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Improving Results of Pancreaticoduodenectomy for Pancreatic Cancer

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Abstract. This report from The Johns Hopkins Hospital reviews the results of pancreaticoduodenal resection during the decade of the 1990s, focusing on two recent publications. The first to be discussed involves a cohort of 650 consecutive patients undergoing pancreaticoduodenectomy (PD), with 443 patients having periampullary adenocarcinomas, 282 of whom had a pathologic diagnosis of pancreatic adenocarcinoma. The second report to be discussed involves the use of adjuvant chemoradiation therapy in a cohort of 174 patients who had successfully undergone PD for pancreatic adenocarcinoma. In both of these cohorts the operative mortality was less than 2%, and the median survival for resected pancreatic adenocarcinoma approximated 20 months.

Pancreaticoduodenectomy (PD) has gained increased usage in recent years, as it has been proven to be a safe, appropriate resectional option in selected patients with malignant and benign disorders of the pancreas and periampullary region. The operative mortality rate following PD is now less than 3% to 4% in many high-volume centers [1–4]. Although the mortality rate has fallen over the last decades, the incidence of postoperative morbidity remains high and can approach 40% to 50%. Common postoperative complications include early delayed gastric emptying, disruption of the pancreatic–enteric anastomosis with subsequent pancreatic fistula, wound infection, hemorrhage, and other problems [5–8]. This article reviews the recent experience at one high-volume center with PD, focusing on the improving results in patients with pancreatic adenocarcinoma.

Patients and Methods

650 Consecutive PDs during the 1990s

A recent report from The Johns Hopkins Hospital documented our experience with all patients undergoing PD from January 1990 through July 1996 [4]. All pathology specimens were reviewed by a single pathologist to determine the primary pathologic diagnosis and the extent of disease. For malignant lesions, resection margins were considered positive if the neoplasm was present at the pancreatic neck, uncinate, bile duct, duodenal, or retroperitoneal soft tissue margin. If the initial margin was positive at frozen section but further resection yielded a negative margin, the margin was considered negative. Lymph nodes were considered positive if any lymph node in the resection specimen contained tumor, regardless of whether it was involved by direct extension or was discontinuous with the primary.

The surgical techniques utilized at our institution have been described previously [9–11]. In brief, the biases at our institution have been to: (1) perform a standard PD, without an extended retroperitoneal lymph node dissection; (2) perform a pylorus-preserving resection, reserving distal gastric resection for neoplasms involving the distal stomach or first portion of the duodenum; and (3) perform partial pancreatectomy, leaving the body and tail of the pancreas in place unless the neoplasm extended into the body of the pancreas. Pancreatic–enteric reconstruction is accomplished by pancreaticojejunostomy, or occasionally via pancreaticogastrostomy [12]. Vagotomy, tube gastrostomy, tube jejunostomy, total parenteral nutrition, and prophylactic octreotide were not routinely used.

Postoperative Adjuvant Chemoradiation following PD for Pancreatic Adenocarcinoma

During this study that spanned 1991–1995 a total of 174 patients with the pathologic diagnosis of pancreatic adenocarcinoma were evaluated by a multidisciplinary group including those from surgery, radiation oncology, medical oncology, and pathology [13]. Patients were offered three options for postoperative treatment after PD, briefly described as follows: (1) *standard therapy,* consisting of external beam radiation therapy to the pancreatic bed (4000–4500 cGy) given with two 3-day courses of 5-fluorouracil (5-FU) (500 mg/m^2/day) followed by weekly bolus 5-FU for four additional months; (2) *intensive therapy,* consisting of external beam radiation therapy to the pancreatic bed (5040–5760 cGy) with prophylactic hepatic irradiation (2340–2700 cGy) given with and followed by infusional 5-FU (200 mg/m^2/day) plus leucovorin (5 mg/m^2/day) for 5 of 7 days a week for 4 months; or (3) *no therapy.* Details of these postoperative therapies and their toxicities and outcomes have recently been reported [13, 14].

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Table 1. 650 Consecutive PDs: pathology.

