mucinous adenoma (IPMA), borderline IPMN (IPMB), and noninvasive and invasive intraductal papillary mucinous carcinoma (IPMC). Invasive IPMC is defined when a histological transition is evidently present between IPMN and pancreatic ductal adenocarcinoma.[11] Pathological diagnosis was performed by pathologists at 3 hospitals (WMU, ACC, TKH), and the central review was done by A.Y. of Kyoto Prefectural University of Medicine in the cases of IPMB and noninvasive and invasive IPMC. In this study, patients' lesions were categorized as benign (IPMA and IPMB) or malignant (noninvasive and invasive IPMC) on the basis of the pathological diagnosis.

The investigation of predictors of malignancy was done for 10 factors: age at time of surgery, sex, presence or absence of symptoms, serum amylase, CA-19-9, CEA, tumor location, size of mural nodules, diameter of MPD, and cyst size of BPD. The surgical indications from diagnostic images in the 2006 international consensus guidelines[4] are supposed to be (1) diameter of MPD

TABLE 1. Characteristics of IPMN Patients Who Underwent Pancreatic Resection (n = 310)

	WMU	ACC	TKH	Total
No. patients	120	115	75	310
Background				
Age at pancreatectomy, mean (SD),[a] y	69.2 (9.1)	65.7 (7.8)	65.7 (8.9)	67.1 (8.7)
Sex, n (%)				
Male	66 (55.0)	72 (62.6)	43 (57.3)	181 (58.3)
Female	54 (45.0)	43 (37.4)	32 (42.7)	129 (41.7)
Symptom +, n (%)	52 (43.3)	29 (25.2)	17 (22.7)	98 (31.6)
Other organ cancer, n (%)	31 (25.8)	31 (27.0)	13 (17.3)	75 (24.2)
Laboratory data				
Amylase level, mean (SD), IU/L	103.0 (106.4)	117.2 (89.6)	143.3 (154.3)	118.0 (115.2)
CEA level, mean (SD), ng/mL	2.6 (2.8)	4.4 (9.0)	2.6 (2.4)	3.3 (5.9)
CA-19-9 level, mean (SD), U/mL	55.8 (190.2)	69.4 (245.6)	32.1 (50.9)	55.1 (192.4)
Image findings				
Tumor location (%)				
Head	74 (61.7)	76 (66.1)	44 (58.7)	194 (62.6)
Body	37 (30.8)	23 (20.0)	24 (32.0)	84 (27.1)
Tail	9 (7.5)	16 (13.9)	7 (9.3)	32 (10.3)
Size of mural nodules, mean (SD), mm	8.8 (8.0)	9.3 (10.5)	8.7 (7.3)	8.9 (8.9)
Diameter of MPD, mean (SD), mm	8.9 (7.8)	7.6 (8.0)	7.9 (6.8)	8.2 (7.6)
Cyst size of BPD, mean (SD), mm	22.7 (16.0)	23.5 (15.7)	30.2 (17.3)	24.8 (16.5)
Type of lesion, n (%)				
MPD	27 (22.5)	18 (15.6)	6 (8.0)	51 (16.4)
Mix	23 (19.2)	20 (17.4)	14 (18.7)	57 (18.4)
BPD	70 (58.3)	77 (67.0)	55 (73.3)	202 (65.2)
Operative procedure				
PD, PpPD/DP, MP, PR/TP, n (%)	79/32/9 (65.8/26.7/7.5)	73/36/6 (63.5/31.3/5.2)	40/33/2 (53.3/44.0/2.7)	192/101/17 (61.9/32.6/5.5)
Pathology				
Benign IPMN, n (%)	58 (48.3%)	59 (51.3%)	33 (44.0%)	150 (48.4%)
Malignant IPMN, n (%)	62 (51.7%)	56 (48.7%)	42 (56.0%)	160 (51.6%)
Noninvasive/invasive, n	37/25	29/27	34/8	100/60

PD indicates pancreatoduodenectomy; PpPD, pylorus-preserving pancreatoduodenectomy; DP, distal pancreatectomy; MP, middle pancreatectomy; PR, partial resection of the pancreas; TP, total pancreatectomy.

10 mm or greater, (2) cyst size of BPD 30 mm or greater, or (3) presence of nodules. The predictive accuracy for malignant IPMN of the surgical indications in the 2006 guidelines[4] was investigated.

Statistical Analysis

The significance of each prognostic factor was assessed by univariate logistic regression analyses. Multivariate logistic regression analysis was used to determine which factors were independent predictors of malignant IPMN in the data set. A receiver operating characteristic (ROC) curve[12] was used to measure the predictive accuracy of each independent predictor of malignant IPMN.

The area under the ROC curve (AUC) expresses how well the factor is able to discriminate between patients with malignant IPMN and those with benign IPMN. Higher values indicate better discrimination: a value of 0.5 indicates no predictive discrimination, whereas 1.0 indicates perfect separation of patients.[13]

We selected the cutoff value for the predicted probability of malignant IPMN. The cutoff value was selected to provide a high sensitivity while at the same time reducing the number of resections of benign IPMN. JMP 7.0.1 statistical software (SAS Institute, Incorporation, Cary, NC) was used in the analysis. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Characteristics of Patients

