ORIGINAL ARTICLE

Pancreatoduodenectomy for Ductal Adenocarcinoma

Implications of Positive Margin on Survival

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Objective: To assess the effect of R0 resection margin status and R0 en bloc resection in pancreatoduodenectomy outcomes.

Design: Retrospective medical record review.

Setting: Mayo Clinic, Rochester, Minnesota.

Patients: Patients who underwent pancreatoduodenectomy for pancreatic adenocarcinoma at our institution between January 1, 1981, and December 31, 2007, were identified and their medical records were reviewed.

Main Outcome Measure: Median survival times.

Results: A total of 617 patients underwent pancreatoduodenectomy. Median survival times after R0 en bloc resection (n=411), R0 non–en bloc resection (n=57), R1 resection (n=127), and R2 resection (n=22) were 19, 18, 15, and 10 months, respectively ($P<.001$). A positive resection margin was associated with death ($P=.01$). No difference in survival time was found between patients undergoing R0 en bloc and R0 resections after reexcision of an initial positive margin (hazard ratio, 1.19; 95% confidence interval, 0.87-1.64; $P=.28$).

Conclusions: R0 resection remains an important prognostic factor. Achieving R0 status by initial en bloc resection or reexcision results in similar long-term survival.

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PANCREATIC DUCTAL ADENOcarcinoma is an aggressive cancer with poor prognosis and an overall 5-year survival rate of 3% to 5%.[1] Morbidity and mortality rates for pancreatoduodenectomy have decreased markedly with advances in operative techniques, patient selection, and postoperative care[2-4]; however, improvement in the form of better oncologic outcomes remains a major challenge. Numerous factors have been shown to affect survival in patients with pancreatic cancer, including tumor size, lymph node status, and histologic grade.[3-9]

Complete resection or R0 resection is an oncologic principle that is commonly and logically believed to be an important predictor of survival in most patients with surgically managed malignant neoplasms. In pancreatic cancer, numerous studies[3,4,10-16] have confirmed the survival advantage of R0 resection. Recently, however, this idea was challenged by Raut et al.[17] They concluded in their study that "there was no statistically significant difference in patient survival or recurrence based on R status."[17(p52)] The use of a standardized approach to patient selection using high-quality cross-sectional imaging explained the absence of any R2 resections in their study.

It has been confirmed that resection improved median survival times throughout a 20-year observation period from 1981 to 2001.[18] In that same study, however, R0 en bloc resection, but not resection margin status, was associated with long-term survival beyond 5 years in a univariate model; this variable, however, did not maintain significance in a multivariate analysis. In light of these findings, our aim in this study was to more fully define the role of R0 en bloc resection and the implications of positive surgical margins in a larger series of patients.

METHODS

After approval from the institutional review board, we searched our surgical index and institutional database to identify all patients who had undergone pancreatoduodenectomy at Mayo Clinic between January 1, 1981, and December 31, 2007. Inclusion criteria mandated that all the patients selected for this study had a confirmed, pathologic diagnosis of pancre-

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Table 1. Location of Positive Margins After Pancreatoduodenectomy for Pancreatic Ductal Adenocarcinoma in 149 Patients

Location of Positive Margin	No. (%) of Patients
Uncinate (SMA) margin	110 (73.8)
Portal vein groove	50 (33.6)
Pancreatic neck	32 (21.5)
Peripancreatic soft tissue	13 (8.7)
Common bile duct	4 (2.7)
Stomach or duodenum	0

Abbreviation: SMA, superior mesenteric artery.

atic ductal adenocarcinoma. Specimens taken before 2002 were reevaluated by a pathologist (T.C.S. or L.Z.). Patients who underwent pancreatoduodenectomy for other neoplasms were excluded from the study.

Patient medical records were reviewed retrospectively for the selected study population. Preoperatively, these patients underwent clinical and radiologic evaluation to determine whether the tumor was able to be resected. Abdominal computed tomography (CT) using a triple-phase pancreas protocol has been used routinely at our institution to identify the pancreatic tumor, assess involvement of adjacent vascular structures, and stage the cancer. Data on patient follow-up for survival and recurrence were retrieved via clinic follow-up appointments, the Mayo Clinic tumor registry, and death certificates.

