VOLUME 27 · NUMBER 17 · JUNE 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Margin Clearance and Outcome in Resected Pancreatic Cancer

David K. Chang, Amber L. Johns, Neil D. Merrett, Anthony J. Gill, Emily K. Colvin, Christopher J. Scarlett, Nam Q. Nguyen, Rupert W.L. Leong, Peter H. Cosman, Mark I. Kelly, Robert L. Sutherland, Susan M. Henshall, James G. Kench, and Andrew V. Biankin

From the Cancer Research Program, Garvan Institute of Medical Research, Sydney; Departments of Surgery and Gastroenterology, Bankstown Hospital, University of New South Wales, Bankstown; Department of Anatomical Pathology, Royal North Shore Hospital, University of Sydney, St Leonards; Department of Surgery, Liverpool Hospital, Liverpool; and Department of Anatomical Pathology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia.

Submitted October 7, 2008; accepted January 7, 2009; published online ahead of print at www.jco.org on April 27, 2009.

Supported by The National Health and Medical Research Council of Australia, The Cancer Council New South Wales, Cancer Institute New South Wales, the Royal Australasian College of Surgeons, and the R. T. Hall Trust.

Written on behalf of the New South Wales Pancreatic Cancer Network.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Andrew V. Biankin, BMedSc, MBBS, FRACS, PhD, Cancer Research Program, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, New South Wales, Australia, 2010; e-mail: a.biankin@garvan.org.au.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2717-2855/$20.00

DOI: 10.1200/JCO.2008.20.5104

ABSTRACT

Purpose
Current adjuvant therapies for pancreatic cancer (PC) are inconsistently used and only modestly effective. Because a high proportion of patients who undergo resection for PC likely harbor occult metastatic disease, any adjuvant trials assessing therapies such as radiotherapy directed at locoregional disease are significantly underpowered. Stratification based on the probability (and volume) of residual locoregional disease could play an important role in the design of future clinical trials assessing adjuvant radiotherapy.

Patients and Methods
We assessed the relationships between margin involvement, the proximity to operative resection margins and outcome in a cohort of 365 patients who underwent operative resection for PC.

Results
Microscopic involvement of a resection margin by tumor was associated with a poor prognosis. Stratifying the minimum clearance of resection margins by 0.5-mm increments demonstrated that although median survival was no different to clear margins based on these definitions, it was not until the resection margin was clear by more than 1.5 mm that optimal long-term survival was achieved.

Conclusion
These data demonstrate that a margin clearance of more than 1.5 mm is important for long-term survival in a subgroup of patients. More aggressive therapeutic approaches that target locoregional disease such as radiotherapy may be beneficial in patients with close surgical margins. Stratification of patients for entry onto future clinical trials based on this criterion may identify those patients who benefit from adjuvant radiotherapy.

J Clin Oncol 27:2855-2862. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in Western societies, with a 5-year survival rate of less than 5%.[1] Operative resection remains the primary treatment modality and the only chance of cure, but only 20% of patients present with localized, nonmetastatic disease that is suitable for resection.[2] Those who undergo resection and receive adjuvant therapy have a median survival of 12 to 22 months[3] and a 5-year survival rate of 20% to 25%.[4]

The rapid demise of a high proportion of patients with pancreatic cancer even after complete surgical resection strongly suggests that occult metastatic disease was present at the time of surgery. Similarly, autopsy findings[5] and studies that assess patterns of disease recurrence show that more than 80% of patients who have potentially curative resections develop liver metastases, with no evidence of local recurrence.[6] This suggests that in pancreatic cancer, long-term survival rates are a better reflection of the adequacy of locoregional therapy than median survival and that adjuvant radiotherapy is only likely to be effective in a subgroup of patients (approximately 20%) where occult metastatic disease is not present. As a consequence, clinical trials that have assessed the therapeutic efficacy of adjuvant radiotherapy to date are grossly underpowered. These assertions are further supported by evidence that only margin-positive patients benefit from the addition of radiotherapy to adjuvant chemotherapy, a finding that was only apparent through a meta-analysis of randomized adjuvant therapy trials for pancreatic cancer.[7]

An additional complicating factor that makes comparison of studies difficult is the lack of

consensus for the definition of margin involvement. The International Union Against Cancer[8] defines R1 as the "presence of residual tumor after treatment," but at this time, there is no international consensus on the histologic definition of R1 for pancreatic cancer. In North America, R1 is defined as the presence of tumor cells at the surface of the resection margin[9,10] (0 mm definition), whereas in many other regions, R1 is defined as the presence of tumor cells within 1 mm of the resection margin,[11-13] extrapolating definitions used for cancers of other organs where close resection margins are associated with an increased risk of local recurrence.[14]

Therefore, the ability to estimate the risk of local recurrence and survival after pancreatectomy for pancreatic cancer is essential for the interpretation of adjuvant trials with respect to the efficacy of radiotherapy, as is stratification of patients for entry into future clinical trials. To address this issue and identify a clinically relevant definition of margin-positive status (R1) that would better reflect outcome after pancreatectomy, we examined the relationship between the degree of surgical margin clearance and long-term survival in a cohort of 365 patients who underwent pancreatectomy for pancreatic cancer in hospitals affiliated with the New South Wales Pancreatic Cancer Network.