The mean age of the patients was 67.1 (SD, 8.7) years, and they included 181 men (58.3%) and 129 women (41.7%). Symptoms were present in 98 patients (31.6%), whereas 212 (68.4%) had no symptoms. The symptoms were abdominal pain in 81 patients, jaundice in 9, and weight loss in 8 patients. Complications with other organ cancer were present in 75 patients (24.2%), including stomach cancer in 30, colon cancer in 14, bile duct cancer in 8, pancreatic cancer in 7, prostate cancer in 5, uterine cancer in 5, liver cancer in 3, and breast cancer in 3 patients. Preoperative laboratory findings were amylase 118.0 (SD, 115.2) IU/L, serum CEA 3.3 (SD, 5.9) ng/mL, and serum CA-19-9 of 55.1 (SD, 192.4) U/mL. Tumor location based on imaging findings was the pancreas head in 194 patients (62.6%), body in 84 patients (27.1%), and tail in 32 patients (10.3%). The mean size of mural nodules was 7.0 (SD, 8.9) mm, the mean diameter of MPD was 6.2 (SD, 7.6) mm, and the mean cyst size of BPD was 25.0 (SD, 16.5) mm (Table 1).

The type of lesion was MPD-IPMN in 51 patients (16.4%), mix-IPMN in 57 patients (18.4%), and BPD-IPMN in 202 patients (65.2%). The operative procedure was pancreatoduodenectomy/pylorus-preserving pancreatoduodenectomy in 192 patients (61.9%), distal pancreatectomy in 73 (23.6%), middle pancreatectomy in 24 (7.7%), total pancreatectomy in 17 (5.5%), and partial resection of the pancreas in 4 patients (1.3%). Pathological diagnosis was benign IPMN in 150 patients (48.4%) and malignant IPMN in 160 patients (51.6%). Among the 160 patients with malignant IPMN, 100 (62.5%) had noninvasive carcinoma, and 60 (37.5%) had invasive carcinoma.

Univariate Analyses

The 10 factors of age at the time of pancreatic resection, sex, presence or absence of symptoms, serum amylase, serum CEA, serum CA-19-9, tumor location, size of mural nodules, diameter of MPD, and cyst size of BPD were tested as predictors of malignancy. The size of mural nodules ($P < 0.0001$), diameter of MPD ($P = 0.0004$), and cyst size of BPD ($P = 0.0044$) were strongly associated with malignant IPMN. Other important prognostic factors were age ($P = 0.0066$) and CA-19-9 ($P = 0.0080$) (Table 2).

TABLE 2. Logistic Regression Univariate Analysis of Factors Associated With Malignant IPMN in Patients Who Underwent Pancreatic Resection

Variables	Relative Risk	95% Confidence Interval		P
Age	1.04	1.01	1.07	0.0066*
Sex				
Male	1			
Female	1.49	0.94	2.34	0.0877
Symptom				
+	1.09	0.67	1.76	0.729
−	1			
Amylase level	1.001	0.996	1.004	0.1253
CEA level	1.08	1.01	1.19	0.0764
CA-19-9 level	1.006	1.003	1.012	0.0080*
Tumor location				
Head	1			0.6443
Body	0.79	0.47	1.31	
Tail	0.87	0.41	1.83	
Size of mural nodules	1.19	1.14	1.24	<0.0001*
Diameter of MPD	1.09	1.04	1.14	0.0004*
Cyst size of BPD	1.02	1.007	1.036	0.0044*

*Statistically significant.

Multivariate Analyses

Multivariable analyses of factors identified as significant by univariate analysis revealed that the size of mural nodules ($P < 0.0001$), diameter of MPD ($P = 0.0347$), and cyst size of BPD ($P = 0.0277$) were statistically significant (Table 3).

ROC Analysis

Receiver operating characteristic analysis was conducted for the cancer diagnosis prediction ability of 3 factors that were significant in multivariate analysis, from which size of mural nodules was found to have very high diagnostic prediction ability with AUC = 0.798. Area under the ROC curve of other factors was 0.643 for diameter of MPD and 0.601 for cyst size of BPD. Area under the ROC curve of surgical indications on diagnostic imaging in the 2006 international consensus guidelines[4] was 0.578 (Table 4).

Size of Mural Nodules and Diagnostic Ability

Mural nodules were detected in 240 (77.4%) of the 310 IPMN patients. Investigation of the cancer diagnostic ability of the size of mural nodules with a cutoff value of 7 mm in the 310 patients revealed that the size of mural nodules was 7 mm or greater in 119 of the 160 malignant IPMN patients (sensitivity, 74.3%) and that the size of mural nodules was less than 7 mm in 109 of the 150 benign IPMN patients (specificity, 72.7%). There were 15 patients (9.4%) who had cancer with no nodules. The mean age of these patients was 69.5 (SD, 6.9) years, and they included 6 men (40.0%) and 9 women (60.0%). The type of lesion in these 15 patients was MPD-IPMN in 3 patients, mix-IPMN in 1 patient, and BPD-IPMN in 11 patients. Pathological findings were noninvasive carcinoma in 14 patients and invasive carcinoma in 1 patient. The mean cyst size in the 11 BPD-IPMN patients was 32.2 (SD, 15.4) mm. The cyst size was less than 30 mm in 6 of these 11 patients (Fig. 1, Table 5).

TABLE 3. Results of Multivariate Analysis Evaluating Risk of Malignant IPMN

Variables	Relative Risk	95% Confidence Interval		*P*
Age	1.028	0.997	1.061	0.0844
CA-19-9 level	1.005	1.001	1.012	0.0819
Size of mural nodules	1.156	1.106	1.214	<0.0001*
Diameter of MPD	1.060	1.001	1.122	0.0347*
Cyst size of BPD	1.020	1.002	1.039	0.0277*

*Statistically significant.