Unique to the practice of the Mayo Clinic is the routine use of frozen-section analysis to assess intraoperatively the margin status and primary tumor, allowing subsequent resection when feasible to achieve negative margins. Subsequently, permanent histologic sections are analyzed for definitive diagnosis, lymph node metastases, and margin status. A systematic approach has been developed and used to assess margin status in accordance with the sixth edition of the American Joint Committee on Cancer guidelines.[19] The surgical margins evaluated routinely include the proximal common hepatic duct; pancreatic neck; uncinate process (also known as the superior mesenteric artery [SMA] margin); posterior, inferior, and superior (soft tissue) pancreatic margin; portal vein groove; and proximal duodenal margin if the patient is undergoing a pylorus-preserving resection. Both the portal vein groove and uncinate (SMA) margins are inked by the surgeon before sending the specimen to the pathology laboratory. In the surgical pathology laboratory, which is located within the operating suites, the specimen is incised in the plane of both the bile and pancreatic ducts facilitated by probes placed in each. Each part is then sliced perpendicular to the pancreatic duct. The tissue at the inked pancreatic margins is shaved at 1- to 2-mm thickness, and all sections are cut at 10 μm, stained with toluidine blue, and examined by a pathologist immediately while the operative procedure continues. The tissue at the uncinate (SMA) margin is sliced in a perpendicular fashion. The portal vein groove margins, the uncinate (SMA) margin, the pancreatic neck, and the common hepatic duct are examined separately and categorized as tumor free (R0) or microscopically involved (R1). The R2 status was based on a description by the surgeon that gross tumor remained. The proximal duodenal and gastric margins are first grossly examined; further microscopic examination is pursued if tumor is visible. The presence of high-grade dysplasia at any margin is also considered positive.

An R0 resection was categorized as R0 en bloc resection, when the tumor was excised in 1 piece without violating the tumor plane, or R0 reexcision, when negative margins were achieved only after sequential reexcision of involved margins. An R1 resection involves a microscopically positive margin(s) anywhere, and an R2 resection involves a grossly positive margin(s) with visible tumor, as determined by the surgeon intraoperatively.

Continuous data are reported as mean (SD) or median (interquartile range), and discrete data are reported as number (percentage). Differences in the categorization of margin status by year groups were tested with the Cochran-Armitage trend test. Cox proportional hazards models were used to construct univariate and multivariate models for death and recurrence or death. Kaplan-Meier–calculated curves were used to depict the overall survival and difference in survival between the different resection margin groups. A time effect was investigated by adding year to the model as a continuous covariate. All statistical tests were 2-sided, and $P < .05$ was considered statistically significant. Statistical analysis was conducted using the SAS statistical software program (version 9.1.3; SAS Institute Inc, Cary, North Carolina).

RESULTS

A total of 617 patients underwent pancreatoduodenectomy for ductal adenocarcinoma between January 1, 1981, and December 31, 2007. Mean age at the operation was 66 (11) years, and males comprised 55.9% of these patients. Five hundred eighty-six (95.0%) of the neoplasms originated in the head of the pancreas, 24 (3.9%) in the uncinate process, and 7 (1.1%) in the pancreatic neck. The mean tumor diameter was 3.3 (1.2) cm. On the basis of International Union Against Cancer tumor staging, neoplasms were staged as T1 (51 [8.3%]), T2 (140 [22.7%]), T3 (422 [68.4%]), and T4 (4 [0.6%]). Positive lymph nodes were present in 334 of 616 patients (54.2%); 241 of the 468 R0 resections (51.5%) and 80 of the 127 R1 resections (63.0%) had positive lymph nodes. Pylorus-preserving resections were performed in 332 of 616 patients (53.9%).

Of the 617 resections, 468 (75.9%) were R0 resections, 411 (87.8%) of which were en bloc resections, whereas the remaining 57 (12.2%) required a subsequent resection to achieve an R0 resection status. Of the 57 patients who underwent margin reexcision, the margins reexcised were as follows: pancreatic neck, 23; SMA margin, 18; and common bile duct, 3. Seven patients had 2 margins reexcised. Three patients had venous resection because of microscopic involvement of the portal vein groove. Three patients had a subsequent venous resection because of involvement of the proximal or distal venous margin.

Final positive margins occurred in 149 (24.1%), with 127 (85.2%) as R1 resections and 22 (14.8%) as R2 resections. The location of the positive margins is indicated in **Table 1**. Of the 149 patients with final positive margins, 135 (90.6%) involved the uncinate (SMA) and/or portal vein groove margins. A linear stapler was used to complete the uncinate margin resection in 156 of 603 patients (25.9%).

