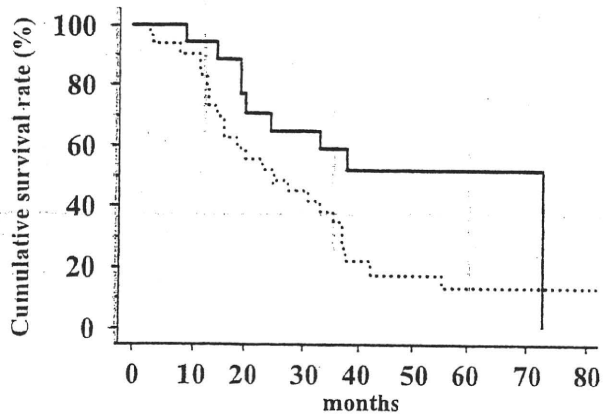
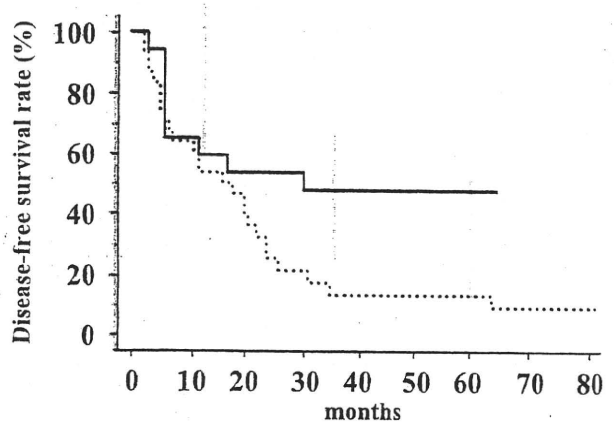


patients at risk	1y	2y	3y	4y	5y	MST
NACRT 18	16	12	8	5	4	-
surgery alone 30	25	15	8	4	2	24 m

Fig. 1　術前放射線化学療法群と切除単独群間の累積生存率の比較（根治切除例）
実線は術前放射線化学療法群（n = 18）で，破線は切除単独群（n = 30）間の生存曲線を示す．両群間に統計学的有意差が認められた（p = 0.0425）．



patients at risk	1y	2y	3y	4y	5y
NACRT 18	10	9	7	4	3
surgery alone 30	16	8	3	2	2

Fig. 2　術前放射線化学療法群と切除単独群間の累積無再発生存率の比較（根治切除例）
実線は術前放射線化学療法群（n = 18）で，破線は切除単独群（n = 30）間の無再発生存曲線を示す．両群間に統計学的有意差が認められた（p = 0.0359）．

Gemcitabine の多施設共同 Phase II 試験の結果より，MST が 26 ヶ月であったと報告している．NACRT は，単施設からの報告をみる限り非常に魅力的であるが，ランダム化試験が行われていないことが問題点である．

まとめると，膵癌に対して NACRT を行い，根治切除例では生存率の改善がみられた．膵癌の 5 年生存率 50% 超を達成するためには，より効果的で副作用の少ない術前治療のレジメを確立してその成績を検証していく必要があると考えられた．

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特集

長期生存膵癌の条件

膵癌術後長期生存を得るための集学的治療戦略

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Multi-Disciplinary Management for Obtaining Long-Term Survivors in Patients with Pancreatic Cancer: Satoi S*1, Toyokawa H*1, Yanagimoto H*1, Kitade H*1, Sonte Kim*1, Yamao J*1, Yamamoto T*1, Hirooka S*1, Matsui Y*1 and A-Hon Kwon*1 (*1Department of Surgery, Kansai Medical University)

We explored the outcome of the multi-disciplinary management for obtaining long-term survivors in patients with pancreatic cancer that extended beyond the pancreas. Our experiences of surgical resection following the pre-operative chemoradiation (pre-CRT) therapy showed that pre-CRT could be associated with a lower rate of lymph node metastasis and a higher rate of R0 resection, resulting in improved prognosis of patients with pancreatic cancer that extended beyond the pancreas.

Key words: Pre-operative chemoradiation, Curative resection, Lymph node metastasis, Overall survival rate, Disease-free survival rate

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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きたし，早期に遠隔臓器に転移することが特徴である．外科的治療が唯一の根治性を追及する方法であるが，膵癌切除例の5年生存率は10%前後と予後不良である[1,2]．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．

今回われわれは，当科における膵癌の治療経験に基づき，膵癌切除例の長期予後を改善するための進展度診断と治療戦略の工夫を提示する．

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1 術前進展度診断

切除により恩恵を受ける症例を適切に選択することが，膵管癌の術前進展度診断のために必要不可欠であり，特に肝転移の有無と血管浸潤の程度が治療内容の選択に大きな影響を与えると考えられる．

2000年から2002年8月まで血管造影下CT（7 mm slice CTHA/CTAP）で行い，2002年9月以降はcine-imaged MDCT（以下MDCT）を使用してきた．MDCTは，動脈相と門脈相を撮像し，検出器構成1.25 mm（4, table移動3.75 mm/rotation，ヘリカルピッチ3のHigh quality (HQ) modeで，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1.25 mm，再構成間隔0.6 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．MDCTと従来法であるCTHA/CTAP/angiography/CECTの両者を用いて，術前進展度診断を行い，肝転移の正診率や，術前CTにおける腫瘍因子の外科的，病理学的腫瘍因子との整合性を比較検討してきた[3]．肝転移の正診率はMDCTで高く，特に10 mm以下の腫瘍性病変はCTHA/CTAP/angiography/CECTに比較して高率に診断可能であった．また，門脈や動脈浸潤の手術所見との整合性を比較すると，MDCTはCTHA/CTAP/angiography/CECTと比較して外科的血管浸潤をより正確に反映していた．しかしながら，MDCTによる術前進展度診断を行い切除可能と診断された症例で，開腹時に予期せぬ遠隔転移症例が約10%にみられたことが問題であり，特に術前治療における患者選択に大きな影響を与えうる問題と考えられた[4]．

2 術前化学放射線療法の治療成績

当科における膵癌の画像上の切除基準は，膵頭部領域では，腫瘍が総肝動脈や上腸間膜動脈と半周以上で接していないこと，門脈進展があっても，完全閉塞に伴う側副血行非形成例で根治切除が可能と考えられる場合としている．膵体尾部領域では，癌が腹腔動脈幹に浸潤していても上腸間膜動脈や胃十二指腸動脈に浸潤していなければ，積極的に腹腔動脈幹合併切除を行っている．

2000年から2005年までに経験した膵癌に対して外科的切除を施行した連続68例を対象としてその成績を検討した．画像上膵外に連続進展を示す膵癌35例（膵癌取扱い規約[5]のT3一部とT4）に対して術前化学放射線療法を行った．再評価により全例でradiological responseは認められず，8例が切除不能となり（23%），最終的に切除27例（Neoadjuvant chemoradiation: NACRT群）と，ほぼ同時期の切除単独群41例の治療成績をretrospectiveに比較検討した．これらの結果はすでに報告しているが[6,7]，今回の報告では観察期間を最低39カ月間（生存例では48カ月間）に延長して生存率を比較検討した．術前化学放射線療法は，全例に40 Gyの非原体照射（2 Gy/日×5日/週，4週間）を施行した．併用化学療法は13例にCDDP＋5FU療法を，22例に塩酸ゲムシタビン（GEM）400 mg/m^{2}を3投1休で投与した．5-FUは200 mg/m^2/日を5日/週で計20日間の持続投与を行い，CDDPは1週目に3 mg/m^2/日を5日間bolus投与し，以降の3週間は6 mg/m^2/日を週2日間投与し，計11回投与とした．両群とも再発・転移診断時には化学療法が行われたが，術後補助化学療法は施行されなかった．

両群間の背景因子に差はなかった．NACRT群では，切除単独群と比較してリンパ節転移率が有意に少なく（32% vs 59%, $p<0.05$），R0率が有意に高率であった（52% vs 22% $p=0.004$）．図1に示すように，NACRT群の累積生存率は，切除単独群と比較して良好な傾向であった（$p=0.0541$）．次に図2に示すように，癌遺残度のR0/1症例において，NACRT群（n＝18）は切除単独群（n＝30）と比較して有意に予後良好であった．さらに図3に示すように無再発生存率もNACRT群で有意に良好であり，1年以内の再発は両群とも同様であったが，その後は経時的に開大がみられ，4年間の観察期間で，最終的にNACRT群では7例（39%）が無再発生存で，切除単独群では2例（7%）が無再発生存で1例が再発生存であった（$p<0.05$）．実5年生存例は切除単独群で3例のみであったのに対して，NACRT群では5例であり，さらに3例が4年以上生存している．

1988年より術前放射線化学療法を行っているMD Anderson Medical CenterのEvansら[8]は，86例のpotentially resectable膵癌に対してGEM 400 mg/m^2，週1回を7週間投与し，同時に30 Gyの対外照射を行った結果，74%が切除可能で，その実5年生存率は36%と報告した．これは，potentially resectable膵癌50例以上で5年以上観察しえたNACRT後切除成績の唯一の報告である．われわれの成績は，症例数が少なく化学療法剤が異なるため解釈には注意が必要であるが，Evansら[8]の成績と同様に約20%に遠隔