Type of Lesion and Predictors of Malignancy

Carcinoma patients were 27 (52.9%) of 51 patients with MPD-IPMN, 38 (66.7%) of 57 patients with mix-IPMN, and 95 (47.0%) of 202 of patients with BPD-IPMN. The number of carcinoma patients was greater with mix-IPMN than with BPD-IPMN ($P = 0.0082$), but no significant differences were seen between MPD-IPMN and mix-IPMN ($P = 0.1454$) or between MPD-IPMN and BPD-IPMN ($P = 0.4504$) (Table 6).

Univariate and multivariate analyses were done with the 10 factors as predictors of malignancy in the MPD-IPMN, mix-IPMN, and BPD-IPMN. It was found that, with MPD-IPMN and mix-IPMN, only the size of mural nodules was a significant factor in univariate analysis (MPD-IPMN $P = 0.0059$, mix-IPMN $P = 0.0013$). With BPD-IPMN, sex ($P = 0.0311$), CA-19-9 ($P = 0.0125$), size of mural nodules ($P < 0.0001$), diameter of MPD ($P = 0.0002$), and cyst size of BPD ($P = 0.006$) were significant factors in univariate analysis, and size of mural nodules ($P < 0.0001$), diameter of MPD ($P = 0.0031$), and sex ($P = 0.0060$) were independent predictors (Table 7). By type of lesion, AUCs related to the carcinoma prediction of size of mural nodules were 0.77, 0.82, and 0.79 in MPD-IPMN, mix-IPMN, and BPD-IPMN, respectively (data not shown).

DISCUSSION

Predictors of malignancy were investigated with objective data in the 310 patients who were the subjects of this study, using standardized preoperative examination modalities, shared definitions of type of lesion, and standardized pathological diagnostic criteria. Many reports have attempted to identify prognostic factors that might influence the management of IPMN patients,[14–16] but this is the first detailed report from an investigation in multiple high-volume centers and with many pancreatic resection patients.

The examination modalities of CT[17] and magnetic resonance cholangiopancreatography[18] have low invasiveness and are most suitable for depicting an overall image of the lesion. Endoscopic ultrasonography,[19,20] endoscopic retrograde cholangiopancreatography,[20] intraductal ultrasonography,[21] and peroral cholangioscopy[22] are invasive, but it is reported that detailed findings can be obtained. Endoscopic ultrasonography in particular is good for depicting papillary protrusions and is useful in measuring nodule size, especially height, and diagnosing lateral spread.[19] It is reported to be a useful diagnostic method in differentiating between benign and malignant tumors with detailed investigations.[20,23] In the present study, EUS measurements were used in all cases for the size of mural nodules within pancreatic ducts, and CT measurements were used for measurements of MPD diameter and cyst size of BPD. Thus, measurements from standardized modalities could be used for these 3 factors.

TABLE 4. Comparison of Predictors by ROC Analysis

Model	AUC
Size of mural nodules	0.798
Diameter of MPD	0.643
Cyst size of BPD	0.601
Surgical indication in the guidelines	0.578

"Guidelines" indicates the international consensus guidelines 2006.[4]

TABLE 5. Diagnostic Ability of Size of Mural Nodules Measured by EUS, n = 310 (Cutoff Value: Nodule Size 7 mm)

Size of Mural Nodules	Pathological Diagnosis	
	Malignant (n = 160)	Benign (n = 150)
<7 mm (n = 150)	41	109
≥7 mm (n = 160)	119	41

The newer WHO classification[24] uses the terms low-grade, intermediate-grade, and high-grade dysplasia in place of adenoma, borderline, and noninvasive carcinoma. However, in this study, the subjects were 310 patients who underwent pancreatic resection at 3 hospitals between 1996 and 2011. Pathologists at these 3 hospitals (WMU, ACC, TKH) diagnosed the lesions as IPMA (mild, moderate, severe) or IPMC (noninvasive, invasive), according to the Classification of Pancreatic Carcinoma Japan Pancreatic Society.[25,26] We used the WHO (2000) histological classification of IPMN,[3] in which pathological diagnosis is classified as IPMA, IPMB, or noninvasive and invasive IPMC.

In this study, the dysplastic changes of adenoma are graded as mild, moderate, or severe, and IPMB is classified as adenoma with severe dysplasia among benign IPMNs.[25,26] When investigating risk factors for malignancy in patients in multiple centers, such standardization of pathological diagnostic criteria and a central review are important.

In the present investigation of 10 objective factors, size of mural nodules measured with EUS and diameter of MPD and cyst size of BPD obtained from CT measurements were significant independent predictors of malignancy (Tables 2 and 3). The size of mural nodules is demonstrated to be a very strong predictor of malignancy, and carcinoma prediction with size of mural nodules only showed high diagnostic ability, with AUC = 0.798. This diagnostic predictive ability for malignancy is better than the AUC = 0.578 obtained with the surgical indications of (1) diameter of MPD of 10 mm or greater, (2) cyst size of BPD of 30 mm or greater, or (3) presence of nodules on diagnostic imaging in the 2006 international consensus guidelines.[4] It has also been reported that whereas the sensitivity of the 2006 guidelines[4] for predicting malignancy of IPMN is high, the specificity is low.[27,28] Therefore, in the revised 2012 guidelines,[10] cyst size of BPD ≥30 mm is a weaker indicator of malignancy than the presence of mural nodules and positive cytology. Branch pancreatic duct IPMN cyst size of 30 mm or greater and MPD dilation of 5 to 9 mm are classified as a "worrisome feature," and EUS observation is recommended to decide a treatment strategy.

