応においても，61％と高率に特異的T細胞が誘導できた(Miyazawa M, et al. Cancer Sci 2010)。また，注射部位の皮膚反応は83％に認め，注射部位反応と臨床効果に相関関係が認められた。

以上から第Ⅱ/Ⅲ相臨床治験であるPEGASUS-PC試験を全国展開し，ペプチドワクチン療法の臨床効果とともに免疫学的パラメータについて探索的検討項目として解析した結果を2013 ASCO GIで報告した。

切除不能膵癌患者を対象に全国35施設の参加で本治験が行われた。その結果，切除不能進行膵癌に対する血管内皮増殖因子受容体2(VEGFR2)エピトープペプチドワクチンとゲムシタビンの併用は，プラセボ＋ゲムシタビンと比べて統計学的に生存期間の延長を示すことができなかった。ただし，実薬群でのみエピトープペプチドワクチン注射に特有の反応である注射部位にびらん・潰瘍が発現した患者(10％)は，潰瘍が発現しなかった患者に比べて生存期間が延長した。

血管内皮増殖因子(VEGF)は膵癌の増殖や転移に関わることが知られている。われわれは，VEGFR2のエピトープペプチドを使ったペプチドワクチンを用いた医師主導型第Ⅰ相臨床試験で良好な結果が得られたため，pivotal studyである第Ⅱ/Ⅲ相臨床治験を行った。試験に用いた薬剤はエルパモチドで，HLA-A24:02拘束性のVEGFR2のエピトープペプチドである。局所進行性・転移により切除不能である膵癌患者153例を，1次治療として，エルパモチドをモンタナイド(IFAアジュバント)1mLと混合した製剤とゲムシタビン(1000mg/m^2)を併用した実薬群(100例)，生理食塩水＋IFAアジュバントにゲムシタビンを併用するプラセボ群(53例)に2：1でランダムに割り付けた。治療スケジュールは，エルパモチドもしくはプラセボを週1回，4週間投与し(day1，8，15，22)，ゲムシタビンはday1，8，15に投与するものを1サイクルとした。なお，治療は病勢進行まで続けられた。登録時患者背景は，2群間で差はなく，Stage Ⅳaが25％，Stage Ⅳbが75％だった。リンパ球が18％未満であったのは2群とも32％で，18％以上であったのが68％だった。薬剤関連有害事象には，グレード3/4の有害事象として，実薬群において白血球減少(31％)，血小板減少(15％)，貧血(22％)，好中球減少(48％)，食欲不振8％，AST上昇3％，注射部位反応2％が認められたが，プラセボ群でも同様に発現しており，これらは同時併用したゲムシタビンによる有害事象と考えられた。

全生存期間(OS)を評価した結果，OS中央値はプラセボ群8.54ヵ月に対し，実薬群8.36ヵ月で，統計学的に有意差は認められなかった。無増悪生存期間や病勢コントロール率も2群間で差はなかった。次に注射部位反応について検討した結果，実薬群において潰瘍が10例に認められ(10％)，プラセボ群には1例も認められなかった。紅斑や硬化などの注射部位反応については実薬群，プラセボ群ともに認められたため，潰瘍がエルパモチドに特有の反応であると考えられた。

そこで潰瘍の形成の有無別にOSを検討した結果，実薬群のうち潰瘍が認められなかった90例のOS中央値が8.15ヵ月だったのに対し，潰瘍が認められた10例のOS中央値は16.0ヵ月と延長していた。実薬群で潰瘍が認められたグループのハザード比は，実薬群で潰瘍なしグループに対して0.713，プラセボ群に対して0.740であった。この結果は，長期にエルパモチドを投与した結果として潰瘍が認められた可能性があるため，3ヵ月時点における解析も行ったが，同じく注射部位反応と生存に相関関係が認められた。

エルパモチドは安全に投与することができ，エルパモチドに特有であった注射部位における潰瘍の発現は生存期間と有意に相関した。現在，われわれは他のエピトープペプチドと混合した製剤(カクテルペプチド)を用い，標準治療不応の膵癌患者を対象とした第Ⅲ相臨床治験(COMPETE-PC試験)を進めている。

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今日の治療指針

私はこう治療している

監修　山口　徹　北原光夫
総編集　福井次矢　高木　誠　小室一成

TODAY'S THERAPY 2014

医学書院

8 肝・胆・膵疾患

（責任編集：持田　智）

9 腎疾患

（責任編集：深川　雅史）

✚「治療のポイント」掲載項目，＊「服薬指導・薬剤情報」掲載項目

Ⓓ 生活指導・食事療法

自己免疫性膵炎の治療経過は長期に及ぶので，生活指導や食事療法が重要である．

1. 生活指導　禁酒，カフェイン飲料や香辛料などの制限や，規則正しい生活などを指導する．
2. 食事療法　腹痛がある例では，代償期の慢性膵炎の治療に準じて，脂肪制限食とする．

ステロイド内服中は，食欲が増進して過食になりがちなので，気をつける．

患者説明のポイント

- 自己免疫性膵炎はステロイドが奏効するが，ステロイド投与量の減量中，維持療法中，投与中止後に再燃することがあるので，定期的に血液や画像検査を受ける必要がある．
- ステロイド治療中は，服用指示に従って，必ず内服しなければいけない．
- ステロイドの胃潰瘍，糖尿病，骨粗鬆症などの副作用について説明する．