PATIENTS AND METHODS

Patients and Data Acquisition

Detailed clinicopathologic and outcome data were collected for a cohort of 365 consecutive patients with a diagnosis of pancreatic ductal adenocarcinoma who underwent pancreatic resection with curative intent (no macroscopic residual disease) from eight teaching hospitals associated with the New South Wales Pancreatic Cancer Network, Sydney, Australia, between 1990 and 2007.

All cases underwent central pathology review by at least one specialist pancreatic histopathologist (J.G.K. and/or A.J.G.) who were blinded to the diagnosis to confirm pancreatic ductal adenocarcinoma and to define histopathologic features in a standardized manner using a synoptic report developed for the purpose.[15] Adenocarcinomas arising in the presence of intraductal papillary mucinous neoplasms or mucinous cystic neoplasms were excluded.

Clinicopathologic information was acquired from hospital notes (clinical history, preoperative imaging reports such as computed tomography, magnetic resonance imaging, ultrasound, and endoscopic ultrasonography, surgeon's operating reports, anesthesiologists reports, and correspondence letters from surgeon's and medical oncologist's consulting rooms). This was initially retrospective, but became prospective in later years. Information from surgeon's notes and imaging reports excluded two patients who had macroscopically involved margins (R2). The date and cause of death was obtained from the New South Wales Cancer Registry and treating clinicians.

There were 295 Whipple pancreaticoduodenectomies and 70 left-sided pancreatectomies used for the final analysis. Ethical approval for the acquisition of data and biologic material was obtained from the human research ethics committee at each participating institution.

The margin status and the closest distance of tumor cells to any surgical resection margin were determined on review of histopathology slides by at least one specialist pancreatic pathologists (A.J.G. and J.G.K.). The surgical resection margins were grouped as pancreatic neck, portal vein/superior mesenteric vein, superior mesenteric artery/retroperitoneal (uncinate), bile duct, proximal gastric/duodenal, and distal duodenal margins for Whipple pancreaticoduodenectomies, and pancreatic transection and retroperitoneal margins for left-sided pancreatectomies. The anterior/serosal margin was considered a surface and not a surgical resection margin.

Table 1. Clinicopathologic Parameters and Outcome (n = 365)

Variable	No. of Patients (n = 365)	%	Median DSS (months)	Log-Rank *P*
Sex				
Female	175	47.9	16.2	
Male	190	52.1	17.5	.3071
Age, years				
Mean	65.9			
Median	67.4			
Range	28.1-86.7			
Outcome				
Follow-up, months				
Range	0-168.6			
Median	15.6			
30-day mortality	15	4.1		
Death				
PC	282	77.3		
Other	12	3.3		
Alive	54	14.8		
Lost to follow-up	2	0.5		
Stage*				
IA	11			
IB	24		21.8	
IIA	113			
IIB	217		15.6	.0432
Differentiation†				
Well	32	8.8		
Moderate	235	64.4	17.1	
Poor	98	26.8	16.2	.2559
Tumor location				
Head	295	80.8	18.3	
Body/tail	70	19.2	11.6	.0013
Tumor size, mm				
≤ 20	84	23.0	27.9	
> 20	281	77.0	15.5	< .0001
Margins, 0 mm				
Clear	233	63.8	19.6	
Involved	132	36.2	13.2	.0003
Lymph nodes				
Negative	148	40.5	22.0	
Positive	217	59.5	15.1	.0003
Perineural invasion				
Negative	109	29.9	21.4	
Positive	256	70.1	16.2	.0020
Vascular invasion				
Negative	202	55.3	18.8	
Positive	163	44.7	16.2	.0147
Chemotherapy‡				
No adjuvant	269	73.7	15.1	
Adjuvant	96	26.3	25.3	.0012
Radiotherapy§				
None	344	94.2	16.7	
Any	21	5.8	22.4	.2921

Abbreviations: DSS, disease-specific survival; PC, pancreatic cancer.
*Stage I tumors versus stage II for survival analysis based on International Union Against Cancer TNM Staging System (ed 6), 2002.
†Well and moderately differentiated tumors grouped together for survival analysis.
‡Gemcitabine, 80 patients (83%) or fluorouracil.
§Analysis compares those patients who received radiotherapy at any time with all others.

Statistical Analysis

Disease-specific survival was used as the primary end point. To investigate the effect of margin distance on survival, the patients were stratified into three subgroups of "clear by up to X mm," "clear by more than X mm," and "involved" for X as 0.5, 1, 1.5, and 2 mms. In addition, survival was analyzed by dichotomizing patients using the different R1 definitions (ie, 0, ≤ 0.5, ≤ 1, ≤ 1.5. and ≤ 2 mm). The median survival was estimated using the Kaplan-Meier method,[16] and the difference was tested using the log-rank test.[17] *P* values of less than .05 were considered statistically significant, and the 3- and 5-year survival rates were estimated using life tables. Statistical analysis was performed using StatView 5.0 Software (Abacus Systems, Berkeley, CA). Cox proportional hazards models were generated for multivariate analysis.