Portal-superior mesenteric vein resection with reconstruction was undertaken in 99 patients (16.0%); of these, 80 underwent R0 resections, and 17 underwent R1 resection because of the presence of tumor cells at the portal vein groove margin, the SMA margin, or both. Two patients were identified as undergoing R2 resection (intraoperatively by the surgeon) after portal vein resection had already been performed. Portal-superior mesenteric vein resection with reconstructions and pylorus-preserving op-

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erations were performed with increased frequency during the more recent years ($P = .002$ and $P < .001$, respectively), whereas the use of a stapler to transect the uncinate margin has decreased and almost been abandoned in more recent years ($P < .001$).

Chemotherapy and/or radiation was administered to 121 of 135 eligible patients with positive margins (89.6%) and 327 of 426 eligible patients with negative margins (76.8%). Neoadjuvant therapy was used in 46 of the 617 patients (7.5%); 22 patients (3.6%) received neoadjuvant chemotherapy and 24 (3.9%) underwent preoperative radiation. Five patients (0.8%) were given intraoperative radiation. Postoperative adjuvant therapy was administered in 448 of 561 patients (79.9%), 397 (88.6%) of whom received chemoradiation therapy, 24 (5.4%) of whom received chemotherapy alone, 7 (1.6%) of whom underwent radiation only, and 20 (4.5%) of whom had no data available.

FACTORS THAT INFLUENCE MARGIN STATUS

Univariate logistic models were constructed to assess the association of factors with positive margins. We found that T3/4 lesions (odds ratio [OR], 11.6; 95% confidence interval [CI], 2.78-48.41; $P < .001$), presence of positive lymph nodes (1.59; 1.09-2.33; $P = .02$), male sex (1.53; 1.05-2.24; $P = .03$), and pylorus-preserving resection (1.59; 1.09-2.32; $P = .02$) were associated with positive margins. Patients who underwent resection of the uncinate margin with a stapler were less likely to have positive margins than those who underwent traditional dissection and division of the uncinate (OR, 0.53; 95% CI, 0.33-0.84; $P = .008$). The mean size of the tumors was 3.1 cm for those resected with a stapler for SMA margin and 3.3 cm for nonstapled tumor resections. Age ($P = .40$), body mass index ($P = .34$), and estimated intraoperative blood loss ($P = .09$) were not associated with margin status. On multivariate analysis, male sex, presence of positive lymph nodes, and pylorus-preserving resections remained associated with the presence of a positive margin(s); use of a linear stapler to transect the uncinate margin continued to demonstrate a decreased association with the presence of positive margins ($P = .04$; **Table 2**).

The relationship of R status, en bloc resection, and portal vein resection was analyzed. Portal vein resection was associated with R1 and R2 resection status ($P < .001$). In particular, patients in whom subsequent resection of margins was required to achieve R0 status had greater odds of having portal vein resection compared with those with an R0 en bloc resection (OR, 3.37; 95% CI, 1.77-6.43; $P < .001$). Similarly, patients with an R1 margin status had greater odds of having a portal vein resection compared with the R0 en bloc resection group (OR, 2.79; 95% CI, 1.69-4.60; $P < .001$). No significant difference was found in odds of portal vein resection between the R2 and R0 en bloc groups (OR, 1.25; 95% CI, 0.36-4.40; $P = .72$).

SURVIVAL BASED ON RESECTION MARGIN STATUS

Median follow-up, treating deaths as censors, was 5.9 years (0-19 years). The median survival for these 617 patients was 18 months. The probability of survival at 1, 2, and 5 years was 69.8%, 36.7%, and 17.4%, respectively. The median recurrence-free survival in this group was 13 months. The probability of recurrence-free survival at 1, 2, and 5 years was 53.6%, 29.9%, and 15.8%, respectively. Tumor recurrence, defined as the presence of tumor on a follow-up CT scan, was observed in 379 of 602 patients (63.0%) during their follow-up periods. Of these patients with tumor recurrence, 52 (13.7%) were first classified as having local recurrence, 291 (76.8%) as having distant recurrence (lungs, liver, or peritoneal metastasis), and 6 (1.6%) as having both local and distant recurrence; data for location of recurrence were unavailable in 30 patients (7.9%).

When the 617 patients were grouped into categories according to margin status (R0 en bloc resections, R0 non–en bloc resections, R1 resections, and R2 resections), median overall survival was 19, 18, 15, and 10 months, respectively (**Figure**, A). The median time to recurrence or death in 602 patients was 14, 12, 12, and 9 months (Figure, B). No difference was found in median overall survival and recurrence-free survival between patients with R0 en bloc resection ($P = .28$) and R0 non–en bloc resection ($P = .71$). Seven of 127 patients (5.5%) with R1 resections had a greater than 5-year survival; of these, the longest survivor lived 9 years. There were no long-term survivors among the R2 resection group.