膵嚢胞，嚢胞性腫瘍
pancreatic cyst and cystic tumor

佐田尚宏　自治医科大学教授・消化器外科学・一般外科学

病態と診断

膵嚢胞は膵に発生する嚢胞性疾患の総称で，腫瘍性嚢胞と非腫瘍性嚢胞がある．非腫瘍性嚢胞は，内腔に上皮が存在する真性嚢胞と，上皮がない仮性嚢胞に分類される．真性嚢胞には先天性（単純性嚢胞など），後天性（貯留嚢胞など）がある．仮性嚢胞は急性膵炎（慢性膵炎の急性増悪を含む），膵外傷後に発生し，多くは自然消褪する．2012年アトランタ分類が改訂され，急性膵炎後の局所合併症はacute pancreatic fluid collection（APFC），acute necrotic collection（ANC），pancreatic pseudocyst（膵仮性嚢胞），walled-off necrosis（WON）に分類された．腫瘍性嚢胞には，膵管内乳頭粘液腫瘍（intraductal papillary mucinous neoplasm：IPMN），粘液性嚢胞腫瘍（mucinous cystic neoplasm：MCN），漿液性嚢胞腫瘍（serous cystic neoplasm：SCN），solid pseudopapillary neoplasm（SPN）などがあり，膵神経内分泌腫瘍，神経原性腫瘍なども嚢胞性腫瘍の形態をとることがある．IPMNは主膵管型と分枝膵管型に分類される．MCNのほとんどは女性の膵体尾部腫瘍で，病理学的には卵巣様間質（ovarian type stroma：OTS）がみられる．SPNは若年女性に好発し，嚢胞性部分と実質部分の混在，被膜内石灰化などが特徴である．

膵嚢胞の診断はUS，CT，MRI（MRCP）などでスクリーニングが行われ，超音波内視鏡検査（endoscopic ultrasonography：EUS），管腔内超音波検査（intraductal ultrasonography：IDUS），内視鏡的逆行性胆管膵管造影（endoscopic retrograde cholangiopancreatography：ERCP）で精査が行われる．

治療方針

膵嚢胞・嚢胞性腫瘍の治療は切除であり，薬物療法はない．臨床症状のない真性嚢胞は治療の対象にならないが，術前確定診断が困難な例がある．仮性嚢胞は自然消褪することが多く，まず経過観察する．発症後4週間を経過して感染が認められる症例は，（経皮，開腹，腹腔鏡的，経口内視鏡的）ドレナージ，necrosectomyの適応となる．嚢胞消化管吻合術（嚢胞胃吻合術，嚢胞空腸吻合術）が実施されることもある．

IPMN，MCNの治療は2012年に改訂された「IPMN/MCN国際診療ガイドライン」に準じて行う．改訂ガイドラインでは悪性度判定にhigh-risk stigmata（確診所見），worrisome feature（疑診所見）を設定，high-risk stigmataは切除対象とし，worrisome featureは切除を考慮する．嚢胞性膵腫瘍では嚢胞径30 mm以上，造影される壁肥厚，主膵管径5-9 mm，壁在結節，尾側の閉塞性膵炎を伴う主膵管狭窄，リンパ節腫脹などをworrisome featureと規定した．SCNの悪性例はきわめてまれで，他の疾患が考えられないときは経過観察可能である．その他の腫瘍性嚢胞は基本的に切除の方針となる．

