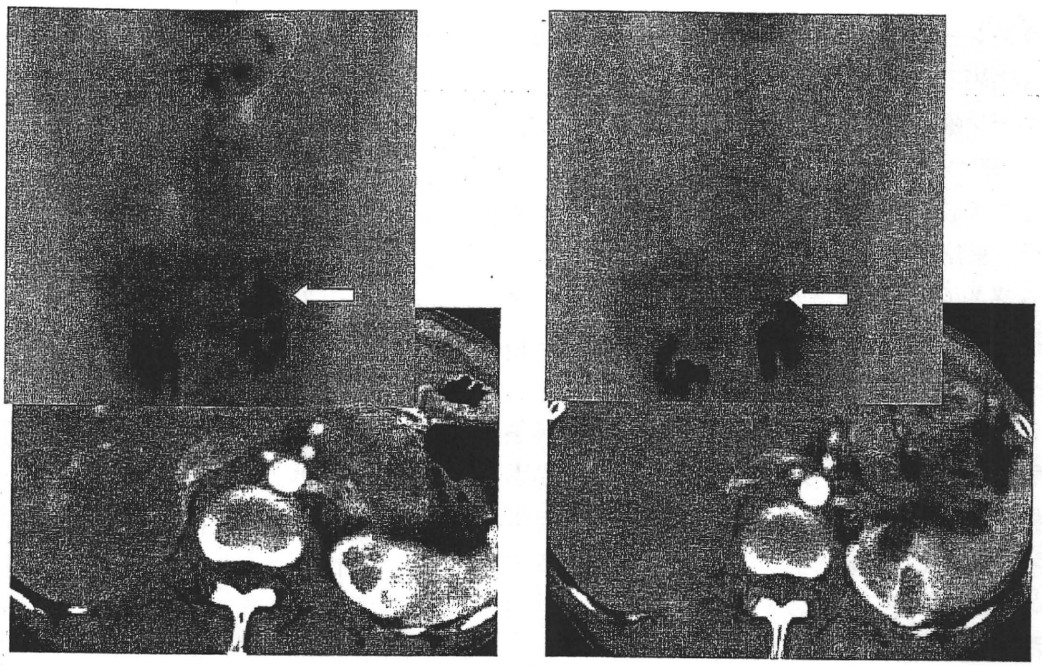

図1　症例：FDG-PET
治療開始後6か月での変化。腫瘍の縮小を認め，左鎖骨上リンパ節転移焼失。

2．進行膵癌に対する第Ⅱ相臨床試験

1）症例登録基準

登録基準は，①組織学的に確定診断された切除不能膵癌患者，②HLA-A24 または HLA-A2 陽性が確認されている，③前治療が行われていない，④performance status (PS) が0または1である，⑤臨床検査で臓器機能が保たれている，⑥20歳以上で本人からの文書による同意が得られていることとしている。

2）投与方法

治療に先立って，患者末梢血リンパ球のペプチド反応性およびペプチド特異的IgG抗体価を検討し，この結果を基に個々の患者に最適なペプチドを最大4種類選択する。これに不完全フロイントアジュバント（ISA 51）を加えてエマルジョン化し，3 mg ペプチド溶液にして最大4種類を毎週皮下投与する。GEM 1,000 mg/m^2 3週投与1週休薬で行い，4週で1クールというプロトコールで継続投与を行った。

1例においては治療開始後6か月時点で左鎖骨上リンパ節転移が消失し，原発巣の描出も極めて困難な症例が認められ，現在もPS 0のまま2年以上外来通院中である（図1）。現在登録を終了し最終結果を解析中である。また第Ⅰ/Ⅱ相臨床試験患者のなかで遠隔転移症例26例の解析では，奏効率27%で病勢コントロール率81%であった。MST は9.5か月で，1年生存率35%と非常に良好な結果であった。さらにこの解析で得られた結果として免疫反応が強く認められた症例は，そうではない患者に比べて生存期間が有意に延長することが認められ，免疫治療のよいレスポンダーと思われた（図2）[19]。

化学療法と免疫療法を併用した場合に特異免疫反応が増強するかどうかという疑問が存在する。われわれの一連の臨床研究からは，特異免疫機能の増強が94%の患者に観察されており，またこの反応はペプチドの用量依存性に出現することが観察された。

シクロフォスファミド，アドリアマイシンなどの化学療法による抗腫瘍効果は，その殺細胞効果だけによるものではなく，宿主免疫による腫瘍排除効果によることが知られている。最近になってGEMにも腫瘍特異的免疫を誘導する作用があることがわかってきた。この作用機序は，抗腫瘍免疫能を抑制するとされる制御性T細胞（Treg）の発見によりかなり明快になってきた。Treg は化学療法剤に対する感受性が他の免疫細胞よりも高いため，化学療法剤で減少し，立ち上がりも遅

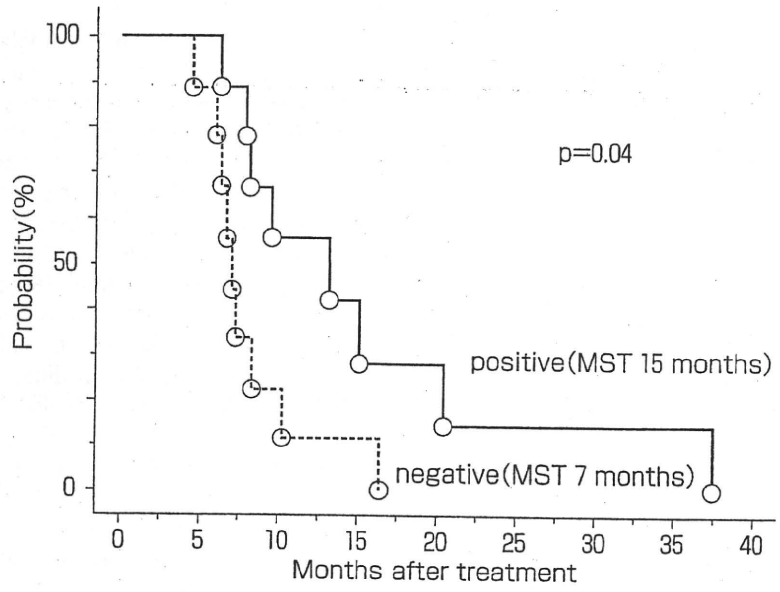

図2 免疫増強効果を示した症例の生存曲線
8回ワクチン接種後の免疫反応評価において，2種類以上のペプチドに対する細胞性免疫増強が得られた症例は，それぞれの非増強症例に比べ有意に生存期間が長い。実線が免疫増強症例，破線が非増強症例の生存曲線を表す。

いとされる。したがって，化学療法施行時は癌細胞が傷害されると同時に抗腫瘍免疫が誘導されやすい状態にあると思われる。このように化学療法と免疫療法の併用は切除不能膵癌症例で極めて新しく，有効性が期待される治療方法の一つになる可能性がある。

おわりに

期待と失望を繰り返してきた癌免疫療法ではあるが，癌ワクチン療法においては，近年化学療法との併用や術後補助療法としての有効性を評価するなど新規のアプローチによって従来では認められなかった臨床効果が期待されるようになり，国際的に承認をめざした開発競争が激化している。しかし，現時点では治療薬として承認されている癌ワクチンはなく，今後の実用化が待望されている。2008年度から新設された先端医療開発特区（スーパー特区）を活用した研究事業に癌ワクチン研究課題が採択され，これまで大学や研究所が主体になって基礎研究，臨床研究（トランスレーショナルリサーチ）の両面において牽引役を果たしてきた時代から一気に癌ワクチン実用化が効率的産学官連携プレーにより，飛躍的に進むものと予想される。

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主題Ⅰ-4 当科における膵頭十二指腸切除術後の膵腸吻合法の工夫と成績

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【目的】膵頭十二指腸切除術(PD、PpPD含む)は、高率に術後合併症が発生し、時に致死的となる場合がある。われわれは術後合併症率を低減するために吻合法の改変や工夫を行ってきたのでそれらの成績を報告する。

【方法】PDの再建方法は膵胆胃(十二指腸)の順に吻合した(結腸前経路)。膵空腸吻合は、2000年から2004年5月までの前期77例は嵌入法で膵管、胆管外瘻術を行い、2004年6月から2006年8月までの中期51例は柿田法変法でomental wrappingを付加し、閉鎖吸引式ドレーンの早期抜去を行い、膵管、胆管外瘻術の適応を制限した(膵管径<3mm、胆管径<10mm)。膵管空腸吻合時には、膵管や膵実質を把持することなく膵管内腔の視野展開が可能なITA holder(Internal Thoracic Artry)や神経鉤(膵管径2mm以下)を活用して安全な吻合を心がけている。2006年9月から2008年9月までの後期78例は中期と同様の吻合法でno stentingとした。前中期群と中後期群の合併症発生率を比較検討した。データは中央値(範囲)で表記した。