Univariate Cox proportional hazards models were constructed to analyze the association of resection margin status with survival and recurrence-free survival. Compared with patients who underwent R0 resection, patients who underwent an R1 resection had a greater risk of death (hazard ratio [HR], 1.40; 95% CI, 1.12-1.76; $P = .003$) and recurrence or death (1.40; 1.13-1.75; $P = .003$). Patients who underwent an R2 resection had a greater risk of death (HR, 2.28; 95% CI, 1.45-3.59; $P < .001$) and a greater risk of recurrence or death (2.20; 1.39-3.46; $P < .001$) than those who underwent an R0 resection.

On multivariate analysis, positive resection margin (R1 and R2) status was associated with death ($P = .01$). The relationship is driven mostly by increased risk in the R2 vs R0 en bloc groups (HR, 2.15; 95% CI, 1.31-3.52; $P = .002$) and less by the increased risk in the R1 vs R0 en bloc groups (1.26; 0.98-1.62; $P = .08$). The addition of year to the multivariate death model caused R1 resection to go from marginal to statistically significant on the multivariate model (HR, 1.31; 95% CI, 1.01-1.69; $P = .04$), indicating that patients who underwent R1 resection had increased risk of

Table 2. Multivariate Analysis of Variables Associated With Positive Margin(s)[a]

Variable	OR (95% CI)	*P* Value
Use of stapler at uncinate margin	0.60 (0.37-0.97)	.04
Pylorus-preserving procedure	1.50 (1.01-2.23)	.04
Male sex	1.55 (1.05-2.30)	.03
Positive lymph nodes	1.55 (1.05-2.28)	.03

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Body mass index was also included in the multivariate model but is not shown because of lack of significance.

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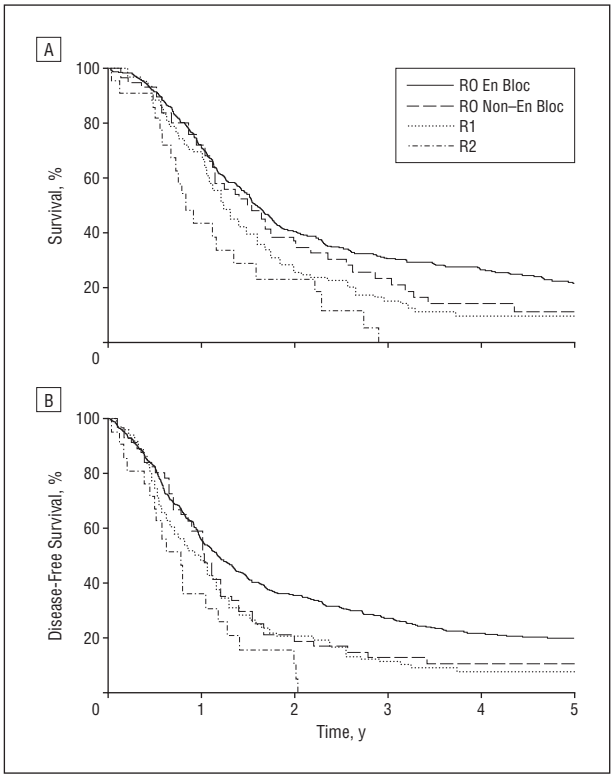

Figure. Kaplan-Meier curves. Time to death (A) and time to recurrence or death (B) in 617 patients with pancreatic ductal adenocarcinoma when categorized into 4 subgroups based on resection margin status (R0 en bloc, R0 non–en bloc, R1, and R2 resections).

death compared with patients who underwent R0 en bloc resection. Other conclusions from the time model were no different from the data given in **Table 3**. No difference in risk of death was seen on multivariate analysis between the R0 en bloc and R0 non–en bloc groups (HR, 1.06; 95% CI, 0.76-1.47; $P=.72$; Table 3). Recurrence-free survival data demonstrated similar findings.