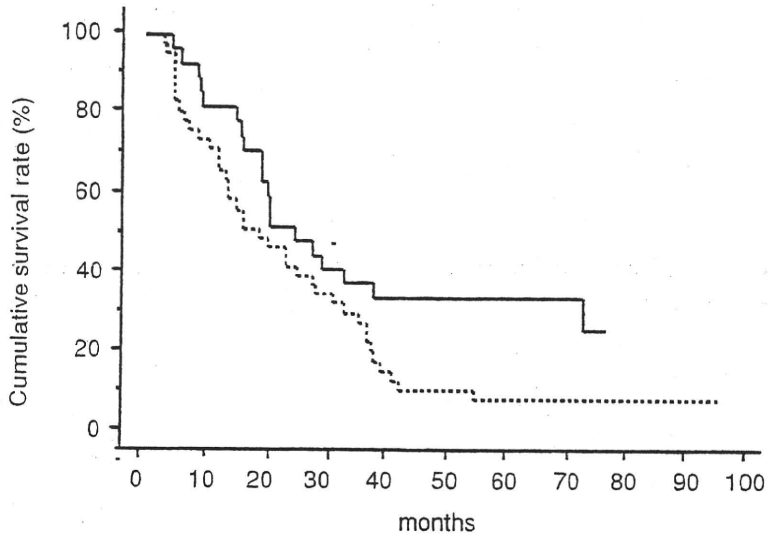

図1　術前化学放射線療法施行後切除27例（NACRT群）と切除単独群41例の累積生存曲線の比較（実線はNACRT群，破線は切除単独群を示す）
NACRT群の累積生存曲線は，切除単独群と比較して良好な傾向であった（p＝0.0541）．NACRT群の実4年生存率は30％であり，切除単独群は9.8％であった．

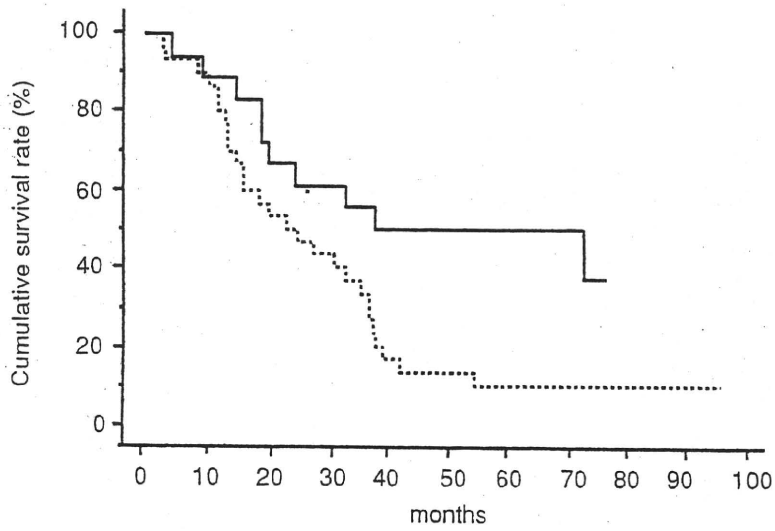

図2　根治切除例（R0/1）の累積生存曲線の比較：NACRT群18例と切除単独30例（実線はNACRT群，破線は切除単独群を示す）
NACRT群根治切除例の累積生存曲線は，切除単独群と比較して有意に良好であった（p＝0.0253）．NACRT群の実4年生存率は43％であり，切除単独群は13％であった．

転移などで切除不能例があるものの，切除されたNACRT群では，切除単独群と比較してリンパ節転移率が低く，根治切除率（R0）が高く，局所再発率が低率であった．結果的に無再発生存率と生存率が良好であり，NACRT群では実4年生存率が50％という良好な成績を示した．

3 新たなる取り組み

今回報告した術前化学放射線療法後切除例の成績は良好であったが，切除前に約20％の症例が脱落していること，今回の化学療法剤ではradiological responseがみられなかったこと，術後1

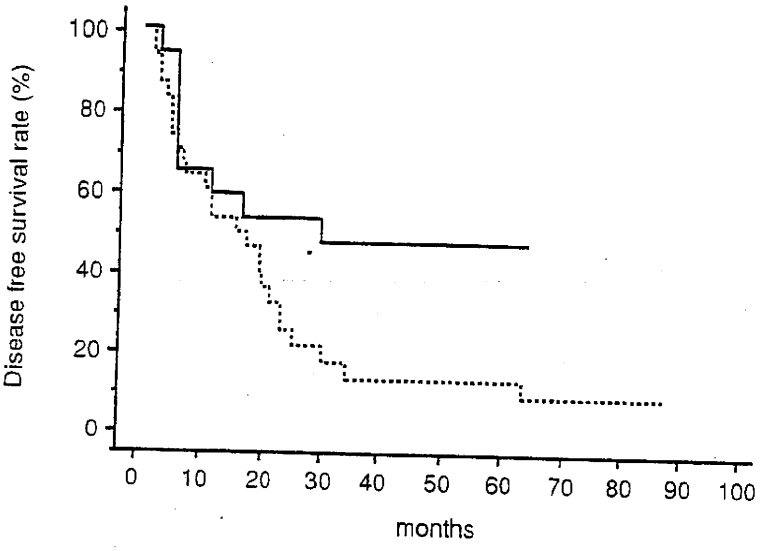

図3　根治切除例（R0/1）の累積無再発生存曲線の比較：NACRT群18例と切除単独30例（実線はNACRT群，破線は切除単独群を示す）
NACRT群の累積無再発生存曲線は，切除単独群と比較して有意に良好であった（p=0.0359）.

年以内の再発率が約50%と不良であること，が問題点として挙げられる．術前化学放射線療法を施行し切除不能であった8例の成績をみると，生存期間中央値は5.5カ月で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．実際，CTの質にもよるが，局所進行膵癌の開腹非切除率は20～57%といわれており，膵癌症例では微小肝腹膜転移の潜在的リスクを考慮する必要がある[9].

これらの問題点を克服するために，われわれは，2008年度より術前化学放射線療法後脱落例を低減するために全例にstaging laparoscopyを行い患者選択を行った上で，当科における切除可能例を対象に，TS1を使用した化学放射線療法を行っている．

実際staging laparoscopyでは，微小肝転移（特に肝表面）や腹膜転移の検出率が高く，さらに超音波検査や血管浸潤同定のための剥離操作を加えるとさらにその正確性は増すといわれている[9]．われわれの施設での経験では，2006年から2008年の切除不能な局所進行膵癌30例に対してstaging laparoscopyを施行した結果，59%に微小遠隔転移を認めたことより，術前化学放射線療法対象患者全例にstaging laparoscopyを施行して遠隔転移例を積極的に除外している．

次に，膵癌に対する新規抗がん剤であるTS1と放射線治療の併用療法に関して，本邦より3件のPhase I試験の結果[10～12]が示されており，その安全性と19～43%のpartial responseが確認されている．さらに最近，韓国のKimら[13]により切除不能膵癌に対するPhase II試験の結果が報告され，partial responseが24%で生存期間中央値が13カ月という良好な成績が示された．TS1を使用した放射線治療を行うことにより腫瘍縮小効果と予後の改善がさらに期待される．また，切除例においては術後の補助化学療法を施行し，再発率の低下を期待している．

まとめると，過去の術前治療で得られた問題点である治療前診断，低い腫瘍縮小効果，術後早期転移の問題点を克服するために，2008年度より術前進展度診断にcine-imaged MDCTを行い切除可能と診断された膵外進展を示すT3/4症例（膵癌取り扱い規約）に対して，微小肝腹膜転移診断のためにstaging laparoscopyを全例に行い，無遠隔転移例を対象にTS1　100 mg/m^2＋50.4 GyのNACRTを行い，3週間後に再評価を行った上で，進行例を除いて切除を行い，補助化学療法を追加するPhase II試験を行っている．

予定症例数は30例で，手術終了後の根治切除率と有効性および安全性を確認することを目的として，現在症例集積中である．

まとめ

難治性膵癌の外科治療において，術前のより正確な進展度診断を行い，適切な患者選択のもと，放射線化学療法後に再評価して切除を行うことにより，長期予後が改善される可能性がある．今後，多施設での切除単独例との比較試験や術前化学療法との比較などを行い，術前放射線化学療法の治療効果を明らかにしていく必要がある．

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Original Paper

Pre-Operative Patient Selection of Pancreatic Cancer Patients by Multi-Detector Row CT

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ABSTRACT

Background/Aims: Accurate pre-operative staging in patients with pancreatic cancer is crucial for avoiding unnecessary laparotomy and for selecting patients accurately for curative resection. In this study, tumor resectability and residual tumor grading in patients evaluated by MD-CT (Multi-detector row CT) or by SD-CT (single-detector CT) were compared to determine whether more accurate imaging has a significant clinical impact on patient selection and surgical outcomes.