膵癌
pancreatic cancer

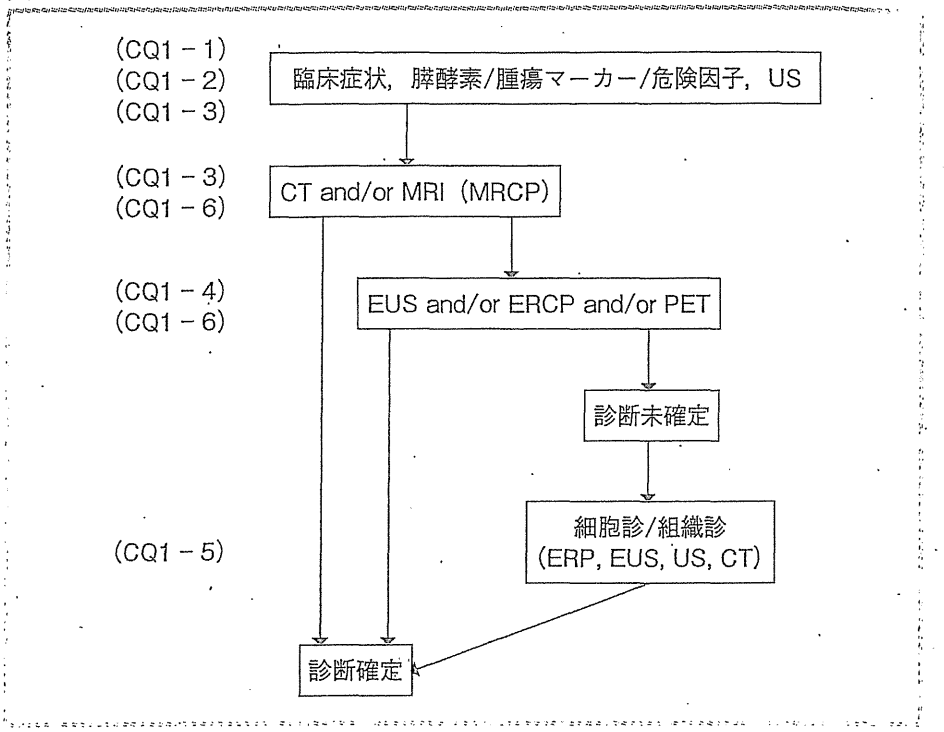
山上裕機　和歌山県立医科大学教授・外科学第2講座

病態と診断

Ⓐ 病態

膵癌は外分泌系の上皮性悪性腫瘍であり，60歳代に最も高頻度にみられ，男性に多い．本邦における膵癌患者は23,000人/年を超え年々増加傾向にあり，臓器別死因は男性5位，女性4位となった．膵癌の発生部位は膵頭部60%，膵体部30%，膵尾部10%と膵頭部に多く発生する．病理学的には浸潤性膵管癌が最も多い組織型であり，膵癌の90%以上を占めている．明らかな原因は不明であるが，危険因子として，家族歴，喫煙，糖尿病，慢性膵炎，腫瘍性膵嚢胞などが挙げられる．

図1　膵癌診断のアルゴリズム



（日本膵臓学会膵癌診療ガイドライン委員会 編：科学的根拠に基づく膵癌診療ガイドライン2009年版，p44，金原出版，2009より転載）

Ⓑ 診断

膵癌の症状は，閉塞性黄疸に伴う黄疸，腹痛，背部痛，体重減少，栄養障害，糖尿病の悪化などが挙げられるが，膵体尾部癌では無症状の症例も多く認められることが特徴である．強固な背部痛は膵癌の上腸間膜動脈・総肝動脈・腹腔動脈の神経叢への浸潤を疑う症状であり，膵癌の局所進行度が高いことを示唆している．

膵癌診断のアルゴリズムが「科学的根拠に基づく膵癌診療ガイドライン2009年版」に示されている（図1）．膵酵素であるアミラーゼ，リパーゼ，トリプシン，エラスターゼ1などの異常は膵疾患全体でみられるため，膵癌を断定できない．腫瘍マーカーとしてCEAやCA19-9などの上昇が重要な所見である．特に，CA19-9は腫瘍マーカーのなかでは有用性が高いが，小膵癌では上昇しないこと，膵炎や胆石などの良性疾患でも上昇する場合があること，ルイスa抗原陰性例では上昇しないことが欠点である．

超音波検査は低侵襲であり，スクリーニングに適した検査である．膵癌は不均一な低エコー腫瘤として描出されるが，膵臓自体が深部に位置することに加え，胃や結腸内のガスによる描出不良域が生じることを理解する必要がある．また，膵管や胆管の拡張が認められた場合は，狭窄をきたす病変がないかを慎重に検査する必要がある．CTでは低吸収域の腫瘤として描出されるが，通常は境界が不明瞭であり，単純CTでは膵癌の診断は困難である．適切な造影条件下にCTを撮影することが小膵癌の診断には必要である．ERCP（内視鏡的逆行性膵胆管造影）では膵管の限局性の狭窄・閉塞と尾側膵管の拡張が典型像となるが，膵液採取による細胞診などの検査ができる．また，最近はEUS-FNA（超音波内視鏡下穿刺吸引細胞診）を施行可能な施設が増加しており，EUSによる詳細な局所進展度診断に加え，穿刺吸引組織診細胞診検査による病理学的診断が可能となり，治療方針の決定に有用である．遠隔転移の検索にはCTやFDG-PETが有用である．

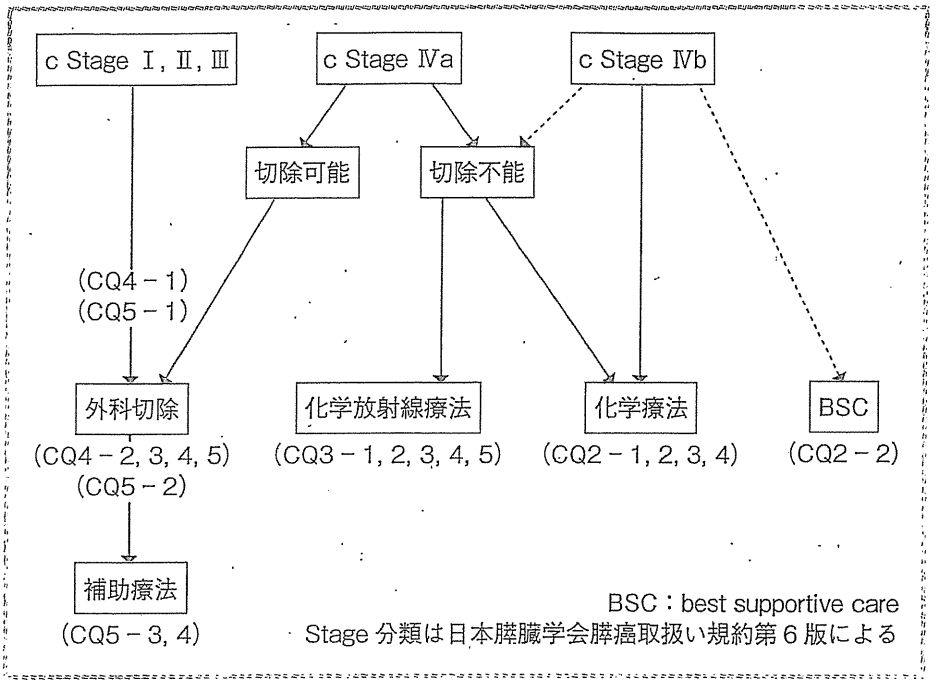
治療方針

膵癌の治療成績は不良であり，難治性癌の代表といえる．膵癌治療のアルゴリズムが前述のガイドラインに示されている（図2）．膵癌の診断時にはすでに遠隔転移や局所進行のため，膵癌の切除率はわずか約30%と低いことが特徴である．

