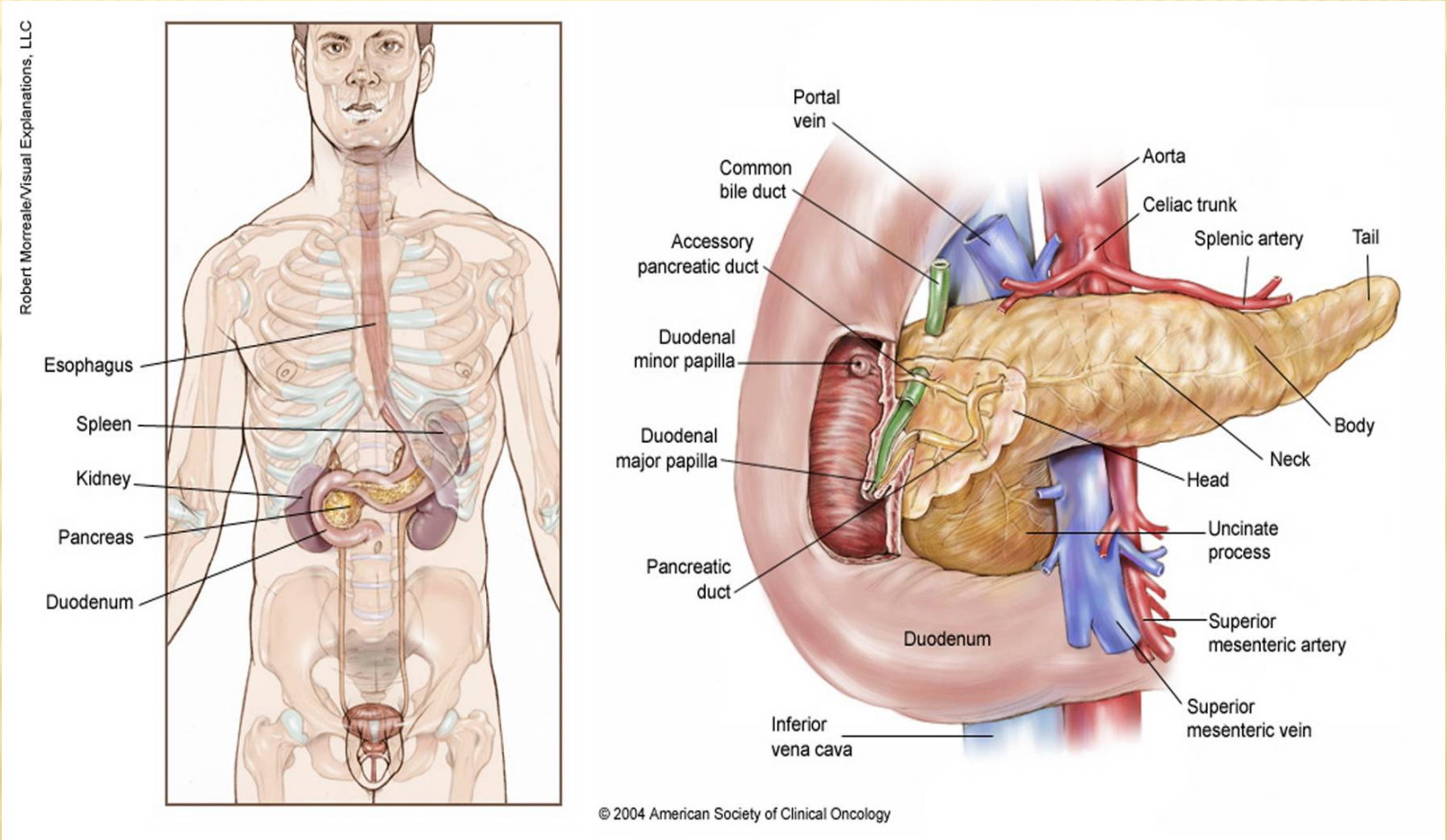
膽胰癌簡介

臺大醫院雲林分院虎尾院區
腫瘤醫學部
陳若白

