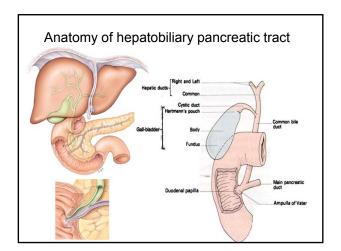
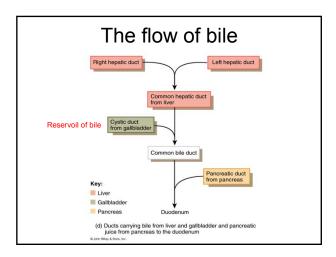
膽胰癌-外科治療 Surgery for biliopancreatic cancer

Yan-Shen Shan, MD, PhD, **Professor**

Institute of Clinical Medicine, College of Medicine, NCKU Division of General Surgery, Department of Surgery, NCKUH Tainan, Taiwan





Pathophysiologic Classification of Jaundice

- Hemolytic Jaundice
- Hepatic Jaundice
- Obstructive Jaundice (Cholestasis): (surgical jaundice)

Intrahepatic (including Klatskin tumor) Extrahepatic

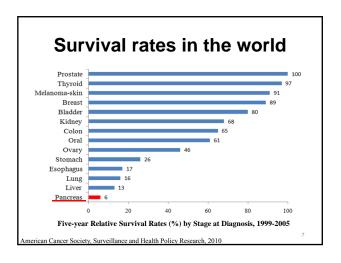
- · Sclerosing cholangitis
- Carcinoma of Ampulla of Vater
- Carcinoma of Pancreas (head)
- Carcinoma of bile ducts · Post-traumatic stricture
- Metastatic
- Lymph nodes of porta hepatis

Surgical procedures depends on etiologies

- · Hepatectomy (R't or L't) with Roux-en-Y hepaticojejunostomy
- Cholecystectomy
- · Choledocholithtomy with T-tube
- Sphincteroplasty
- · Pancreaticoduodenectomy



Management of pancreatic cancer in NCKUH



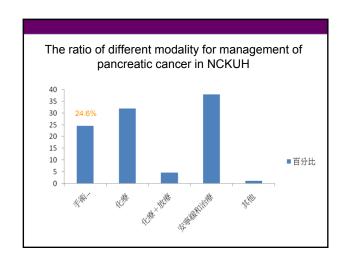
Pancreatic Cancer

- Adenocarcinoma of the pancreas continues to be a most formidable disease:
 - The 4th leading cause of cancer-related death in USA
 - The 8th leading cause of cancer-related death in Taiwan (2014)
 - Median survival of metastatic/unresectable pancreatic cancer: 4-6 months

Why the prognosis is poor in pancreatic cancer?

- Early metastasis: clinical early but molecular late
- 2. Lower resectability (15-20%), poor prognosis in resectable patients
- 3. Low efficiency in chemotherapy
- Special role of pancreas in GI tract: malnutrition, infection (fungus, GNB)

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Why the prognosis is poor in pancreatic adenocarcinoma?

- Early metastasis: clinical early but molecular late
- 2. Lower resectability
- 3. Low efficiency in chemotherapy
- 4. Special role of pancreas in GI tract: malnutrition, infection (fungus, GNB)

How can we improve the resectability?

Staging of pancreatic cancer Primary Tumor (T) cannot be determin T0 No evidence In situ Limited to pancreas, 2cm or less in greatest dimension T2 Limited to pancreas, more than 2cm in greatest dimension Extends beyond pancreas but without invaxis or SMA Regional Lymph Nodes (N) Cannot be as No regional lymph node metastasis Regional lymph node metasta Distant Metastasis (M) Cannot as MO No distant metastasis Distant metastasis Tram et al. "Diagnosis, Staging, and Surveillance of Pancreatic Cancer ." Am. J. Roentgenol. May 2003 180:1311-1323