Ⓐ 切除可能膵癌

膵癌の根治的な治療法は外科的切除であるが，切除例の多くは進行癌であるため，日本膵臓学会の癌登録データにおける切除例の1年，3年，5年生存率はそれぞれ70.6%，30.3%，18.8%と不良である．膵癌切除例の予後規定因子は癌遺残のないR0切除と術後の補助化学療法である．ゲムシタビン塩酸塩

図2　膵癌治療のアルゴリズム



（日本膵臓学会膵癌診療ガイドライン委員会 編：科学的根拠に基づく膵癌診療ガイドライン 2009年版，p45，金原出版，2009より転載）

（GEM）による術後補助化学療法の有効性が，ヨーロッパや本邦で無作為化比較試験によって証明されている（CONKO－001試験，JSAP－02試験）．本邦では歴史的に拡大郭清が行われてきたが，どのような症例に拡大郭清をすべきか今後の検証が必要である．また，膵体部癌では腹腔動脈神経叢や脾動脈根部への浸潤をきたしやすく，そのような症例は切除不能と診断されたり，膵体尾部切除術を行っても高率に再発することがある．しかし，腹腔動脈合併切除術を併施することで，長期生存例も報告されるようになってきた．われわれはR0切除率を高めるために，術前治療を行った後に積極的に膵体尾部切除術＋腹腔動脈合併切除術を行っている．

Ⓑ 切除不能膵癌

切除不能症例に対しては，GEMやテガフール・ギメラシル・オテラシルカリウム配合剤（S－1）を用いた化学療法が中心となる．約800例を対象としたGEM単独，S－1単独，両者併用の3群による臨床試験（GEST試験）が行われ，2011年の米国臨床腫瘍学会（ASCO 2011）で，S－1はGEMに対するS－1の非劣性が示されたが，GEMとS－1併用による優越性を認めなかった．しかし，どの群においても高率に2次治療が行われており，膵癌においても1次治療不応後の2次治療が重要なことを示唆している．S－1を長期継続投与するために，S－1隔日投与に関する臨床試験が進行中である．

一方，GEMの登場以来，より優れた治療の開発を目的とした他の抗癌剤との併用療法も積極的に試みられたが，そのほとんどは第III相試験でGEM単独に対する延命効果を証明できなかった．それらのなかで，EGFRチロシンキナーゼ阻害薬のエルロチニブ（タルセバ）との併用療法はGEM単独に対する生存期間の優越性が示された（MST：GEM＋エルロチニブ群6.24か月 vs. GEM群5.91か月）．エルロチニブの主な副作用は，食欲不振，下痢，疲労，ざ瘡様皮疹などであるが，重篤な有害事象は少ないものの間質性肺炎がわが国の治験では8.5％に認められており注意を要する．さらに，生存期間の差が大きくなかったことから副作用やコストに見合う臨床的意義を疑問視する声もあり，GEM単独に置き換わる位置づけにはなっていない．

HLA－A 2402患者を対象にvascular endothelial growth factor（VEGF）を標的としたペプチドワクチン療法の治験（PEGASUS－PC試験）が行われた．詳細な解析結果はまだ報告されていないが，どのようなsubsetの患者に有効性を認めたか非常に興味がもたれる．現在，新たなるペプチドワクチンの治験が進行中である．

℞ 処方例

ジェムザール注　1回1,000 mg/m²　点滴静注（30分）　第1，8，15日　3週連続投与し4週目は休薬

ティーエスワン配合カプセル（20 mg）　80 mg/m²　分2　朝・夕食後　28日間連続投与後

Masao Tanaka
Editor

Intraductal Papillary Mucinous Neoplasm of the Pancreas

Springer

Chapter 3
Natural History and Malignant Transformation of Branch Duct IPMN

Hiroyuki Maguchi and Satoshi Tanno

Abstract The number of reports published on the follow-up data of patients with BD-IPMN has been increasing. Accumulating evidence from independent 12 studies revealed that the mean frequency of morphological changes of BD-IPMN, such as increased cyst size, increased MPD diameter, and/or appearance or enlargement of MNs, was 27.4 % (range, 14.9–61.8 %) of 1,293 followed-up patients (follow-up period, 2.6–8.1 years). Surgical resection was carried out in 9.9 % (range, 0–22.2 %) of all cases. Among the resected cases, 27.3 % were diagnosed histologically as malignant. During the follow-up period, malignant transformation was observed in only 2.7 %. BD-IPMNs without MNs have a low risk for malignant transformation regardless of cyst size at the initial diagnosis. Malignant transformation is associated with signs of progression especially appearance or enlargement of MNs and/or an increase in the MPD diameter. On the other hand, PDAC develops independently in the pancreas distinct from BD-IPMN. The mean frequency of PDAC occurrence was 2.8 % (range, 1.4–8.0 %) of all cases during the follow-up.

In conclusion, careful attention should be paid to the occurrence of PDAC in the entire pancreas in addition to progression of BD-IPMN when performing follow-up examinations in patients with BD-IPMN.