【結果】前期に対して中期群の経口摂取開始日や腹腔ドレーン抜去日は有意に早期であり($p<0.0001$)、後期群ではその傾向がさらに顕著となった。中期群のISGPF基準による膵液漏発生率(Grade B／C、6%)や、胃内容排泄遅延(DGE、6%)は前期群(19%、23%)と比較して有意に低率であった($p<0.05$)。全合併症率も同様の結果であった(39% vs 64%、$p=0.0109$)。後期群の膵液漏(14%)、DGE(8%)、全合併症(51%)率は中期群と比較して差は無かった。在院死、再手術および出血性合併症は前期(0%、4%、1%)、中期(2%、2%、0%)、後期(3.8%、2.5%、0%)で差は認めなかった。胆管空腸縫合不全や術後胆管炎の頻度は前期(1.3%、13%)、中期(2%、7.8%)、後期(0%、7.7%)で有意な差は無かった。在院日数に関して、前期(41日、18－132)、中期(24日、11－73)、後期(13日、8－101)と時間推移と共に有意に短縮した($p<0.05$)。

【結語】膵腸吻合法の変更により、膵液漏やDGEなど合併症率が低下し、膵胆管外瘻術をno stentingに変更後も合併症率に有意差なく在院日数が減少した。

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膵癌に対する腹腔鏡下細胞診と生検の意義*

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要約：膵癌は画像上遠隔転移がないと判断されても開腹時に微小肝，腹膜転移で非切除となることが10～20%と報告されている。膵癌の治療選択肢として個別化治療を行うためには，治療前の進展度診断はきわめて重要であり，腹腔鏡検査は微小肝・腹膜転移の描出と微量な腹水細胞診断に有用である。われわれは2007年より，画像上切除可能膵癌でCA19-9≧150 U/ml かつ腫瘍長径≧30 mmの症例と，切除不能局所進行膵癌症例に対して，微小遠隔転移診断目的に腹腔鏡検査を施行してきた。結果として腹腔鏡検査は，より正確な進展度診断となり，切除可能例では開腹非切除率の低下，そして切除不能局所進行膵癌症例に対しては治療方法の選択（化学療法か化学放射線療法）に有用であった。さらに今後，術前治療における微小遠隔転移症例を対象とするようなstaging migrationを低減するためにも有効である可能性が示唆された。

Key words：微小遠隔転移，洗浄細胞診，腹水細胞診，集学的治療

はじめに

膵癌は解剖学的特殊性ならびに高い生物学的悪性度から容易に周囲組織に浸潤性進展を来し，遠隔臓器に転移して発見されることが多いという特徴がある。外科的治療が唯一の根治性を追及する方法であるが，膵癌切除例ですら，その5年生存率は10%前後と予後不良である[1～3)]。このことは，膵癌に対する切除単独治療の限界を示唆しているとも考えられる[4)]。

膵癌の診断時に切除可能症例と判断される症例は15～20%にすぎず，さらにそれらの症例の中でおよそ10%前後の割合で開腹時に微小肝腹膜転移の存在により非切除となることが報告されている[5,6)]。われわれが以前より報告しているように，多列検出器CT（Multidetector row CT：MDCT）を使用することにより，血管浸潤の正診率や肝転移診断率が高まるもの[7)]，10 mm以下の微小肝腹膜転移の画像診断は画像診断が格段に進歩した現在でも限界がある。

膵癌における腹腔鏡検査の意義は，画像上遠隔転移が同定できない症例での微小肝腹膜転移や少量の癌性腹水の診断による正確な治療前進展度診断が可能となることにある[8,9)]。これにより，画像上切除不能局所進行例の遠隔転移診断による治療方法の選択（化学療法か化学放射線療法か），切除可能例の遠隔転移診断による開腹非切除率の低減や術前治療におけるstaging migrationの低減などが可能となる。

今回，われわれは2007年から2009年までの3年間で経験した画像上切除可能膵癌16例や切除不能局所進行39例において，微小遠隔転移診断のために腹腔鏡検査を施行してきたので，その経験に基づいて腹腔鏡検査における細胞診や組織診断の意義について報告する。

Ⅰ．腹腔鏡検査の対象と術前検査

当科では，2007年より画像上切除不能局所進行膵癌

* Clinical Significance of Cytological and Histological Results on Staging Laparoscopy in Patients with Pancreatic Cancer

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全例と，画像上切除可能症例において，非切除性に対する高危険群をCA19-9≧150 U/ml かつ腫瘍長径≧30 mm と設定し，高危険群に対して腹腔鏡検査を行ってきた。切除不能局所進行例は39例が，切除可能例は61例の内，高危険群16例が対象となった。

MDCTはAquilion® CT system（Toshiba Medical Systems, Tochigi, Japan）を使用して，動脈相，門脈相と平衡相を撮像し，検出器構成1.0 mm×64，横隔膜下肝臓の高さから腎下縁までスキャンし，スライス厚1.0 mm，再構成間隔0.5 mmの画像を再構成して，このデータをワークステーション（AquariusNet Viewer, TeraRecon Inc., San Mateo, CA, USA）へ転送した。動脈相と門脈相のデータからvolume dataを再構成し，軸位・冠状断・矢状断の画像を作成した上でシネ画像として繰り返し観察した。

当科における画像上切除可能例は，①膵頭体部癌では，腫瘍が総肝動脈，腹腔動脈や上腸間膜動脈と半周性未満で接していること，②門脈浸潤があっても切除することにより根治性が期待されること，③遠隔転移がないこと（傍大動脈リンパ節転移含む），④穿刺可能な腹水貯留がないことである。膵体尾部癌では，大動脈浸潤がないこと，上腸間膜動脈と半周性未満で接していること，腹腔動脈幹浸潤があっても上腸間膜動脈浸潤が半周性で胃十二指腸動脈に進展していない症例，と規定している。一方で，切除不能局所進行症例は，画像上遠隔転移（傍大動脈リンパ節転移含む）や穿刺可能な腹水貯留がなく，切除可能の基準に入らない局所進行例としている。傍大動脈リンパ節転移は，PET検査で異常集積のある場合，と規定している。また，穿刺可能な腹水貯留症例の場合には積極的に超音波ガイド下に経皮的腹水細胞診を行っている。

また，内視鏡的細胞診や組織診断で治療前に膵癌の診断が得られていない場合（膵癌の疑い含む），腹腔鏡や開腹にて生検を行い，原則，細胞学的もしくは組織学的に膵癌と診断されてから治療を行う方針としている。

Ⅱ．腹腔鏡検査の方法

全身麻酔下に臍横部の15 mm程度の皮膚切開から12 mm trocarを留置して，腹腔鏡を挿入する。さらにもう2ヵ所にtrocarを留置する。まず，腹腔全体を観察し腹膜結節の有無を確認する。必要時には既往手術例でみられる癒着を剝離する。当科では，既往手術に関係なく腹腔鏡検査で積極的に癒着剝離を行い，腹腔内の観察困難時にはためらうことなく小開腹下に観察

図1　腹腔鏡下膵生検

を行っている。次に肝表面の観察に移り，肝表面の結節の有無を確認する。次に，ダグラス窩に少量の腹水が存在している場合には，可能な限り頭低位としてダグラス窩に貯留している腹水内に腹腔鏡を潜水させて，腹膜翻転部の結節の有無を検査する。その後，腹水を採取して術中細胞診検査に提出する。腹水の存在がない場合には，生理食塩水100 mlで腹腔内を洗浄し，同様に腹膜翻転部の結節の有無を確認した後，50 mlの洗浄液を採取し，細胞診検査に提出している。全例に腹水細胞診もしくは洗浄細胞診を施行した。さらに，2本の腸鉗子を用いて横行結腸を挙上し，結腸間膜の結節の有無，Treiz靭帯の空腸から回腸末端部までの小腸間膜の結節の有無，その他の結腸や直腸間膜の結節の有無を調べる。腹膜や肝表面に白色調充実生結節を認める場合には，腹腔鏡下超音波検査で明らかに嚢胞性病変と確認される場合を除き，生検を行い術中迅速検査で転移の有無を確認している。さらに，超音波検査で肝内部の結節性病変の有無をチェックしている。上記の手技を行い，術前に内視鏡的細胞診や組織診検査にて腺癌と診断されていない場合にのみ，網嚢や小網を開放し膵腫瘍を肉眼的に確認し，18 G trucut needle biopsyを使用した超音波ガイド下膵生検を行っている（図1）。

Ⅲ．切除不能局所進行例における腹腔鏡検査成績

画像上，切除不能局所進行膵癌症例は，腹腔鏡検査で微小遠隔転移がなければ化学放射線療法を，転移があれば全身化学療法を施行する方針としている。過去3年間に経験した画像診断上，切除不能局所進行膵癌症例は41例あり，内39例に腹腔鏡検査を行った。残りの2例はperformance statusが2以上の症例で腹腔

表 1　腹腔鏡検査における腺癌診断率

		切除可能	局所進行	p 値
細胞診	腹水	0/3（0%）	13/17（76%）	0.03
	洗浄	5/13（38%）	10/22（45%）	0.73
肝生検		3/16（19%）	7/39（18%）	1.00
腹膜生検		1/16（6%）	12/39（31%）	0.08
遠隔転移率		5/16（31%）	21/39（67%）	0.03

鏡検査を拒否されたため，化学療法を施行した。年齢の中央値 64（42～82）歳，膵体部癌比率 50%，最大腫瘍径 41（21～91）mm であった。表 1 に示すように，細胞診陽性率は（59%，23/ 39）であった。腹膜転移 12 例（31%），肝転移 7 例（18%）に認め，何らかの遠隔転移を認めた症例は 26 例（67%）で，微小転移を認めない切除不能局所進行癌症例は 13 例（33%）にすぎなかった。なお，腹腔鏡検査で遠隔転移を認めない局所進行膵癌の 1 例（膵体尾部欠損例）で化学放射線療法後に腫瘍縮小を認めたため，膵全摘，門脈ならびに総肝動脈合併切除を行い，組織学的根治切除となり，術後 9ヵ月現在無再発生存例を経験している。