Pathology	No.	%
Periampullary adenocarcinoma	443	68
Pancreatic	282	43
Ampullary	70	11
Distal bile duct	65	10
Duodenal	26	4
Other	207	32
Chronic pancreatitis	71	11
Neuroendocrine tumor	31	5
Pancreatic cystadenoma	25	4
Ampullary adenoma	21	3
Pancreatic cystadenocarcinoma	14	2
Gastrointestinal stromal tumor	10	2
Miscellaneous	35	5

From Yeo et al. [4], with permission.

Results

650 Consecutive PDs during the 1990s

During the 6 years 7 months of this recent report [4], 650 patients underwent PD. The mean age of the patients was 63 years (range 18–89 years); 54% of the patients were male, 46% were female, and 91% were Caucasian. The median intraoperative blood loss was 625 ml; the median units of red blood cells transfused was zero; and the median operative time was 7 hours. Pylorus-preserving resection was performed in 82% of the patients, partial pancreatectomy in 95%, and pancreatic anastomosis via pancreaticojejunostomy in 67%.

Table 1 presents the pathologic diagnoses of the 650 resected specimens. Periampullary adenocarcinoma was found in 443 of the patients (68%), with the distribution being 242 patients (43%) with pancreatic cancer, 70 patients (11%) with ampullary cancer, 65 patients (10%) with distal bile duct cancer, and 26 patients (4%) with duodenal cancer. Of the remaining 207 patients without periampullary adenocarcinoma (32%), the most common findings were chronic pancreatitis, neuroendocrine tumors, pancreatic cystadenoma, ampullary adenoma, and pancreatic cystadenocarcinoma. Thirty-five patients (5%) were classified as having a miscellaneous pathologic diagnosis, including four patients with metastatic cancer to the head of the pancreas, three patients with gallbladder cancer, and the others with other more uncommon diagnoses.

Detailed pathologic findings from the 443 patients with periampullary adenocarcinoma are shown in Table 2. Of the 282 pancreatic adenocarcinomas, the mean tumor diameter was 3.2 cm, the median tumor diameter was 3 cm; most of the patients (63%) had moderately differentiated tumors. Patients with pancreatic adenocarcinoma underwent margin-negative resection in 71% of the cases, and 70% of all resections were associated with positive lymph nodes in the resection specimen. Tumor diameter was smallest for ampullary and distal bile duct cancers (median 2 cm) and largest for duodenal tumors (median 4.8 cm).

Multiple factors were evaluated by univariate analysis to determine their impact on survival in the 443 patients with periampullary cancer (Table 3). Parameters that influenced survival included estimated intraoperative blood loss, site of the primary tumor, tumor diameter, resection margin status, resected nodal status, tumor differentiation, and need for reoperation.

Table 2. Pathologic details from the 443 patients with resected periampullary adenocarcinoma.

Parameter	Pancreatic ($n = 282$)	Ampullary ($n = 70$)	Distal bile duct ($n = 65$)	Duodenal ($n = 26$)
Tumor diameter				
Mean	3.2 ± 1.6*	2.3 ± 1.4	2.1 ± 0.8	4.8 ± 2.8**
Median	3.0	2.0	2.0	4.8
Tumor diff. (%)				
Well	6	8	3	4
Moderate	63	69	69	70
Poor	31	23	28	26
Margin status (%)				
Negative	71	97	91	96
Positive	29***	3	9	4
Node status (%)				
Negative	30	56	43	38
Positive	70****	44	57	62

From Yeo et al. [4], with permission.
diff.: differentiation.
*$p = 0.05$ compared to tumor diameter of ampullary and distal bile duct tumors; **$p = 0.05$ compared to tumor diameter of pancreatic, ampullary, and distal bile duct tumors; ***$p < 0.05$ compared to positive margin status of ampullary, distal bile duct, and duodenal tumors; ****$p < 0.05$ compared to positive nodal status of ampullary and distal bile duct tumors.

A multivariate analysis was undertaken using a Cox proportional hazards model, with the goal being to determine which of the above univariate factors were independent predictors of survival. The hazard ratios and probability values are listed in Table 4. Two of the factors listed are independent predictors of prolonged survival: presence of a duodenal primary lesion and absence of reoperation. Both of these parameters have hazard ratios less than 1 and highly significant probability values. The remaining four factors are related to the pathologic analysis of the resection specimen. In order of worsening prognosis, they include tumor diameter ≥ 3 cm (hazard ratio = 1.47), positive resection margin status (hazard ratio = 1.63), lymph node metastases (hazard ratio = 1.93), and poor tumor differentiation (hazard ratio = 3.76).