Keywords BD-IPMN • BD-IPMNs without MNs • Follow-up • Guideline 2012 • Malignant transformation • MNs • Morphological changes • MPD diameter • Natural history • Pancreatic ductal adenocarcinoma (PDAC) • PDAC concomitant with IPMN • Progression

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3.1 Introductory Remarks

IPMNs can be classified into three types, i.e., main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed type, based on imaging study and/or the histology in the revised guidelines (Tanaka et al. 2012). The frequency of malignant BD-IPMN such as IPMN with high-grade dysplasia or noninvasive cancer and IPMN with an associated invasive cancer is lower than that of MD-IPMN and mixed type (Tanaka et al. 2012). Patients with BD-IPMN who do not have any sign of malignancy may be managed conservatively.

Although the natural history of BD-IPMN is not well established, there have been an increasing number of reports published on the follow-up data in patients with BD-IPMN.

3.2 Morphological Change of BD-IPMN During the Follow-Up Period

The published reports on the follow-up of BD-IPMN were summarized in Table 3.1 (Kobayashi et al. 2005; Lee et al. 2007; Rautou et al. 2008; Tanno et al. 2008; Guarise et al. 2008; Sawai et al. 2010; Uehara et al. 2011; Maguchi et al. 2011; Arlix et al. 2012; Bae et al. 2012; Ohno et al. 2012; Khannoussi et al. 2012). Total number of cases was 1,293. The range of mean initial cyst size and main pancreatic duct (MPD) diameter was 15–28 mm and 2.4–3.8 mm, respectively. Almost all

Table 3.1 Morphological changes of BD-IPMN during follow-up

		Initial imaging findings				
Author (year)	Number of cases	Cyst size (mm)	MPD (mm)	MN (absent/present)	Progression (%)	Follow-up period (year)
Kobayashi et al. (2005)	47	28	–	10/37	7 (14.9)	3.5
Lee et al. (2007)	45	28	–	–	10 (22.2)	3.5
Rautou et al. (2008)	121	15	–	–	33 (27.3)	2.8
Tanno et al. (2008)	82	20	3	0/82	13 (15.9)	8.1
Guarise et al. (2008)	52	17	2.8	11/41	11 (21.2)	2.6
Sawai et al. (2010)	103	18	3	–	29 (28.2)	4.9
Uehara et al. (2011)	100	21	3.8	5/95	28 (28.0)	5.1
Maguchi et al. (2011)	349	19	3	0/349	62 (17.8)	3.7
Arlix et al. (2012)	47	15	2.4	0/47	18 (38.3)	6.4
Bae et al. (2012)	152	22	–	–	94 (61.8)	2.6
Ohno et al. (2012)	142	22	2.5	61/81	35 (24.6)	3.5
Khannoussi et al. (2012)	53	–	–	–	15 (28.3)	7.0
Total	1,293				355 (27.4)	

MPD main pancreatic duct, *MN* mural nodule

cases were suspected to have a low risk of malignancy. The mean follow-up period ranged from 2.6 to 8.1 years.

Among these, the mean frequency of morphological changes on the imaging findings, such as increased cyst size, increased MPD diameter, and/or appearance or enlargement of mural nodules (MNs), was 27.4 % (335/1,293) (range, 14.9–61.8 %) of all cases during the follow-up period.

There are several reasons for varying the range in frequency. The most obvious reason may be the different definition of the progression of BD-IPMN especially in cyst size. Some authors have defined cyst size changes of 5–10 mm or greater as progression (Rautou et al. 2008; Maguchi et al. 2011) because of the difficulty in the accurate measuring of a grape-like dilated cyst. However, Bae et al. (2012) reported that 94 (61.8 %) of 152 patients showed an increase in cyst size, and the mean incremental rate of cyst size growth was 0.0038 cm/month. Arlix et al. (2012) also reported that 18 (38.3 %) of 47 patients showed an increased cyst size, and the mean enlarged size was less than 3 mm.

Other reasons include differences in the patient characteristics at the initial diagnosis, the difference of imaging modalities in each institution, and the difference of the follow-up periods.

3.3 Malignant Transformation of BD-IPMN During the Follow-Up

The number of resected cases with BD-IPMN during the follow-up was shown in Table 3.2 (Kobayashi et al. 2005; Lee et al. 2007; Rautou et al. 2008; Tanno et al. 2008; Guarise et al. 2008; Sawai et al. 2010; Uehara et al. 2011; Maguchi et al. 2011; Arlix et al. 2012; Bae et al. 2012; Ohno et al. 2012; Khannoussi et al. 2012). The mean frequency of resected cases was 9.9 % (128/1,293) (range, 0–22.2 %) of all cases. Of 128 BD-IPMNs, 35 (27.3 %) cases were diagnosed histologically as malignant (noninvasive 25 and invasive 10). Therefore, the frequency of malignant transformation was only 2.7 % (35/1,293) in total during the follow-up period, whereas the remaining patients without surgical resection may have a risk of malignant transformation in the future.

Thirty-two (91.4 %) of 35 patients with malignant BD-IPMNs exhibited obvious signs of progression such as increased cyst size, increased MPD diameter, and/or appearance or enlargement of MNs. Three (8.5 %) malignant cases having no change of cyst size or MPD diameter showed an appearance of a solid mass at the periphery of the cyst during the follow-up (Kobayashi et al. 2005).