Guideline for Surgery

RESECTABLE

No distant metastases Clear fat plane around celiac and superior mesenteric arteries (SMA) Patent superior mesenteric vein (SMV)/portal vein

BORDERLINE RESECTABLE

Severe unilateral or bilateral SMV/portal impingement <180 degree tumor abutment on SMA Abutment or encasement of hepatic artery, if reconstructible SMV occlusion, if of a short segment, and reconstructible

UNRESECTABLE

Distant metastases

Greater than 180 degrees SMA encasement, any celiac abutment Unreconstructible SMV/portal occlusion

Aortic invasion or encasement

Surgical procedures for pancreatic cancer

- Pancreatic head cancer: Pancreaticoduodenectomy (Whipple, PD) or pylorus-preserving pancreaticduodenectomy (PPPD)
- Body and tail pancreatic cancer: Distal pancreatectomy

History of Pancreaticodoudenectomy

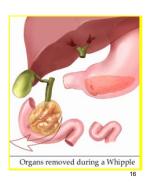
- · 1912: Walter Kausch
- 1935: Allen Whipple
 - Two-stage: P-duct ligation
 - 1942: One-stage
 - PJ anastomosis
 - · Mortality:31%
- 1942: Kenneth Watson
 - Pylorus-preserving PD (PPPD)





Major Procedures in PD and PPPD

- · Expose phase (evaluation of resectability)
- · Removal phase
- · Reconstruction phase



Reconstruction phase in Whipple

- · Hepaticojejunostomy
- Pancreaticojejunostomy (pancreaticogastrostomy): duct-to-mucosa (with or without stent, internal or external), invagination
- Gastrojejunostomy







Reconstruction phase in In PPPD

- · Hepaticojejunostomy
- Pancreaticojejunostomy (pancreaticogastrostomy): duct-to-mucosa (with or without stent, internal or external), invagination
- · Duodenojejunostomy





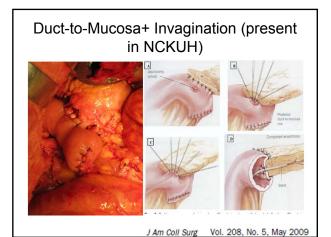


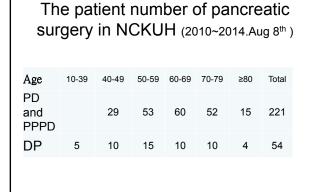
Surgical Mortality and Morbidity (before 2009)

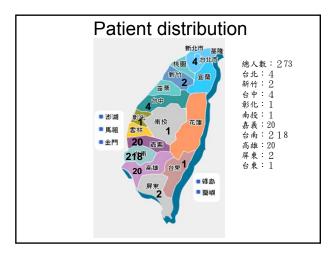
- Surgical mortality
 - < 5%, even 0% in high volume hospital
 - 2.6% in NCKUH, 4.8% in Taipei VGH
- Surgical morbidity
- in experienced centers: 46% 59%
- around 40% in NCKUH (including 26% DGE
- and 7.6% pancreatic leakage)

 35.6% in Taipei VGH

Duct-to-Mucosa +Invagination







Mortality in pancreatic surgery:

1/221 (0.45%) in PD and PPPD, 1/54 (1.9%) in DP morbidity: around 10%, hospital:12 days

- 82 y/0, borderline resectable pancreatic head cancer,
- PD with total pancreatectomy and portal vein resection
- · Postoperative complication: late SMV stricture with small molecular heparin treatment
- · Died 29days after resection due to suspicion of sepsis (didn't survey for sign of DNR)

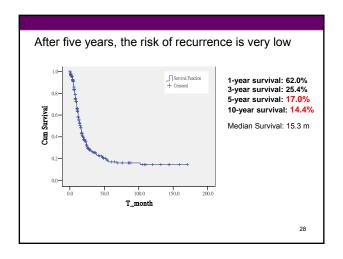
Resectable pancreatic cancer: Stage I and Stage II