With regard to the diagnostic ability of the size of mural nodules from EUS observations, the sensitivity and specificity for differentiating between benign and malignant IPMN are reported to be good with a cutoff value of 5 mm in BPD-type IPMN.[23] In

TABLE 6. Type of Lesion and Pathological Diagnosis

Pathology	MPD-IPMN (n = 51)	Mix-IPMN (n = 57)	BPD-IPMN (n = 202)	Total (n = 310)	*P*
Malignant	27 (52.9%)	38 (66.7%)	95 (47.0%)	160 (51.6%)	0.1454*
Benign	24 (47.1%)	19 (33.3%)	107 (53.0%)	150 (48.4%)	0.0082†
					0.4504‡

*MPD versus mix.
†Mix versus BPD.
‡MPD versus BPD.

the present study, good results for diagnostic ability, showing sensitivity of 74.3% and specificity of 72.7%, were obtained when the cutoff value for the size of mural nodules observed with EUS was 7 mm. Size of mural nodules by EUS measurements with a cutoff value of 7 mm is thought to be useful as a surgical indication criterion for IPMN.

There are also reports that pancreatic juice cytology is useful in diagnosing malignancy,[9,29,30] but currently there are no standardized diagnostic criteria for all institutions. There are also reports of differences in sensitivity of pancreatic juice cytology depending on the collection method[31,32] and that cytological diagnosis of pancreatic juice is indeed difficult even for experienced pathologists and cytologists.[33] When investigating patients at multiple institutions, it is difficult to standardize diagnostic criteria for cytology, so it was not used in the analysis in the present study.

In the classification of MPD-IPMN, there is no strict definition regarding the size of the lesion existing in the MPD, and even with a classification of BPD-IPMN, there are cases in which the lesion also spreads to the MPD. In fact, there are cases that are difficult to clearly classify as MPD-IPMN or BPD-IPMN. Classification of IPMN into MPD-IPMN, mix-IPMN, and BPD-IPMN is reported to be useful,[4] but there is currently no international consensus. In this study, cases in which the lesion was in the MPD only were taken to be MPD-IPMN, and other cases were classified as mix-IPMN or BPD-IPMN with an MPD diameter of 1 cm as the reference.

TABLE 7. Multivariate Analysis of All Univariate Predictive Parameters for Type of Lesion

Variable	Relative Risk	95% Confidence Interval		*P*
MPD-IPMN (n = 51)				
Size of mural nodules	1.136	1.048	1.258	0.0059*
Mix-IPMN (n = 57)				
Size of mural nodules	1.243	1.108	1.450	0.0013*
BPD-IPMN (n = 202)				
Sex				
Male	1			
Female	2.732	1.352	5.709	0.0060*
CA-19-9 level	1.005	1.000	1.013	0.1444
Size of mural nodules	1.174	1.107	1.257	<0.0001*
Diameter of MPD	1.271	1.087	1.496	0.0031*
Cyst size of BPD	1.024	0.996	1.055	0.0992

*Statistically significant.

There were significantly more cases of carcinoma in mix-IPMN than in BPD-IPMN, whereas no significant difference was seen between MPD-IPMN and BPD-IPMN (Table 6). This is thought to be influenced by the fact that patients who had pancreatic resection at multiple centers were investigated retrospectively, and the surgical indications were not consistent at each of the institutions.

Looking at predictors of malignancy by type of lesion, the only significant factor in MPD-IPMN and mix-IPMN was size of mural nodules (Table 7). In BPD-IPMN, size of mural nodules, diameter of MPD, and sex were significant independent factors, but cyst size of BPD was not a significant predictor of malignancy (Table 7). Several recent studies reported that the size of mural nodules was a more significant factor than the cyst size in BPD for predicting the malignancy of BPD-IPMN.[9,23,30] The size of mural nodules from EUS measurements also showed high diagnostic predictive ability for malignancy in an investigation with groups by type of lesion with MPD-IPMN, mix-IPMN, and BPD-IPMN, having AUCs of 0.77, 0.82, and 0.79, respectively.

In the present investigation using objective data, the size of mural nodules observed by EUS was shown to be a significant predictor of malignancy, but there were 15 (9.4%) of 160 patients who had carcinoma with no nodules (Fig. 1). Eleven of these 15 patients had BPD-IPMN, and the pathological finding was noninvasive carcinoma in 14 of the 15 patients. It is also reported that among cases of BPD-IPMN with no nodules, 6 (8.2%) of 73 patients who underwent pancreatic resection had carcinoma and that 5 of these 6 had noninvasive carcinoma.[29] Nearly all of these cases were noninvasive carcinoma,

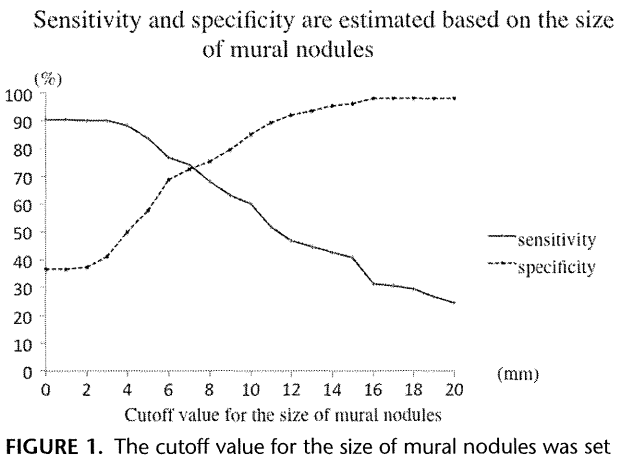


FIGURE 1. The cutoff value for the size of mural nodules was set every 1 mm from 0 to 20 mm, and sensitivity and specificity were calculated and plotted.

but the probability of carcinoma in patients without nodules is conjectured to be nearly 10%.