Methodology: One hundred-fifty consecutive patients with pancreatic cancer evaluated from January 2000 to April 2005 were included in this retrospective study. Seventy pancreatic cancer patients underwent pre-operative evaluation using SD-CT and angiography (5-7 mm slice thickness, 1st period 2000-2002), and 80 patients underwent MD-CT (1.25 mm slice thickness, 2nd period 2002-2005).

Results: The introduction of MD-CT had a significant impact on the selection of suitable patients, this group showing a lower frequency of surgical intervention in cases of incurable disease (p=0.0383). Pre-operative evaluation using MD-CT in the resected cases also provided a higher percentage of accurate R0/R1 grading relative to SD-CT evaluations (p=0.0164).

Conclusion: MD-CT imaging has a significant impact on preventing unnecessary exploratory surgery and on the selection of appropriate pancreatic cancer patients for surgical resection.

KEY WORDS: Resectability; Potentially resectable tumor; Incurable tumor; Unresectable tumor; Grading of residual tumor; Overall survival rate; Disease-free survival rate; CTHA, CTAP; Angiography.

ABBREVIATIONS: CT During Hepatic Arteriography (CTHA), CT During Arterioportgraphy (CTAP)

INTRODUCTION

Pancreatic cancer is a lethal disease with poor prognosis. Even after radical operation, the five-year survival rate varies between 10-30% (1-4). At the time of pancreatic cancer diagnosis, only 15-20% of patients have potentially resectable disease without evidence of major vessel involvement or distant metastases (5). For these cases, surgical resection remains the only potentially curative treatment. Since the management of patients with incurable disease should be primarily non-surgical, it is essential to select patients who may benefit from surgery by staging cancers accurately. Relapsed disease, particularly at an early post-operative phase, can also affect surgical outcome adversely in pancreatic cancer patients. Underestimation of pre-operative tumor extension, inability to perform surgical clearance of the tumor, and biological features of the tumor all can contribute to early relapse of the tumor, even in patients who have undergone curative resection.

We reported previously that the accuracy of multi-detector row CT (MD-CT) for detection of pancreatic cancer liver metastasis or vascular involvement was superior to single detector (SD) CT (6). Between 2000 and 2002, SD-CT and abdominal angiography were used routinely for pre-operative staging. In September 2002, we began applying MD-CT for pre-operative evaluation of pancreatic cancer patients. In addition to the superior spatial resolution of MD-CT and the possibility of multi-planar reconstructions, MD-CT images with thinner collimation provide more accurate and detailed information than images from conventional contrast-enhanced CT (7,8). We hypothesized that using MD-CT to improve the accuracy of liver metastasis and vascular invasion diagnoses would reduce the frequency of unnecessary laparotomy, resulting in improved surgical results for eligible pancreatic cancer patients.

The goal of this study was to compare tumor respectability and residual tumor grading between patients examined before or after the introduction of MD-CT.

METHODOLOGY

One hundred-fifty consecutive patients with ductal adenocarcinoma of the pancreas that were evaluated between January 2000 and April 2005 in Kansai Medical University Hospital were included in the study (**Table 1**). After clinical diagnosis of pancreatic cancer using ultrasonography, CT, MRCP, ERCP, endoscopic ultrasonography, cytological examination of the bile juice and/or biopsy of the bile duct mucosa

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(conducted at the Department of Gastroenterology), all patients were referred to the Department of Surgery for pre-operative evaluation of tumor extension. Pre-operative staging was focused on (1) the detection of liver or lymph-node metastases, (2) identifying tumor vascular involvement, and (3) obtaining information about the anatomy of the celiac trunk and superior mesenteric arteries. Cases involving an endocrine tumor of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, or anaplastic cancer were excluded.

Patients in the study were classified according to radiological results into one of four groups: "incurable", "locally advanced", "potentially resectable", and "unresectable". "Incurable" cases involved diagnosis of peritoneal carcinomatosis or distant organ metastasis. "Locally-advanced" cases consisted of patients without any distant organ metastasis, but with (1) vascular involvement of a major peripancreatic artery (defined as tumor in-growth with >50% vessel contiguity in the celiac trunk, common or proper hepatic artery or superior mesenteric artery), (2) extended obstruction of the portal vein to distal branches of the superior mesenteric vein, or (3) with cavernous transformation of the porta hepatic. At the time of laparotomy, patients demonstrating tumors with any of the features above were classified as "unresectable" and were not treated surgically. Patients with no distant organ metastasis or tumor extension to a major peripancreatic artery [as defined in (1)] were classified into the "potentially resectable" group. Patients with tumors that invaded the portal vein were also classified as candidates for surgical resection but only in the absence of extended obstruction of the portal vein to distal branches of the superior mesenteric vein, or cavernous transformation of the porta hepatis. Patients with cancer in the pancreatic body and tail, with celiac trunk invasion and without SMA invasion, were classified as "potentially resectable" candidates for curative resection.

The following strategy was basically applied for treatment of the remaining pancreatic cancer patients: Patients with potentially resectable cancer underwent only surgical resection, primarily. Patients with locally advanced cancer received chemo-radiation (possibly followed by surgical resection), and patients with distant organ metastasis received systemic chemotherapy. MD-CT or SD-CTs/angiography was performed for tumor staging at least two weeks before surgery, chemotherapy or chemo-radiotherapy. Informed consent from each patient included in the study was obtained in accordance with the provisions of the Declaration of Helsinki. Patient data were obtained from the prospective database of Pancreatic Disease at Kansai Medical University Hospital.

MD-CT was used to evaluate 80 patients with pancreatic cancer from September 2002 to April 2005 (2nd term). Subsequently, staging laparoscopy was performed during the 2nd term on patients who showed ring-enhanced lesions or nodular low-attenuation lesions (less than 10-mm diameter) of the liver on MD-CT. Seventy patients with pancreatic cancer who underwent pre-operative evaluation using SD-CT/angiography between January 2000 and August 2002 (1st term) served as the historical control group. During this period, staging laparoscopy was not performed. All operations were performed by two experienced hepato-pancreato-biliary surgeons who were in agreement about the extent of the surgery to be performed.

Table 1. Patient Characteristics

	1st term	2nd term	*p* value
Time	2000.1-2002.8	2002.9-2005.4	
Number of patients	70	80	
Age	64 (47-82)	65 (39 - 83)	n.s.
Gender (Male : Female)	31 : 39	37 : 43	n.s.
Incurable cases	27 (39%)	48 (60%)	0.0138
Reason (local:distant)	8:19	10:38	n.s.
Potentially resectable cases	43 (61%)	32 (40%)	0.0138
Resected cases	33 (47%)	29 (36%)	n.s.
R0 (%)	6 (18)	15 (52)	0.0164
R1 (%)	13 (39)	8 (28)	
R2 (%)	14 (43)	6 (20)	
Unresected cases	10 (14%)	3 (4%)	0.0383
Reason (local:distant)	2:8	0:3	n.s.

Unresectable case: patients who had no indication for surgical resection on laparotomy. Incurable case: patients who had no indication for laparotomy due to detection of distant metastasis and/or locally advanced tumor during pre-operative radiological examination. Local, locally advanced disease; distant, distant metastasis. R0, negative margin; R1, positive microscopic margin; R2, positive gross margin

Settings for contrast-enhanced Multidetector row CT (MD-CT)

Since September 2002, MD-CT imaging on patients with pancreatic cancer has been performed using a Hi-speed advantage QX/I (General Electric Medical System, Milwaukee, WI). Arterial and portal phase images were collected using a 1.25 mm × 4-detector configuration and a multi-slice pitch of 3 (High quality mode), with a table speed of 3.75 mm/rotation. After reconstruction of the raw scans, data from serial 1.25-mm thick slices with a 0.6-mm interval were transferred to a workstation (Advantage Window 3.1). The scans were evaluated by an experienced hepatopancreatobiliary surgeon and a consultant radiologist. At the top of axial scans, 2D and 3D coronal and sagittal anatomical reconstructions were also performed. A recent publication from this unit6 provides more detailed information.

CT during hepatic arteriography (CTHA) and CT during arterioportgraphy (CTAP)

Between January 2000 and August 2002, patients with pancreatic cancer underwent CTHA/CTAP at the time of pre-operative angiography. As described previously (6), whole-liver scanning (single-slice helical CT: thickness 7 mm, interval 7 mm, 120 kV, 250 mA, 0.8 sec/rotation) was done for

CTAP and CTHA. CTHA/CTAP/angiography findings were evaluated independently by an experienced radiologist, and conventional SD-CT was performed with a slice thickness of 5 mm.

Comparison of pre-operative patient selection and grading of residual tumor with different pre-operative radiological modalities

Pre-operative patient selection and grading of residual tumors (R classification) were compared between 29 patients that underwent resection after pre-operative MDCT evaluation in the 2nd term, and 33 patients evaluated by SD-CT/angiography in the 1st term (**Table 1 and 2**). Residual tumors were graded as follows: R0, radical resection with tumor-free resection margins; R1, palliative resection with microscopically proven tumor on resection margins; R2, palliative resection with macroscopically tumor-positive margins. For strict evaluation of surgical margins, intra-operative frozen or permanent pathological sections from the dissected stump of the extra-pancreatic nerve plexus around the celiac trunk or the superior mesenteric artery (SMA) and from retroperitoneal tissues were routinely used. All pathological findings were evaluated by an experienced pathologist according to the General Rules for Clinical and Pathological Management of Carcinoma of the Pancreas of the Japan Pancreas Society (9). Tumor staging was graded as M1 (stage IVb) when para-aortic lymph node metastasis was detected. There was one in-hospital death in each period.