In addition, a multicenter study in Japan (Maguchi et al. 2011) reported that all nine malignant BD-IPMN cases exhibited progression, although all seven patients with benign BD-IPMN had no progression during the follow-up period.

These findings support the notion that malignancy is associated with signs of progression.

Table 3.2 Resected cases of BD-IPMN during follow-up

Author (year)	Number of resected cases (%)	Malignancy of resected cases		Histological findings of malignancy	
		Progression	No change	Noninvasive	Invasive
Kobayashi et al. (2005)	6 (12.8)	0/3	3[a]/3		3[a]
Lee et al. (2007)	10 (22.2)	2/10		1	1
Rautou et al. (2008)	8 (6.7)	4/8		4	
Tanno et al. (2008)	7 (8.5)	1/7		1	
Guarise et al. (2008)	0				
Sawai et al. (2010)	11 (10.7)	3/8	0/3	2	1
Uehara et al. (2011)	1 (1)	1/1		1	
Maguchi et al. (2011)	29 (8.3)	9/22	0/7	8	1
Arlix et al. (2012)	5 (10.2)	0/5			
Bae et al. (2012)	18 (11.8)	3/18		2	1
Ohno et al. (2012)	30 (21.1)	9/30		6	3
Khannoussi et al. (2012)	3 (5.7)	0/3			
Total	128 (9.9)	32/115	3[a]/13	25	10

[a]No change of cyst size and MPD diameter except the appearance of a solid mass at the periphery of the cyst

Table 3.3 Progression and malignancy of BD-IPMN without MN during follow-up

Author (year)	Number of cases	Progression (%)	Malignant (%)	IPMN with an associated invasive carcinoma (%)	Follow-up period (year)
Kobayashi et al. (2005)	29	0	0	0	3.5
Tanno et al. (2008)	82	13 (15.9)	1 (1.2)	0	8.1
Guarise et al. (2008)	41	4 (9.7)	0	0	2.6
Uehara et al. (2011)	95	7[a] (7.4)	2 (2.1)	1(1.1)	5.1
Maguchi et al. (2011)	349	62 (17.8)	9 (2.6)	1 (0.3)	3.7
Arlix et al. (2012)	47	18 (36.7)	0	0	6.4
Total	643	104 (16.2)	12(1.9)	2(0.3)	

[a]Appearance of MN alone

3.4 Progression and Malignancy of BD-IPMN Without MNs

The presence of MNs has been reported to be strongly suggestive of malignancy. Table 3.3 shows the follow-up data of BD-IPMN patients who had no MNs at the initial diagnosis (Kobayashi et al. 2005; Tanno et al. 2008; Guarise et al. 2008; Uehara et al. 2011; Maguchi et al. 2011; Arlix et al. 2012). The mean frequency of progression was 16.2 % (104/643) of all cases during the follow-up period. Twelve (1.9 %) cases were found to be malignant by histological examination, and only two (0.3 %) cases were IPMN with an associated invasive cancer.

These findings suggest that BD-IPMNs without MNs have a low risk of progression and malignant transformation. They are suitable for management without surgery and do not need short interval surveillance.

Table 3.4 Initial cyst size in relation to progression and malignancy

Author (year)	Number of cases (%)	Progression (%)	Malignant (%)
Tanno et al. (2008)			
<3 cm	72 (87.8)	10 (13.9)	1 (1.4)
≧3 cm	10 (12.2)	3 (30.0)	0
Maguchi et al. (2011)			
<3 cm	287 (82.2)	49 (17.1)	6 (2.1)
≧3 cm	62 (17.8)	13 (21.0)	3 (4.8)

3.5 Cyst Size in Relation to Progression and Malignancy

Cyst size >3 cm was previously thought to be one of the predictors of malignancy. Therefore, a BD-IPMN >3 cm was included in the consensus criteria for resection in the first guidelines (Tanaka et al. 2006).

Several studies have validated the safety of this guideline for surgical treatment of BD-IPMN >3 cm and revealed that the specificity is quite low (Rodriguez et al. 2007; Tang et al. 2008; Pelaez-Luna et al. 2007). These reports suggest that a BD-IPMN size of >3 cm is a weaker indicator of malignancy than the presence of MNs (Tanaka et al. 2012).

There was few number of long-term follow-up data in patients with BD-IPMN >3 cm. Table 3.4 shows the initial cyst size in relation to progress and malignancy during the follow-up (Tanno et al. 2008; Maguchi et al. 2011). Two studies demonstrated that there was no significant difference in the frequency of progression and malignancy in the resected cases between initial cyst size of less than 3 and 3 cm or greater.

With accordance to this, the revised guideline 2012 recommends that the indication for resection is more conservative (Tanaka et al. 2012). BD-IPMN >3 cm without any signs of further risk stratification can be observed without immediate resection.

3.6 Predictive Sign of Malignancy During Follow-Up

Although malignancy is associated with sign of progression of BD-IPMN during follow-up, adequate predictive signs of malignancy have not been defined. Many investigators proposed signs of malignancy as the appearance or the enlargement of MNs and/or an increase in MPD diameter (Lee et al. 2007; Tanno et al. 2008; Sawai et al. 2010; Uehara et al. 2011; Maguchi et al. 2011; Ohno et al. 2012). It is still controversial whether an increase in cyst size alone is an adequate predictive sign of malignancy (Rautou et al. 2008; Bae et al. 2012; Kang et al. 2011) or not (Lee et al. 2007; Tanno et al. 2008; Sawai et al. 2010; Uehara et al. 2011; Maguchi et al. 2011; Ohno et al. 2012).

