

Whipple procedure: Significant morbidity with marginal benefit

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Grand Rounds

November 15, 2010



Objectives

- Statistics
 - What is a whipple procedure?
 - Pancreatic cancer has poor prognosis
 - Little benefit to surgery alone.
 - Quality of life/Palliation
 - Closing Remarks
- 

Pancreatic Cancer

Estimated New Cases*

				Males	Females				
Prostate	192,280	25%				Breast	192,370	27%	
Lung & bronchus	116,090	15%				Lung & bronchus	103,350	14%	
Colon & rectum	75,590	10%				Colon & rectum	71,380	10%	
Urinary bladder	52,810	7%				Uterine corpus	42,160	6%	
Melanoma of the skin	39,080	5%				Non-Hodgkin lymphoma	29,990	4%	
Non-Hodgkin lymphoma	35,990	5%				Melanoma of the skin	29,640	4%	
Kidney & renal pelvis	35,430	5%				Thyroid	27,200	4%	
Leukemia	25,630	3%				Kidney & renal pelvis	22,330	3%	
Oral cavity & pharynx	25,240	3%				Ovary	21,550	3%	
Pancreas	21,050	3%				Pancreas	21,420	3%	
All Sites	766,130	100%				All Sites	713,220	100%	

- Accounts for 2% of new cancer diagnoses.
- Equally common among males and females

Pancreatic Cancer

Estimated Deaths

			Males	Females			
Lung & bronchus	88,900	30%		Lung & bronchus	70,490	26%	
Prostate	27,360	9%		Breast	40,170	15%	
Colon & rectum	25,240	9%		Colon & rectum	24,680	9%	
Pancreas	18,030	6%		Pancreas	17,210	6%	
Leukemia	12,590	4%		Ovary	14,600	5%	
Liver & intrahepatic bile duct	12,090	4%		Non-Hodgkin lymphoma	9,670	4%	
Esophagus	11,490	4%		Leukemia	9,280	3%	
Urinary bladder	10,180	3%		Uterine Corpus	7,780	3%	
Non-Hodgkin lymphoma	9,830	3%		Liver & intrahepatic bile duct	6,070	2%	
Kidney & renal pelvis	8,160	3%		Brain & other nervous system	5,590	2%	
All Sites	292,540	100%	All Sites	269,800	100%		