RESULTS

Cohort Characteristics

The cohort of 365 patients (Table 1) consisted of 175 women and 190 men. The mean age at diagnosis was 66 years, with a median age of 67 and range of 28 to 87 years. The median follow-up for all patients was 15.6 months (range, 0 to 169 months). Fifty-four patients (14.8%) were alive at the census date (August 2007). The 30-day mortality rate was 4.1%. Two hundred eighty-two patients (77.3%) died from pancreatic cancer, 12 patients (3.3%) died of other causes, and two

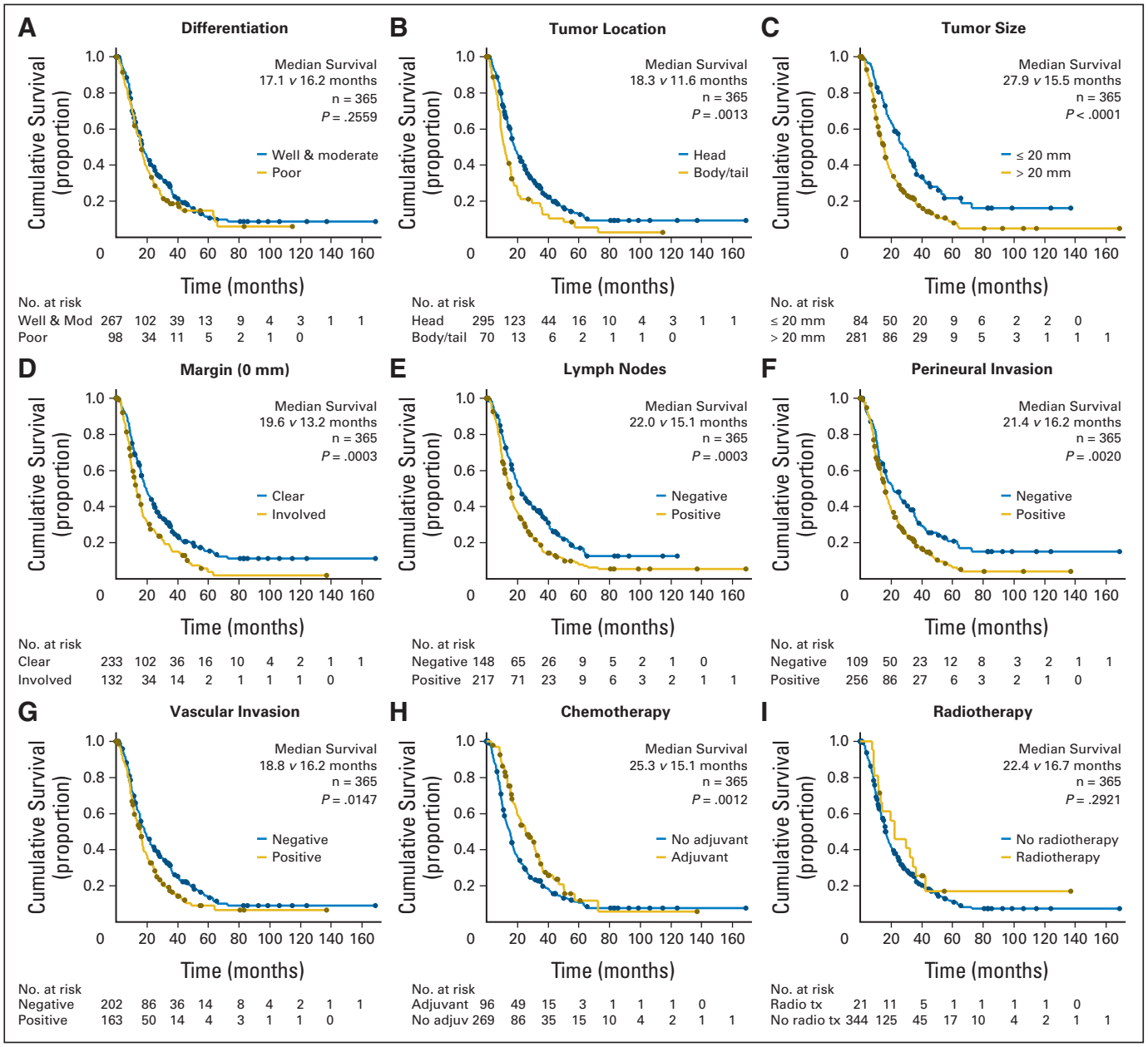

Fig 1. Kaplan-Meier survival curves for (A) differentiation, (B) tumor location, (C) tumor size, (D) margin involvement (R1 = 0 mm), (E) lymph node metastases, (F) perineural invasion, (G) vascular space invasion, (H) adjuvant chemotherapy and (I) radiotherapy (RADIOTX).

patients (0.5%) were lost to follow-up. The median disease-specific survival was 16.8 months, with 3- and 5-year survival rates of 23.8% and 11.4%, respectively. The majority of tumors were moderately differentiated (64%), followed by poor differentiation (27%), and only 9% of tumors were well differentiated. Most tumors were located in the head of the pancreas (81%) and were more than 20 mm in maximal diameter (77%). Lymph node metastases were present in 217 (60%) of 365 patients, perineural invasion was present in 256 patients (70%), and vascular space invasion was present in 163 patients (45%). Twenty-six percent of patients received adjuvant chemotherapy (gemcitabine or fluorouracil). Before 1998, adjuvant chemotherapy for pancreatic cancer was not the standard of care in Australia. Twenty-one patients (6%) received radiotherapy.