Statistical analysis

All data are expressed as median values and range. Data analysis was undertaken using Statview Version 5.0 for Windows (Abacus Concepts, Inc. USA). When appropriate, chi-square or Fisher's exact tests were used for comparison of categorical variables. Kaplan-Meier curves of disease-free survival and overall survival were generated, and comparisons between the groups were performed using log-rank test.

RESULTS

Comparison of pre-operative patient selection and grading of residual tumor with different pre-operative radiological modalities.

Based on SD-CT/angiography images in the 1st term, 27 of 70 patients (39%) were classified as primary incurable or locally advanced cases. Among the 43 patients (61%) that were classified as potentially resectable, 10 patients (14%) underwent surgical exploration without pancreatic resection and 33 patients (47%) underwent resection (**Table 1**). In the 2nd term, 80 patients were pre-operatively evaluated by MD-CT. Among 10 patients who displayed suspicious small metastases (less than 10-mm diameter) in the liver on MD-CT, subsequent staging laparoscopy confirmed the presence of liver metastases in seven, and the other three patients underwent pancreatectomy. In total, 48 of 80 patients (60%) in the 2nd term were not eligible for pancreatectomy, 29 patients (36%) underwent surgical resection and 4% underwent unnecessary laparotomy (**Table 1**). Thus, introduction of MD-CT followed by staging laparoscopy in selected patients not only resulted in a higher frequency of primary diagnosed incurable or locally advanced cases, but also in fewer unresectable cases who underwent unnecessary laparotomy, relative to SD-CTs/angiography ($p<0.02$).

Table 2. Clinical Characteristics of Resected Cases in the 1st and 2nd Term

	1st term	2nd term	*p* factor
Total number of patients	*33*	*29*	n.s.
Age	64 (52-78)	65 (47 - 83)	n.s.
Gender(Male : Female)	17 : 16	13 : 16	n.s.
CA19-9 (U/ml)	93 (5-8470)	89 (1-9116)	n.s.
Site of primary lesion			
Head : Body-tail	24 : 9	23 : 6	n.s.
Tumor size (mm)	30 (13-90)	32 (16-80)	n.s.
Co-morbid disease (+:-)	16:17	16:13	n.s.
Pre-operative chemo-radiation (+:-)	8:25	20:9	p=0.0008
Type of surgery (PD:PpPD:TP:DP)	21:1:2:9	19:3:0:7	n.s.
PV resection (+:-)	8:25	5:24	n.s.
CA resection (+:-)	1:32	1:28	n.s.
Operative duration (min)	510(266-900)	565(265-815)	n.s.
Extent of blood loss (ml)	1390(450-5503)	1140(400-7250)	n.s.
Stage I:II:III:IVa:IVb	2:3:3:13:12	2:0:9:12:6	n.s.
Pathological differentiation (well:mod:por:other)	10:16:6:1	4:20:0:5	n.s.

The data was expressed as median (range). PD, pancreaticoduodenectomy; PpPD,pylorus preserving PD; TP,total pancreatectomy; DP,distal pancreatectomy; PV, portal vein; CA, Celiac trunk; mod,moderately; por,poorly; other, papillary/adenosquamous cell carcinoma.

There were few significant differences in the clinical backgrounds of the 29 patients in the 2nd term relative to the 33 patients in the 1st term (**Table 2**). Patients in the 2nd term were significantly more likely to be treated pre-operatively with chemo-radiotherapy (p=0.0008). The frequency of portal vein resection, which was performed in 24% of 1st term and 21% of 2nd term patients, was not statistically different. In each term, distal pancreatectomy with celiac trunk resection was performed in one patient (3%). Of the cases that underwent pancreatectomy with vascular resection, 27% of tumors were R0 grade, 40% R1 and 33% R2. Although 25% of all R2-grade cases underwent this procedure, there was no significant difference in the frequency of R2 tumors resected in pancreatectomies with or without vascular resection.

In comparisons of residual tumor staging, the frequency of R0/1 in patients evaluated by MD-CT (80%) was significantly higher ($p<0.05$) than R0/1 evaluated by SD-CT/angiography (57%). The frequency of R2 grading was only 20% in the 2nd term, significantly less ($p<0.05$) than in the 1st term. All grade R1 cases showed microscopic tumor invasion to the retroperitoneal tissue or the stump of extra-pancreatic nerve plexus between the SMA and the pan-

creatic parenchyma. In contrast, R2 cases primarily showed major vessel invasions such as SMA, celiac trunk or common hepatic artery.

DISCUSSION

In this study, the pre-operative patient selection was compared to surgical resectability, and grading of residual tumor of patients with pancreatic cancer evaluated by MD-CT (slice thickness of 1.25 mm in the axial, coronal and sagittal phases) relative to conventional SD-CT/angiography (standard slice thickness of 5-7 mm). In selected patients, introduction of MD-CT followed by staging laparoscopy not only yielded a higher frequency of incurable or locally advanced cases during primary diagnosis, but also in fewer unresectable cases, relative to conventional forms of CT. Furthermore, the frequency of grade R0/1 tumors in patients evaluated by MD-CT was significantly higher than in patients evaluated by SD-CT/angiography. These data demonstrate that routine pre-operative imaging by MD-CT can significantly reduce the frequency of unnecessary surgical exploration and improve the selection of appropriate pancreatic cancer patients for surgical resection.

Technical developments in contrast enhanced MD-CT are useful not only for examination of thinner sections (which allow less partial-volume averaging to pick out mass lesions in solid organs, as well as different orthogonal plane display), but also for increased imaging speed (which allows greater bolus injection and a correspondingly higher concentration of iodine load to the portal vein and to the liver for better metastatic discernment). A faster injection rate also allows better segmentation of contrast phases. MD-CT cine-images with thin collimation in the axial, coronal and sagittal phases can provide detailed information in regions around peri-pancreatic major vessels and small liver metastases.

It is widely accepted that surgical resection is the only curative treatment that offers a significant chance for long-term survival in pancreatic cancer patients (10,11). Patients diagnosed with distal metastases, where the main treatment goal is to improve quality of life using less invasive procedures, should be managed non-surgically. Accurate staging to select patients who may benefit from resection is essential. Recent reports indicate that approximately one-third of patients diagnosed with resectable pancreatic tumors on CT were then found to have unresectable tumors upon surgery (12-15). This type of incorrect diagnosis is most often due to undetected vascular invasion, or small peritoneal or liver metastases. We reported previously that the accuracy of diagnosis of liver metastasis and vascular involvement by MD-CT in patients with pancreatic cancer was favorable compared to radiological findings from SD-CTs/angiography (6). Others have also reported that the sensitivity and specificity of vascular involvement diagnosis are 80-100% for MD-CT (16,17). These findings, and our experiences, lead us to conclude that accurate evaluation of liver metastasis and vascular involvement by MD-CT could result in fewer surgical cases without resection, and more curative cases relative to patients evaluated by SD-CT/angiography.

The problem of undetected metastases has led many surgeons to perform staging laparoscopy and laparoscopic biopsy routinely in an effort to avoid unnecessary laparotomy (12-14,18) . In this study staging laparoscopy was performed in selected cases to confirm the presence of liver metastasis detected by MD-CT, because use of the operating room for pancreatic surgery was limited in our hospital. In cases where MD-CT detected a small liver mass (<10 mm in diameter, and not definitive for the diagnosis of liver metastasis), laparoscopic exploration, ultrasonography and biopsy were used for confirmation. The 4% frequency of unresectable cases found in the 2nd term of this study would be considered acceptable in usual clinical practice. Thus, we suggest that routine staging laparoscopy after MD-CT pre-operative evaluation is not essential for selecting resectable cases with reasonable accuracy.