- 4th Leading cause of cancer death
- High mortality

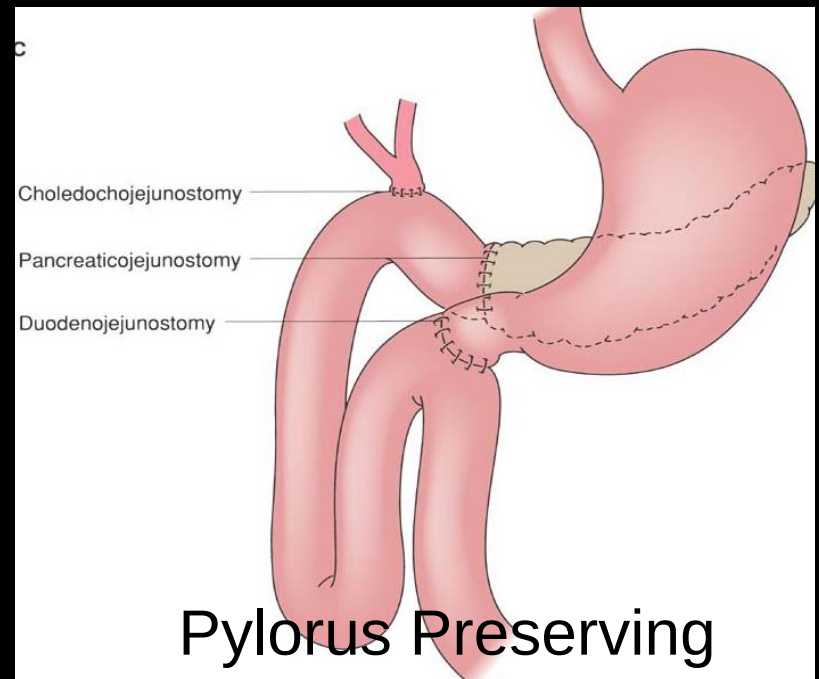
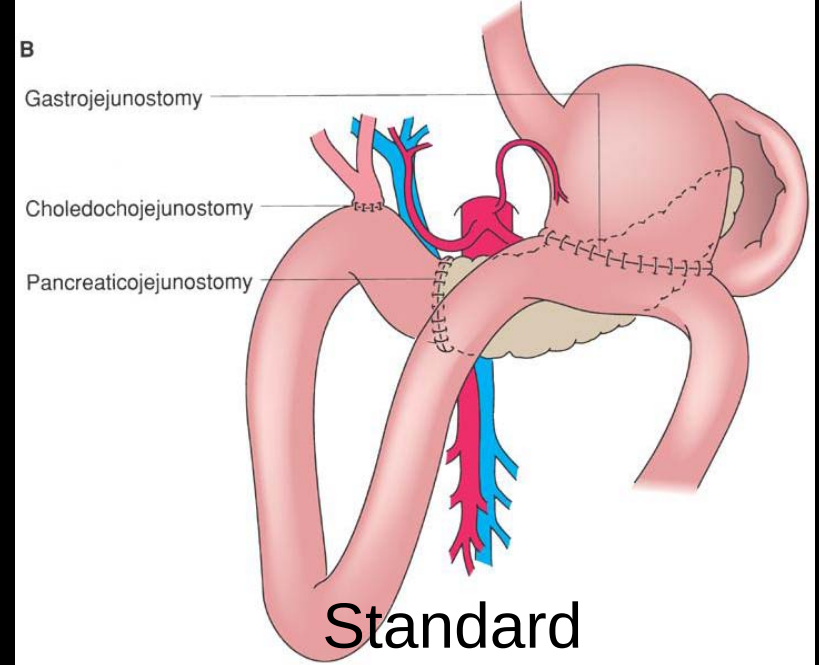
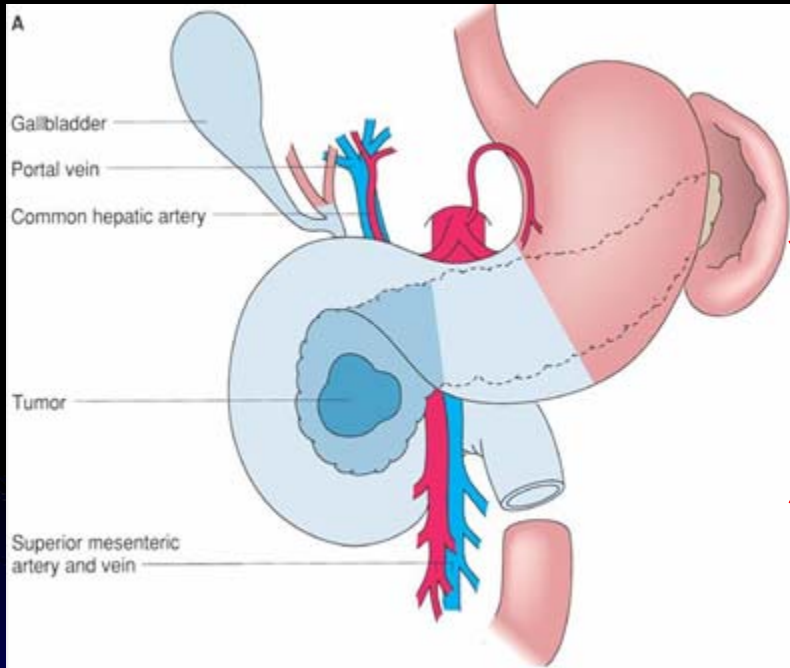
Whipple procedure



Surgical treatment for peri-ampullary tumors

- 1st performed by AO Whipple in 1932
- High mortality (30%)