The location of positive margins was also associated with both death and recurrence or death ($P<.001$). A positive SMA margin conferred a trend for greater risk of death (HR, 1.24; 95% CI, 0.97-1.60; $P=.09$) and a marginally increased risk of recurrence or death (1.27; 1.00-1.63; $P=.05$). Those patients with positive margins at the pancreatic neck, common bile duct, or peripancreatic soft tissue had a greater risk of death (HR, 1.97; 95% CI, 1.38-2.81; $P<.001$) and recurrence or death (1.87; 1.32-2.65; $P<.001$). A positive portal vein groove margin had no demonstrable disadvantage on survival (HR, 1.05; 95% CI, 0.72-1.53; $P=.81$) or recurrence or death (1.02; 0.72-1.46; $P=.89$), although the portal vein groove margin was evaluated only in the latter part of the study.

COMMENT

Although oncologic procedures for curative resection in pancreatic cancer should always be directed toward obtaining negative margins, ambiguity exists regarding the effect of margin status on survival. Although many authors have shown that a positive resection margin is a poor prognostic indicator,[3,4,10-16,20] some have provided evidence that questions the importance of an R0 resection.[17] In our study, we reaffirmed the importance of achieving an R0 resection whether via an en bloc resection or reexcision.

Table 3. Multivariate Cox Proportional Hazards Model for Death

Variable [a]	HR (95% CI)	*P* Value
Age at operation	1.02 (1.01-1.03)	<.001
Tumor grade		
Moderate differentiation	1.00 [Reference]	
Poor differentiation	1.62 (1.23-2.13)	<.001
Dedifferentiation	2.12 (1.53-2.95)	<.001
T stage		
T1	1.00 [Reference]	
T2	1.25 (0.83-1.87)	.29
≥T3	1.44 (0.98-2.11)	.06
Lymph node status	1.45 (1.19-1.77)	<.001
Blood loss >500 mL	1.37 (1.12-1.67)	.002
Resection type		
R0 en bloc	1.00 [Reference]	
R0 non–en bloc	1.06 (0.76-1.47)	.72
R1	1.26 (0.98-1.62)	.08
R2	2.15 (1.31-3.52)	.002

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Other variables that were included in the multivariate model but are not shown because of a lack of statistical significance include male sex and use of a stapler.

Both univariate and multivariate analysis demonstrated increased risk for death and recurrence or death for patients undergoing R1 and R2 resections vs R0 resections. Interestingly, when analyzing patients who underwent R0 resection vs R1 resections only (ie, excluding R2 resections) by multivariate modeling, R1 resection was not an independent risk factor for death. Although this finding seems to validate those of Raut et al[17] (whose study did not include any patients undergoing R2 resection), analyzing our data with consideration for practice changes over time reveals a trend for decreased survival and recurrence or death in patients who underwent R1 resection compared with those who underwent R0 en bloc resection. Specifically, early in the study period, our usual practice was to resect the uncinate process after mobilization of the portal vein and superior mesenteric vein, without actually visualizing the SMA. In 1997, we introduced the performance of en bloc periadventitial dissection of the SMA margin in patients with pancreatic head cancer. Moreover, it was at this time we also incorporated precise pathologic margin identification and routine marking of portal vein groove and SMA margin with ink. However, adoption of periadvential dissection and precise margin marking was gradually adopted in our multisurgeon practice. This is why we chose to use time as a continuous covariate in the multivariate model rather than attempting to compare the first and second halves of the study period. When statistical models were rerun with time as a continuous covariate, R0 en bloc resection had a significant survival benefit over R1 resection ($P=.04$). This finding further emphasizes the significance of improved operative techniques to permit better margin identification and the importance of organized pathologic assessment of margins.

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The difference in median survival times observed in our patients and those patients described by Raut et al[17] is noteworthy. Our median survival times for the R0 and R1 groups were 19 and 15 months, respectively, whereas the M. D. Anderson Cancer Center[17] reported median survival times of 28 and 21 months for the 2 groups, respectively. Neoadjuvant therapy was used in more than 70% of patients in their study, whereas only 3.9% of our patients received neoadjuvant chemoradiation. The neoadjuvant treatment strategy used at the M. D. Anderson Cancer Center defers operation for a few months, which allows exclusion of nonresponders with early disease progression from their surgical group. Their series did not include patients before 1990 (our study commenced in 1981); thus, more modern imaging and careful patient selection allowed avoidance of any R2 resections. Their use of periadventitial dissection of the SMA margin and pathologic assessment were consistent throughout their study, and although this is our current practice, adoption was gradual during the 26-year time frame of the study. These observations perhaps explain the differences in median survival times observed in our respective studies and the lack of agreement on the impact of R1 margin status on survival.