Factors that define resectability include the sur-

Table 3. Resection Rates in Patients with Potentially Resectable Pancreatic Cancer Based on Different Imaging Modalities

	Imaging studies	n*	potentially resectable	resected	resection rate % (R0:1:2:%)	reason for unresected distant	local
Rumstadt *et al.*.27	CT	398	194	172	89 (NR)	NR	NR
White *et al.*.28	CT	103	68	38	56 (68:NR:NR)	18%	26%
Friess *et al.*.29	CT	119	102	71	70 (NR)	14%	16%
Saldinger *et al.*.30	CT	NR	52	36	69 (78: NR:NR)	6%	25%
Vollmer *et al.*.18	CT	84	84	47	56 (NR)	26%	17%
	Lap	84	60	47	78 (NR)	7%	13%
Jimenez *et al.*.12	Lap	125	31	23	74 (NR)	3%	23%
Ellsmere *et al.*.13	MD-CT	NR	44	23	52 (66:17:17)	18%	30%
Vargas *et al.*. 17	MD-CT	59	25	22	88 (95:5:0)	12%	0%
In this study							
2000-2002	CT	70	43	33	77(18:39:43)	18%	5%
2002-2005	MD-CT	80	32	29	91(52:28:20)	9%	0%

*Number of patients with pancreatic cancer. MD-CT, multidetector row-CT; NR, not reported; Lap, staging laparoscopy
Resection rate, resected number/potentially resectable number

geon's opinion on the necessity of venous or arterial resection (19-20), and whether high-risk margins for resection of a tumor are acceptable. In our center, pancreatectomy with portal vein or celiac trunk resection was performed in some cases in which resection had been predicted to generate surgical- or pathological-free margins. During the period of this study, surgical indication was fixed, and two experienced surgeons performed all resections. Relative to SD-CT/angiography, pre-operative evaluation using MD-CT led to a higher frequency of curative resection and fewer cases of palliative resection. The frequency of R0 resected cases in the 1st and 2nd term (18% and 52%, respectively) was relatively low; however in the 2nd term, the frequency of R0/R1 in resected cases was 80% (an acceptable value). Because we examined pathological specimens of the surgical stump of perineural and retroperitoneal fat tissues between the pancreatic parenchyma and the SMA or the CA strictly, the frequency of R1-grade resected cases was relatively high. All 1st- and 2nd-term R1-grade cases showed positive microscopic margins of perineural and retroperitoneal fat tissues, but no extended invasion into major peri-pancreatic arteries. The significant decrease observed in the frequency of R2-grade tumors in the 2nd term was attributed to cases involving extended invasion to the major peri-pancreatic artery. Thus, a use of MD-CT contributes to accurate pre-operative imaging of major peri-pancreatic vessel invasion. Relatively high rates of R2 operation at our facility may also be due to broad surgical indications. To reduce frequency of R2 resection, "potentially resectable" cases categorized in this study should be defined as tumor ingrowth with vessel contiguity less than 0-25%, but not less than 50% in the major peri-pancreatic artery.

A caveat to interpreting the increase in curative resection in the 2nd term as significant is that, in addition to surgical resection, there is a difference in the number of patients receiving pre-operative chemo-radiation therapy (CRT) between the 1st and 2nd terms. A group at Duke University has reported that pre-operative CRT, in particular, can result in down-staging of pancreatic cancers (21,22). Breslin *et al.* at the M. D. Anderson Cancer Center have suggested that patient survival time with potentially resectable pancreatic cancer is maximized by a combination of chemoradiation and pancreaticoduodenectomy (23). Authors of a recent review from Sweden suggested that neo-adjuvant therapy represents an interesting solution to the poor prognosis of pancreatic cancer, although trials that include random controls are lacking (24). In this study, the frequency of grade-R2 tumors in cases with CRT was similar to that in cases without CRT, and both univariate and multivariate analyses showed that CRT was not an independent factor for curative resection (data not shown). Overall, the effect of neo-adjuvant therapy on patients with pancreatic cancer is presently unclear and will require further study. In interpreting the results of this retrospective analysis, variables including type of operation, rate of portal vein and celiac trunk resection, operative time and extent of blood loss, showed no significant differences between the 1st term and the 2nd term (Table 2). However, we were unable to take other underlying variables, such as pre-operative chemoradiotherapy and an extended study period of approximately five years, into account.

Overall, nearly 80% of patients evaluated with staging laparoscopy underwent successful resection, relative to an average of 70% (range 56-89%) of patients evaluated with CE-CT (**Table 3**). Better detection of unsuspected distant metastases likely contributed to this increase in successful resection but is not likely to contribute significantly to any changes in the detection of locally advanced disease following staging laparoscopy. Clearly, laparoscopy can prevent unnecessary laparotomy in patients with CT-occult metastases that then appear as peritoneal or surface liver metastases (25,26). In the conventional CE-CT or staging laparoscopy cases, the most common cause of unresectability (around 20%) was the presence of locally advanced disease. These data question the value of laparoscopy in the detection of mesenteric or retroperitoneal vessel involvement. In contrast, thin-collimation MD-CT cine-images of axial, coronal and sagittal phases provide detailed information around peri-pancreatic major vessels. MD-CT data from this report, and from Vargas *et al.*, demonstrate that extended vascular invasion is not the most common cause of unresectability. Previously, Ellesmere *et al.* had reported that locally advanced disease was present in approximately 30% of cases evaluated with laparotomy, however, the MD-CT scanning parameters of their study included 5 mm-thick reconstruction slices, relative to the 0.6 mm-thick slices of our protocol.

In conclusion, the use of MD-CT, which allows extremely thin collimation and the acquisition of high-resolution images of the pancreas, has a significant impact on the prevention of unnecessary surgical exploration and the selection of appropriate pancreatic cancer patients for surgical resection.

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Surgical Results After Preoperative Chemoradiation Therapy for Patients With Pancreatic Cancer

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Objectives: The results of surgical therapy alone for pancreatic cancer are disappointing. We explored surgical results after neoadjuvant chemoradiation therapy (NACRT) for patients with pancreatic cancer that extended beyond the pancreas.

Methods: Sixty-eight consecutive patients with pancreatic cancer who underwent pancreatic resection were included. Twenty-seven patients underwent surgical resection after NACRT (NACRT group). The other 41 patients were classified as surgery-alone group. Surgical results were compared in patients who underwent curative resection (R0/1) who were followed up for at least 25 months and underwent no adjuvant therapy.

Results: A lower frequency of lymph node metastasis was observed in the NACRT group ($P < 0.05$). The frequency of residual tumor grading in the NACRT group was significantly different from that in surgery-alone (R0/1/2%, 52/15/33 vs 22/51/27; $P = 0.0040$). In R0/1 cases, overall survival and disease-free survival rates in the NACRT group (n = 18) were significantly longer than in surgery-alone (n = 30, $P < 0.05$). The rate of local recurrence in the NACRT group was significantly less than in surgery-alone (11% vs 47%, $P = 0.0024$).

Conclusions: This single-institution experience indicates that NACRT is able to increase the resectability rate with clear margins and to decrease the rate of metastatic lymph nodes, resulting in improved prognosis of curative cases with pancreatic cancer that extended beyond the pancreas.

Key Words: curative resection, retrospective analysis, gemcitabine, 5-FU, CDDP, survival analysis

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The results of surgical therapy alone for pancreatic ductal cancer are still disappointing. Surgical resection for patients with pancreatic cancer at an early stage, which corresponds to cancer growth within pancreatic parenchyma, is the only curative treatment option; however, both distant and local/regional patterns of relapse are common within a year, even after curative resection.[1] In approximately 50% of resected pancreatic tumors, the surgical margins contain tumor cells.[2] The aggressive features of pancreatic cancer can lead to a dismal prognosis, and surgery alone is not optimal for achieving locoregional control of pancreatic cancer.[3,4]

To achieve 5-year survival exceeding 50% in patients with pancreatic cancer, Traverso LW advocated appropriate patient selection for curative resection by accurate staging, balanced resection, centralized treatment in high-volume centers, and the use of an effective adjuvant or neoadjuvant therapy.[4] Neoadjuvant (preoperative) chemoradiation therapy (NACRT) has several possibilities such as improved patient selection after the restaging evaluation, increased resectability rate with clear margins (R0 resection),[5] decreased rate of metastatic lymph nodes, and decreased rate of local relapse.[6] We previously reported that preoperative chemoradiation (5-fluorouracil [5-FU] or gemcitabine + 40 Gy) enabled the selection of 24 of 32 patients for surgery and resulted in acceptable toxicity.[7]

The objectives of this retrospective study were to compare the pathological results, overall survival (OS) and disease-free survival (DFS) rates, and type of recurrence in pancreatic cancer patients who underwent surgical resection after NACRT with those of patients who underwent surgery alone.

MATERIALS AND METHODS

One hundred seventy-five consecutive patients with a clinical diagnosis of pancreatic ductal adenocarcinoma were evaluated for the staging of tumor extension between January 2000 and December 2005 in Kansai Medical University Hospital. Cases involving an endocrine tumor of the pancreas, intraductal papillary mucinous cancer, acinar cell cancer, anaplastic cancer, duodenal cancer, distal common bile duct cancer, or ampullary cancer were excluded. During this period, 68 consecutive patients with pancreatic cancer who underwent pancreatic resection were included in this study. All tissues of the resected patients were pathologically proven ductal adenocarcinoma of the pancreas. Between 2001 and 2004, NACRT was performed in 35 patients who had radiologically diagnosed pancreatic cancer that extended beyond the pancreas (T3/T4 pancreatic cancer by TNM staging), and who were regarded as potentially resectable ([PR] n = 19) and locally advanced ([LA] n = 16), defined by National Comprehensive Cancer Network (NCCN) guideline.[8] Treatment consisted of concurrent radiotherapy (40 Gy within 4 weeks), and chemotherapy with 5-FU and cisplatin (CDDP) ([FP] n = 13) or with gemcitabine ([GEM] n = 22), as described in the previous article.[7] Finally, 27 patients (PR, n = 16; LA, n = 11; FP, n = 8; GEM n = 19) underwent surgical resection (NACRT group). The other 41 patients were classified as the surgery-alone group that consisted of pancreatic cancer patients who had a tumor limited to the pancreas (T1/T2 TNM staging) between 2001 and 2004, and the resected cases from 2000 and from 2005. Forty-eight patients with residual tumor staging of R0/1 were abstracted from 68 resected patients between 2000 and 2005, and the clinical and pathological characteristics, OS rate, DFS rate, and type of relapse were compared (NACRT group, n = 18; surgery-alone group, n = 30). All patients were followed up for at least 25 months and underwent no adjuvant chemotherapy.