Two types

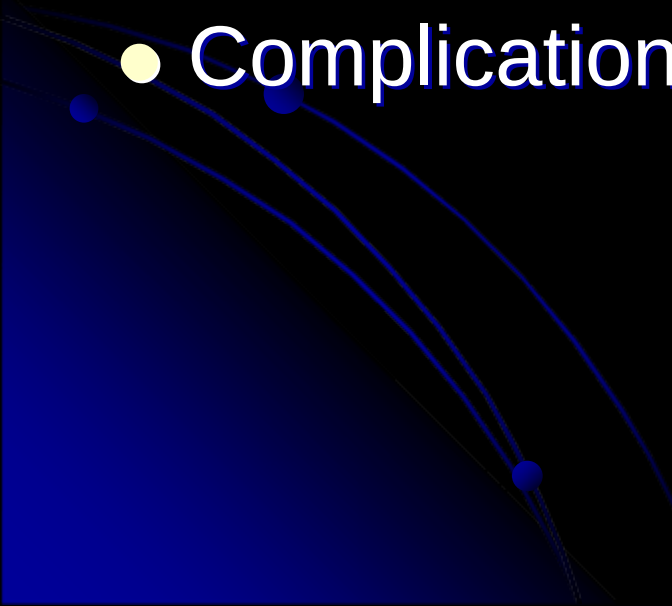


Similar results with respect to morbidity and mortality

Surgical resection

- 80-90% of patients present with advanced unresectable disease
- Preoperative staging with CT scan/MRI, EUS, and FNA important to select candidates
- Diagnostic laparoscopy or staging laparotomy sometimes required

What is the debate?

- Does surgery improve survival? Slightly
 - Benefit of 6-18 months.
 - Requires adjuvant therapy to see results
 - Toxicity of adjuvant therapy
 - Complications of large surgery
- 

Poor Prognosis

TABLE 1
AJCC 6th Edition TNM Staging System for Pancreatic Cancer

Definitions of TNM

TX	Primary tumor cannot be assessed			
T0	No evidence of primary tumory			
Tis	Carcinoma in situ			
T1	Tumor limited to the pancreas, 2 cm or less in greatest diameter			
T2	Tumor limited to the pancreas, greater than 2 cm in greatest diameter			
T3*	Tumor extends beyond pancreas but no involvement of celiac axis or superior mestenteric artery			
T4*	Tumor involves the celiac axis or the superior mestenteric artery (unresectable)			
NX	Regional nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Regional lymph node metastasis			
MX	Distant metastasis cannot be assessed			
M0	No distantant metastasis			
M1	Distant metastasis			
Stage grouping				
Stage 0	Tis	N0	M0	Localized within pancreas
Stage IA*	T1	N0	M0	Localized within pancreas
Stage IB*	T2	N0	M0	Localized within pancreas
Stage IIA	T3	N0	M0	Locally invasive, resectable
Stage IIB*	T1,2, or 3	N1	M0	Locally invasive, resectable
Stage III*	T4	Any N	M0	Locally advanced, unresectable
Stage IV	Any T	Any N	M1	Distant metastases