Ⅳ．切除可能症例（高危険群）における腹腔鏡検査成績

過去 3 年間の 61 例の切除可能膵癌症例の内，CA19-9≧150 U/ m*l* かつ腫瘍長径≧30 mm を開腹非切除の高危険群と設定して，16 例（26%）に腹腔鏡検査を施行した。本来全例に行うべきかもしれないが，本邦における保険適応の問題や手術室利用の制限などを鑑みて，合理的な運用を考慮したときに，過去の報告にあるように，開腹非切除症例の高危険群は CA19-9 値と腫瘍径とする報告が多い[10,11]。当科における過去の症例の検討では，CA19-9≧150 U/ m*l* かつ腫瘍長径≧30 mm の因子の非切除性に対する正診率が有意に高かったために，両因子を採用して前向きに腹腔鏡検査施行例の選別を行ってきた。年齢の中央値 66(42～82)歳，膵体部癌比率 31%，最大腫瘍径 35（30～70）mm であった。これらの高危険群 16 例に腹腔鏡検査を行ったところ，5 例（31%）に遠隔転移を認め，不要な開腹手術が避けられた。さらに，微小遠隔転移による非切除例の術後在院日数の中央値（範囲）は 4 日（2～9 日）で，術後より化学療法開始までの日数の中央値（範囲）は 9 日（6～27）日と短期間であった。一方で，開腹非切除の低危険群である 45 例は直接開腹術が行われたが，2 例に遠隔転移を認めた。結果的に 61 例の開腹非切除率は3%となり，当該期間の過去の症例の 21%（腹腔鏡検査無し）と比較すると有意に低率であった（p＜0.05）。最終的に切除施行した 54 例は 96%が根治切除となった。

表 2　部位別腹腔鏡下生検診断率

切除可能膵癌症例			
部位	生検件数	腺癌	非悪性
肝	6	3	3
腹膜	1	1	0
膵	1	0	1
切除不能局所進行症例			
部位	生検件数	腺癌	非悪性
肝	8	7	1
腹膜	12	12	0
膵	4	4	0

Ⅴ．腹腔鏡検査における細胞診・生検の意義

表 1 が示すように，画像上切除可能 16 例の内，微量腹水細胞診が 3 例，洗浄細胞診が 13 例に行われた。結果的に腹水細胞診陽性例は皆無で，洗浄細胞診で腺癌診断例は 5 例で，内 3 例は他部位に遠隔転移がなく洗浄細胞診のみ腺癌診断例であった。一方で，画像上切除不能局所進行例で 17 例の微量腹水細胞診と 22 例の洗浄細胞診が行われた。腹水細胞診で腺癌診断率は 76%（13/ 17）で，洗浄細胞診で腺癌診断率は 45%（10/ 22）であり，全体で 59%（23/ 39）であった。洗浄細胞診で腺癌診断例の内 5 例が他部位に遠隔転移なく洗浄細胞診のみ腺癌診断例であった。両群間の比較では，切除可能膵癌の腹水細胞診での腺癌診断率は有意に低率であった（p＝0.031）。

組織診断の検討では（表 2），腹腔鏡検査における腹腔内観察において，肝や腹膜に白色調で充実性腫瘤を認めた場合，腹腔鏡下生検が行われ，術中迅速病理検査に提出された。結節の大きさは，大網に長径 15 mm の結節を認めた 1 例を除き，長径 5 mm 以下の大きさであった。画像上切除可能例で 8 件の内 4 件が腺癌と診断され，切除不能局所進行例で 24 件の内，23 件の腺癌診断例があり，局所進行例で有意に高率であった（p＝0.0086）。病変の部位別には，腹膜転移と膵生検の診断率は 94%（17/ 18）であったことに対して，肝生検では 71%（10/ 14）と低率であった。4 例の非悪性病変は，肝表面の炎症性病変，瘢痕組織や壊死組織という結果であった。肝表面に存在する長径 5 mm 以下の白色調充実生腫瘤の肉眼的鑑別は困難であるため，組織診断が重要であると考えられた。

膵生検は膵頭部癌2例と膵体尾部3例に行われた。これらの症例は2008年以前の症例であり，2008年度より消化器内科が積極的にEUS-FNAを施行する方針となり，それ以降腹腔鏡下膵生検を施行する症例は皆無となった。腹腔鏡下膵生検は，腫瘍撒布の面から安全性は確立されていないため，特に切除可能例の生検ではなるべく避ける方針をとっている。結果的に4例が腺癌と診断されたが，残りの1例は炎症性細胞のみと診断され，開腹下に生検を行った際に，膵腫瘤内より膿性排液を認めたため慢性膵炎の可能性を考え閉腹したものの，1ヵ月後に膵頭十二指腸切除術を施行し通常型膵癌の診断を得た症例である。

VI. 合併症とport site recurrence

過去3年間で，切除可能ならびに局所進行膵癌に対して55例の腹腔鏡検査を行ってきた。手術時間中央値68（20～192）分で，100 m*l*以上の出血を来した症例は認めなかった。7例（13%）に開腹手術を必要としたが，その内訳は，腫瘍が膵体部から門脈や動脈に進展しており腹腔鏡下生検が危険と考えられた4例，上腹部手術既往1例，高度の癒着を伴う急性虫垂炎を合併した1例，既往手術のない高度癒着1例であった。合併症は小腸損傷の2例で，うち1例は術中損傷，他1例は術後1日目に腹膜炎症状を呈し，小開腹下に修復を必要とした小腸の小穿孔（3 mm径）症例であった。後者では治療開始が1週間遅延したが，その後は予定通りの治療が行われた。

晩期合併症の一つとして，port site recurrenceの出現があげられ，当科でも1例を経験している。局所進行膵癌症例で治療経過中に肝転移や腹水病変が出現した後にport site recurrenceを認めた症例であったが，同転移巣の増大速度は緩やかで最終的に肝転移，癌性腹膜炎により死亡した。

ま と め

今回の腹腔鏡検査では，画像上切除不能局所進行膵癌症例の67%の症例で，切除可能例の11%の症例（5例は腹腔鏡，2例は開腹で診断）で何らかの微小遠隔転移を認めており，膵癌の悪性度の高さを再認識することとなった。局所進行例では，腹水細胞診陽性率や何らかの遠隔転移率が切除可能例と比較して有意に高率であり，遠隔転移例が多数を占めた。また，局所進行例における生検の診断率が高く，同症例で白色調充実性腫瘤を認める場合は，転移病変である可能性が高いと考えられる。

新地ら[9]は同様の検討を行い，腹腔鏡検査で遠隔転移例（化学療法施行）と真の局所進行例（化学放射線療法施行）とに分類したとき，局所進行例の生存期間が有意に延長したことを報告している（生存期間中央値：13.6ヵ月 vs 5.9ヵ月）。当施設においても，微小遠隔転移の有無によって治療方法を変更しており，遠隔転移例では全身化学療法を，局所進行例では化学放射線治療を行っている。画像上同定できない微小転移を診断可能な腹腔鏡検査は，進展度診断別の個別化治療の選択に有用である。

また，画像上切除可能膵癌に対しては，術前化学放射線療法を施行後に腫瘍増大や遠隔転移の新規出現例を除き切除術を行っている。当科を含めた数施設が以前より報告しているように，術前治療では約20%の症例が遠隔転移のために切除不能となっている[12~14]。当科での術前化学放射線療法後切除不能例の生存期間中央値は5.5ヵ月で1年以上生存した症例は皆無であった。これらの症例では化学放射線療法施行前よりCT画像では捉えきれない微小肝・腹膜転移が存在していた可能性も否定できない。これらの経験を踏まえて，遠隔転移症例には放射線治療を行うことなく，全身化学療法の継続が重要と考えており，術前治療を行う症例には腹腔鏡検査を行い，微小遠隔転移の診断に努めている。また，術前治療を行わない症例においても，遠隔転移の高危険群に対して腹腔鏡検査を行うことにより微小遠隔転移を効率的に診断することが可能であった。

腹腔鏡検査は，腹水や洗浄細胞診，肝や腹膜結節の組織診，内視鏡的細胞診断や組織診断困難例では，腹腔鏡用超音波ガイド下に膵腫瘤生検も可能である。上腹部手術既往例では，癒着による術野の制限のため，開腹を必要とすることがあるが，およそ1時間程度で施行可能であり，在院日数も術後3日程度と短期間である。昨今の本邦における手術室利用の制限という面や健康保険報酬の面からは，腹腔鏡検査の施行は制限されているのが現状であるが，術前治療を行う場合や切除不能局所進行膵癌症例では積極的に腹腔鏡検査を行い，細胞診や組織診断を行って正確な進展度診断に基づいた治療方針の決定に必要不可欠な検査法と考えられる。

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ORIGINAL ARTICLE

Is a Nonstented Duct-to-Mucosa Anastomosis Using the Modified Kakita Method a Safe Procedure?

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Objectives: After standardization of the perioperative management of pancreaticoduodenectomy, we retrospectively compared results in nonstented pancreaticojejunostomy with external-stented pancreaticojejunostomy.