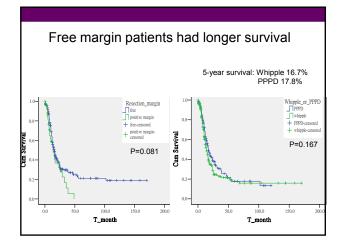
- · Patients with resectable disease, standard treatment is surgical resection
- · Surgery offers only chance for cure but
 - ~Following potentially curative PD, disease recurs in 80-90% of patients
 - ~Median survival ranges: 13-20 months
- 5 year survival rate: ~20% ~Most common sites of first recurrence are liver metastasis and local-regional failure

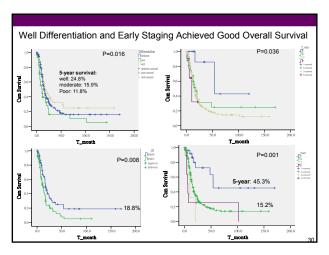
How about Taiwan's results? (before 2011)

- Six medical centers: NCKUH, NTUH, VGHTC, VGHKH, TMH, Changhua-Christian Hospital
- · Pancreatic head cancer

		Operation method Whipple PPPD (n=307) (n=124)		Univariate	Multivariate P-value
Characteristics				P-value	
Sex	Male	196	70	0.153	0.581
	Female	111	54		
Age (years), mean ± SD		64.7 ± 10.1	64.9 ± 12.4	0.883	0.567
Blood loss (ml), mean ± SD		847.7 ± 809.3	648.3 ± 541.7	0.021	0.363
Operation time (min), mean ± SD		407.0 ± 140.0	366.0 ± 152.7	0.065	
Resection margin:	R0:R1	231:42	89:10	0.194	
	Poor	34	19	0.385	
Differentiation	Moderate	218	79		
	Well	43	17		
LN	Positive	124	25	0.046	0.777
	Negative	78	29		
Recurrence	Yes	200	85	0.834	
	Nil	89	36		
Survival	Yes	91	71	0.807	







Multivariate analysis of prognostic factors for recurrencefree survival in patients with pancreatic head cancer

	Di	sease-free surviva	ıl
Parameter	OR	95% CI	P-value
Age	1.011	0.997-1.025	0.128
Differentiation (poor/moderate or well)	0.617	0.372-1.023	0.061
Stage (I/II-IV)	5.405	1.730-16.95	0.004

Multivariate analysis of prognostic factors for overall survival in patients with pancreatic head cancer

Parameter	Disease-free survival				
rarameter	OR	95% CI	P-value		
Age	1.006	0.984-1.028	0.614		
Preoperative drainage (yes/ nil)	0.665	0.427-1.037	0.072		
Differentiation (poor/ moderate or well)	0.607	0.287-1.287	0.405		
LN (positive/ negative)	0.638	0.408-1.000	0.050		
T stage (T1/T2-4)	3.230	0.514-20.00	0.212		

Locally Advanced Pancreatic Cancer:

Stage III (T4, N0-1,M0)

- Surgically unresectable tumor (extension or involving the surrounding vessels or organs) without evidence of distant mets.
- 26% of pancreatic cancer at diagnosis
- The median survival is less than 12 months. despite the use of chemotherapy, chemoradition, or both.
- SEER: 5-year survival rate is 8.7%

AJCC 6th ed. New York, NY: Springer, 2002,pp157-164

Therapeutic Modalities Used in Locally Advanced Pancreatic Cancer:

No universal protocol

- Chemotherapy
- Radiation
- Pancreatic enzymes and diabetic medications Stents; ERBD/ PTCD
- Palliative surgery

Possible curative surgery following neoadjuvent treatment

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How to Improve Resectability

· Methods:

SMA approach

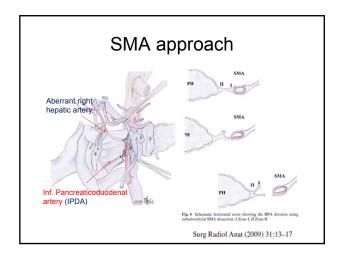
Neo-adjuvant therapy for locally advanced therapy

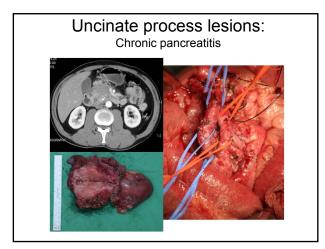
Chemotherapy

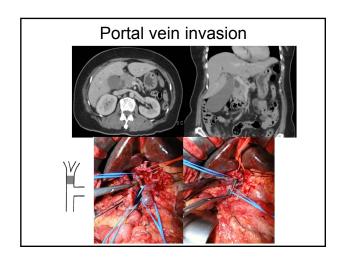
Concurrent chemoradiation

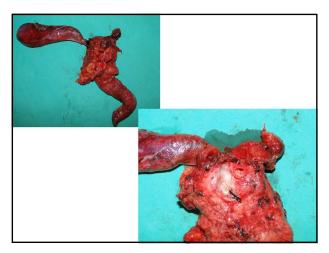
SMA approach

- Indications
 - Uncinate process lesions
 - Major vessel resection

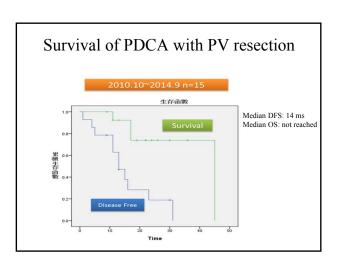


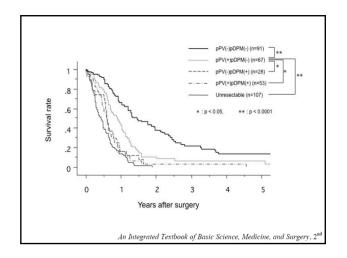


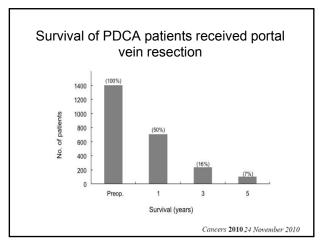




			NC	KU	H init	ial e	experie	ence		
A g e	S	Dx TMN	Length of vein resected	OP time (min)	PV clamping time (min)	Blood loss (ml)	Complications	Mortality	LOS	Survival (m)
62	F	T3N1	2cm	300	NA	700	Bleeding pneumonia	n	58	54
48	М	T3N1	2cm	302	NA	800	n	n	25	13
42	М	T3N1	3cm	430	42	450	n	n	15	>9
62	М	T3N1	4.5cm	442	28	600	Hemobilia (PTCD)	n	13	>9
73	М	T3N1	2cm	450	14	1600	n	n	25	>7
62	F	T3N1	3cm	390	14.5	1000	n	n	14	+







How to improve resectability in LAPC, borderline, or uncinate pancreatic cancer

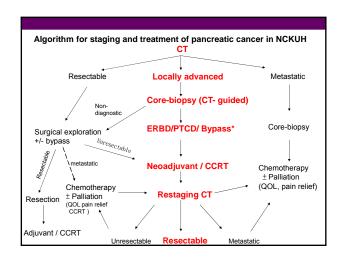
· Methods:

SMA approach

Neo-adjuvant therapy for locally advanced therapy

Chemotherapy

Concurrent chemoradiation



Criteria of locally advanced pancreatic cancer in NCKUH

- Unresectable locally advanced pancreatic ca: failed exploratory laparotomy computed tomography (CT)
- The criteria of CT: tumor involved confluence of portal and splenic vein, superior mesentery artery, severe peri-tumor soft tissue invasion, and extensive lymphoadenopathy in the celiac trunk.