The combination of cytology and diameter of MPD[9,29] and pancreatic juice CEA measurements[23] are reported to be effective in identifying carcinoma patients among IPMN patients without nodules. There is also a report of a carcinoma predicting nomogram using multiple factors based on risk ratio.[30] For more accurate identification of carcinoma cases in the future, more detailed investigation of large numbers of patients at multiple centers and formulation of a carcinoma predictive model based on multiple versatile and objective factors will be necessary.

REFERENCES

1. Ohashi K, Murakami Y, Maruyama M, et al. Four cases of mucous secreting pancreatic cancer. *Prog Diagn Endosc.* 1982;20:348–351.
2. Kloppel G, Solcia E, Longnecker DS, et al. *World Health Organization International Histological Typing of Tumors of the Exocrine Pancreas.* Berlin, Germany: Springer; 1996:1–61.
3. Longnecker DS, Adler G, Hruban RH, et al. Intraductal papillary-mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, eds. *World Health Organization Classification of tumors. Pathology and Genetics of Tumors of the Digestive System.* Lyon, France: IARC Press; 2000:237–241.
4. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology.* 2006;6:17–32.
5. Salvia R, Fernandez-del Castillo C, Bassi C, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg.* 2004;239:678–685.
6. Terris B, Ponsot P, Paye F, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol.* 2000;24:1372–1377.
7. Sugiyama M, Izumisato Y, Abe N, et al. Predictive factors for malignancy in intraductal papillary-mucinous tumours of the pancreas. *Br J Surg.* 2003;90:1244–1249.
8. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg.* 2004;239:788–797.
9. Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. *Ann Surg.* 2007;246:644–651.
10. Tanaka M, Castillo CF, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology.* 2012;12:183–197.
11. Yamaguchi K, Kanemitsu S, Hatori T, et al. Pancreatic ductal adenocarcinoma derived from IPMN and pancreatic ductal adenocarcinoma concomitant with IPMN. *Pancreas.* 2011;40:571–580.
12. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29–36.
13. Harrell FE Jr, Califf RM, Pryor DB, et al. Evaluating the yield of medical tests. *JAMA.* 1982;247:2543–2546.
14. Jang JY, Kim SW, Ahn YJ, et al. Multicenter analysis of clinicopathologic features of intraductal papillary mucinous tumor of the pancreas: is it possible to predict the malignancy before surgery? *Ann Surg Oncol.* 2005;12:124–132.
15. Nagai K, Doi R, Kida A, et al. Intraductal papillary mucinous neoplasms of the pancreas: clinicopathologic characteristics and long-term follow-up after resection. *World J Surg.* 2008;32:271–278.
16. Yang AD, Melstrom LG, Bentrem DJ, et al. Outcomes after pancreatectomy for intraductal papillary mucinous neoplasms of the pancreas: an institutional experience. *Surgery.* 2007;142:529–534.
17. Kawamoto S, Lawler LP, Horton KM, et al. MDCT of intraductal papillary mucinous neoplasm of the pancreas: evaluation of features predictive of invasive carcinoma. *AJR Am J Roentgenol.* 2006;186:687–695.
18. Albert J, Schilling D, Breer H, et al. Mucinous cystadenomas and intraductal papillary mucinous tumors of the pancreas in magnetic resonance cholangiopancreatography. *Endoscopy.* 2000;32:472–476.
19. Kobayashi G, Fujita N, Noda Y, et al. Mode of progression of intraductal papillary-mucinous tumor of the pancreas: analysis of patients with follow-up by EUS. *J Gastroenterol.* 2005;40:744–751.
20. Yamao K, Nakamura T, Suzuki T, et al. Endoscopic diagnosis and staging of mucinous cystic neoplasms and intraductal papillary-mucinous tumors. *J Hepatobiliary Pancreat Surg.* 2003;10:142–146.
21. Furukawa T, Oohashi K, Yamao K, et al. Intraductal ultrasonography of the pancreas: development and clinical potential. *Endoscopy.* 1997;29:561–569.
22. Yamao K, Ohashi K, Nakamura T, et al. Efficacy of peroral pancreatoscopy in the diagnosis of pancreatic diseases. *Gastrointest Endosc.* 2003;57:205–209.
23. Hirono S, Tani M, Kawai M, et al. The carcinoembryonic antigen level in the pancreatic juice and mural nodule size are predictors of malignancy for branch duct type intraductal papillary mucinous neoplasms of the pancreas. *Ann Surg.* 2012;255:517–522.
24. Adsay NV, Fukushima N, Furukawa T, et al. Intraductal neoplasms of the pancreas. In: Bosman FT, Carneiro F, Hruban RH, et al, eds. *WHO Classification of Tumors of Digestive System.* Lyon, France: WHO Press; 2010:304–313.
25. Japan Pancreatic Society. *Classification of Pancreatic Carcinoma.* 2nd ed. Tokyo, Japan: Kanehara & Co Ltd; 2003.
26. Japan Pancreatic Society. *Classification of Pancreatic Carcinoma.* 3rd ed. Tokyo, Japan: Kanehara & Co Ltd; 2011.
27. Nagai K, Doi R, Ito T, et al. Single-institution validation of the international consensus guidelines for treatment of branch duct intraductal papillary mucinous neoplasms of the pancreas. *J Hepatobiliary Pancreat Surg.* 2009;16:353–358.
28. Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. *Am J Gastroenterol.* 2007;102:1759–1764.
29. Sadakari Y, Ienaga J, Kobayashi K, et al. Cyst size indicates malignant transformation in branch duct intraductal papillary mucinous neoplasm of the pancreas without mural nodules. *Pancreas.* 2010;39:232–236.
30. Shimizu Y, Kanemitsu Y, Sano T, et al. A nomogram for predicting the probability of carcinoma in patients with intraductal papillary-mucinous neoplasm. *World J Surg.* 2010;34:2932–2938.
31. Del Favero G, Fabris C, Angonese C, et al. Cytology in the diagnosis of pancreatic cancer. *Int J Pancreatol.* 1988;3(suppl 1):S137–S141.
32. Nakaizumi A, Tatsuta M, Uehara H, et al. Usefulness of simple endoscopic aspiration cytology of pancreatic juice for diagnosis of early pancreatic neoplasm. A prospective study. *Dig Dis Sci.* 1997;42:1796–1803.
33. Yamaguchi K, Nakamura M, Shirahane K, et al. Pancreatic juice cytology in IPMN of the pancreas. *Pancreatology.* 2005;5:416–421.