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121,000 pt from NCD

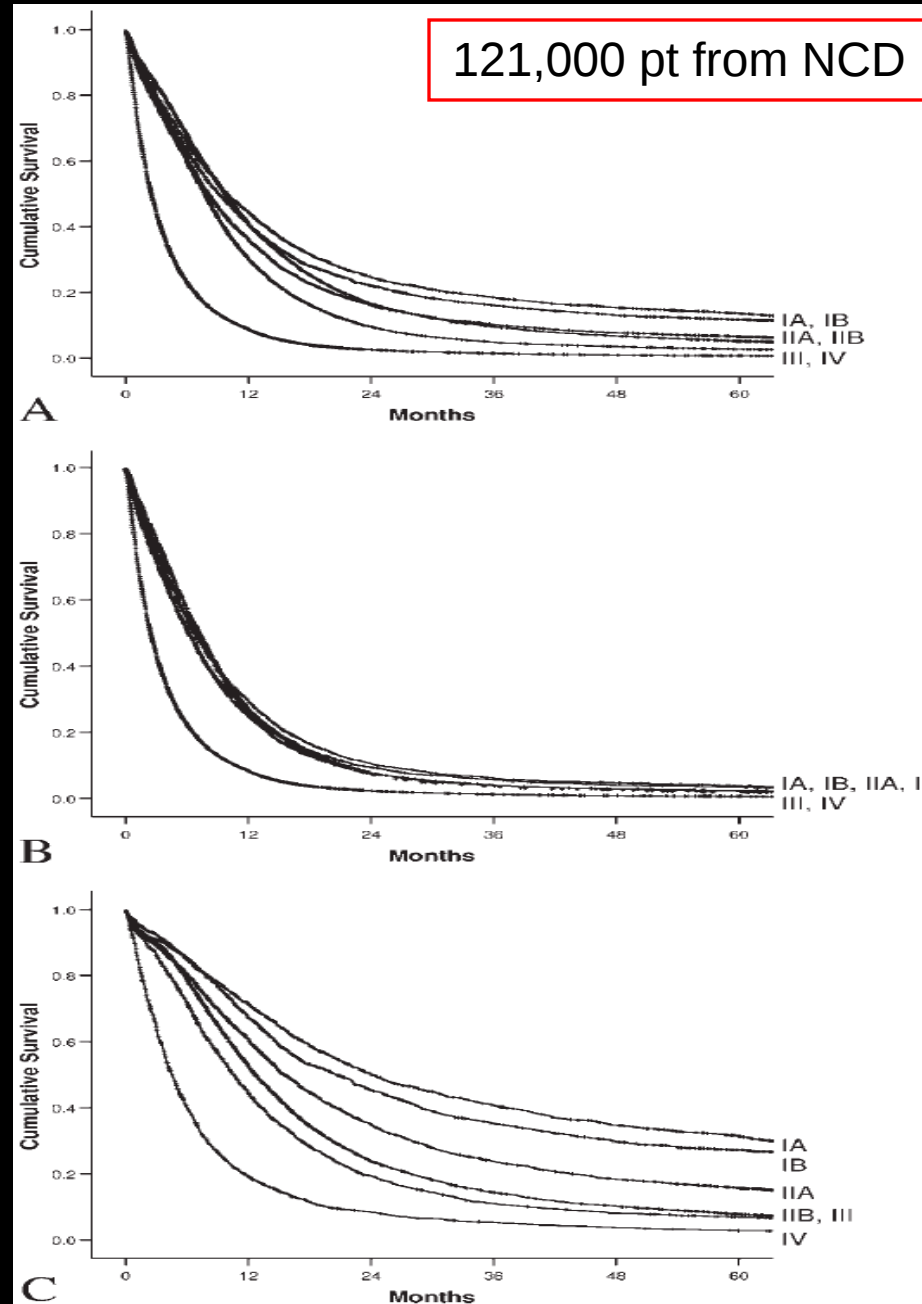


FIGURE 1. Observed 5-year survival for patients with pancreatic adenocarcinoma based on the AJCC Cancer Staging Manual 6th Edition. (A) All patients, (B) nonresected patients, (C) pancreatotomy patients.