As shown in the previous article,[9,10] local tumor unresectability was defined as (1) vascular involvement of a major

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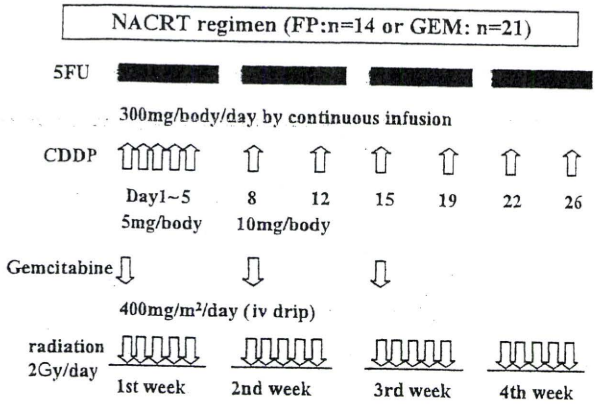

FIGURE 1. The regimen of NACRT.

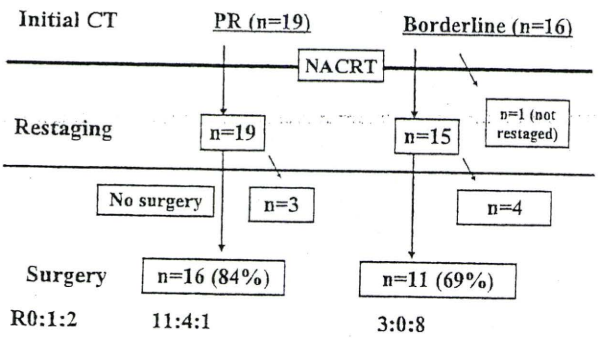

FIGURE 2. Clinical course of the NACRT group. PR indicates potentially resectable; borderline, borderline resectable in the NCCN guidelines.

peripancreatic artery (defined as tumor ingrowth with >50% vessel contiguity in the celiac trunk [CA], common or proper hepatic artery, or superior mesenteric artery); (2) extended obstruction of the portal vein to distal branches of the superior mesenteric vein; or (iii) with cavernous transformation of the porta hepatis. Patients with peritoneal carcinomatosis or distant organ metastasis were also excluded from this study. On the other hand, patients with cancer in the pancreatic body and tail, with CA invasion, and without superior mesenteric artery (SMA) invasion were also classified as candidates for the Appleby operation. All operations were performed by 2 experienced hepatopancreatobiliary surgeons who were in agreement about the extent of surgery to be performed. Preoperative staging was performed using contrast-enhanced computed tomography (CECT), abdominal angiography, CT-assisted hepatic arteriography, and CT during arterial portography before August 2002, and using CE multidetector row CT after September 2002.[9,10]

The detailed eligibility criteria were reported in the previous article.[8] Informed consent was obtained from all patients according to institutional regulations, and this study was approved by the local ethics committee. Patient data were obtained from the prospective database of pancreatic disease at Kansai Medical University Hospital.

Treatment Protocol

Patients received a continuous infusion of 5-FU (200 mg/m^2 5 times per week, 1–4 weeks), accompanied by CDDP (3 mg/m^2 on days 1–5, 6 mg/m^2 on days 9, 12, 14, 19, 23, and 26) in the FP-NACRT arm (Fig. 1). Gemcitabine at a dose of 400 mg/m^{-2} per day was given intravenously over 30 minutes starting 2 hours before radiotherapy 3 times weekly for 4 weeks in the GEM-NACRT arm (Fig. 1). Concomitantly, 10 mg of azasetron was routinely given before chemotherapy administration. Chemoinfusion was started approximately 60 minutes before radiation therapy. The protocol for radiation therapy was as follows. A total of 40 Gy was concurrently delivered in 2-Gy fractions to the tumor bed Monday through Friday for 4 weeks by a linear accelerator using megavoltage photon beams (6 MV). The clinical target volume was delineated slice by slice on the planning CT scan using CT simulation software. It encompassed the gross tumor volume as defined by the preoperative CT scan, plus a margin of 0.8 cm. Also included were retroperitoneal paraaortic lymphatic vessels between the CA and the upper mesenteric artery to the anterior level of the vertebral bodies. The gross tumor volume was defined as the gross tumor mass detected by CT scans. The planning target volume included the clinical target volume, with a 1-cm margin. Usually, a 4-field approach was chosen using anteroposterior and left and right lateral beams.

Surgical resection was performed 3 to 4 weeks after NACRT completion if none of the following were found: disease progression to an unresectable status (as previously mentioned) as determined by repeated abdominal CECT, a prohibitive decline in performance status, or other evidence of metastatic disease. Pancreatectomy was performed with portal vein resection, if portal vein resection was predicted to provide a surgical- or pathological-free margin. For resected patients, curative surgery was performed with extended lymph node dissection including paraaortic lymph nodes. Median time from the last day of NACRT to surgical resection was 28 days (range, 15–60 days). If tumor progression was evident, additional treatment with chemotherapeutic regimens was determined on an individual basis.

TABLE 1. Patient and Operative Factors of the NACRT and Control Groups

	NACRT	Control	P
Total no. patients	27	41	
Age	64 (47–74)	66 (50–83)	n.s.
Gender (male/female)	10:17	23:18	n.s.
CA19-9, U/mL	110 (1–8116)	89.7 (1–9116)	n.s.
Comorbid disease (+/−)	14:13	23:18	n.s.
Site of primary lesion			
Head/body-tail	21:6	28:13	n.s.
Tumor size, mm	30 (16–80)	30 (13–90)	n.s.
CDRS (PR/borderline)	16:11	24:17	n.s.
Type of surgery (PD/TP/DP)	20:1:6	27:1:13	n.s.
PV resection (+/−)	4:23	12:29	n.s.
CA resection (+/−)	2:25	1:40	n.s.
Operative duration, min	560 (325–840)	515 (265–900)	n.s.
Extent of blood loss, mL	1390 (400–6420)	1045 (390–7250)	n.s.

Data are expressed as the median (range).

Borderline indicates borderline resectable; CA19-9, carbohydrate antigen 19-9; CDRS, criteria defining resectability status; DP, distal pancreatectomy; n.s., not significant; PD, pancreaticoduodenectomy; PR, potentially resectable; PV, portal vein; TP, total pancreatectomy.

TABLE 2. Tumor Factors of the NACRT and Control Groups

	NACRT	Control	P
Total no. patients	27	41	
Site of primary lesion			
Head/body-tail	21:6	28:13	n.s.
Tumor size, mm	30 (16–80)	30 (13–90)	n.s.
Pathological differentiation (well/mod/por/other)	6:18:1:2	10:22:5:4	n.s.
Stage I–III : IVa/IVb	10:17	13:28	n.s.
LN mets positive/negative	11:16	28:13	0.0440
INF β/γ	19:8	33:8	n.s.
Ly 0/1:2/3	16:11	13:28	0.0440
V 0/1:2/3	22:5	20:21	0.0102
Ne 0/1:2/3	7:20	6:35	n.s.
Ch positive/negative	12:15	22:19	n.s.
Du positive/negative	14:13	20:21	n.s.
S positive/negative	12:15	16:25	n.s.
Rp positive/negative	16:11	28:13	n.s.
PV positive/negative	8:19	15:26	n.s.
A positive/negative	6:21	7:34	n.s.
PL positive/negative	9:18	19:2	n.s.
R grading 0:1:2 (n)	14:4:9	9:21:11	0.0040
R grading 0:1:2, %	52:15:33	22:51:27	
Radiological response*			
Grade Ia:Ib:II	12:6:9	N/E	

Data are expressed as the median (range).

Mod indicates moderately; por, poorly; other, papillary/adenosquamous cell carcinoma; R0, negative margin; R1, positive microscopic margin; R2, positive gross margin; LN met, lymph node metastasis; INF, mode of histological infiltration; Ly, grade of infiltration of the lymphatic vessels; V, grade of venous infiltration; Ne, grade of perineural invasion; Ch, grade of invasion to intrapancreatic common bile duct; Du, grade of invasion to the duodenum; S, grade of invasion to the anterior capsule; Rp, grade of invasion of the retroperitoneal tissue; Pv, grade of invasion of the portal vein; A, grade of invasion of the large artery; Pl, invasion of the extrapancreatic nerve plexus.

*Radiological response was defined as the amount of degenerated cancer cells.

Ia indicates less than 33% population of degenerated cancer cells; Ib, between 34% and 66%; II, more than 67%.