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Case 1

- 55 year-old male
- Left flank dull pain with radiation to back since June, 2003
- · Decrease of appetite
- · Weight loss (3 kg/month)
- PPU, subtotal gastrectomy + BII, 30 years ago
- Abdominal echo (June 16, 2003): pancreatic tail mass

Tumor marker	CEA	CA125	CA199	CA153	
July 9, 2003	1.2	11.6	4.9	10.2	48

Abdominal CT Pancreatic tail tumor (7x6x4 cm) with stomach invasion



Exploration: Unresectable,

A huge pancreatic tail tumor fixed to retroperitoneum with invasion to stomach, spleen, liver, diaphragm, mesocolon, and SMA root Biopsy: adenocarcinoma

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Treatment - CCRT

Regimen:

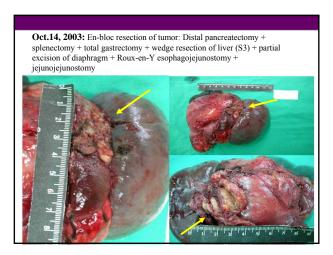
- Radiotherapy with 4500 cGy/25Fx
- Chemotherapy with Gemcitabine 400 mg/m²
 + Oxaliplatin 30 mg/m² · q2w x III
- After radiotherapy, chemotherapy with Gemcitabine 1000 mg/m² ,q2w x III

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Sep.25, 2003 After CCRT: Abdominal CT: Pancreatic tail tumor (2x2x1 cm), R/O splenic hilum invasion with splenic infarction

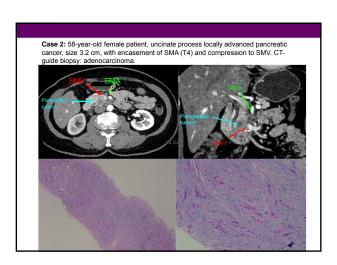


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Pathological Report

- Retroperitoneum pancreatic bed: fibrosis
- Pancreas: adenocarcinoma, poorly differentiated adenocarcinoma
- LN metastasis: negative
- · Stomach adenocarcinoma by invasion
- Liver (S3): negative
- Spleen: negative



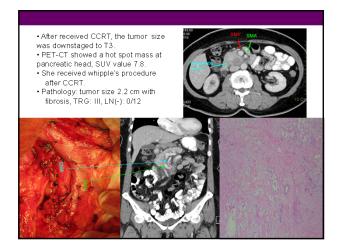
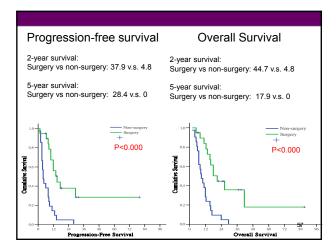
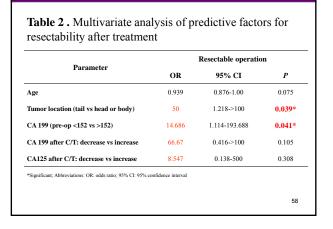


Table 1. The demographics of patients with locally advanced pancreatic cancer after gemcitabine-based treatment Characteristics No. of patients Sex (M:F) 26: 14 Age (years), mean (range) 63.5 (39-80) Location 17: 18: 5 Treatment: Chemotherapy#: Chemoradiation (CCRT)* 25: 15 CT: resectable 20 (9: 7: 4) 17 (42.5%) 5: 7: 5 Whipple: central pancreatectomy: distal pancreatectomy 14: 2: 1 R0: R1: R2 resection Overall survival, median (mean± SD), months 12.5 (22.5 ± 4) 21 (33.1 ± 7) vs 9.0 (10.5 ± 2) 18.2 (9.0 ± 3) Surgery v.s. non-surgery Progressive survival, median (mean± SD), months Surgery v.s. non-surgery 15 (32.1 ± 6) vs 4.0 (6.7 ± 2) #: 20 patients received phase I/II GOFT, 6 patients with GOFS, *: 5 patients received CCRT Tainan program, 8 patien received gem induction chemotherapy and reduced dose gem with R/T BMC Surgery 2014