J Hepatobiliary Pancreat Sci (2013) 20:590–600
DOI 10.1007/s00534-013-0616-0

ORIGINAL ARTICLE

Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

Sohei Satoi · Hiroki Yamaue · Kentaro Kato · Shinichiro Takahashi · Seiko Hirono · Shin Takeda · Hidetoshi Eguchi · Masayuki Sho · Keita Wada · Hiroyuki Shinchi · A. Hon Kwon · Satoshi Hirano · Taira Kinoshita · Akimasa Nakao · Hiroaki Nagano · Yoshiyuki Nakajima · Keiji Sano · Masaru Miyazaki · Tadahiro Takada

Published online: 10 May 2013

Abstract
Purpose A multicenter survey was conducted to explore the role of adjuvant surgery for initially unresectable pancreatic cancer with a long-term favorable response to non-surgical cancer treatments.
Methods Clinical data including overall survival were retrospectively compared between 58 initially unresectable pancreatic cancer patients who underwent adjuvant surgery with a favorable response to non-surgical cancer treatments over 6 months after the initial treatment and 101 patients who did not undergo adjuvant surgery because of either unchanged unresectability, a poor performance status, and/or the patients' or surgeons' wishes.
Results Overall mortality and morbidity were 1.7 and 47 % in the adjuvant surgery group. The survival curve in the adjuvant surgery group was significantly better than in the control group ($p < 0.0001$). The propensity score analysis revealed that adjuvant surgery was a significant

Electronic supplementary material The online version of this article (doi:10.1007/s00534-013-0616-0) contains supplementary material, which is available to authorized users.

S. Satoi · A. H. Kwon
Department of Surgery, Kansai Medical University, Moriguchi, Japan

H. Yamaue (✉) · S. Hirono
Second Department of Surgery, Wakayama Medical University School of Medicine, Wakayama, Japan
e-mail: yamaue-h@wakayama-med.ac.jp

K. Kato · S. Hirano
Department of Surgical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

S. Takahashi · T. Kinoshita
Department of Hepatobiliary Pancreatic Surgery, National Cancer Center Hospital East, Kashiwa, Japan

S. Takeda · A. Nakao
Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan

H. Eguchi · H. Nagano
Department of Surgery, Graduate School of Medicine, Osaka University, Suita, Japan

M. Sho · Y. Nakajima
Department of Surgery, Nara Medical University Graduate School of Medicine, Nara, Japan

K. Wada · K. Sano
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

H. Shinchi
Department of Surgical Oncology, Kagoshima University, Kagoshima, Japan

M. Miyazaki
Department of General Surgery, Chiba University, Graduate School of Medicine, Chiba, Japan

T. Takada
The Japanese Society of Hepato-Biliary-Pancreatic Surgery, Tokyo, Japan

independent prognostic variable with an adjusted hazard ratio (95 % confidence interval) of 0.569 (0.36–0.89). Subgroup analysis according to the time from initial treatment to surgical resection showed a significant favorable difference in the overall survival in patients who underwent adjuvant surgery over 240 days after the initial treatment.

Conclusion Adjuvant surgery for initially unresectable pancreatic cancer patients can be a safe and effective treatment. The overall survival rate from the initial treatment is extremely high, especially in patients who received non-surgical anti-cancer treatment for more than 240 days.

Keywords Adjuvant surgery · Unresectable pancreatic cancer · Chemotherapy · Radiotherapy · Super-responder

Introduction

Pancreatic cancer is a lethal disease, and contributes to the increasing number of cancer deaths worldwide. Only 20 % of patients can be treated by surgery, and the overall 5-year survival rate is less than 5 % [1, 2]. Irrespective of the treatment strategy adopted, prognosis in patients with unresectable pancreatic cancer continues to be disappointing, with a median survival of 8–14 months [3–7]. These patients rarely have a chance to live more than 3 years.