Follow-Up

After the completion of all treatments, patients were evaluated by physical examination every month, chest radiography, and CECT every 3 months. The development of a new low-density mass in the region of the pancreas bed and root of the mesentery was considered evidence of local recurrence even in the absence of symptoms. Cytological or histological confirmation of recurrent disease was not routinely required. Radiographic evidence of a new low-density region in the liver or lung was considered evidence of distant recurrence; biopsy was rarely performed. Peritoneal recurrence was defined as new ascites on physical examination or on CT and was confirmed by cytological examination of ascites. Sites of recurrent disease were documented at the time of initial recurrence. If the patients had any useful tumor markers at the first admission, these were checked again for confirmation of recurrence. In all patients, the date of first treatment was chosen as the starting point for survival analysis. All patients had a minimum follow-up of 25 months.

End Points and Statistical Analysis

The countable data were expressed as the median and range. The χ test or Fisher exact test was used for comparison of categorical variables when appropriate. The OS and DFS rates were calculated from the start of study treatment until death or the final date of follow-up and determined by the Kaplan-Meier method. Patients alive at the time of the study report were censored. The log-rank test was applied for the comparison of survival rates between different groups. Results were considered significant at $P < 0.05$.

RESULTS

Clinical Course of the NACRT Group

From 2001 to December 2004, 35 patients diagnosed as having pancreatic cancer were treated with NACRT using FP or GEM. Fourteen patients received FP-NACRT, and 21 patients received GEM-NACRT. According to NCCN guidelines, the 35 patients were divided into PR (n = 19) and borderline (n = 16), as shown in Figure 2. After NACRT, 34 patients were restaged using CECT or CE multidetector row CT, and 1 patient refused restaging. Three patients in the PR category (16%) did not undergo surgical resection because of liver metastasis, and 5 patients in the borderline category (31%) who had peritoneal metastasis (n = 2), liver metastasis (n = 1), and progressive disease (n = 1), in addition to 1 patient who refused restaging, did not undergo surgical resection. Finally, 16 patients (84%) in PR and 11 patients (69%) in borderline underwent surgical resection. The frequency of R0/1 in PR was 94%, significantly superior to 27% in borderline ($P < 0.0001$).

When radiological response was defined as the amount of degenerated cancer cells, only 9 patients (33%) in this NACRT regimen had more than 67% population of degenerated cancer cells (Table 1).

TABLE 3. Patient and Operative Factors in R0/1 Cases of the NACRT and Surgery-Alone Groups

	NACRT	Surgery-Alone	P
Total no. patients	18	30	
Age	65 (51–74)	68 (50 – 83)	n.s.
Gender (male/female)	7:11	18:12	n.s.
CA19-9, U/mL	90 (1–8116)	87 (1–9116)	n.s.
Comorbid disease (+/−)	10:8	18:12	n.s.
Site of primary lesion			
Head/body-tail	15:3	18:12	n.s.
Tumor size, mm	29 (16–80)	30 (13–90)	n.s.
PR/borderline	15:3	21:9	n.s.
Type of surgery (PD/TP/DP)	15:0:3	17:1:12	n.s.
PV resection (+/−)	3:15	9:21	n.s.
CA resection (+/−)	1:17	1:29	n.s.
Operative duration, min	557 (330–795)	512 (265–900)	n.s.
Extent of blood loss, mL	1078 (400–6420)	970 (390–5030)	n.s.

Data are expressed as the median (range).

Borderline indicates borderline resectable (NCCN, criteria defining resectability status); DP, distal pancreatectomy; LN, lymph node; PD, pancreaticoduodenectomy; PR potentially resectable; PV, portal vein; TP, total pancreatectomy.

TABLE 4. Tumor Factors in R0/1 Cases of the NACRT and Control Groups

	NACRT	Surgery Alone	P
Total no. patients	18	30	
Pathological differentiation (well:mod:por:other)	5:11:1:1	8:16:2:4	n.s.
Stage I-III/IVa/IVb	10:8	13:17	n.s.
LN met positive:negative	6:12	18:12	n.s.
INF β:γ	12:6	27:3	n.s.
Ly 0/1:2/3	12:6	11:19	n.s.
V 0/1:2/3	15:3	14:16	0.0158
Ne 0/1:2/3	5:13	4:26	n.s.
Ch positive/negative	8:10	13:17	n.s.
Du positive/negative	10:8	12:18	n.s.
S positive/negative	12:15	16:25	n.s.
Rp positive/negative	7:11	18:12	n.s.
PV positive/negative	2:16	8:22	n.s.
A positive/negative	1:17	2:28	n.s.
PL positive/negative	3:15	11:19	n.s.
Radiological response			
Grade Ia:Ib:II	7:4:7	N/E	

Data are expressed as the median (range).

Mod indicates moderately; por, poorly; other, papillary/adenosquamous cell carcinoma; LN met, lymph node metastasis; INF, mode of histological infiltration; Ly, grade of infiltration of the lymphatic vessels; V, grade of venous infiltration; Ne, grade of perineural invasion; Ch, grade of invasion to intrapancreatic common bile duct; Du, grade of invasion to the duodenum; S, grade of invasion to the anterior capsule; Rp, grade of invasion of the retroperitoneal tissue; Pv, grade of invasion of the portal vein; A, grade of invasion of the large artery; Pl, invasion of the extrapancreatic nerve plexus.

Comparisons of Surgical Results Between NACRT and Surgery-Alone Groups

The operative and tumor characteristics of all resected patients are listed in Tables 1 and 2. There were no significant differences in patient and operative characteristics between NACRT and surgery-alone groups. On comparison of tumor characteristics, significantly lower frequencies of lymph node metastasis, infiltration of lymphatic vessels, and venous infiltration in the NACRT group were found relative to those in the surgery-alone group ($P < 0.05$). Moreover, the frequency of pathologically curative resection (R0) in the NACRT group was significantly higher that that in the surgery-alone group (R0/1/2%, 52/15/33 vs 22/51/27; $P = 0.0040$). On abstracting R0/1 cases in NACRT and surgery-alone groups (Tables 3 and 4), although there was a tendency of a lower frequency of lymph node metastasis and infiltration of lymphatic vessels in the NACRT group relative to the surgery-alone group, a significant difference was not achieved. A significantly lower frequency of venous infiltration only was found in the NACRT group relative to the surgery-alone group ($P = 0.0158$). There was no difference in the survival curve of R2 cases between them.

Comparisons of OS and DFS Rates

All patients were followed up for at least 25 months without adjuvant chemotherapy. The median follow-up time after NACRT was 20.5 months (range, 3–84 months) for all patients and 56 months (range, 34–84 months) for censored patients. No

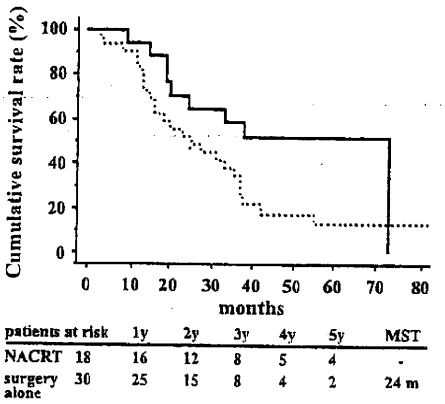

FIGURE 3. Overall survival rates in the NACRT and surgery-alone groups. Solid line indicates NACRT group; broken line, surgery-alone group. MST indicates median survival time.

treatment death occurred. Although the 1-, 3-, and 5-year OS rates in the NACRT group were 85%, 39%, and 34%, superior to 68%, 30%, and 9% in the surgery-alone group ($P = 0.0792$), there was no significant difference. The median survival time in the NACRT and surgery-alone groups was 24.5 and 18.5 months, respectively.

When patients who underwent curative resection (R0/1) were abstracted from all patients, there was a significant difference in the OS curve between the NACRT and surgery-alone groups (OS rates at 1 year, 3 years, and 5 years: 94%, 59%, and 52% in the NACRT group versus 83%, 34%, and 13% in the surgery-alone group; $P = 0.0425$; Fig. 3). The median survival time in the NACRT group was not reached, and in the surgery-alone group was 24 months. At a minimum of 36 months' follow-up, 8 patients in the NACRT group (44%) and 5 patients in the surgery-alone group (17%) were alive. Disease-free survival rates at 1 year, 3 years, and 5 years were 59%, 47%, and 47% in the NACRT group, significantly better than 53%, 12%, and 8% in the surgery-alone group (Fig. 4, $P = 0.0359$). Although the DFS rate at 1 year was similar, the difference in the DFS curve dramatically extended over 1 year after surgical resection. At the minimum follow-up of 25 months, 8 patients (44%) in the NACRT group and only 2 patients (7%) in the surgery-alone group were disease-free, and a significant difference was found between them ($P = 0.0024$). In the

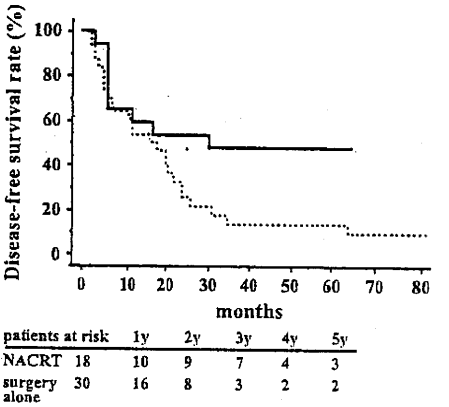

FIGURE 4. Disease-free survival rates in the NACRT and surgery-alone groups. Solid line indicates NACRT group; broken line, surgery-alone group.