TABLE 4
Observed Survival in Patients With Pancreatic Adenocarcinoma, 1992–1998

All patients	No. of patients (%)	Observed survival					Median survival (mo)
		1-y	2-y	3-y	4-y	5-y	
Stage IA	5298 (4.4%)	44.4%	24.6%	18.5%	15.3%	13.6%	10.0
Stage IB	6662 (5.4%)	40.6%	22.0%	16.1%	13.0%	11.7%	9.1
Stage IIA	12,332 (10.1%)	36.1%	16.2%	10.2%	7.7%	6.5%	8.1
Stage IIB	14,398 (11.8%)	40.9%	16.5%	9.6%	6.7%	5.1%	9.7
Stage III	15,831 (13.0%)	30.2%	9.5%	4.8%	3.5%	2.7%	7.7
Stage IV	67,192 (55.2%)	8.8%	2.5%	1.4%	0.9%	0.7%	2.5
Total	121,713						4.4
Nonresected patients							
Stage IA	3412 (4.4%)	29.2%	10.5%	6.2%	4.6%	3.8%	6.8
Stage IB	4298 (5.4%)	26.0%	9.4%	5.7%	4.0%	3.4%	6.1
Stage IIA	8486 (10.1%)	25.0%	7.7%	4.1%	2.8%	2.4%	6.2
Stage IIB	6570 (11.8%)	26.9%	7.7%	3.8%	2.6%	2.0%	6.7
Stage III	12,981 (13.0%)	27.0%	7.3%	3.4%	2.4%	1.8%	7.2
Stage IV	64,454 (55.2%)	8.3%	2.3%	1.2%	0.8%	0.6%	2.5
Total	100,201						3.5
Pancreatectomy patients							
Stage IA	1886 (8.8%)	71.3%	50.2%	40.7%	34.7%	31.4%	24.1
Stage IB	2364 (11.0%)	67.3%	45.4%	35.3%	29.6%	27.2%	20.6
Stage IIA	3846 (17.9%)	60.7%	34.9%	23.8%	18.4%	15.7%	15.4
Stage IIB	7828 (36.4%)	52.7%	23.8%	14.4%	10.2%	7.7%	12.7
Stage III	2850 (13.2%)	44.5%	19.3%	11.0%	8.1%	6.8%	10.6
Stage IV	2738 (12.7%)	19.2%	8.4%	5.3%	3.7%	2.8%	4.5
Total	21,512						12.6

Whipple alone

Author	No. Patients	Median Survival	Overall survival (5 yr)
GITSG	22	11	0
Bakkevold	31	11	8
EORTC	54	13	8
ESPAC-1	69	17	8

Gastrointestinal tumor study group,
European org. for research & treatment of cancer
European study group for pancreatic cancer

Adjuvant therapy

Author	No. Patients	Therapy	Median Survival (Months)	Overall survival (5 yr)%
GITSG	43	5FU + XRT	21	19
John Hopkins	366	5FU + XRT	21	16
EORTC	114	5FU + XRT	16	10
ESPAC-1	289	5FU + Leucovorin 5FU + XRT	22	21
Virginia Mason	43	5FU + XRT + interferon + cisplatin	44	42

Toxicity of Adjuvant Therapy

- ESPAC - 20% with Grade 3 or 4 toxicity
- EORTC - 44% with Grade 1-3 toxicity
 - Unable to receive full dosing of 5-FU
- Virginia Mason – 70% Grade 1-3 toxicity
 - 40% required hospitalization

Patients unable to receive therapy and/or poor quality of life

Morbidity

Table 1. Recent Series Reporting Complications after Pancreaticoduodenectomy

First author	Study dates	n	Method of data collection	Severity grading used	Timing of complications recorded	Morbidity (%)	Mortality (%)	Median LOS (d)	Reoperation (%)	Pancreatic leak (%)
Current series	2001–2003	204	Prospective	Yes	Yes	47	1	9	9	12
Yeo ⁴	1990–1996	650	Prospective	No	No	41	1.4	13	4.0	14
Lowy ⁵	1991–1995	120	Prospective	No	No	27	0.9	15	1.8	25
Buchler ⁷	1993–1999	331	Prospective	No	No	38.4	2.1	14	3.9	2.1
Adam ⁸	1994–2001	301	Prospective	No	No	42	3	15	7	9
Gouma ⁶	1997–1999	151	Prospective	No	No	41	0.7	15	8	5
Balcom ¹⁷	1998–2000	489	Retrospective	No	No	37	1	NR	2	11
Grobmyer ¹⁸	1994–1998	59	Retrospective	No	No	NR	3.4	NR	NR	17
Aranha ¹⁹	1992–2002	152	Retrospective	No	No	NR	0	NR	0.7	15
Sato ²⁰	1992–1997	62	Retrospective	No	Yes	NR	1.6	NR	NR	15
Brooks ²¹	1993–1998	111	Retrospective	No	No	42	0	12	NR	14

- Grobmyer et al J Am Coll Surg 2007;204:356–64.