Factors associated with a significantly better survival on univariate analysis included tumors of the pancreatic head (median survival 18.3 *v* 11.6 months; $P = .0013$) compared with those of the body/tail, tumor size $\leq$ 20 mm (27.9 *v* 15.5 months; $P < .0001$), absence of direct margin involvement (19.6 *v* 13.2 months; $P = .0003$), absence of lymph node metastases (22.0 *v* 15.1 month; $P = .0003$), absence of perineural invasion (21.4 *v* 16.2 months; $P = .0020$), absence of vascular space invasion (18.8 *v* 16.2 months; $P = .0147$), and administration of adjuvant chemotherapy (25.3 *v* 15.1 months; $P = .0012$; Fig 1).

Multivariate models using Cox proportional hazards analysis demonstrated that tumor location, tumor size, direct margin involvement, lymph node metastases, vascular space invasion, and adjuvant chemotherapy were independent prognostic factors (Table 2A to C).

Involved margin based on an R1 = 0 mm definition occurred in 132 (36%) of 365 patients. The most commonly involved was the superior mesenteric artery (SMA)/retroperitoneal margin with 76 patients (58%), followed by the neck or the pancreatic transection margin with 64 patients (49%), the bile duct margin with six patients (4.5%), and portal vein (PV)/superior mesenteric vein (SMV) margin with four patients (3%). Proximal gastric/duodenal and distal duodenal margins were not involved in any of the patients. Of the 132 patients with positive margins, 116 (87.9%) had one positive margin, 15 (11.4%) had two positive margins, and one (0.8%) had four positive margins. Appendix Tabel A2 (online only) shows the breakdown of involved margins for Whipple and left-sided pancreatectomies.

Degree of Margin Clearance and Survival

To investigate the relationship between degree of margin clearance and disease-specific survival, univariate analyses were performed using different R1 definitions, with the close margin group as a separate variable (Fig 2). In these analyses, patients who had a margin clearance of either 0 to 0.5, 0 to 1, 0 to 1.5, or 0 to 2 mm had equivalent median survival times to those with clear margins (ie, > 0.5 mm, > 1 mm, > 1.5 mm, or > 2 mm, respectively). However, the long-term survival rates for each of these groups were worse compared with those with clear margins and were equivalent to those with involved margins until a clearance of 2 mm was present (Table 3). This suggests that a margin clearance of more than 1.5 mm is associated with long-term survival equivalent to margins of a greater distance, whereas margin clearances of less than 1.5 mm had a long-term survival which was closer to that of patients with directly involved resection margins.

Table 2. Multivariate Analysis

R1 Definition and Variable	Hazard Ratio	95% CI	*P*
A. PC (n = 365), R1 = 0 mm			
Differentiation, poor	1.22	0.93 to 1.57	.1602
Tumor location, body/tail	1.58	1.17 to 2.14	.0029
Tumor size, > 20 mm	1.61	1.20 to 2.17	.0016
Margin involvement, positive	1.48	1.15 to 1.89	.0020
Lymph node metastases, positive	1.57	1.22 to 2.01	.0004
Perineural invasion, positive	1.24	0.95 to 1.63	.1174
Vascular invasion, positive	1.28	1.01 to 1.63	.0445
Adjuvant chemotherapy	0.62	0.46 to 0.81	.0007
B. PC (n = 365), R1 = 0 mm			
Tumor location, body/tail	1.59	1.18 to 2.15	.0026
Tumor size, > 20 mm	1.60	1.19 to 2.15	.0020
Margin involvement, positive	1.46	1.14 to 1.86	.0029
Lymph node metastases, positive	1.56	1.21 to 2.00	.0005
Perineural invasion, positive	1.23	0.94 to 1.62	.1368
Vascular invasion, positive	1.31	1.03 to 1.66	.0303
Adjuvant chemotherapy	0.61	0.46 to 0.81	.0006
C. PC (n = 365), R1 = 0 mm (final model)			
Tumor location, body/tail	1.62	1.19 to 2.18	.0018
Tumor size, > 20 mm	1.63	1.21 to 2.19	.0013
Margin involvement, positive	1.48	1.15 to 1.89	.0019
Lymph node metastases, positive	1.58	1.23 to 2.03	.0003
Vascular invasion, positive	1.34	1.05 to 1.70	.0177
Adjuvant chemotherapy	0.61	0.46 to 0.80	.0005
D. PC (n = 365), R1 = 1.5 mm			
Differentiation, poor	1.22	0.93 to 1.59	.1475
Tumor location, body/tail	1.66	1.23 to 2.25	.0011
Tumor size, > 20 mm	1.59	1.18 to 2.15	.0024
Margin involvement, positive	1.36	1.06 to 1.74	.0161
Lymph node metastases, positive	1.60	1.25 to 2.06	.0002
Perineural invasion, positive	1.22	0.93 to 1.61	.1605
Vascular invasion, positive	1.25	0.98 to 1.59	.0706
Adjuvant chemotherapy	0.61	0.46 to 0.81	.0006
E. PC (n = 365), R1 = 1.5 mm			
Differentiation, poor	1.21	0.93 to 1.58	.1637
Tumor location, body/tail	1.69	1.25 to 2.28	.0007
Tumor size, > 20 mm	1.62	1.20 to 2.18	.0017
Margin involvement, positive	1.39	1.09 to 1.78	.0083
Lymph node metastases, positive	1.64	1.27 to 2.10	.0001
Vascular invasion, positive	1.28	1.00 to 1.63	.0469
Adjuvant chemotherapy	0.61	0.46 to 0.81	.0005
F. PC (n = 365), R1 = 1.5 mm (final model)			
Tumor location, body/tail	1.69	1.25 to 2.29	.0006
Tumor size, > 20 mm	1.60	1.19 to 2.16	.0020
Margin involvement, positive	1.36	1.07 to 1.74	.0130
Lymph node metastases, positive	1.62	1.26 to 2.07	.0002
Vascular invasion, positive	1.31	1.03 to 1.66	.0296
Adjuvant chemotherapy	0.61	0.46 to 0.80	.0005