Methods: The study population included 129 consecutive patients who underwent pancreaticoduodenectomy between 2004 and 2008. The postoperative mortality and morbidity were compared between 51 patients with restrictive use of external stenting (group A) and 78 patients without external stenting (group B). The patient with a pancreatic duct of less than 3 mm in diameter was 31% in group A and 46% in group B.

Results: There were no differences in postoperative morbidity and mortality between the 2 groups. Although the frequency of overall postoperative pancreatic fistula development was significantly higher in group B than in group A (44% vs 27%, $P = 0.0004$), there was no difference in grade B/C postoperative pancreatic fistula rate (group A: 5.9% vs group B: 14.1%). The length of in-hospital stay in group B was significantly shorter than group A (13 vs 24 days, $P < 0.0001$). There were no differences in postoperative morbidity and mortality between subgroups that were consisted of patients with small pancreatic duct diameter.

Conclusion: This retrospective single-center study showed that nonstented duct-to-mucosa anastomosis was a safe procedure and was associated with a shortened in-hospital stay.

Key Words: grade B/C, pancreatic duct diameter less than 3 mm, early drain removal, in-hospital stay, morbidity, mortality

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In recent years, pancreaticoduodenectomy (PD), including pylorus-preserving PD (PpPD), has been increasingly performed to treat a variety of diseases of the pancreas and periampullary region. Advances in surgical techniques and appropriate perioperative management have improved the short-term outcome of PD. In most high-volume centers, the mortality rate has decreased to less than 5%, although postoperative morbidity rates remain at approximately 40%.[1–8] To reduce the frequency of postoperative pancreatic fistula (POPF) development, we introduced the following departmental guidelines[9]: (i) modified Kakita method[10] for performing a pancreaticojejunostomy (PJ), (ii) omental wrapping around the PJ, (iii) early removal of closed-suction drain, and (iv) restrictive use of pancreatic and biliary duct stenting. Following those approaches, postoperative morbidity (39%), frequency of grade B/C pancreatic fistula (6%), and delayed gastric emptying (6%) have all been significantly reduced. According to this policy, external stents were inserted across the anastomosis to drain the pancreatic duct in the limited number of patients who had a pancreatic duct diameter of less than 3 mm and/or with bile duct diameter of less than 10 mm. However, there have been reports of some severe complications associated with the stenting tube.[11–13] These have included acute pancreatitis due to subsequent occlusion or bending of the stenting tube, late anastomotic stenosis after iatrogenic injury sustained when withdrawing the external stenting tube, or hepatic abscess formation caused by internal stent migration.[11–13] After standardization of the anastomotic method and perioperative management of PD,[9] since September 2006, we have performed nonstented PJ even in patients with a pancreatic duct diameter of less than 3 mm and/or with a bile duct diameter of less than 10 mm. The data on postoperative complications were collected from the prospective database in Kansai Medical University. We herein retrospectively compared the results from nonstented PJ with external-stented PJ after pancreaticoduodenectomy.

MATERIALS AND METHODS

From June 2004 to September 2008, 129 consecutive patients with pancreatic and periampullary disease underwent PD including PpPD by 2 pancreatic surgeons at Kansai Medical University Hospital. Cases were excluded from the study if they had undergone: duodenal-preserving pancreatic head resection (n = 1), medial segment–preserving pancreatectomy (n = 1), median pancreatectomy (n = 3), total pancreatectomy (n = 3), PD without PJ (post–median pancreatectomy, n = 1), partial pancreatectomy (n = 5), and emergent PD for patients with the lasting duodenal bleeding from gastrointestinal tumor (n = 1). The PJ was performed using the modified Kakita method as described in a previous paper.[9] Briefly, 8 absorbable interrupted stitches were placed in the pancreatic duct and jejunal mucosa in end-to-side fashion, and an approximation of the jejunal wall and the pancreatic stump was made using 3 or 4 nonabsorbable interrupted penetrating stitches. We routinely used the internal thoracic artery (ITA) holder to obtain good visualization of the anastomosis.[14] Duct-to-mucosa anastomosis can be difficult to perform when the pancreatic duct is not dilated and the lumen of duct is easily flattened in patients with normal pancreatic parenchyma, and the insertion of an ITA holder into the duct lumen in such cases enables excellent visualization without retaining the duct or pancreatic remnant. Before closing the abdomen, the omentum was wrapped around the pancreatic anastomosis. Routinely, 2 closed-suctioned drains were placed in the pancreatic anastomosis area. Our policy was to remove drains early between 3 and 6 days after the operation in patients without infection-induced systemic inflammatory response syndrome (SIRS)[15] when POPF defined by the International Study group of Pancreatic Fistula[16] was absent or grade A, or when fluid drained was less than 200 mL/d. When POPF was clinically diagnosed as grade B, the perianastomotic drain was

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replaced, and in some cases, closed lavage was performed with 500 to 3000 mL of natural saline solution, depending on the amylase level in the drained fluid. On developing POPF, all attempts were made to maintain per os and enteral feeding. All patients with obstructive jaundice first underwent endoscopic nasogastric/retrograde bile drainage or percutaneous transhepatic drainage, and it was performed in 61% of patients. All patients received prophylactic antibiotics intraoperatively and for 1 or 2 days postoperatively. The nasogastric tube was routinely removed on postoperative day (POD) 1 after confirmation that the volume of drainage fluid was less than 200 mL/d. Postoperative enteral nutrition through a jejunostomy tube was initiated at POD 3 in all patients. Oral food intake was initiated at POD 5 or 6. Once the patient was getting 50% of required nutrition from an oral diet, enteral nutrition was stopped, and the jejunostomy tube was finally withdrawn at POD 21 at an outpatient clinic. Peripancreatic drainage fluid was collected, and the amylase level was measured and monitored on PODs 3 and 6 and every 3 days thereafter as needed. The date of discharge from hospital was decided by the senior surgeons and was taken once the patient could take more than 50% of solid food served and was afebrile with falling C-reactive protein levels less than 5 mg/dL. No patients had prophylactic octreotide to prevent POPF development and thromboembolic prophylaxis with low-molecular-weight heparin. All complications were prospectively recorded into a prospective pancreatic database.

Group A

Group A consisted of 51 consecutive patients who underwent PD from June 2004 to August 2006; in these patients, the semiclosed external stenting of pancreatic and biliary ducts (polyethylene tube; Sumitomo Bakelite Co, Tokyo, Japan) was used in cases with a pancreatic duct of less than 3 mm in diameter (16 patients, 31%) and with a bile duct of less than 10 mm in diameter (13 patients, 25%). This group has the same population as presented in the previous article.[9]

Group B

Group B consisted of consecutive 78 patients who underwent PD from September 2006 to September 2008. All patients underwent PJ without external stenting of the pancreatic and biliary duct. In this group, 36 patients (46%) had a pancreatic duct of less than 3 mm in diameter.

Definition of Postoperative Complications

The overall general and surgery-related complications were recorded in this study. These included delayed gastric emptying, POPF, wound dehiscence, intra-abdominal infection, abdominal abscess formation, cardiopulmonary disorder, hemorrhagic complication, peritoneal/pleural effusion, anastomotic leakage, marginal ulcer formation, and diarrhea and other complications. Each day that a patient demonstrated clinical symptoms of SIRS[15] was recorded. Sepsis was considered to be present if a patient had any complication involving clinical symptoms of infection-induced SIRS that continued for more than 2 inpatient days. Clinical symptoms of SIRS within the first 4 PODs were excluded as a systemic response to surgical stress.

The POPF was defined according to the International Study group of Pancreatic Fistula criteria.[16] Abdominal abscess, including liver abscess, was defined as a collection of pus or infected fluid confirmed by ultrasound, computed tomography–guided aspiration and culture, or a second laparotomy. Delayed gastric emptying was defined according to the International Study Group of Pancreatic Surgery.[17] Wound dehiscence was diagnosed as an open wound with or without the clinical presence of pus or microbiological findings of bacteria. Intra-abdominal infection was regarded as radiological findings of fluid collection (pleural effusion and/or ascites) or microbiological findings of bacteria with infection-induced SIRS. Peritoneal/pleural effusion was defined as more than 200 mL/d of drained fluid beyond the 14th POD. Anastomotic leakage was radiologically diagnosed by leakage of contrast agents from the anastomosis. Upper gastrointestinal endoscopy for marginal ulcer formation was performed when patients showed signs of appetite loss, epigastralgia, or bloody discharge from the nasogastric tube or in the stools. Hemorrhagic complication was defined as intra-abdominal or intestinal bleeding requiring blood transfusion, operation, and/or radiological intervention. Aspartate aminotransferase or alanine aminotransferase levels of more than twice the upper limit of normal reference indicated postoperative liver dysfunction, including cholangitis. Death of a patient for any reason was regarded as in-hospital death.

Statistical Analysis

Mortality and morbidity after PD were calculated for each group and were compared between groups A and B. Patient variables included age, sex, clinical diagnosis, comorbid disease, obstructive jaundice, operative variables, preoperative blood tests, and preoperative chemoradiation. Operative variables included the type and duration of operation, estimated blood loss, type of blood transfusion, and extent of operation, including resection of adjacent organs and portal vein. All data were entered into an electronic database on a personal computer, and continuous variables are expressed as median values and ranges. Statistical analyses including Mann-Whitney U test and Fisher exact test were performed using StatView Version 5.0 for Windows (SAS, Inc, Cary, NC). The profound factors identified by the univariate analysis were further examined by multivariate analysis using logistic regression analysis to determine independent significant factors for grade B/C POPF after PD. $P < 0.05$ was considered significant.