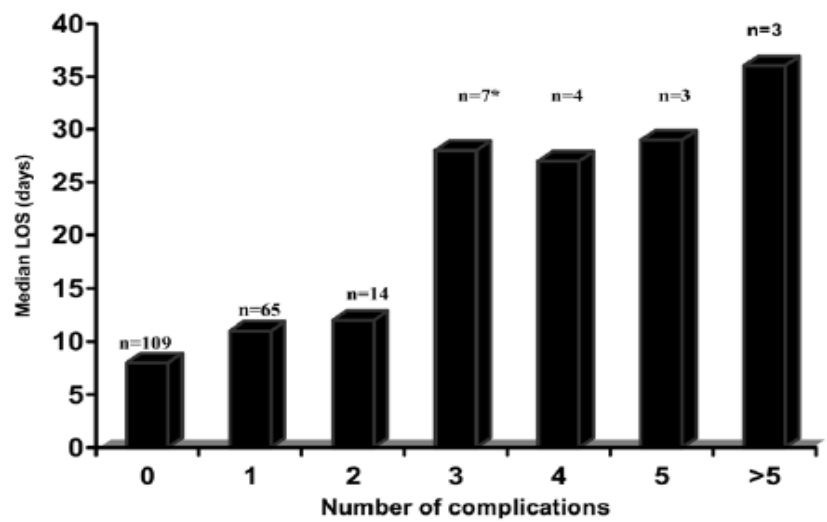
Defining Morbidity after Pancreaticoduodenectomy: Use of a Prospective Complication Grading System

Stephen R Grobmyer, MD, Fredric M Pieracci, MD, Peter J Allen, MD, Murray F Brennan, MD, FACS,
David P Jaques, MD, FACS

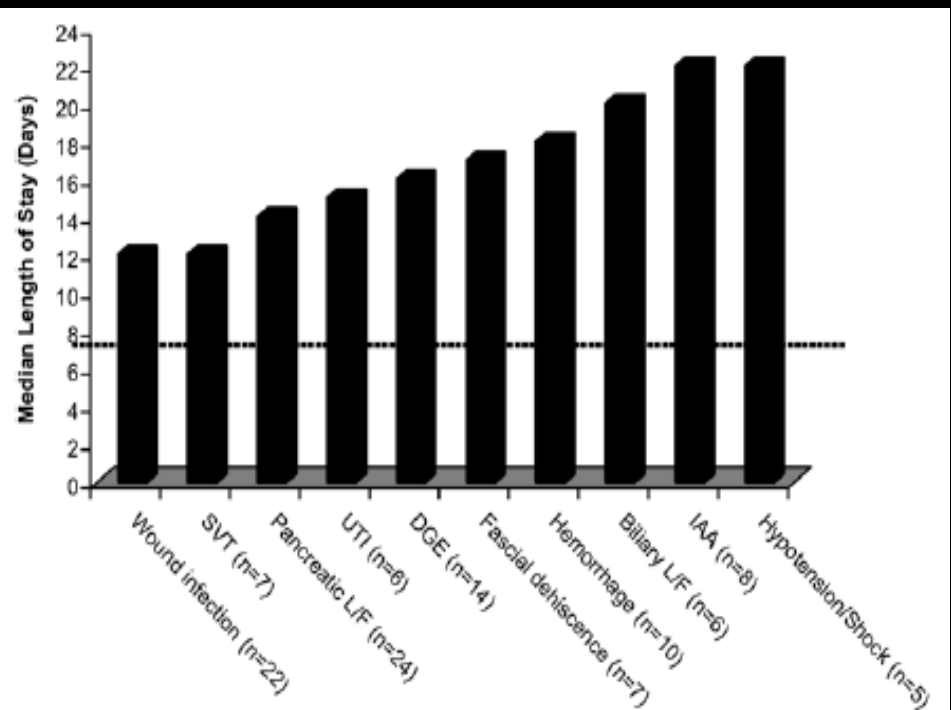
- Retrospective review of prospective database at MSK
- 204 patients underwent Whipple procedure from 2001-2003
 - ~50% for pancreatic adenocarcinoma
- Used to predict peri-operative morbidity and mortality