Postoperative Adjuvant Chemoradiation following PD for Pancreatic Adenocarcinoma

This study specifically addressed the role of postoperative adjuvant chemoradiation therapy in patients undergoing PD for pancreatic adenocarcinoma [13]. During the period from October 1991 through September 1995, a total of 174 patients underwent PD for pancreatic adenocarcinoma. There was one in-hospital death (0.6%), leaving 173 patients who survived the operative period. Of these patients, 57% elected to receive standard adjuvant therapy, 12% elected the intensive therapy regimen, and 31% received no therapy. The median survival for the entire cohort was 19 months, with actuarial 1-, 2-, 3-, and 4-year survival rates of 68%, 36%, 29%, and 24%, respectively (Fig. 1). There were no significant differences in survival based upon age, gender, or race.

Tumor characteristics and postoperative factors were evaluated by univariate analysis. As listed in Table 5, tumor diameter, resection margin status, and resected lymph node status either achieved or approached statistical significance as factors influencing survival. Additionally, patients receiving either type of adju-

Table 3. Univariate analysis for 443 patients with periampullary adenocarcinoma.

Parameters not influencing survival		
Age		
Gender		
Race		
Type of resection: pylorus-preserving vs. classic		
Extent of resection: partial vs. total pancreatectomy		
Type of anastomosis: pancreaticojejunostomy vs. pancreaticogastrostomy		
Venous resection		
Operative time		
Transfusion status		
Postoperative length of stay		
Postoperative complications		
Parameters influencing survival	**Hazard ratio**	***p***
Estimated blood loss (ml)		
< 700	1.00	0.006
≥ 700	1.51	
Tumor site		
Pancreas	1.00	—
Bile duct	1.07	0.768
Ampullary	.56	0.006
Duodenum	.26	0.002
Tumor diameter (cm)		
< 3	1.00	0.036
≥ 3	1.37	
Margin status		
Negative	1.00	< 0.001
Positive	2.08	
Node status		
Negative	1.00	< 0.001
Positive	2.21	
Tumor differentiation		
Well	1.00	—
Moderate	1.97	0.139
Poor	2.81	0.028
Reoperation		
Yes	1.00	0.003
No	.36	

From Yeo et al. [4], with permission.

Table 4. Multivariate analysis for 443 patients with periampullary adenocarcinoma.

Parameter	Hazard ratio	*p*
Duodenal primary	0.29	0.004
No reoperation	0.22	< 0.001
Tumor diameter ≥ 3 cm	1.47	0.02
Margin positive	1.63	0.007
Node positive	1.93	< 0.001
Poorly differentiated	3.76	0.008

From Yeo et al. [4], with permission.

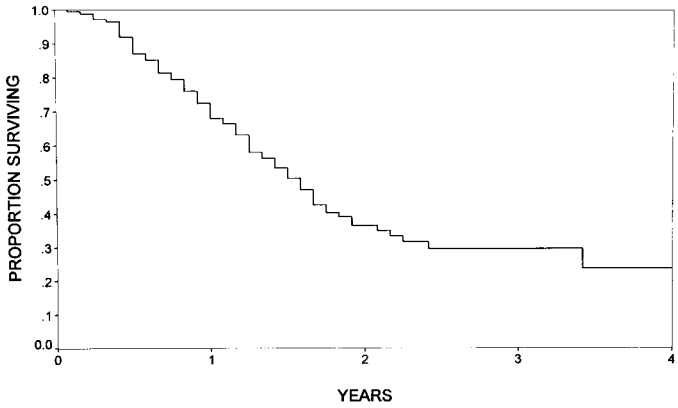

Fig. 1. Actuarial survival curve (Kaplan-Meier) for all patients undergoing PD for adenocarcinoma of the head, neck, or uncinate process of the pancreas ($n = 174$) from October 1991 through September 1995. (From Yeo et al. [13], with permission.)