NACRT group, all patients disease-free for more than 1 year have survived between 36 and 65 months.

There were no significant differences in OS and DFS rates between the use of GEM- and 5-FU–based chemoradiation. Moreover, there was no significant difference in survival curves between patients with R0 and R1 resection.

Type of Recurrence in Patients Who Underwent Curative Resection (R0/1)

The major pattern of recurrence was distant metastasis such as the liver and peritoneum (39%) in the NACRT and local recurrence (47%) as well as distant metastasis (43%) in the surgery-alone group. The frequency of local recurrence in the NACRT group was 11%, significantly lower than 47% in the surgery-alone group ($P = 0.0024$).

DISCUSSION

Even after curative resection, patients with pancreatic cancer face a 50% to 80% local recurrence rate and a 25% to 50% chance of developing distant metastases at the peritoneum and liver. The dreadful prognosis associated with this disease has mandated studies of combined multimodality therapies with both radiation and chemotherapy.[11,12] Crane et al[13] mentioned that NACRT had its own intrinsic advantages in that it theoretically increased the vulnerability of cancer cells because of intact vasculature, better tumor cell oxygenation, and the probability of sterilizing cells at the resection margin. Neoadjuvant CRT can clinically provide improved patient selection because patients with rapidly progressive systemic disease are identified as part of the restaging evaluation performed after NACRT before the planned surgery. Another advantage is better tolerability, which consecutively allows multimodal treatment in a higher number of patients, and the avoidance of late radiation-related toxicity. Furthermore, NACRT is able to facilitate resectability with free margins and a low frequency of lymph node metastasis. The Duke University group[14] reported that NACRT was associated with a marked reduction in the incidence of pancreatic leak, as well as leak-associated morbidity and mortality. On the other hand, Tse et al[15] referred to the theoretical disadvantages of potential overtreatment for a subset of patients with early-stage disease or with benign disease and of the potential risk of biliary stent–related morbidity.

Our previous study demonstrated that 5-FU/CDDP- or GEM-based CRT could reduce pain at a high rate without affecting Karnofsky performance status and body weight, resulting in acceptable toxicity.[7] Subsequently, we attempted to compare surgical results after NACRT in patients with pancreatic cancer that extended beyond the pancreas with patients who underwent surgery alone in this study. As a result, a lower frequency of lymph node metastasis and a higher frequency of pathologically curative resection were observed in the NACRT group. In patients who underwent curative resection, OS and DFS rates in the NACRT group were significantly longer than in the surgery-alone group. At a minimum follow-up of 25 months, the actual DFS rate in the NACRT group was 44%, significantly better than 7% in the surgery-alone group. Moreover, the frequency of local recurrence in the NACRT group was significantly less than in the surgery-alone group.

Neoadjuvant CRT ultimately leads to patient selection, as patients who show tumor progression during chemoradiation do not undergo surgery. As many as approximately 20% to 40% of patients initially presenting with resectable pancreatic tumors, but which had become unresectable at restaging evaluation, avoided unnecessary laparotomy.[7,16–22] In this article, 16% of PR and 31% of borderline resectable patients in the NACRT group were excluded from the subsequent surgical resection.

In general, the favorable prognostic factors for survival and recurrence in patients with pancreatic cancer have been reported as curative resection and negative lymph node metastasis.[4,5] The quality of surgery and examination of the pathological specimens can vary. Raut et al[23] proposed the term *SMA margin*, which indicates perivascular soft tissue, primarily perineural and mesenteric tissue, adjacent to (and posterior to) the right lateral border of the proximal SMA. In pancreatic cancer, the retroperitoneal margin is very close and often positive. It seems reasonable to conclude that locoregional therapy in pancreatic cancer can be optimized with complete gross tumor resection and treatment of microscopic disease at the SMA margin with chemoradiation. Factors that define resectability include the surgeon's opinion on the necessity of venous or arterial resection and whether high-risk margins for tumor resection are acceptable. In this study, our surgical indication included not only "potentially resectable" but also "borderline resectable," defined by NCCN,[9] and subsequently, we allowed R2 resection in this study. We performed aggressive pancreatectomy with portal vein or CA resection in some cases in which resection had been predicted to generate surgical-free margins. During this study, surgical indication was fixed, and 2 experienced surgeons performed all resections. Two pathologists closely examined pathological specimens of the dependently removed surgical stump of perineural and retroperitoneal fat tissues between the pancreatic parenchyma and the SMA or CA under surgical exposition of the right-sided adventitia of the proximal SMA and CA. Some authors reported that the frequency of pathologically curative resection (R0) after NACRT was 60% to 90%,[7,16,17,19–23] which was similar to our results of 52% (69% in PR and 27% in borderline resectable cases). It has been reported that the frequency of negative lymph node metastasis after NACRT and surgical resection was 40% to 80%, lower than after surgery alone.[7,16,17,19,21,22] In this experience, 59% negative lymph node metastasis in the NACRT group was significantly higher than 32% in the surgery-alone group. Better patient selection and the direct effect of chemoradiation in the NACRT group are able to facilitate resectability with free margins and a low frequency of lymph node metastasis. On the other hand, 20 (29%) of 68 resected patients had R2 residual tumor staging. There were no differences in survival analysis between R2 surgery in the NACRT and surgery-alone groups. Although it is difficult to interpret the results in a small population, surgical results in R2 cases after NACRT were disappointing.

Previous studies have shown that surgery alone yielded local recurrence rates of 50% to 80%, whereas preoperative chemoradiation reduced local failure rates to 5% to 13%.[7,17,20–22,24] The low local recurrence rate (11%) in the NACRT group at a minimum follow-up of 25 months was encouraging and was similar to previous reports.[7,17,21,22] Interestingly, there was a similar DFS rate within 1 year in the NACRT and surgery-alone groups with the absence of adjuvant chemotherapy, but a significant difference of the DFS curve over 1 year was observed among those who underwent curative resection. When all observed patients were followed up for 2 years, 44% of patients in the NACRT group were disease-free, significantly better than 7% in the surgery-alone group. All surviving patients in the NACRT group have been disease-free with a range of follow-up of 36 and 65 months, and the median survival time in the NACRT group was not reached. Over time, the difference in the DFS curve was clearly extended. It is important to note that all patients did not undergo adjuvant

chemotherapy, but patients with recurrent disease underwent weekly GEM administration on recurrence.

The median survival time in 5-FU–based neoadjuvant trials ranged from 15.7 to 45 months, which compares favorably with the survival rate of patients in the observation arms of previous randomized adjuvant trials (range, 11–19 months),[25,26] and is similar to that of the treatment arms of randomized adjuvant trials (range, 20–44 months).[25,27,28] The M.D. Anderson Cancer Center group[29] reported favorable results that the median survival time in GEM-based chemoradiation was 33 months, and most patients were noted to have greater than 50% nonviable tumor cells in the specimen, and 2 pathological complete responses were noted. Moreover, a phase II trial of neoadjuvant GEM (400 mg/m^2) with concurrent radiation of 30 Gy showed that 61 (73%) of 71 patients underwent surgical resection, and the median survival time was 36 months at 2 years' follow-up.[30] A phase II multi-institutional trial of NACRT using full-dose GEM conducted at the University of Michigan[16] demonstrated that 17 of 20 patients underwent surgical resection with 94% R0 grading, and the median survival time and 2-year OS rate were 26 months and 61%, respectively, after a median follow-up of 18 months. Thus, some studies of NACRT have demonstrated favorable outcomes compared with similar series of patients treated with surgery alone; however, the efficacy results must be interpreted with caution because the reports of NACRT for pancreatic cancer are heterogeneous with regard to patient population, treatment methods, modalities, and limited accrual. The University of Liverpool group[27,31] criticized that some studies using NACRT resulted in a median survival time of 9 to 39 months, and the largest comparative study found that neither the survival nor the pattern of disease recurrence was significantly different between neoadjuvant and adjuvant therapy. There have been no randomized controlled trials of neoadjuvant therapy despite the positive outcomes of single-institutional series of neoadjuvant therapy. New trials are being developed to address the neoadjuvant therapy question.[32,33] Brunner et al[32] initiated a multicenter prospectively randomized phase II study that aimed to answer the question of whether NACRT with GEM and CDDP can prolong the OS of patients with ductal adenocarcinoma of the pancreatic head in comparison with primary resected patients.

Chemoradiation therapy followed by curative resection seems to improve survival in patients with pancreatic cancer that extended beyond the pancreas in this study; however, several questions remain controversial: Should therapy be given preoperatively or postoperatively? Which chemoagent with external radiation has the high efficacy to induce tumor cell necrosis? How long is needed? How much radiation and chemotherapy should be used? More effective and less toxic regimens are necessary for neoadjuvant therapy to realize the ultimate goal of maximizing the number of patients who receive curative resection with less frequent metastatic lymph nodes, resulting in 50% or more 5-year survival rates.

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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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