RESULTS

Patient Demographic and Baseline Characteristics Including Surgical Details

Baseline and operative characteristics of the 129 patients enrolled in the study are shown in Table 1. Most variables did not differ significantly between the 2 groups. However, compared with group B (n = 78), in group A (n = 51), the operation time was significantly longer ($P = 0.0086$), and external pancreatic stenting and bile duct stenting were more frequently performed ($P < 0.0001$).

Postoperative Complications

The postoperative course was complicated in 47% of the 129 patients. As shown in Table 2, there were no differences in the frequency of overall complications, septic complications, reoperation, and in-hospital death between the 2 groups. Among the listed complications, although the frequency of overall POPF was significantly higher in group B compared with group A patients (group A: 27% vs group B: 44%; $P = 0.0004$), there was no difference in the incidence of grade B/C of POPF (group A; 5.9% vs group B; 14.1%). Most POPF was classified as grade A (group A: 57%, group B: 68%) that was not clinically relevant.

TABLE 1. Patient Demographics and Baseline Characteristics

Parameters	Group A (n = 51)	Group B (n = 78)	*P*
Pancreatic duct diameter (≥3 mm:<3 mm)	35 (69):16 (31)	42 (54):36 (46)	NS
Pancreatic duct drainage (+:−)	16:35	0:78	<0.0001
Bile duct drainage (+:−)	13:38	0:78	<0.0001
Age, y	68 (51–84)	66 (36–90)	NS
Male-female ratio	33:18	51:27	NS
Disease (P:B:A)	29:9:13	46:13:19	NS
Benign-malignant ratio	4:47	13:65	NS
Total bilirubin, mg/dL	0.7 (0.3–4.7)	0.7 (0.2–3.6)	NS
AST, U/L	24 (12–77)	25 (13–236)	NS
Amylase, U/L	70 (11–473)	78 (17–300)	NS
Albumin, g/dL	3.7 (2.3–4.5)	3.9 (1.9–4.8)	NS
WBC, $\times 10^2$/mL	50 (31–98)	52 (24–124)	NS
Hb, g/dL	11.6 (8.3–14.1)	11.5 (7.7–15.8)	NS
Comorbid disease (−:+)	19:32	24:54	NS
DM (−:+)	32:19	53:25	NS
Jaundice (−:+)	18:33	32:46	NS
CRT (+:−)	7:44	5:73	NS
Type of operation (PD:PpPD)	33:18	42:36	NS
Operation time, min	523 (355–795)	468 (275–714)	0.0086
Blood loss, mL	1140 (212–6420)	952 (272–5238)	NS
Transfusion (allo:auto:none)	16:30:5	22:49:7	NS
Resection of other organs (+:−)	7:44	19:59	NS
Day of drain removal, POD	7 (4–30)	4 (3–50)	<0.0001
In-hospital stay, POD	24 (11–73)	13 (8–101)	<0.0001

Table shows median value (range) or number of patients (%).

NS indicates not statistically significant; P:B:A, pancreatic disease–biliary disease–ampullary disease; AST, aspartate aminotransferase; WBC, white blood cell count; Hb, hemoglobin; DM, diabetes mellitus; CRT, preoperative chemoradiation therapy; allo, allogenic blood transfusion; auto, autologous blood transfusion; none, no transfusion.

The leakage of PJ, as shown radiologically, was found in only 1 patient in group B. As shown in Table 2, there were no differences in the incidences of other complications. One patient (2%) in group A died at POD 31 after laparotomy because of the development of intestinal necrosis due to sudden onset of superior mesenteric arterial thrombosis. Two patients in group B required relaparotomy because of leakage of colonic anastomosis (n = 1) and intra-abdominal abscess after intractable POPF (n = 1). In group B patients, there were 3 in-hospital death caused by pneumonia (n = 2) and liver failure after leakage of colonic anastomosis. No bleeding complications or POPF-related mortality were reported in this study. The median length of postoperative in-hospital stay was significantly shorter in group B compared with group A: 13 days (range, 11–73 days) vs 24 days (range, 8–101 days), respectively ($P < 0.0001$). In more details, the length of in-hospital stay was (group B vs group A) 64% vs14% (in-hospital of <14 days), 19% vs 55% (15–29 days), and 17% vs 31% (>29 days).

Identification of Risk Factors for Grade B/C POPF

Multivariate logistic regression analyses were used to identify the risk factors associated with grade B/C POPF (Table 3). These risk factors were extracted from the results of univariate analysis for grade B/C POPF. A pancreatic duct with a diameter of less than 3 mm was the only independent risk factor for grade B/C POPF in this study.

TABLE 2. Comparison of Postoperative Complications

Parameters	Group A (n = 51)	Group B (n = 78)	*P*
Overall complications	20/51 (39%)	40/78 (51%)	NS
Septic complications	10/51 (20%)	9/78 (12%)	NS
Reoperation	1/51 (2.0%)	2/78 (2.5%)	NS
In-hospital death	1/51 (2.0%)	3/78 (3.8%)	NS
Pancreatic fistula	7/51 (14%)	34/78 (44%)	0.0004
Grade B/C	3/51 (5.9%)	11/78 (14%)	NS
DGE	3/51 (6%)	6/78 (8%)	NS
Grade A/B/C	0/1/2	3/1/2	NS
Drain infection	3/51 (5.8%)	6/78 (8%)	NS
Abdominal abscess	2/51 (3.9%)	6/78 (8%)	NS
Hemorrhage	0/51 (0%)	0/78 (0%)	NS
Wound dehiscence	10/51 (20%)	12/78 (15%)	NS
Pneumonia	1/51 (2.0%)	3/78 (3.8%)	NS
Bile leakage	1/51 (2.0%)	0/78 (0.0%)	NS
Marginal ulcer	1/51 (2.0%)	0/78 (0.0%)	NS
Peritoneal/pleural effusion	6/51 (12%)	2/78 (3%)	NS
Liver dysfunction	4/51 (7.8%)	6/78 (7.7%)	NS

Figure represents number of patients (%).

NS indicates not statistically significant; DGE, delayed gastric emptying; fluid collection, pleural effusion and/or ascites.

TABLE 3. Logistic Regression Analysis Using Perioperative Parameters for POPF (Grade B/C)

Category	Risk Factors	P	Relative Risk	95% CI
POPF (grade B/C)	P-duct >3 mm	—	1	
	P-duct <3 mm	0.0098	6.391	1.564–26.121

This table shows the most relevant factors in each category by multivariate analysis. The risk factor used for multivariate analysis was abstracted from the results of univariate analyses.

CI indicates confidence interval; P-duct, diameter of pancreatic duct.

Comparison of Postoperative Complications Between the 2 Subgroups in Patients With a Pancreatic Duct With a Diameter of Less Than 3 mm

In groups A and B, 31% (16/51) and 46% (36/78) of patients, respectively, had a pancreatic duct of less than 3 mm in diameter. Regarding the patients' background, there was no difference between the 2 groups (data were not published). Although there was a tendency for a higher frequency of overall POPF in group B versus group A, this did not reach statistical significance. As shown in Table 4, there were no differences between the 2 subgroups in the incidences of grade B/C POPF, delayed gastric emptying, intra-abdominal abscess formation, and other postoperative complications. In comparison of grade B/C POPF rate of 2 groups in patients with a pancreatic duct with a diameter of more than 3 mm, no significant difference was found (data not shown).

DISCUSSION

After the introduction of PD by Kausch[18] and Whipple et al,[19] the mortality rate after PD was approximately 20% in the 1970s. However, in more recent decades, morbidity and mortality rates have decreased because of improvements in perioperative management and preoperative patient selection. The development of POPF often results in severe complications, such as sepsis, intra-abdominal abscess and bleeding, and delayed gastric emptying. The safe reconstruction of pancreaticoenteric continuity after PD continues to be a challenge for the pancreatic surgeon. Although the mortality rates in high-volume centers have fallen in the past 10 years to less than 5%, morbidity still remains at 30% to 50% after PD.[1–7] To date, many efforts have been made to reduce the occurrence of POPF and mortality after PD, including the use of octreotide,[20] methods of pancreaticoenterostomy,[21–23] pancreatic duct stenting,[24,25] drain management,[26] and use of surgical microscopy.[27]

Previously, we reported rates of 5.5% for in-hospital mortality, 56% for postoperative complications, and 31% for septic complications in 198 patients who underwent PD.[8] Consequently, departmental guidelines to reduce postoperative morbidity after PD were developed and could lead to the standardization of perioperative management of PD and to a lower incidence of grade B/C POPF, delayed gastric emptying, and overall complications.[9] In that study, external stenting of the pancreatic duct was used in the limited number of patients with a pancreatic duct of less than 3-mm diameter and with a biliary duct of less than 10-mm diameter. Theoretically, external or internal stenting may help divert the pancreatic secretion away from the anastomosis.[24,25] However, severe complications associated with the stenting tube have been reported[11,12] and include acute pancreatitis due to subsequent occlusion or bending of the stenting tube or late anastomotic stenosis after iatrogenic injury sustained when withdrawing the external stenting tube.[11,12] Recently, Rezvani et al[13] reported that internal stent migration caused liver abscess formation, which was treated by percutaneous transhepatic interventional radiological approach. We have also experienced a very rare case in the early 1990s, when a patient died due to intractable pancreatojejunal anastomotic leakage after withdrawal of the external stenting tube. Other concerns were the occurrence of a catheter-related infection. Based on these experiences, we changed our procedures from duct-to-mucosa anastomosis using external stenting, to nonstented anastomosis.