Table 5. Factors influencing survival after PD: tumor characteristics and postoperative factors.

		Univariate analysis			
Parameter	No.	Median survival (months)	1-Year survival (%)	2-Year survival (%)	*p*
Entire cohort	174	19.0	68	36	—
Tumor characteristics					
Diameter (cm)					
< 3	76	26.0	79	53	< 0.001
≥ 3	98	14.5	60	25	
Resection margins					
Positive	51	15.0	60	28	0.095
Negative	123	18.5	71	40	
Lymph nodes					
Positive	130	16.5	63	34	0.077
Negative	44	19.5	83	43	
Differentiation					
Well/moderate	126	18.0	70	37	0.614
Poor	48	16.0	62	37	
Postoperative factor: adjuvant therapy					
Yes	120	19.5	80	39	0.003
No	53	13.5	54	30	
Standard	99	21.0	80	44	0.002*
Intensive	21	17.5	70	22	0.252*
None	53	13.5	54	30	

From Yeo et al. [13], with permission.
*p values vs. no therapy.

vant therapy ($n = 120$) had a median survival of 19.5 months and a 2-year survival of 39% (Fig. 2), which are significantly increased compared to the 53 patients who received no therapy (13.5 months and 30%; $p = 0.003$). Moreover, the patients receiving standard adjuvant therapy ($n = 99$) had a significantly ($p < 0.002$) longer median survival (21 months) and increased 2-year survival (44%) compared to the outcome in the no therapy group (13.5 months and 30%, respectively). The intensive therapy group had no survival advantage when compared to the standard therapy group (Fig. 3).

The toxicity of the adjuvant therapy regimens could best be evaluated in the subset of patients undergoing adjuvant therapy at The Johns Hopkins Hospital. In the group of 99 patients undergoing *standard* postoperative adjuvant chemoradiation therapy, 19 patients received their treatment at The Johns Hopkins Hospital; 18 were able to complete the intended regimen, and no patient required hospitalization during the chemoradiation therapy. The mean dose of radiation delivered was 4380 cGy. During adjuvant therapy 70% of patients lost weight (mean loss was 7% of body weight), whereas 30% of patients gained weight. The toxicity of the *intensive* regimen was acceptable but was increased compared

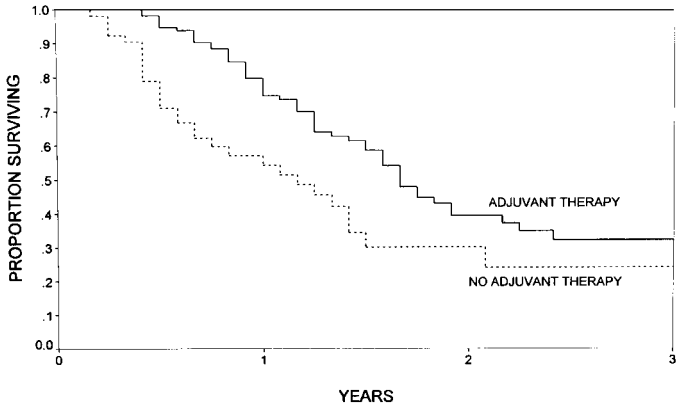

Fig. 2. Actuarial survival curves for patients undergoing PD comparing patients receiving adjuvant therapy ($n = 120$) to those declining adjuvant therapy ($n = 53$), ($p = 0.003$). (From Yeo et al. [13], with permission.)

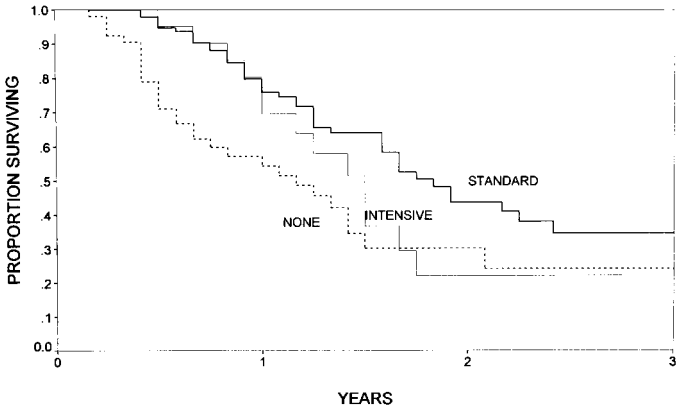

Fig. 3. Actuarial survival curves for patients undergoing PD comparing standard therapy ($n = 99$), intensive therapy ($n = 21$), and no therapy ($n = 53$). Standard therapy versus no therapy, $p = 0.002$. Intensive therapy versus no therapy, $p = 0.252$. (From Yeo et al. [13], with permission.)