3.7 Pancreatic Ductal Adenocarcinoma in Patients with BD-IPMN

Pancreatic ductal adenocarcinoma (PDAC) may develop independently in the pancreas separately from IPMNs, especially in BD-IPMN (Tanaka et al. 2012; Yamaguchi et al. 2002). The frequency of PDAC concomitant with IPMN was 4.1–9.3 % in the resected case studies (Yamaguchi et al. 2002; Ingakul et al. 2010; Kanno et al. 2010; Tanno et al. 2010a; Yamaguchi et al. 2011).

During the last several years, an increasing number of reports for the occurrence of PDAC in follow-up patients with IPMN have been published (Sawai et al. 2010; Uehara et al. 2011; Maguchi et al. 2011; Tada et al. 2006; Uehara et al. 2008; Tanno et al. 2010b; Ikeuchi et al. 2010) (Table 3.5). The mean frequency of occurrence of PDAC concomitant with IPMN was 2.8 % (range, 1.4–8.0 %) during follow-up. It is noted that the frequency (2.8 %, 30/1,085) was similar to the frequency of malignant transformation of BD-IPMN (2.7 %, 35/1,293) during the follow-up.

These findings suggest that BD-IPMN may be an indicator for a precancerous state of the pancreas and that PDAC may have not infrequently occurred in the pancreas distinct from BD-IPMN.

The long-term prognosis of the patients with BD-IPMN is still unclear. However, a multicenter study in Japan (Maguchi et al. 2011) described that the patients with PDAC distinct from BD-IPMN had a poor prognosis, whereas patients with malignant BD-IPMNs, including noninvasive and invasive carcinomas, had a relatively better prognosis after surgical treatment.

In conclusion, special attention should be paid to the occurrence of PDAC in the entire pancreas when performing follow-up examinations in patients with BD-IPMN including postoperative status, and shorter interval surveillance is required.

Table 3.5 Occurrence of PDAC in patients with BD-IPMN during follow-up

Author (year)	Number of cases	Number of PDAC concomitant with IPMN (%)	Follow-up period (year)
Tada et al. (2006)	197[a]	5 (2.6)	3.8
Uehara et al. (2008)	60	5 (8.0)	7.3
Tanno et al. (2010b)	89	4 (4.5)	5.3
Ikeuchi et al. (2010)	145	5 (3.4)	4.6
Sawai et al. (2010)	103	2 (1.9)	4.9
Maguchi et al. (2011)	349	7 (2.0)	3.7
Ohno et al. (2012)	142	2 (1.4)	3.5
Total	1,085	30 (2.8)	

[a]Included pancreatic cyst

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Effect of Daikenchuto (TJ-100) on Postoperative Bowel Motility and on Prevention of Paralytic Ileus after Pancreaticoduodenectomy: A Multicenter, Randomized, Placebo-controlled Phase II Trial (The JAPAN-PD Study)

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We conducted a multicenter, randomized, controlled trial in patients with pancreaticoduodenectomy to investigate the efficacy of Daikenchuto (TJ-100), which is a Kampo medicine (traditional Japanese herbal medicine), for its effect on postoperative bowel motility and for prevention of postoperative paralytic ileus. This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) time to having the first postoperative passage of flatus. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the Gastrointestinal Symptom Rating Scale (GSRS) Score (Japanese Version) and visual analogue scale, the change ratio of abdominal circumference, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery. Two hundred and twenty patients are required in the study (110 patients per group).

Key words: pancreaticoduodenectomy – Japanese herbal medicine (TJ-100) – postoperative paralytic ileus – surgical site infection

INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the most extensive surgical procedures with high incidence of morbidity for patients with periampullary disease. Improved surgical skills and modern perioperative care reduced the mortality rate, but there is still a high morbidity rate, which remains about 40–50% (1, 2). In these days, several investigators have reported that a fast-track program reduced the incidence of morbidity and the postoperative hospital days in PD (3, 4). To keep normal state of the digestive function is an essential factor affecting the recovery of postoperative paralytic ileus in the fast-track program. Daikenchuto (TJ-100), which is a traditional Japanese herbal medicine, has been used for the prevention and treatment of postoperative ileus in Japan (5, 6). TJ-100 extract powder (Tsumura & Co., Tokyo, Japan) is manufactured as an aqueous extract containing

2.2% Japanese pepper, 5.6% processed ginger, 3.3% ginseng and 88.9% maltose syrup powder. To date, there has been no prospective study investigating the effect on the normalization of bowel peristalsis after PD. Therefore, we have started a multicenter, randomized, placebo-controlled phase II trial of TJ-100 to evaluate its efficacy for supporting postoperative bowl motility and preventing postoperative paralytic ileus after PD.

PROTOCOL DIGEST OF THE STUDY

Objective

Postoperative paralytic ileus after surgery for intraperitoneal organ is one of the common complications (>90% in many series) and recognized as an inevitable response to intraperitoneal surgery (7–9). The JAPAN-PD study is a multicenter, randomized, double-blinded, placebo-controlled, phase II trial, and planned to implement for patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of pancreas who are expected to undergo PD to investigate an enhancement effect of the bowel motility and the prevention effect of TJ-100 for postoperative paralytic ileus after PD.

Resources

A research grant from a non-profit organization: epidemiological and clinical Research Information Network (ECRIN).