Table 3. Complications after Pancreaticoduodenectomy

Complications	Events	% of patients
Anastomotic leak, pancreas	24	12
Wound infection	22	11
Delayed gastric emptying	14	7
Hemorrhage (10 events/9 patients)	10	5
Intraabdominal abscess	8	4
Fascial dehiscence or evisceration	7	3
Supraventricular arrhythmia	7	3
Urinary tract infection	6	3
Anastomotic leak, biliary	6	3
Hypotension, shock	5	2
Cellulitis	3	1.5
Clostridium difficile colitis	3	1.5
Congestive heart failure, left ventricular dysfunction	3	1.5
Myocardial infarction	3	1.5
Renal failure	3	1.5
Apnea or hypoxia	2	1.0
Atelectasis	2	1.0
Catheter-related infection	2	1.0
Deep venous thrombosis	2	1.0
Dehydration	2	1.0
Anastomotic leak, intestinal	2	1.0
Gastrointestinal bleeding	2	1.0
Pleural effusion	2	1.0
Pneumonitis	2	1.0
Sepsis	2	1.0
Acute respiratory distress syndrome	1	0.5
Angina, cardiac ischemia	1	0.5
Aspiration	1	0.5
Cardiopulmonary arrest	1	0.5
Catheter-related infection	1	0.5
Constipation	1	0.5
Delirium tremens	1	0.5
Fever	1	0.5
Fluid imbalance	1	0.5
Gastroesophageal reflux disease	1	0.5
Hypoxia (congestive heart failure)	1	0.5
Ileus, paralytic	1	0.5
Interstitial pneumonitis and fibrosis	1	0.5
Prolonged intubation	1	0.5
Salivary gland infection	1	0.5
Small bowel obstruction	1	0.5



3 or more complications = LOS ↑



Quality of Life

Quality of Life and Outcomes After Pancreaticoduodenectomy

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John J. Huang, MD,* Charles J. Yeo, MD,* Taylor A. Sohn, MD,* Keith D. Lillemoe, MD,* Patricia K. Sauter, RN,* JoAnn Coleman, RN,* Ralph H. Hruban, MD,†‡ and John L. Cameron, MD*

*From the Departments of *Surgery, †Oncology, and ‡Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland*

- 323 patients
- Whipple procedure from 1981-1997
 - Surgery within last 6 months
 - ~30% for pancreatic adenocarcinoma
- Control group – Recent lap chole and normal age matched controls
- Received questionnaire to assess physical, psychological, social aspects of life

Table 4. QUALITY OF LIFE ASSESSMENT BY PANCREATICODUODENECTOMY SUBGROUPS

Domains	Benign Pathology (n = 83)		Malignant Pathology (n = 109)		LC Patients (n = 37)
	Chronic Pancreatitis (n = 34)	Other Benign Disease (n = 49)	Pancreatic Adenocarcinoma (n = 54)	Other Cancers (n = 55)	
Physical (15 items)	74%*	80%	77%*	81%	83%
Psychological (10 items)	75%*	80%	78%*	81%	82%
Social (5 items)	79%*	81%	83%	81%	84%

LC, laparoscopic cholecystectomy.

QOL was assessed by a visual analogue scale, with the highest score being 100% in each domain.

* $P < .05$ vs. LC patients.