Table 6. Multivariate analysis.

Factor	*p*	Hazard ratio
Tumor diameter ≥ 3 cm	< 0.001	2.278
Intraoperative blood loss ≥ 700 ml	0.014	1.754
Positive resection margins	0.055	1.586
Intensive therapy	0.04	0.495
Standard therapy	< 0.001	0.347

From Yeo et al. [13], with permission.

to that of the *standard* therapy. A description of the early evaluation of this regimen has been reported by Carducci et al. [14].

Using a Cox proportional hazards model, a multivariate analysis was undertaken to determine which of the univariate prognostic factors were independent predictors of survival in this cohort of 174 patients with pancreatic adenocarcinoma treated via PD. The probability values and hazard ratios for the final multivariate model are listed in Table 6. Tumor diameter ≥ 3 cm was a powerful independent predictor of decreased survival. Intraoperative blood loss ≥ 700 ml also influenced survival in a negative fashion, as did the presence of positive resection margins. Notably, the use of either of the two adjuvant therapy protocols had a significant impact on survival, with both having hazard ratios < 1, indicating improvement in survival with therapy. Standard therapy appeared to be a more powerful independent predictor of survival than was intensive therapy, based on both its smaller probability value and its smaller hazard ratio.

Discussion

The surgical history of the treatment of periampullary tumors encompasses the past century. Halsted reported the first successful resection of an ampullary tumor in 1899, describing a local ampullary resection [15]. In 1912 Kausch performed the first successful PD in two stages [16]. Despite many early attempts at combined pancreaticoduodenal resection during the early part of the twentieth century, until 1935 most ampullary cancers were managed by a transduodenal approach similar to that first reported by Halsted. In 1935 Whipple et al. reported three patients with ampullary carcinoma treated by a two-stage PD [17]. In 1937 Brunschwig [18] reported extending the indications for PD to include cancer of the head of the pancreas. During the 1940s and 1950s, PD was typically accomplished as a one-stage procedure; it was applied to patients with all forms of periampullary neoplasms and was performed with increasing frequency. However, during this era, PD was a formidable operation that carried a hospital mortality approaching 25% in some series reported through the 1970s, leading some to suggest that its use be abandoned [19, 20].

It is of note that exceptions to this high mortality rate existed. In particular a report by Howard in 1968 described 41 consecutive patients treated by PD without a hospital death [21]. In recent years, dramatic improvements in hospital morbidity, mortality, and survival after PD have been reported. Trede et al. [22] reported 118 consecutive resections with no operative mortality in 1990, whereas a report from our institution in 1993 described 145 consecutive PDs without an in-hospital death [2]. Most recently at our institution, 190 consecutive patients have been reported without in-hospital mortality [4]. Overall, many centers have now reported hospital mortality rates less than 4%, with the mortality rate approaching 1% in selected series.

This information notwithstanding, PD remains a formidable operation, with a median operative time of 7 hours and a median estimated intraoperative blood loss of 625 ml. In recent years the indications for PD have been expanded, concomitant with the declining morbidity and improving patient survival. The procedure, although applied most commonly with curative intent for periampullary adenocarcinoma, is also indicated for a variety of other periampullary neoplasms and for nonneoplastic conditions such as chronic pancreatitis. In addition, a recent report from our institution has suggested that PD, when performed with perioperative morbidity and mortality rates similar to those achieved for palliative bypass procedures, may be associated with improved long-term survival in patients with locally advanced periampullary adenocarcinoma who would have otherwise been treated via palliative bypass [23].