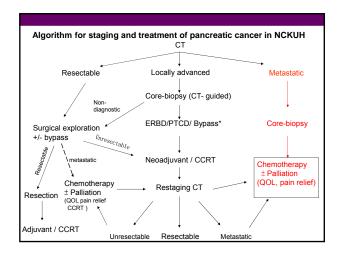


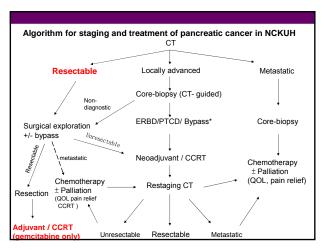


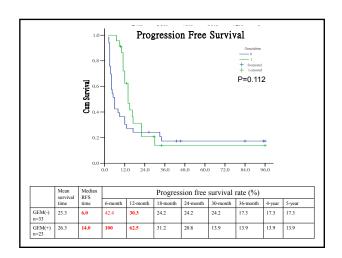
P	Recurrence-free survival			
Parameter	OR	95% CI	P	
Age	0.990	0.914-1.072	0.806	
Sex: male/female	3.196	0.617-16.552	0.166	
CA 199 (pre-C/T <294 vs >294)	1.776	0.357-8.850	0.483	
CA 199 (pre-op <152 vs >152)	26.32	3.300-200	0.002*	
CA 199 (post-op <82 vs >82)	2.137	0.524-8.696	0.290	
CEA (post-op <6 vs >6)	2.604	0.749-9.091	0.132	
CA 125 (pre-op <32.8 vs >32.8)	55.56	6.579-500	<0.001*	

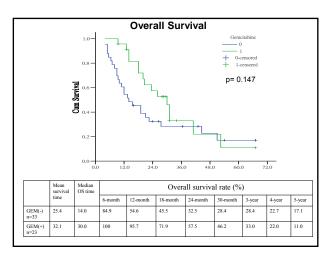
Recurrent Site	Surgery (n=17)	Non-surgery (n=23)
Liver	8	21
Peritoneum	6	12
Others (bone, lung, soft tissue, brain)	4	5
Loco-regional	1	0
Disease free	3	0

m2 Dr. Shan will insert slide with additional column RRR, 2010/11/14



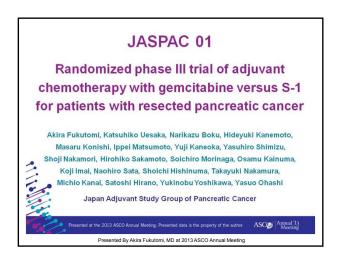


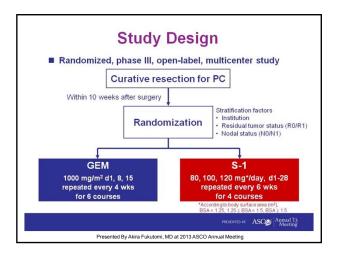


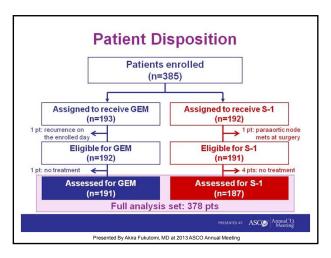


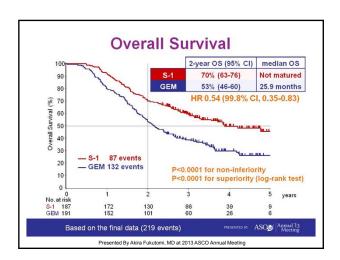
The benefit of postoperative adjuvant therapy