Fifty-seven patients required reexcision of margins to obtain R0 status. Early in the study period before periadventitial dissection of the SMA margin was used, reexcision of this margin was undertaken in 18 patients. Given our current practice of periadventitial dissection of the SMA margin, if reported as positive on frozen section currently, reexcision of this margin is not feasible. Our decision to perform portal vein resection is based on our ability to safely mobilize the portal-superior mesenteric vein from the portal vein groove. Although frozen section analysis of the portal vein groove margin is now performed routinely, we have used margin positivity in this location as a reason to perform sequential, non–en bloc portal vein resection in only 3 patients. The implications of positive portal vein groove margins will require further investigation.

When stratifying patients who undergo R0 resections into en bloc and reexcision categories, we found no difference in survival or recurrence or death. Schmidt et al[21] confirmed that reexcision of an isolated pancreatic neck margin by use of total pancreatectomy to achieve an R0 resection improved survival when compared with a cohort of patients undergoing pancreatoduodenectomy with an isolated positive pancreatic neck margin (R1). Considering all of this, we advocate an aggressive approach to obtain negative margins even if this requires a sequential reexcision. Given our current practice of periadventitial dissection of the SMA margin and the investigative status of the implications of a positive portal vein groove margin, sequential reexcision to achieve R0 status is practically limited to the pancreatic neck, common hepatic duct, and proximal duodenal-gastric margins.

Most patients with an R1 status had positive margins at the uncinate (SMA) margin (71.7%), where the presence of the SMA leaves little room for subsequent resection. The uncinate margin remains one of the most vexing areas of pancreatic cancer resection and, as our data suggest, a significant obstacle to achieving long-term survival after pancreatic cancer resection. An analysis was performed to compare the use of a stapler device to accomplish the uncinate (SMA) margin transection to standard surgical techniques. We found that patients who underwent stapled resection were less likely to have positive margins even though the tumor size for patients in the stapler and nonstapler groups was similar. This finding may be attributed to bias because staplers were more likely to be used early in our series when pathologic assessment was not as systematic. We have gradually abandoned its use in more recent years, as evidenced by decreasing frequency in its use in the latter half of the study ($P < .001$), and do not advocate its use in handling the uncinate margin. Our preferred practice is to perform periadventitial skeletonization of the right side of the SMA.

Although our data showed that portal vein groove margin positivity did not confer a prognostic disadvantage ($P = .81$), univariate analysis showed that patients who underwent portal vein resection with reconstruction were more likely to have a positive margin ($P = .002$), which is associated with poor survival. This discrepancy can be explained by the fact that the portal vein groove margin was not identified and assessed by frozen sections until 1997, when we adopted a more meticulous and precise operative and pathologic approach, and that margin positivity in this location prompted portal-superior mesenteric vein resection in only 3 patients.

Tumor stage, histologic differentiation of the tumor, age at operation, male sex, pylorus preservation, and increased blood loss investigated in multivariate models were associated with poor prognosis in terms of both survival and recurrence or death similar to previous findings.[3-9,12,13,15,22] Pylorus-preserving pancreatoduodenectomy and portal vein resection with reconstruction were performed in more recent years, coinciding with a more standardized pathologic evaluation of specimens at our institution. These changes in practice, which occurred during the long span of time that our study covers (1981-2007), likely represent an opportunity for bias.

All patients underwent an abdominal CT as preoperative screening to avoid operating on patients with unresectable neoplasms. Despite this, 22 patients were deemed to have an R2 resection status based on the surgeon's assessment that residual tumor remained. Seventeen of these occurred in the earlier part of the study (before 1999), whereas CT failed to identify R2 lesions in 5 patients during the last 8 years (2000-2007). We believe that advancements in CT imaging, especially the development of the triple-phase pancreas protocol, has been instrumental in minimizing the number of R2 resections more recently. Careful patient selection should ideally allow elimination of R2 resections.

Achieving an R0 resection remains an important task in pancreatic cancer surgery. Although the change in our pathologic methods and operative technique during the 26-year period of this study represents a major limitation of this study, analysis of R status with respect to time indicates that R0 resection holds a survival benefit over R1 resections. This likely represents the complex pattern in which pancreatic cancer presents, recurs, and, all too often, results in death. Given this, any survival advantage achieved by R0 resection appears to be accom-

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plished equally by a 1-time en bloc resection or reexcision, highlighting the importance of intraoperative frozen section analysis of margins when attempting curative resection of pancreatic head tumors.

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