The overall postoperative mortality in the series of 650 consecutive patients reported here was 1.4% [4]. These results reflect the dramatic decline in the postPD mortality rates that have occurred over the past decade. There is no question that many factors contribute to this decline in mortality rates: careful patient preoperative assessment, improved surgical technique, and improve-

ments in perioperative care (including major improvements in interventional radiology and critical care management). In addition, recently published data from two large statewide registries have shown a relation between hospital volume for complex pancreatic resection and perioperative mortality rates. Gordon et al. [24] have used data from the Maryland Health Services Cost Review Commission to show that hospital mortality after PD was six times higher among patients treated at low-volume facilities than among patients treated at a high-volume regional provider (i.e., The Johns Hopkins Hospital). Similarly, Lieberman et al. [25] used data from the New York State Department of Health Statewide Planning and Research Cooperative System to show that both crude and standardized (risk-adjusted) perioperative mortality rates after pancreatic resection were inversely related to hospital volume. These studies and others have clearly shown that the experience in a high-volume institution is associated with lower perioperative mortality and duration of hospitalization, when controlling for patient characteristics and co-morbidities. These data suggest that regionalization of care as concerns complex pancreatic resection would have a substantial impact on both the cost and outcome of patients undergoing this procedure.

The issue of the use of adjuvant chemoradiation after PD for adenocarcinoma of the pancreas remains somewhat unsettled. The most widely known trials of adjuvant chemoradiation after pancreatic resection were reported by the Gastrointestinal Tumor Study Group in 1985 and 1987 [26, 27]. Both of these studies were flawed by small sample sizes, slow patient accrual rates, and the inclusion of patients with adenocarcinoma of the body and tail of the pancreas. In the recent study from Johns Hopkins [13], the components of the standard therapy regimen were based on the encouraging data from the GITSG, using a 5-fluorouracil (5-FU)-based chemotherapeutic regimen in combination with and following external beam radiation therapy to the pancreatic bed. There are, however, four differences between our standard therapy group and the GITSG regimen. First, our standard therapy group was composed exclusively of patients with adenocarcinoma confined to the head, neck, or uncinate process of the pancreas, resected via PD. Second, the length of time for the administration of weekly bolus 5-FU after external beam radiation therapy was decreased from 2 years to 4 months. Third, our patients could receive standard therapy regardless of resection margin status. Fourth, the dose of radiation was increased to a ceiling of 4500 cGy. By both univariate and multivariate analysis, our results show that adjuvant chemoradiation is associated with a favorable effect on survival. We recognize that our study is limited methodologically by its nonrandomized design. It has been our practice to recommend adjuvant chemoradiation therapy to our resected patients since the GITSG results were published. We therefore are biased in support of the use of adjuvant therapy.

Résumé

En se basant sur deux publications récentes, on résume l'expérience de la duodénopancréatectomie effectuée à l'Hôpital Johns Hopkins pendant la décennie 1990. La première publication concerne une cohorte de 650 patients consécutifs ayant eu une duodénopancréatectomie, 443 pour adénocarcinome périampullaire, et 282 pour adénocarcinome du pancréas, confirmé histologiquement. La deuxième partie concerne 174 patients ayant eu une radiochimiothérapie adjuvante après duodénopancréatectomie pour adénocarcinome du pancréas. Dans les deux cohortes, la mortalité opératoire était inférieure à 2%, et la survie médiane, après résection, de 20 mois environ.

Resumen

Este trabajo del Johns Hopkins Hospital revisa los resultados de la duodenopancreatectomía en la década de 1990, a la luz de dos publicaciones recientes. La primera, comprende una cohorte de 650 pacientes a los que se les practicó una duodenopancreatectomía; 443 padecían de un adenocarcinoma periampular, de los que 282 fueron diagnosticados anatomopatológicamente, de forma definitiva, de adenocarcinoma pancreático. La segunda publicación incluye un colectivo de 174 pacientes en los que, tras realizar con éxito una duodenopancreatectomía por adenocarcinoma de páncreas, se les administró un tratamiento quimio-radioterápico adyuvante. En ambas cohortes la mortalidad operatoria fue menor del 2% y la supervivencia media, para los adenocarcinomas resecados, fue, aproximadamente, de 20 meses.

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