In this study, there were no differences in grade B/C POPF and other major complications between the 2 groups. The overall incidence of POPF was significantly higher in group B than in group A, and there was a trend for a higher frequency of overall POPF in patients with small-diameter pancreatic ducts in group B, relative to group A. However, nonstented PJ did not increase the frequency of grade B/C POPF cases that were considered to be clinically important, even in patients with small-diameter pancreatic ducts. In this study, the methods used for PJ and perioperative management have been standardized. The population analyzed was relatively homogeneous as to clinical background, underlying diseases, clinical diagnosis, and type of operation; however, there was a tendency for more patients in group B to have small-diameter pancreatic ducts than in group A (46% vs 31%, respectively). Although the significantly higher rate of overall POPF in group B might be associated with relatively higher frequency of patients with small-diameter pancreatic ducts in this group, nonstented PJ might also, in part, have led to the increased rate of grade A POPF. Logistic regression analysis showed that the only risk factor for grade B/C POPF was small-diameter pancreatic ducts, as shown in Table 3. Subgroup analysis of patients with small-diameter pancreatic ducts showed that there was no difference between the 2 subgroups in the overall incidence of POPF, grade B/C POPF, or other complications.

External stenting across PJ anastomosis is widely used by surgeons[9,24,25,28] and may have the potential to drain pancreatic enzymes away from the PJ anastomosis. However, it was unclear whether nonstented PJ was a safe procedure. Roder et al[28] reported in a prospective study that the rate of pancreatic fistula in the external stenting group was decreased, relative to the nonstenting group. Nevertheless, as a proportion of the patients

TABLE 4. Comparison of Postoperative Complications in Subgroup of Patients in Groups A and B With a Pancreatic Duct With a Diameter of Less Than 3 mm

Parameters	Group A (n = 16)	Group B (n = 36)	P
Overall complications	8/16 (50%)	23/36 (64%)	NS
In-hospital death	0/16 (0%)	1/36 (2.8%)	NS
Pancreatic fistula	5/16 (31%)	21/36 (58%)	NS
Grade B/C	3/16 (19%)	8/36 (22%)	NS
DGE	1/16 (6.2%)	3/36 (8.3%)	NS
Grade A/B/C	0/1/0	2/0/1	NS

Figure represents number of patients (%).

NS indicates not statistically significant; DGE, delayed gastric emptying.

underwent PJ using the invagination technique, the findings were based on a heterogeneous population regarding the anastomotic technique used. In contrast, Imaizumi et al[12] retrospectively proposed that a stenting tube was unnecessary even in the normal pancreas if the duct-to-mucosa anastomosis performed was satisfactory. Recently, Poon et al[24] reported results from a prospective randomized trial in 120 patients over a 6-year period, which showed that external drainage of the pancreatic duct with a external stent reduced the leakage rate of PJ after PD. The differences between this study relative to ours were the longer study period, the longer period that the drains were left inserted, and the higher frequency of hemorrhagic complications, and in-hospital deaths due to POPF. In our study, the median POD that the drain was removed was 7 in group A and 4 in group B, which were earlier than POD 10 or more reported by Poon et al.[24] Moreover, there were no hemorrhagic complications or POPF-related mortality in this present study, which was also of a shorter duration than that reported by Poon et al[24] (4 years 4 months vs 6 years 4 months, respectively). The main limitation to our study was the small sample size and the retrospective nature of the analysis, which could have biased the outcome, although the study was conducted throughout by the same staff who all followed standard perioperative management procedures for the relative short study period. It is difficult to elucidate the reason for the difference in results, although the one thing they had in common was that they were single-center studies. To explore further the reasons for the different findings, it will be necessary to run a multicenter trial with the standardization of the anastomotic method and perioperative management across sites.

In this study, we would like to emphasize the shorter postoperative in-hospital stay in group B, relative to group A. In Japan, most patients do not leave the hospital until they have completely recovered because they do not have to pay for the total cost of hospital stay. In the patients who required removal of an external stenting tube, there was a tendency to later discharge from hospital. Therefore, it might be reasonable to assume that the abolishment of external stenting would be associated with shorter in-hospital stay.

Poon et al[24] proposed that stenting of the pancreatic duct allowed more precise placement of sutures, thus protecting the pancreatic duct from suture injury and reducing the risk of iatrogenic pancreatic duct occlusion, pancreatitis, and fistula formation. Indeed, duct-to-mucosa anastomosis with nonstenting can be difficult to perform when the pancreatic duct is not dilated and the lumen of duct is easily flattened in patients with normal pancreatic parenchyma. However, insertion of an ITA holder into the duct lumen enables excellent visualization without retaining the duct or pancreatic remnant.[14] In some cases, a stay-suture may be placed to open the lumen of the pancreatic duct; however, when the suture is pulled, there is a risk in that the suture material can cut easily into the pancreatic duct or parenchyma. Using an ITA holder can minimize incidental laceration of the pancreatic duct or parenchyma by replacing the need for a stay-suture; it can also minimize trauma by protecting the pancreatic duct from crush injuries caused by forceps. Thus, we firmly believe that duct-to-mucosa anastomosis without pancreatic duct stenting, and using the ITA holder, is a safe procedure.

In summary, this retrospective analysis showed that there were no differences in postoperative mortality and morbidity including grade B/C POPF development, between patients who underwent stented and nonstented PJ after PD. The multivariate analysis showed that the only risk factor for grade B/C POPF was a pancreatic duct diameter of less than 3 mm. In conclusion, the nonstented PJ using the modified Kakita method can be safely performed and is associated with a reduced length of in-hospital stay.

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Reinforcement of Pancreticojejunostomy Using Polyglycolic Acid Mesh and Fibrin Glue Sealant

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Objectives: To examine whether pressure-tight reinforcement of pancreaticojejunostomy (PJ) using polyglycolic acid (PGA) mesh and fibrin glue sealant can reduce the incidence of postoperative pancreatic fistula (POPF).

Methods: The study population included 128 consecutive patients who underwent pancreaticoduodenectomy between September 2006 and January 2010. Postoperative mortality and morbidity among 50 patients who underwent reinforcement of PJ anastomosis using PGA mesh and fibrin glue were compared with 78 patients (historical controls).

Results: The 2 groups demonstrated no significant differences in frequencies of overall or septic complications, reoperation, or in-hospital death. No significant difference in the frequency of POPF, delayed gastric emptying, or intra-abdominal abscess was found between groups. There was no difference between the 2 groups in the number of necessary interventions, and no bleeding complications or POPF-related mortality occurred. The median length of postoperative in-hospital stay between the 2 groups was similar: 13 days (range, 8–101 days) versus 14 days (range, 8–61 days). Similar findings were observed in a subgroup analysis consisting of patients with a pancreatic duct diameter smaller than 3 mm.

Conclusion: This retrospective single-center study showed that reinforcement of PJ anastomosis using PGA mesh and fibrin glue provided no significant benefit in reducing the frequency of POPF.

Key Words: pancreatic fistula, ISGPF, grade B/C, in-hospital stay, morbidity, mortality

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In recent years, mortality and morbidity in pancreaticoduodenectomy (PD; including pylorus-preserving PD) patients have decreased owing to advances in surgical techniques and appropriate perioperative management. In most high-volume centers, mortality has decreased to less than 5%, although postoperative morbidity remains at approximately 40%.[1–5] Many attempts to reduce the frequency of development of postoperative pancreatic fistulas have been made, including use of octreotide,[6] alternative methods of pancreaticoenterostomy,[7–9] pancreatic duct stenting,[10,11] drain management,[12] and use of surgical microscopy.[13]

At our center, the frequencies of postoperative morbidity (39%), grade B/C pancreatic fistula (6%), and delayed gastric emptying (6%) were all reduced significantly in response to departmental guidelines[14] that specify duct-to-mucosa anastomosis for pancreaticojejunostomy (PJ) and early removal of closed-suction drains. The subsequent introduction of nonstented duct-to-mucosa anastomosis has also been shown to reduce in-hospital stay time, with no significant increase in risk.[15] Nonetheless, postoperative pancreatic fistula (POPF) is still one of the most frequent causes of morbidity in this center.

Since October 2008, our physicians have attempted to reduce the frequency of POPF by reinforcing anastomosis of PJ with polyglycolic acid mesh (PGA, Neoveil, Gunze, Osaka, Japan) and fibrin glue sealant (Bolheal, Chemo-Sero Therapeutic Institute, Kumamoto, Japan). Polyglycolic acid mesh felt is a bioabsorbable recombinant membrane made of a synthetic polymer with a celluloselike structure. Reports of concomitant use of PGA mesh and fibrin glue sealant to prevent air leakage,[16] cerebrospinal leakage,[17] bile leakage,[18] and pancreatic fistula after pancreaticogastrostomy[19] suggest that these materials may reinforce compromised tissues subject to high pressure. The purpose of this study was to examine whether pressure-tight reinforcement of PJ using PGA mesh and fibrin glue could prevent POPF. We herein compare the clinical results from reinforcement of PJ anastomosis (n = 50) retrospectively with historical controls (n = 78).