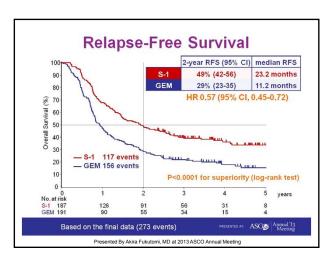
- In our experience, postoperative adjuvant can delay the median recurrence time about 8 months, and prolong patient median survival to 30 months and within 3year survival benefit
- CONKO-001 trial also proved Gem treatment can prolong PFS after resection

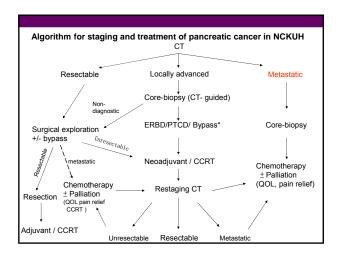












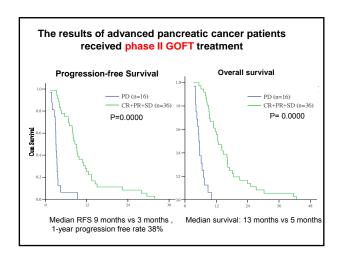
	State and Development State	
Characteristics	P	atients numbe
Eligible patients		13
Sex (M; F)		6: 7
Age (years)	Median	67
	Range	57-78
Disease status	Locally advanced	7
	Metastatic	6
Karnofsky score	100	8
	90	3
	70	1
	50	1
ECOG score	0	9
	1	2
	2	2

GOFT for pancreatic cancer (phase I)

TABLE 3 Objective Tumor Response						
	F	Response(%				
Dose lev	el Patients	CR	PR	SD	PD	rate
1	6	1	2	2	1	50
2	6	0	4	1	1	66.7
3	1	0	0	1	0	0
Total	13	1	6	4	2	53.8

CR: complete response; PR: partial response; SD: stable disease; PD: progression disease.

Shan YS HepatoGastroenterology 2007



The Feasibility of Metastasectomy for Pancreatic Cancer in Modern Era

Pulmonary Metastasectomy

- First described case in 1882
 - Incidental resection during chest wall resection
- First long-term survivor in 1939
 - Metastatic renal cell carcinoma
 - Survived 23 years after resection
- · Survival benefits in
 - Colorectal cancer, soft tissue sarcoma, renal cell carcinoma, etc.

Abeloff: Abeloff's Clinical Oncology, 4th ed.

Pulmonary Metastasectomy

- · Criteria for resection
 - Appear to be completely resectable
 - Adequate cardiopulmonary reserve
 - Technical feasibility
 - Controlled primary tumor site
 - Absence of extra-pulmonary metastatic disease

Abeloff: Abeloff's Clinical Oncology, 4th ed.

Hepatic Metastasectomy

- · First attempt before World War II
- Metastasectomy rather than formal lobectomy
- · Colorectal cancer
 - Often isolated liver metastasis
 - 5-year survival improved after metastectomy
- · Gastric cancer and pancreatic cancer
 - Short mean survival
 - Often widespread metastases

Abeloff: Abeloff's Clinical Oncology, 4th ed

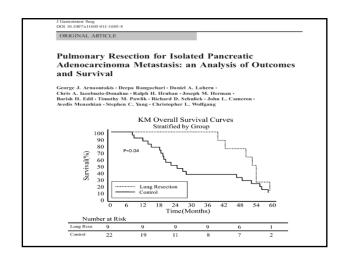
Metastasectomy in Pancreatic Cancer

- · No study about hepatic metastasectomy
- One study about pulmonary metastasectomy in 2011/07
- Inclusion criteria for pulmonary metastectomy
 - Primary diagnosis of pancreatic cancer
 - No distant metastases at the time of diagnosis
 - Pancreaticoduodenectomy
 - Isolated pulmonary metastasis