NOTE. A to C: Cox multivariate models, with C being the final model when R1 was defined as 0 mm clearance. D to F: Cox multivariate models, with F being the final model when R1 was defined as 1.5 mm clearance.
Abbreviation: PC, pancreatic cancer.

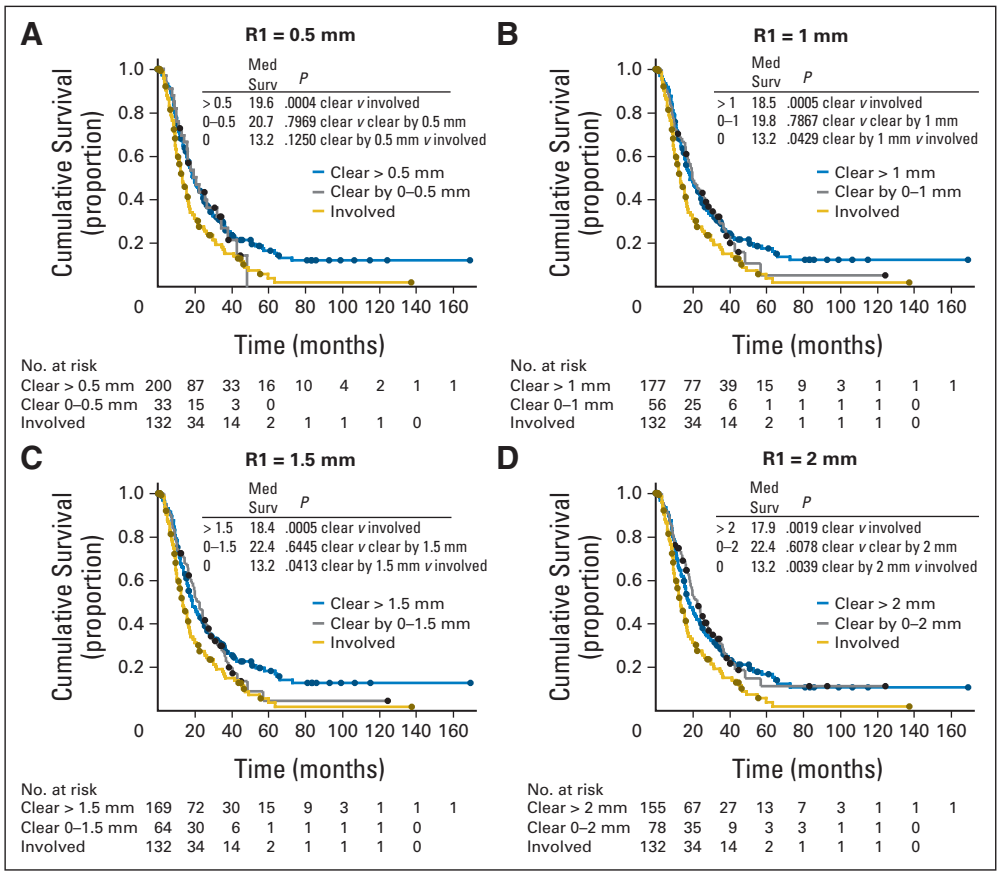

Fig 2. Kaplan-Meier survival curves for all patients stratified in three subgroups in each case with a different margin distance (involved, clear by 0 to X mm and clear by > X mm) for distances of (A) 0.5 mm, (B) 1 mm, (C) 1.5 mm, and (D) 2 mm. Med Surv, median survival.

Dichotomizing into "clear" and "involved" groups using the above different R1 definitions (0 mm, ≤ 0.5 mm, ≤ 1 mm, ≤ 1.5 mm, and ≤ 2 mm) showed that the differences in survival between the clear and the involved groups were not as great as the distance of margin clearance increased. However, until a margin clearance of more than 1.5 mm was achieved, there was still a statistically significant difference between the two groups (Appendix Fig A1, online only). In addition, margin status using an R1 definition of 1.5 mm was an independent predictor of survival in multivariate analysis (Table 2D to 2F).