MATERIALS AND METHODS

From September 2006 to January 2010, 128 consecutive patients with pancreatic and periampullary disease underwent PD including pylorus-preserving PD at Kansai Medical University Hospital. Pancreaticojejunostomy was performed using the modified Kakita method as described previously.[14] Before closing the abdomen, the omentum was wrapped around the pancreatic anastomosis. The patients underwent PJ without external or internal stenting of the pancreatic and biliary ducts. Routinely, 2 closed-suctioned drains were placed in the pancreatic anastomosis area. Peripancreatic drainage fluid was collected and amylase levels were measured and monitored on postoperative days 3 and 6 and every 3 days thereafter as needed. All patients received prophylactic antibiotics intraoperatively and for 1 or 2 days postoperatively.

Our policy was to remove drains early (between 3 and 6 days after the operation) in patients with no infection-induced systemic inflammatory response syndrome (SIRS),[20] no POPF or grade A POPF (as defined by the International Study Group of Pancreatic Fistula [ISGPF][21]), and with less than 200 mL/d of fluid drainage. When POPF was clinically diagnosed as grade B, the perianastomotic drain was replaced 6 or 7 days after the operation, and, depending on amylase levels in the drained fluid, closed lavage was performed continuously with 500 to 3000 mL/d of natural saline solution. In patients developing POPF, all attempts were made to maintain per os or enteral feeding.

Among the 59% of patients with obstructive jaundice, we performed endoscopic nasogastric/retrograde bile drainage or percutaneous transhepatic drainage. Nasogastric tubes were removed routinely on postoperative day (POD) 1 after confirmation that fluid drainage volume was less than 200 mL/d. In patients who underwent tube enterostomy, initiation of postoperative

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enteral nutrition through a jejunostomy tube was started on POD 3 and oral food intake on POD 4 to 6. Once the patient could ingest at least 50% of required nutrition orally, enteral nutrition was stopped; the jejunostomy tube was then withdrawn at an outpatient clinic on POD 21. Hospital discharge dates were determined by senior surgeons, with requirements that patients ingest at least 50% of solid foods served, are afebrile, and display C-reactive protein levels reduced to less than 5 mg/dL. No patients received either prophylactic octreotide to prevent POPF development or thromboembolic prophylaxis with low–molecular weight heparin. All complications were recorded prospectively in a pancreatic database.

We divided the 128 PD patients into 2 study groups: group A and group B. The historical control patients in group A consisted of 78 consecutive patients who underwent PD between September 2006 and September 2008. Within this group, 36 patients (46%) had pancreatic ducts less than 3 mm in diameter. This group included the same population presented in a previous report.[15] Group B consisted of 50 consecutive patients who underwent PD between October 2008 and January 2010. After PJ reconstruction, hepaticojejunostomy, gastro(duodeno)jejunostomy, and Braun anastomosis in these patients, we performed peritoneal cavity lavage with 3000 to 5000 mL of natural saline. After drying the PJ anastomosis, reinforcement was performed using PGA mesh and fibrin glue sealant as described below.

Fibrin glue was prepared from a mixture of solutions A and B. Solution A contained 80 mg/mL human fibrinogen, 7 U/mL human plasma-derived coagulation factor XIII, and 1000 kinetics isotope effects bovine aprotinin. Solution B contained 250 IU/mL human thrombin and 5.9 mg/mL of calcium chloride. Polyglycolic acid mesh was first cut to a size that covered the circumference of the anastomosis. After applying 0.5 mL of solution A to the PJ anastomosis, the PGA mesh was wrapped around the site for complete coverage. Upon confirming proper attachment of the PGA mesh to the anastomosis, a mixture of solution A and B was sprayed onto the PGA mesh using a double-barrel syringe connected to a Y-shaped catheter (Fig. 1). After 2 minutes of drying, the omentum was then wrapped around the pancreatic anastomosis.

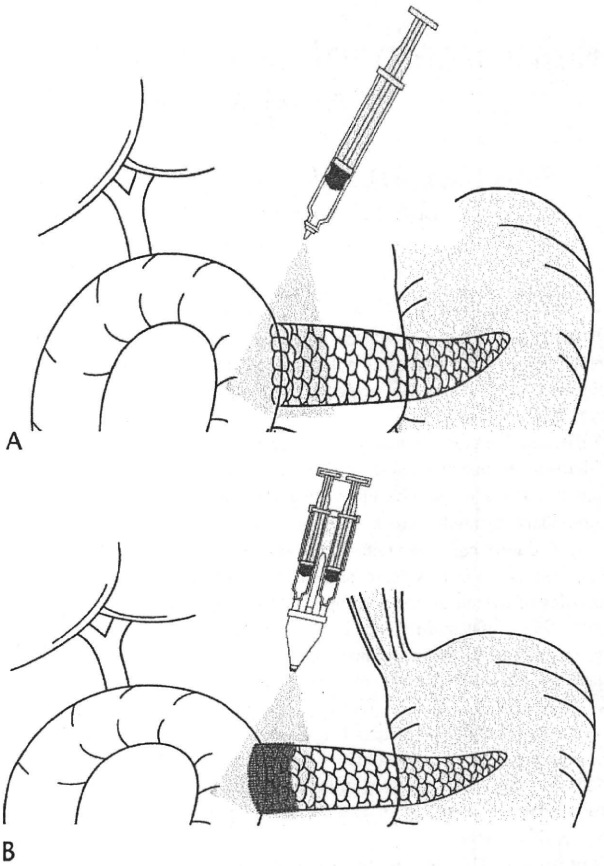

FIGURE 1. A, Solution A (0.5 mL) was applied to the anastomosis where PGA mesh would be installed. B, A single piece of PGA mesh that wraps completely around the PJ anastomosis was used. After confirming that the mesh attached closely to the anastomosis, a mixture of solution A and B was sprayed onto the PGA mesh using a double-barrel syringe connected to a Y-shaped catheter.

Definition of Postoperative Complications

General and surgery-related complications, including POPF, delayed gastric emptying, wound dehiscence, intra-abdominal infection, abdominal abscess formation, cardiopulmonary disorder, hemorrhagic complication, peritoneal/pleural effusion, anastomotic leakage, and others, were recorded prospectively throughout the study. The number of days that patients demonstrated clinical symptoms of SIRS[20] was recorded. Sepsis was defined as complications involving clinical symptoms of infection-induced SIRS that continued for more than 2 inpatient days, although clinical symptoms of SIRS within the first 4 postoperative days were excluded as a systemic response to surgical stress. Complications, including POPF,[21] delayed gastric emptying,[22] and postoperative hemorrhagic,[23] were defined by standards adopted by the ISGPF. Abdominal abscesses including liver abscess, wound dehiscence, intra-abdominal infection, peritoneal/pleural effusion, anastomotic leakage, and postoperative liver dysfunction, were defined as described in the previous report.[14,15] In-hospital death of a patient for any reason was recorded.

Statistical Analyses

Mortality and morbidity after PD between groups A and B were compared. Patient variables included age, sex, clinical diagnosis, comorbid disease, obstructive jaundice, operative variables, and preoperative blood tests (Table 1). All data were entered into an electronic database on a personal computer. Continuous variables are expressed as median and range values. Statistical analyses including the Mann-Whitney U test and the Fisher exact test were performed using Statview Version 5.0 for Windows (Abacus Concepts, Inc, Piscataway, NJ). $P < 0.05$ was considered significant.

RESULTS

Patient Demographic and Baseline Characteristics Including Surgical Details

Baseline and operative characteristics of the 128 patients enrolled in the study are shown in Table 1. No variables differed significantly between the 2 groups.

Postoperative Complications

Postoperative course was complicated in 51% of the group A patients and 60% of the group B patients. As shown in Table 2, there were no differences in the frequencies of overall complications, septic complications, reoperation, and in-hospital death between the 2 groups. The groups showed no significant differences in additional complications, including

TABLE 1. Patient Demographics and Baseline Characteristics

Parameters	Group A (n = 78)	Group B (n = 50)	*P*
Age, y	66 (36–90)	66 (33–82)	0.374
Male/female	51:27	31:19	0.710
Disease (P:B:A)	46:13:19	27:6:17	0.452
Benign/malignant ratio	13:65	7:43	0.805
Total bilirubin, mg/dL	0.7 (0.2–3.6)	0.7 (0.3–6.2)	0.975
AST (U/L)	25 (13–236)	24 (11–78)	0.703
Albumin (g/dL)	3.9 (1.9–4.8)	3.8 (1.9–4.7)	0.399
WBC, $\times 10^2$/mL	52 (24–124)	55 (34–93)	0.299
Hemoglobin, g/dL	12 (8–16)	12 (8–16)	0.794
Comorbid disease (−:+)	24:54	20:30	0.341
Diabetes mellitus (−:+)	53:25	41:9	0.101
Jaundice (−:+)	32:46	20:30	1.000
Type of operation (PD/PpPD)	42:36	22:28	0.365
Operation time, min	468 (275–714)	440 (327–711)	0.347
Blood loss, mL	952 (272–5238)	884 (110–3853)	0.459
Transfusion (allo/auto/none)	22:49:7	19:23:8	0.155
Resection of other organs (+:−)	19:59	15:35	0.541
Pancreatic duct diameter, >3 mm:≤3 mm	42 (54):36 (46)	24 (48):26 (52)	0.588

Table shows median value (range) or number of patients (%).