J Gastrointest Surg DOI 10.1007/s11605-011-1605-8

Pulmonary Resection for Isolated Pancreatic Adenocarcinoma Metastasis: an Analysis of Outcomes and Survival

George J. Arnaoutakis - Deepa Rangachari - Daniel A. Laheru -Chris A. Iacobuzio-Donahue - Ralph H. Hruban - Joseph M. Herman -Barish H. Edli - Timothy M. Pawlik - Richard D. Schulick - John L. Cameron -Awdis Menchilan - Stephen C. Yang - Christopher L. Wolfgang



Case I

• Name: 莊○蘭

Age: 58 years old

Gender: female

Diagnosis



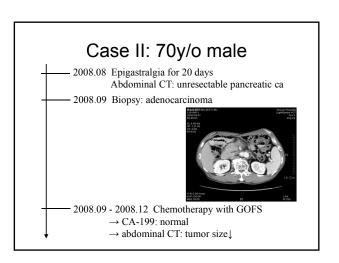
 Pancreatic ductal adenocarcinoma status post Whipple's operation on 2009/04/01 2009.06 Elevated CA-199 level (325.76)
Abdominal CT: liver metastases

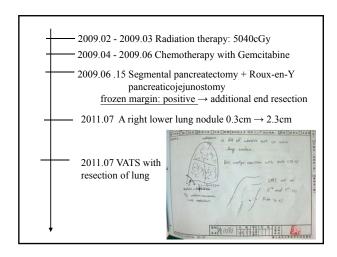
2009.06 - 2009.11

Chemotherapy with Gemcitabine, Oxaliplatin and 5-Fu
+ oral Sunitinib (GOFS)
→ CA-199: normal
→ abdominal CT: negative

2009.11 - 2010.11 Normal CA-199
2011.02 Elevated CA-199 (34.85), Abdominal CT: (-)
2011.05 CA-199 level increased to 82.26
Abdominal MRI: liver metastases

2011.06 Partial hepatectomy * II
2011.06 - 2011.08 Chemotherapy with GOFS
2011.08 Abdominal CT: negative
2015.0628 admitted to hospiece due to liver meta and peritoneal seeding





	ectomy			
Age	Sex	Treatment	Metastectomy	Survival
58	F	C/T (GOFS)	Hepatectomy	-, 6Y2m
70	М	CT (GOFS, Gem) R/T	Lung resection	+
50	М	GOFL	Whipple	+
38	М	GOFL	Hepatectomy	-
58	М	Adjuvant (Gem)	Lung resection	+

Metastasectomy in Pancreatic Cancer

- · Good biology for resection
 - Relatively long interval between initial resection of the pancreatic primary and relapse
 - Isolated and stable disease over time
 - Favorable response to systemic therapy

Milestones for management of pancreatic cancer in NCKUH

- 2003 Tainan pancreatic group: 成大醫院, 台南市醫,奇美,新樓,嘉基, 大林慈濟, 聖馬爾定等共七家醫院, 執行治療計劃 (GOFT, phase I and II), CCRT, MDT team for pancreatic cancer
- 2004 建立成大醫院治療guideline
- 2008 國家衛生院加入
- 2010, Oct 成大成立上消化道癌症團隊
- 2011 PEP02, phase II, 2^{nd} line treatment, (BJC, 2013)
- 2011 Cooperation with OSUCCC
- 2014 MM398, phase III, 2nd line treatment (completed)

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Conclusion

- Pancreaticoduodenectomy for pancreatic head cancer
 - Surgical mortality: decreased
 - Surgical morbidity: high and unchanged, decreased in experienced team
- Neoadjuvant therapy can downstage the severity of pancreatic cancer in some patients to increase the resectibility and patients survival.
- SMA approach can be performed safely to increase resectability
- Under new chemotherapy, matastectomy may be suitable for some selected patients.

Thank You!



"I think a life for music is a well-spent one, and that's what I have dedicated mine to." Pavarotti