Medical oncologists or pancreatic surgeons have identified candidates for surgical resection in patients with initially unresectable pancreatic cancer who favorably responded to multimodal treatment. Additional surgical resection during multimodal treatment is called "adjuvant surgery" [8]. The role of adjuvant surgery has not been fully determined because the number of patients who received this type of treatment was very small in each institution. Is adjuvant surgery a safe or effective treatment option for patients with unresectable pancreatic cancer? When should a shrunken tumor be removed in the process of maintaining chemotherapy and/or radiation therapy? There is no study indicating the clinical efficacy, safety and optimal timing of adjuvant surgery. There are long-term survivors and a comparable survival rate among this subset of patients after surgical resection following multimodal treatment [8–12]. However, the duration of multimodal treatment before pancreatectomy varies from a few months to several years in previous reports [8–12]. The clinical data on initially unresectable pancreatic cancer patients with a favorable response to chemo(radio)therapy over 6 months were collected as a project study of pancreatic surgery under the supervision of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS), to assess the role of adjuvant surgery in the clinical setting.

Patients and methods

A multicenter survey was conducted to collect clinical data on patients who underwent adjuvant surgery for initially unresectable pancreatic cancer following a favorable response to chemo(radio)therapy over 6 months from 2001 to 2009. Detailed data on 58 patients (adjuvant surgery group) were retrospectively collected from 39 out of 150 training institutes for highly advanced surgery registered by the committee of JSHBPS in 2009. The study criterion was initially unresectable pancreatic cancer patients who underwent surgical resection following the achievement of stable disease (SD), partial response (PR), or complete response (CR) defined by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1 [13]) over 6 months after initiating non-surgical anti-cancer treatments. The clinical data on 101 patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments who did not undergo surgical resection was collected as a control group from the same 39 centers. The unresectability of pancreatic cancer was based on the clinical criteria in each institute.

All patients had cytologically or pathologically proven ductal adenocarcinoma of the pancreas. The clinical variables shown in Table 1 were collected. Radiological assessment was performed according to RECIST version 1.1 [13]. The pathological parameters included residual tumor grading, Evans classification [14], and tumor staging according to TNM classification [15]. Serial data on tumor markers such as carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), DUPAN-2 or Span-1 were collected every 1–3 months during multimodal treatment. Post-operative follow-up data included serial data on tumor markers, adjuvant chemotherapy, the date and the primary site of disease recurrence, the date and cause of death, and the last follow-up date. The observation period was defined as the time from the initial treatment to the date of death for censored patients or the last follow-up date for non-censored patients. This study was performed in accordance with the precepts of the Helsinki Declaration, and was approved by the local ethics committee.

Statistical analysis

Continuous variables were expressed as median values and range. All parameters were compared between the adjuvant surgery and control groups. Statistical analyses, including the Mann–Whitney *U* test for continuous variables, and chi-squared statistics or Fisher's exact test for categorical variables, were performed using SAS software version 9.2 (SAS Institute, Cary, NC, USA). The primary outcome

Table 1 Clinical backgrounds in the adjuvant surgery and control groups

Parameters	Category	Adjuvant surgery (n = 58)	Control[a] (n = 101)	p value
Sex	Male	37 (63.8 %)	59 (58.4 %)	0.61
	Female	21 (36.2 %)	42 (41.6 %)	
Age (years)	Median (min–max)	62.5 (40–80)	65 (41–85)	0.01
Reason for unresectability	Local advance	41 (70.7 %)	56 (55.4 %)	0.07
	Distant organ metastasis			
	Overall	17 (29.3 %)	45 (44.6 %)	
	Peritoneal metastasis[b]	1 (1.7 %)	17 (16.8 %)	0.003
Tumor diameter	Median (min–max)	30 (16–75)	35 (13–76)	0.009
Tumor location	Ph	31 (53.4 %)	50 (49.5 %)	0.74
	Pbt	27 (46.6 %)	51 (50.5 %)	
Change in tumor marker[c]	Increase	4 (6.9 %)	4 (40 %)	0.46
	Decrease or no tumor marker	54 (93.1 %)	97 (96.0 %)	
Tumor marker (number of patients showing an increased level)	CA19-9	40 (69.0 %)	83 (82.2 %)	0.06
	Others	12 (20.7 %)	8 (7.9 %)	
	None	6 (10.3 %)	10 (9.9 %)	
CA19-9	Median (min–max)	313 (9–13080)	440 (11–144400)	0.13
Chemotherapy	GEM base	53 (91.4 %)	89 (88.1 %)	0.60
	Others	5 (8.6 %)	12 (11.9 %)	
Gemcitabine (g)	Median (min–max)	28.2 (0–173.6)	28.0 (0–168)	0.55
	≥28 g	29 (50 %)	50 (49.5 %)	1.00
	<28 g	29 (50 %)	51 (50.5 %)	
S-1 (mg)	Median (min–max)	3850 (0–53768)	6300 (0–64120)	0.19
	≥5650 mg	26 (44.8 %)	52 (51.5 %)	0.51
	<5650 mg	32 (55.2 %)	49 (48.5 %)	
Radiotherapy	Done	26 (44.8 %)	19 (18.8 %)	0.001
	None	32 (55.2 %)	82 (81.2 %)	
Immunotherapy	Done	2 (3.4 %)	6 (5.9 %)	0.71
	None	56 (96.6 %)	95 (94.1 %)	
TNM by UICC	II	10 (17.2 %)	14 (13.9 %)	0.63
	III	31 (53.4 %)	45 (44.6 %)	
	IV	17 (29.3 %)	42 (41.6 %)	
RECIST	CR	7 (12.1 %)	2 (2.0 %)	<0.0001
	PR	39 (67.2 %)	38 (37.6 %)	
	SD	12 (20.7 %)	61 (60.4 %)	
Duration until PR/CR[d]	Median (min–max)	151.5 (21–919)	174 (36–1669)	0.11