Allo indicates allogenic blood transfusion; AST, aspartate aminotransferase; auto, autologous blood transfusion; none, no transfusion; P:B:A, pancreatic disease: biliary disease: ampullary disease; PpPD, pylorus preserving pancreaticoduodenectomy; WBC, white blood cell count.

POPF. Postoperative pancreatic fistula (grade B/C) occurred in 11 patients (14%) in group A, and in 5 patients (10%) in group B. Pancreaticojejunostomy anastomotic leakage was detected radiologically in one patient each in groups A (1%) and B (2%). Ultrasonography-guided drainage was performed in 3 patients in group A and one in group B. Drain exchange was performed in 6 group A and 3 group B patients. Additional therapeutic antimicrobial agents were administered intravenously in 2 patients in group A and one patient in group B. There was no significant difference in the number of interventions necessary between the 2 groups. There was no significant difference between the groups in maximum amylase levels in drainage fluids during

TABLE 2. Comparison of Postoperative Complications

Parameters	Group A (n = 78)	Group B (n = 50)	*P*
Overall complications	40/78 (51%)	30/50 (60%)	0.367
Septic complications	9/78 (12%)	9/50 (18%)	0.312
Reoperation	2/78 (2.5%)	0/50 (0%)	0.520
In-hospital death	3/78 (3.8%)	1/50 (2.0%)	1.000
Pancreatic fistula	34/78 (44%)	17/50 (34%)	0.355
D-Amy (U/L)	1339 (402–64,227)	1139 (365–12,537)	0.162
Grade B/C	11/78 (14%)	5/50 (10%)	0.591
PJ anastomotic leakage	1/78 (1%)	1/50 (2%)	1.000
DGE	6/78 (8%)	7/50 (14%)	0.369
Grade A/B/C	3/1/2	5/0/2	0.420
Drain infection	6/78 (8%)	5/50 (10%)	0.750
Abdominal abscess	6/78 (8%)	3/50 (6%)	1.000
Hemorrhage	0/78 (0%)	0/50 (0%)	—
Wound dehiscence	12/78 (15%)	9/50 (18%)	0.808
Pneumonia	3/78 (3.8%)	2/50 (4%)	1.000
Bile leakage	0/78 (0%)	0/50 (0%)	—
Peritoneal/Pleural effusion	2/78 (3%)	6/50 (12%)	0.06
Liver dysfunction	6/78 (7.7%)	9/50 (18%)	0.095
In-hospital stay (POD), d	13 (8–101)	14 (8–61)	0.765

Table shows median value (range) or percentage of patients (%).

D-amy indicates the highest amylase level in fluid drained from each patient who had POPF; DGE, delayed gastric emptying.

TABLE 3. Comparison of Postoperative Complications in A and B Subgroups of Patients With a Pancreatic Duct Diameter Less Than 3 mm

Parameters	Group A (n = 36)	Group B (n = 26)	*P*
Overall complications	23/36 (64%)	20/26 (77%)	0.403
In-hospital death	1/36 (2.8%)	0/26 (0%)	1.000
Pancreatic fistula	21/36 (58%)	13/26 (50%)	0.608
Grade B/C	8/36 (22%)	5/26 (19%)	1.000
DGE	3/36 (8.3%)	5/26 (19%)	0.262
Grade A/B/C	2/0/1	3/0/2	0.443

Table represents number of patients (%).

postoperative days 3 to 6. Two patients in group A required relaparotomy owing to colonic anastomotic leakage after PD with right hemicolectomy for pancreatic caner (n = 1) and intra-abdominal abscess after intractable postoperative pancreatic fistula (n = 1). Three in-hospital patient deaths occurred in group A: two were due to pneumonia and one was due to liver failure after leakage of colonic anastomosis. In group B, no patient required reoperation, and one patient died of pneumonia on POD 44. No bleeding complications or POPF-related mortality were reported in this study. The median length of postoperative in-hospital stay was similar between the 2 groups: 13 days (range, 8–101 range) for group A versus 14 days (range, 8–61 days) for group B. No adverse events, such as allergic reaction associated with PGA mesh/fibrin glue, occurred.

Postoperative Complications in Subgroups of Patients With a Small Pancreatic Duct

Although 46% (36/78) of group A patients and 52% (26/50) of group B patients had a pancreatic duct less than 3 mm in diameter, there was no difference in overall complications, POPF, or DGE between patients in these subgroups (Table 3).

DISCUSSION

Since October 2008, our center has clinically applied pressure-tight reinforcement of PJ anastomosis using PGA mesh and fibrin glue with the goal of reducing POPF (grade B/C) after PD. In this retrospective study, we found that patient characteristics, perioperative parameters, and postoperative morbidity and mortality were comparable between the PGA mesh/fibrin glue group (n = 50) and the historical control group (n = 78). The results of this study indicate that mesh-and-glue reinforcement around the site of PJ anastomosis did not decrease the frequencies of grade B/C POPF, overall POPF, POPF-related complications, or overall morbidity and mortality. Comparisons of experimental and control subgroups including only patients with a pancreatic duct diameter less than 3 mm showed similar findings.

In recent decades, morbidity and mortality rates after PD have decreased owing to improvements in perioperative management and preoperative patient selection. The development of POPF often results in severe complications, including sepsis, intra-abdominal abscess and bleeding, and delayed gastric emptying. Safe reconstruction of pancreaticoenteric continuity after PD continues to be a challenge for the pancreatic surgeon. At our center, we have established criteria for removal of nasogastric tubes and drains, for initiation of per os and hospital discharge, and for managing patients perioperatively according to a defined clinical pathway. With this institutional standardization of perioperative management in place, we examine here the clinical efficacy of pressure-tight reinforcement of PJ anastomosis using PGA mesh and fibrin glue to reduce POPF.

Because pressure-tight closure of PJ anastomosis cannot be achieved by simple suturing, application of fibrin glue has the potential to decrease pancreatic leakage by mechanically sealing the anastomosis. Fibrin glue is a tissue adhesive composed of human fibrinogen and thrombin. In few previous nonrandomized studies, fibrin glue sealant has been reported to reduce the incidence of pancreatic fistula.[24,25] A prospective randomized trial conducted by Lillemoe et al[26] that tested the use of fibrin glue alone for reinforcement of PJ in 124 patients who underwent PD showed no statistically different rates of mortality, pancreatic fistula, or intra-abdominal complications between patients in treatment and control groups.

Since fibrin glue is not stable in a wet field, it is possible that the proximity of the glue alone to vigorous irrigation and suction applied during surgery could render it inactive. For this reason, the use of PGA mesh (which in itself does not aid in tissue adherence) in combination with fibrin glue has been predicted to stabilize and enhance the action of fibrin glue. Polyglycolic acid mesh is a nonwoven sheet of high water absorbability that is made of synthetic polymer with a celluloselike structure. Because of its high molecular weight, fibrinogen in the glue solution does not penetrate the PGA sheet. As a result, spraying of combined fibrinogen and thrombin between tissue defects and the sheet allows formation of secure fibrin connections.[19] Although PGA mesh itself cannot seal tissue defects, PGA in combination with fibrin glue sealant has been used to seal anastomoses and render them more resistant to high pressure.

Reports state that the pressure required for breaking a seal consisting of PGA mesh and fibrin glue was 55 mm Hg at an intestinal wall defect[27] and 70.6 mm Hg at a visceral pleural defect.[28] Uemura et al[19] were the first to report that the combined use of PGA felt and fibrin glue as an adjunct to pancreaticogastrostomy was extremely favorable in preventing POPF (as defined by ISGPF). Although they reported a favorable 12% incidence of POPF (without any grade B/C) overall in a relatively small group of 25 consecutive patients who underwent PD, this group was not compared with any control group. The technical differences reported by Uemura et al[19] were in doing the PJ and in using a single piece of PGA mesh to wrap the anastomosis.

In the 40-month study described here, postoperative morbidity and mortality among 50 patients in whom this type of reinforcement was applied were compared with a historical control group consisting of 68 patients without reinforcement of PJ anastomosis. The population analyzed was relatively homogeneous in clinical background, underlying diseases, clinical diagnosis, and type of operation. The main limitation to our study is the retrospective nature of the analysis, which could have biased the outcome; however, it should be noted that a common staff followed standardized perioperative management procedures throughout the relatively short study period.

Although previous reports on the concomitant use of PGA mesh and fibrin glue for sealing tissue defects were favorable,[27,28] we did not observe similar results for sealing anastomoses of PJ. Since anastomoses between solid organs and the intestine present irregularities, PGA mesh may not be capable of covering these junctions effectively. As a result, pancreatic juices could leak out through invisible gaps between the PGA mesh/fibrin glue and the anastomosis. Nevertheless, the use of PGA mesh and fibrin glue did not promote any statistical increase in postoperative morbidity such as intra-abdominal infection, abdominal abscess formation, or septic complications.

In conclusion, this retrospective analysis showed that reinforcement of PJ anastomosis using PGA mesh and fibrin glue provided no benefit in reducing the frequency of POPF.

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