Endpoints

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus lasting over 72 h after surgery and (ii) the time to having the first postoperative passage of flatus. In this study, the postoperative paralytic ileus is defined as the delay of the first postoperative flatus for over 72 h (3.0 days) after surgery (7–9), or the status requires some intervention of treatment for ileus. Every 12 h are counted as 0.5 postoperative day and 24 h as 1.0 postoperative day. The secondary endpoints are the incidence of postoperative paralytic ileus in cases that combined with/without enteral alimentation, QOL assessment by the GSRS Score (Japanese Version) and visual analogue scale about abdominal pain and abdominal distention, the change ratio of abdominal circumference on postoperative day 3 and operative day just after surgery, the incidence of postoperative complication, the number of postoperative hospital days, the incidence of surgical site infection and the incidence of postoperative small bowel obstruction within 2 years after surgery.

Eligibility Criteria

Inclusion Criteria

(i) Patients with periampullary tumors (extrahepatic bile duct tumor, tumors of ampulla of Vater and duodenal tumor) and pancreatic tumors (pancreatic cancer, intraductal papillary mucinous neoplasm of the pancreas, pancreatic endocrine tumor and pancreatic neuroendocrine tumor) of the head of the pancreas who are scheduled to undergo PD.
(ii) Age of at least 20 years and older at the time of registration.
(iii) All patients provided written informed consent before initiation of study-related procedures.

Exclusion Criteria

(i) Clinically problematic cardiac disease.
(ii) Liver cirrhosis or active hepatitis.
(iii) Severe pulmonary disease (interstitial pneumonia, pulmonary fibrosis, pulmonary emphysema etc.).
(iv) Chronic renal failure requiring hemodialysis.
(v) Other malignant disease that can influence the adverse effect.
(vi) Patients with tumors requiring resection of colon.
(vii) Patients who are expected to have severe intra-abdominal adhesion due to past surgical history or past peritonitis history.
(viii) Patients who had used gastrointestinal prokinetic medication, antipsychotic medication or antidepressants.
(ix) Patients who had used Japanese herbal (Kampo) medicines within 4 weeks before registration.
(x) Pregnant or lactating women.
(xi) Any other medical condition that makes the patient unsuitable for including into the study according to the opinion of the investigator.

Registration

An eligibility report form is sent to the registration center at ECRIN. Eligible patients are centrally randomized to either Arm A (TJ-100) or Arm B (placebo) using primary disease, the presence of preoperative therapy, the presence of pylorus ring in the remnant stomach and the institution as balancing variables. Information regarding the necessary follow-up tests is then sent from the registration center at ECRIN.

Treatment Methods

ARM A

In the TJ-100 group, TJ-100 at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and

postoperative day 1, TJ-100 were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

ARM B

In the placebo group, placebo at a dose of 5 g was administered orally as a solution three times daily immediately before meals or every 8 h for 17 consecutive days (15 g/day from preoperative day 3 to postoperative day 14). On the operative day (only once immediately after operation) and postoperative day 1, placebo were administered as a diluent via enteral feeding tube (10 Fr), which terminates in jejunum to prevent aspiration pneumonia.

Criteria of Dose Reduction and Discontinuation of the Protocol Treatment

In cases where Grade 2 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the patient will be administered reduced dose of the test drug to a dose of 2.5 g, and in case where Grade 3 postoperative diarrhea or other clinical adverse effects (CTCAE version 4.0 criteria) are observed, the protocol treatment will be immediately discontinued.

Data Collection

Data will be collected prospectively for all patients including history, physical examination, laboratory data, pathologic examination, perioperative clinical information and complications.

Study Design and Statistical Analysis

This clinical trial primarily evaluates the co-primary endpoints: (i) the incidence rate of postoperative paralytic ileus for over 72 h after surgery and (ii) the time to have the first postoperative passage of flatus. The multiplicity issue (inflation of the type I error) due to analyzing two endpoints is dealt with using the Bonferroni method. That is, the significance levels for both tests are set at 2.5% to control the overall type I error rate. The sample size was calculated on the basis that the incidence rate of postoperative paralytic ileus for 72 h after surgery was expected to be 90% for the placebo group. In case the effect of reducing the incidence of postoperative paralytic ileus is assumed to be 20% for the TJ-100 group (that is, incidence rate = 70%), the least number of patients to provide the 85% power necessary to confirm the superiority of a group was calculated to be 94 per group for a two-sided 2.5% significance level test. Furthermore, given the number of patients, 84% statistical power is retained to prove the superiority in terms of time to occurrence of postoperative paralytic ileus for the hazard ratio of 0.62. The significance level for this inference is also set at 2.5%. Taking exclusion from analysis of about 15% into account, the number of patients to be accrued was set at 110 per treatment arm (220 in total). The first primary endpoint, incidence rate of postoperative paralytic ileus for 72 h after surgery, will be compared between the two treatment groups using the χ^2 test. The second primary endpoint, time to having the first postoperative passage of flatus, will be analyzed by constructing Kaplan–Meier curves as time-to-event plots. Differences between the curves are tested for significance using log-rank statistics.

PARTICIPATING INSTITUTIONS

Eleven leading Japanese institutions and hospitals (all of them are high volume center in pancreatic surgery) for PD are participating in this trial.

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Conflict of interest statement

None declared.

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Predictors of Malignancy in Intraductal Papillary Mucinous Neoplasm of the Pancreas

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

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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

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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

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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.