Data are the number (%) or median (range) unless otherwise specified

Met metastasis, *Ph* pancreas head, *Pbt* pancreas body and tail, *CA19-9* carbohydrate antigen 19-9, *GEM* gemcitabine, *RECIST* Response Evaluation Criteria In Solid Tumors, *CI* confidence interval, *CR* complete response, *PR* partial response, *SD* stable disease

[a] The reasons for initially unresectable pancreatic cancer in the control group were locally advanced tumors in 56 (54 %, 50 arterial invasions and 6 portal vein invasions with long segment) and distant organ metastases in 45 (46 %, 19 liver, 17 peritoneal metastasis or peritonitis carcinomatosa, 7 cervical or para-aortic lymph nodes, and 2 lung). Eighty-nine patients received gemcitabine-based chemotherapy, and 73 patients had S-1 chemotherapy

[b] Peritoneal metastasis includes peritonitis carcinomatosa

[c] Tumor marker: this category is divided into increased tumor marker and decreased or no tumor marker

[d] The days between the initiation of treatment and the identification of a partial/complete response of the tumor according to the RECIST criteria

variable was overall survival, defined as the time from non-surgical anti-cancer treatments to death or the last follow-up date. Comparisons of the overall survival between the two groups were made using the log-rank test. In addition, profound factors identified by the univariate analysis were further examined by multivariate Cox proportional-hazard

models to determine independent significant factors for survival.

A propensity score methodology was used to provide adjustments since a propensity score can calculate the conditional probability of receiving a treatment given all potential confounders measured. The propensity score analysis required calculation of the conditional probabilities for the adjuvant surgery group using a multivariate logistic regression to generate a propensity score [16]. The selection of variables for calculating the propensity score was based on the potential association with the overall survival results (sex, age, radiation therapy or not, tumor marker decrease or not during non-surgical anti-cancer treatment, PR/CR vs SD, tumor size, amount of gemcitabine administration, reason for unresectability). Model discrimination was assessed with C-statistics, and model calibration was assessed with Hosmer–Lemeshow statistics. The propensity score was subdivided into quartiles as shown in Table A (Electronic Supplementary Material). The treatment effect was separately estimated within each quartile, and quartile estimates were combined to give an overall estimate of adjuvant surgery. A survival analysis using Cox proportional-hazard models was used. The hazard ratio and 95 % confidence intervals were calculated for all estimates. A 2-tailed p value less than 0.05 was considered to be statistically significant.

Results

Clinical background in the adjuvant surgery and control groups

Tables 1 and 2 show that the reason for the initially unresectable pancreatic cancer was 41 locally advanced tumor and 17 distant organ metastases in the adjuvant surgery group. Fifty-three patients received gemcitabine-based chemotherapy, and 32 patients had S-1 chemotherapy. The radiological response of SD, PR, or CR was found in 7, 39, and 12 patients, respectively. The median duration between the initial therapy and the detection of PR/CR was 150 days (21–739). The median duration between the

Table 2 Type of surgery in the adjuvant surgery group

Reasons for UN	Locally advanced ($n = 41$)					Metastasis ($n = 17$)			Total number (%)
	SMA/(PV) ($n = 16$)	CHA/(PV) ($n = 8$)	CA/CHA/GDA ($n = 9$)	CA/SMA ($n = 5$)	PV ($n = 3$)	Liver ($n = 13$)	No 16 LN[a] ($n = 3$)	P ($n = 1$)	
Operation type									
PD[b]	13	7	0	1	2	7	0	0	30 (51)
TP	0	1	0	1	1	0	0	0	3 (5)
DP	3	0	3	0	0	5	3	1	15 (26)
DPCAR	0	0	6	3	0	1		0	10 (17)
Combined resections of other organs									
None	5	2	3	0	0	5	2	1	18 (31)
PV/SMV	9	4	2	1	3	4	0	0	23 (40)
Ad	0	0	6	3	0	1	1	0	11 (19)
CA/CHA	0	0	6	3	0	1	0	0	10 (17)
CHA	0	2	0	–	0	0	0	0	2 (3)
SMA	1	0	0	0	0	0	0	0	1 (2)
Liver	0	0	0	0	0	5 Bx2	0	0	5 (9)
Colon	1	0	0	0	0	1	0	0	2 (3)
Pathological findings									
CR[c]	1	1	2	1	0	1	1	0	7 (12)
R0/1/2[d]	36/5/0					12/4/1			

Data are the number (%) or median (range) unless otherwise specified

UN unresectability, *SMA* superior mesenteric artery, *CHA* common hepatic artery, *CA* celiac axis, *GDA* gastroduodenal artery, *PV* portal vein, *LN* lymph node, *P* peritoneal metastasis, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *DPCAR* DP with celiac axis resection, *TP* total pancreatectomy (TP), *SMV* superior mesenteric vein, *Ad* adrenal, *Bx* biopsy, *CR* complete response

[a] No 16 LN, paraaortic lymph node

[b] Includes pylorus preserving PD

[c] Complete pathological response was defined as the absence of identifiable tumor cells in the resected specimen. The pathological examination was done using 5-mm specimens slices according to the standard method defined by the Japan Pancreas Society

[d] Residual tumor grading; R0, negative microscopic margin; R1, positive microscopic margin; R2, positive gross margin