Whipple Pancreaticoduodenectomy Subgroup Analysis

Because body/tail cancers may be considered different from those arising in the pancreatic head, we performed analysis on the 295 patients who underwent Whipple pancreaticoduodenectomy (Fig 3). In this subgroup, similar to all patients in the cohort, significantly better long-term survival was only seen when more than 1.5-mm clearance was present (Appendix Table A3, online only). In the 70 patients with body/tail cancers, there were only seven patients who had a margin clearance of between 0 and 1.0 mm, with no patients between 1 and 1.5 mm, limiting interpretation of the influence of margin clearance in this subgroup (Appendix Fig A2). This suggests that the predominant effect seen in the overall analysis was due to the Whipple subgroup.

DISCUSSION

The inherent biologic aggressiveness of pancreatic cancer results in a high proportion of patients presenting with overt metastatic disease. The rapid demise of a significant number of patients treated with potentially curative surgery suggests that a large proportion of patients staged as having locoregional disease have occult distant metastases. As a consequence, past trials of adjuvant therapies targeting locoregional disease (ie, radiotherapy) are grossly underpowered,[18-21] significantly impairing the ability to draw meaningful conclusions. Stratification of patients for future clinical trials so that they are sufficiently powered is therefore essential to improve outcomes with currently available treatment modalities.[22] This stratification may be applied based on refinement of current TNM staging, as described in this study.

Here we present evidence that the degree of margin clearance is important for long-term survival in patients who had pancreatectomies as part of their treatment for pancreatic cancer. Those patients who had resection margins with tumor closer than 1.5 mm had median survivals similar to those with greater clearance, suggesting that a similar proportion of patients had occult metastatic disease. On the other hand, their long-term survival was equivalent to those with directly involved margins, and it was not until a margin clearance of more than 1.5 mm was present that the proportion of long-term survivors became equivalent to patients

Table 3. Subgroup Analysis Using Different Margin Clearance (R1) Definitions

R1 Definition and Subgroup	No. of Patients (n = 365)	Median Survival (months)	Difference	3-Year Survival	Difference	5-Year Survival	Difference	*P* (log-rank)
0 mm								
Clear	233	19.6		28.0		15.5		
Involved	132	13.2	6.4	16.1	11.9	3.9	11.6	.0003*
≤ 0.5 mm								
Clear > 0.5 mm	200	19.6		28.0		16.6		.0004*
Clear by 0-0.5 mm	33	20.7	−1.1	26.9	1.1	0	16.6	.7969†
Involved	132	13.2	7.5	16.1	10.8	3.9	−3.9	.1250‡
≤ 1 mm								
Clear > 1 mm	177	18.5		27.5		17.6		.0005*
Clear by 0-1 mm	56	19.8	−1.3	29.2	−1.7	5.3	12.3	.7867†
Involved	132	13.2	6.6	16.1	13.1	3.9	1.4	.0429‡
≤ 1.5 mm								
Clear > 1.5 mm	169	18.4		28.9		18.5		.0005*
Clear by 0-1.5 mm	64	22.4	−4.0	25.0	3.9	4.6	13.9	.6445†
Involved	132	13.2	9.2	16.1	8.9	3.9	0.7	.0413‡
≤ 2 mm								
Clear > 2 mm	155	17.9		27.5		16.7		.0019*
Clear by 0-2 mm	78	22.4	−4.5	28.6	−1.1	11.2	5.5	.6078†
Involved	132	13.2	9.2	16.1	12.5	3.9	7.3	.0039‡

*P value for "clear" versus "involved."
†P value for "clear" versus "clear by X mm."
‡P value for "clear by X mm" versus "involved."

who had margins of greater distance. These findings suggest that in the case of pancreatic cancer, a margin clearance of 1.5 mm would be a useful definition of R1 in both a clinical and a trial setting.

Evidence that indirectly supports a potential role for radiotherapy for involved or close resection margins comes from randomized clinical trials[20,21] and large single-institution experiences,[23] which assessed the role of adjuvant protocols, including radiotherapy. A meta-analysis of randomized controlled trials of adjuvant therapy for pancreatic cancer by Stocken et al[7] demonstrated that chemotherapy was beneficial in patients who had clear resection margins, but not in margin-positive patients. This suggests that chemotherapy may have been most effective in patients with a low risk of residual local disease. In contrast, patients who had involved resection margins had a benefit from receiving radiotherapy as part of their adjuvant protocols. Patients with close resection margins (< 1.5 mm) may have a better response to adjuvant radiotherapy compared with frankly involved margins as a result of the probable low volume of residual local disease and potentially constitute a subgroup that is most likely to have the greatest benefit. In addition, a recent publication from the Johns Hopkins Hospital reporting their experience in using fluorouracil-based chemoradiotherapy as standard adjuvant therapy showed approximately equivalent benefits in all subgroups.[23]

Different therapeutic approaches and pathology reporting may account for the discrepancies seen between studies that assess the relationship of margin involvement and survival. Several studies have shown that standardized pathology reporting increases the margin positivity rate.[10,12,24] Raut et al[10] reported on the experience of 360 consecutive pancreaticoduodenectomies for pancreatic ductal adenocarcinoma from The University of Texas M. D. Anderson Cancer Center, where standardized histopathology reporting was used. The authors demonstrated that margin clearance was a statistically significant variable on univariate, but not on multivariate analysis. Potential reasons why our study differed on multivariate analysis may be due to the fact that the majority of patients in the study by Raut et al received neoadjuvant therapy, which may have influenced the survival of R1 patients more than R0 patients. In addition, the significance and viability of tumor cells at the resection margin histologically after neoadjuvant therapy is yet to be defined.