Table 5. FUNCTIONAL OUTCOME ASSESSMENT BY PANCREATICODUODENECTOMY SUBGROUPS

Parameters	Benign Pathology (n = 83)		Malignant Pathology (n = 109)		LC Patients (n = 37)
	Chronic Pancreatitis (n = 34)	Other Benign Disease (n = 49)	Pancreatic Adenocarcinoma (n = 54)	Other Cancers (n = 55)	
Weight loss (lb)	10†	11†	24†	10†	1
Abdominal pain (%)	29†	18†	41†	18†	4
Thirst (%)	29†	18†	15†	7*	3
Frequent urination (%)	47†	33†	33†	33†	5
Fatigue (%)	29*	24*	28*	25*	14
Foul stool (%)	47†	37†	59†	42†	4
Diabetes (%)	41†	27*	33†	24*	8
Normal activity (%)	97	97	92	98	97

LC, laparoscopic cholecystectomy.

Healthy controls were not given the functional outcome assessment questionnaire.

* $P < .05$ vs. LC patients.

† $P < .005$ vs. LC patients.

Conclusions

- Whipple procedure is overrated with minimal mortality benefit
- Large amount of associated morbidity
- Quality of life important in patient who had months to live
- Most benefit seen after resection due to adjuvant therapies
- “Biology is king”
 - Until better adjuvant therapy available, little progress will be made in terms of survival

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Welcome to Colorado



Morbidity

Randomized clinical trial of pylorus-preserving duodenopancreatectomy *versus* classical Whipple resection – long term results

C. A. Seiler, M. Wagner, T. Bachmann, C. A. Redaelli, B. Schmied, W. Uhl, H. Friess and M. W. Büchler

130 pts over approx. 5.5 consecutive years

	Total (n = 130)	Standard Whipple (n = 66)	Pylorus-preserving Whipple (n = 64)	p
Surgical morbidity				
Delayed gastric emptying*	50 (38.5)	30 (45)	20 (31)	0.096†
Bleeding	6 (4.6)	4 (6)	2 (3)	0.680‡
Fistula	3 (2.3)	1 (2)	2 (3)	0.999‡
Infection (wound or abscess)	8 (6.2)	4 (6)	4 (6)	0.999‡
Medical morbidity				
Pulmonary	17 (13.1)	10 (15)	7 (11)	0.435†
Cardiocirculatory	8 (6.2)	5 (8)	3 (5)	0.465‡
Renal	8 (6.2)	3 (5)	5 (8)	0.489‡
Other	4 (3.1)	1 (2)	3 (5)	0.361‡
Relaparotomy	3 (2.3)	1 (2)	2 (3)	0.616‡
Overall morbidity (%)	80 (61.5)	45 (68.2)	35 (54.7)	0.071†
Mortality	3 (2.3)	2 (3)	1 (2)	0.999‡

Pancreatic Cancer: Adjuvant Therapy

Study	No Pts	R1 Rxn (%)	Treatment Median Survival	Control Arm Median Survival	P
GITSG (1985) Kaiser et al, Arch Surg 1985	49	0	5FU + XRT 21.0 months	No chemo/XRT 10.9 months	0.035
EORTC-40891 (1999) Klinkenbijl et al, Ann Surg 1999	114 (214)	21	5FU + XRT 17.1 months	No chemo/XRT 12.6 months	0.09
ESPAC-1 (2004) Neoptolmemos et al, N Eng J Med 2004	289	18	5FU + Leucovorin 20.1 months 5FU + XRT 15.9 months	No Chemo 15.5 No Chemo/XRT 17.9 months	0.009 0.05
RTOG 9704 (2006) Regine et al, J Clin Oncol 2007	380 (512) (head lesions)	>35	Gem-5FU/EBRT-Gem 20.6 months	5FU-5FU/EBRT-5FU 16.9 months	0.33
CONKO-001 (2007) Oettle et al, JAMA 2007	368	19	Gemcitabine 22.1 months DFS 13.9 months	No chemo 20.1 months DFS 6.9 months	0.06 0.001
Kosuge (2006) Jpn J Clin Oncol	88		5-FU + cisplatin 15.8	Observation 12.5	0.94