In conclusion, these data suggest that a resection margin of more than 1.5 mm is important for the long-term survival of a subgroup of patients. Close resection margins (< 1.5 mm) may be a marker of increased risk of local disease recurrence, which is reflected in long-term survival rates, and not in median survival, because the majority of patients die of metastatic disease. More aggressive approaches that target locoregional disease, such as adjuvant radiotherapy, in this subgroup of patients may improve their long-term survival. It would be potentially informative if past clinical trials were retrospectively analyzed to examine the role of radiotherapy in patients with close surgical margins. Moreover, stratification of patients based on margin status for entry into future clinical trials, which include radiotherapy protocols, may provide sufficient power to accurately define the role of adjuvant radiotherapy in the routine management of pancreatic cancer. The presence of tumor cells within 1.5 mm of resection margins may be either a surrogate marker of histopathologic sampling procedures or tumor biology. Until biomarkers of therapeutic responsiveness for locoregional therapies are validated,[25-30] this approach, which includes greater attention to histopathology reporting, may be a potentially significant step toward personalized therapy for pancreatic cancer.

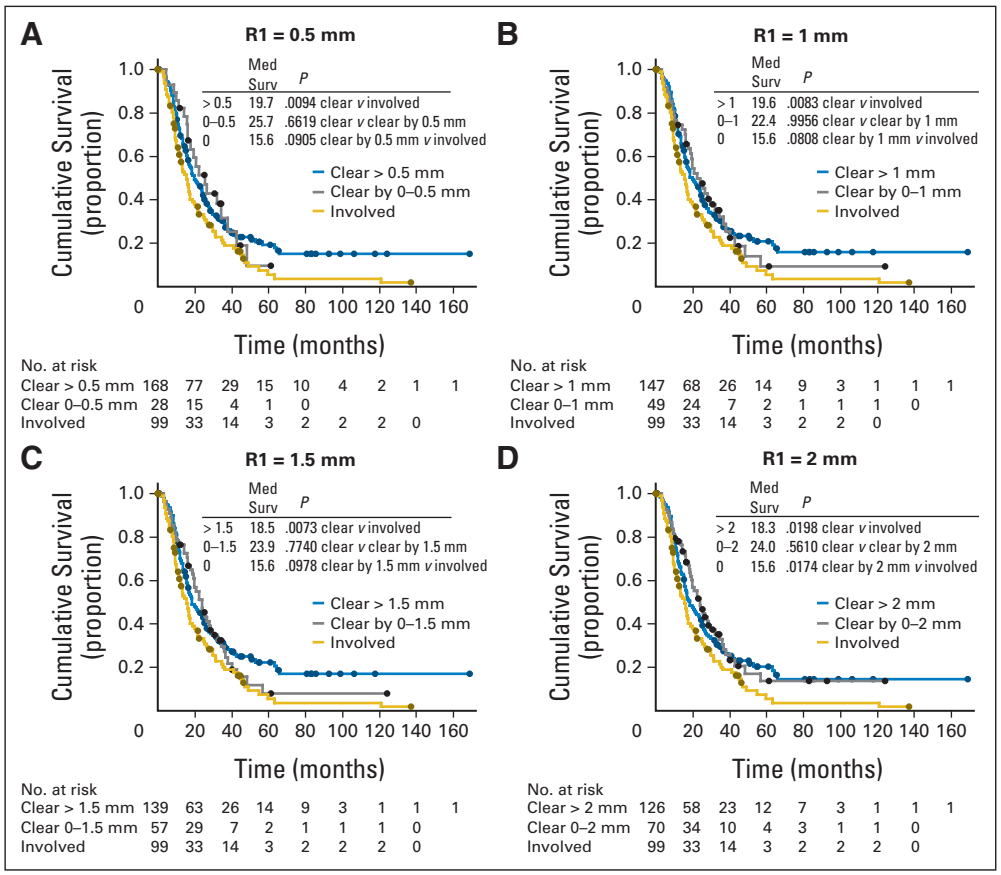

Fig 3. Kaplan-Meier survival curves for patients who underwent Whipple pancreaticoduodenectomy for pancreatic head tumors stratified in three subgroups in each case with a different margin distance (involved, clear by 0 to X mm and clear by > X mm) for distances of (A) 0.5 mm, (B) 1 mm, (C) 1.5 mm, and (D) 2 mm. Med Surv, median survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: David K. Chang, Amber L. Johns, Neil D. Merrett, Anthony J. Gill, Emily K. Colvin, Christopher J. Scarlett, Nam Q. Nguyen, Rupert W.L. Leong, Peter H. Cosman, Mark I. Kelly, Robert L. Sutherland, Susan M. Henshall, James G. Kench, Andrew V. Biankin
Administrative support: Robert L. Sutherland
Provision of study materials or patients: Neil D. Merrett, Peter H. Cosman, Andrew V. Biankin
Collection and assembly of data: David K. Chang, Amber L. Johns, Neil D. Merrett, Anthony J. Gill, Emily K. Colvin, Christopher J. Scarlett, Nam Q. Nguyen, Rupert W.L. Leong, Peter H. Cosman, Mark I. Kelly, Susan M. Henshall, James G. Kench, Andrew V. Biankin
Data analysis and interpretation: David K. Chang, Amber L. Johns, Neil D. Merrett, Anthony J. Gill, Emily K. Colvin, Christopher J. Scarlett, Nam Q. Nguyen, Rupert W.L. Leong, Peter H. Cosman, Mark I. Kelly, Robert L. Sutherland, Susan M. Henshall, James G. Kench, Andrew V. Biankin
Manuscript writing: David K. Chang, Amber L. Johns, Susan M. Henshall, James G. Kench, Andrew V. Biankin
Final approval of manuscript: David K. Chang, Amber L. Johns, Neil D. Merrett, Anthony J. Gill, Emily K. Colvin, Christopher J. Scarlett, Nam Q. Nguyen, Rupert W.L. Leong, Peter H. Cosman, Mark I. Kelly, Robert L. Sutherland, Susan M. Henshall, James G. Kench, Andrew V. Biankin

REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008
2. Yeo CJ, Cameron JL, Sohn TA, et al: Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: Pathology, complications, and outcomes. Ann Surg 226:248-257, 1997
3. Cameron JL, Riall TS, Coleman J, et al: One thousand consecutive pancreaticoduodenectomies. Ann Surg 244:10-15, 2006
4. Neoptolemos JP, Dunn JA, Stocken DD, et al: Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: A randomised controlled trial. Lancet 358:1576-1585, 2001
5. Barugola G, Falconi M, Bettini R, et al: The determinant factors of recurrence following resection for ductal pancreatic cancer. JOP 8:132-140, 2007
6. Schnelldorfer T, Ware AL, Sarr MG, et al: Long-term survival after pancreatoduodenectomy for pancreatic adenocarcinoma: Is cure possible? Ann Surg 247:456-462, 2008
7. Stocken DD, Buchler MW, Dervenis C, et al: Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer 92:1372-1381, 2005
8. Sobin LH, Wittekind C: UICC TNM Classification of Malignant Tumours. New York, NY, Wiley-Liss, 2002
9. Hruban RH, Pitman MB, Klimstra DS: Tumors of the Pancreas. Washington, DC, American Registry of Pathology, Armed Forces Institute of Pathology, 2007
10. Raut CP, Tseng JF, Sun CC, et al: Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg 246:52-60, 2007
11. Campbell F, Bennett MK, Foulis AK: Minimum Dataset for the Histopathological Reporting of Pancreatic, Ampulla of Vater and Bile Duct Carcinoma.

London, United Kingdom, Royal College of Pathologists, 2002

12. Esposito I, Kleeff J, Bergmann F, et al: Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 15:1651-1660, 2008

13. Verbeke CS: Resection margins and R1 rates in pancreatic cancer: Are we there yet? Histopathology 52:787-796, 2008

14. Wibe A, Rendedal PR, Svensson E, et al: Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. Br J Surg 89:327-334, 2002

15. Gill AJ, Johns AL, Eckstein R, et al: Synoptic reporting improves histopathological assessment of pancreatic resection specimens. Pathology 6:1-7, 2008

16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

17. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer 35:1-39, 1977

18. Neoptolemos JP, Stocken DD, Friess H, et al: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 350:1200-1210, 2004

19. Klinkenbijl JH, Jeekel J, Sahmoud T, et al: Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: Phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 230:776-782, 1999; discussion 782-784

20. Kalser MH, Ellenberg SS: Pancreatic cancer: Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 120:899-903, 1985

21. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer: Gastrointestinal Tumor Study Group. Cancer 59:2006-2010, 1987

22. Maitournam A, Simon R: On the efficiency of targeted clinical trials. Stat Med 24:329-339, 2005

23. Herman JM, Swartz MJ, Hsu CC, et al: Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol 26:3503-3510, 2008

24. Verbeke CS, Leitch D, Menon KV, et al: Redefining the R1 resection in pancreatic cancer. Br J Surg 93:1232-1237, 2006

25. Biankin AV, Morey AL, Lee CS, et al: DPC4/Smad4 expression and outcome in pancreatic ductal adenocarcinoma. J Clin Oncol 20:4531-4542, 2002

26. Segara D, Biankin AV, Kench JG, et al: Expression of HOXB2, a retinoic acid signaling target in pancreatic cancer and pancreatic intraepithelial neoplasia. Clin Cancer Res 11:3587-3596, 2005

27. Skalicky DA, Kench JG, Segara D, et al: Cyclin E expression and outcome in pancreatic ductal adenocarcinoma. Cancer Epidemiol Biomarkers Prev 15:1941-1947, 2006

28. Murphy NC, Scarlett CJ, Kench JG, et al: Expression of LMO4 and outcome in pancreatic ductal adenocarcinoma. Br J Cancer 98:537-541, 2008

29. Chang DK, Merrett ND, Biankin AV: Improving outcomes for operable pancreatic cancer: Is access to safer surgery the problem? J Gastroenterol Hepatol 23:1036-1045, 2008

30. Colvin EK, Chang DC, Merrett ND, et al: Individualized therapy for pancreatic cancer. J Gastroenterol Hepatol 23:1779-1782, 2008

Acknowledgment

We thank all the members and administrative staff of the New South Wales Pancreatic Cancer Network. For the full list of members, please see www.pancreaticcancer.net.au.