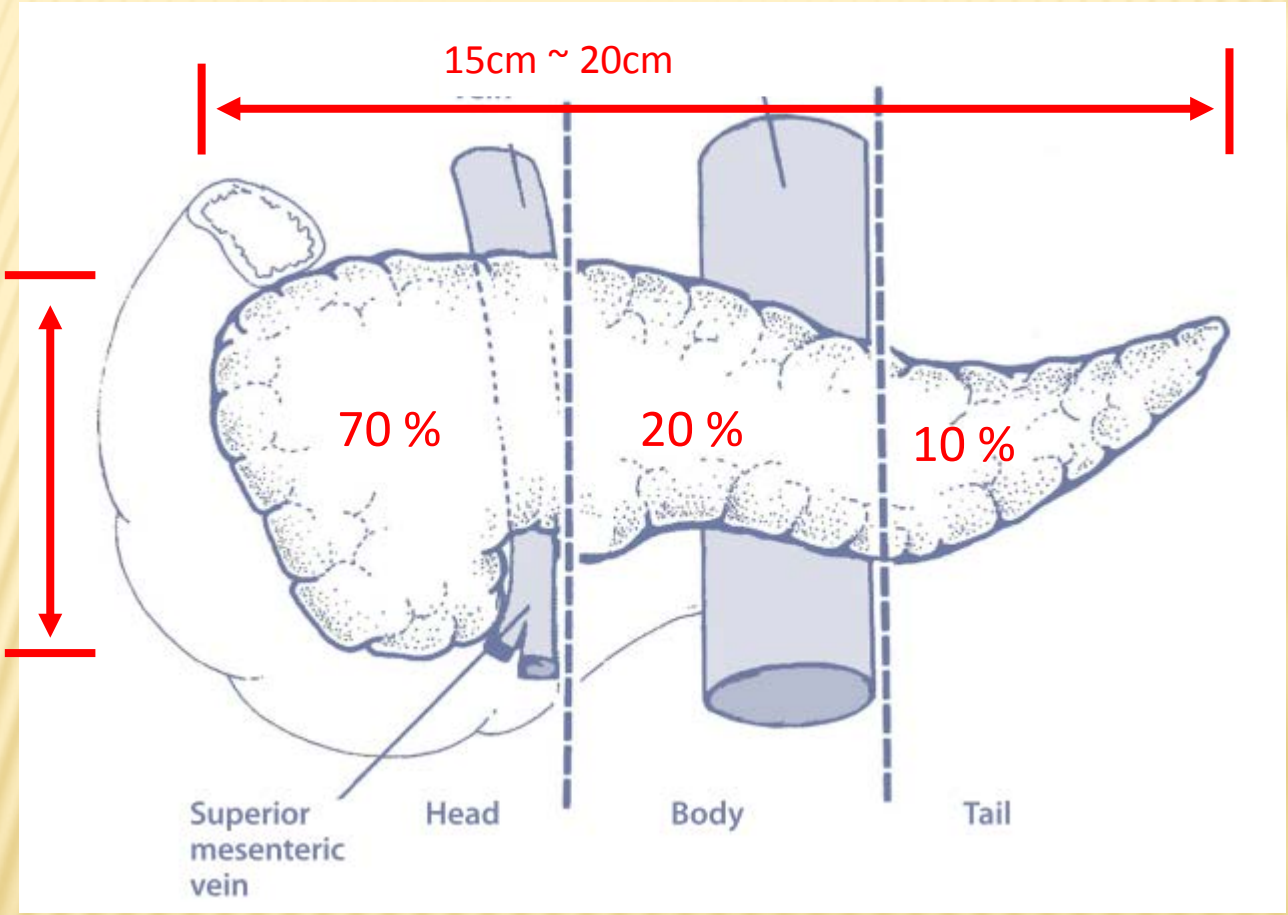
JUNE 27 , *2015*

胰臟癌

胰臟解剖位置

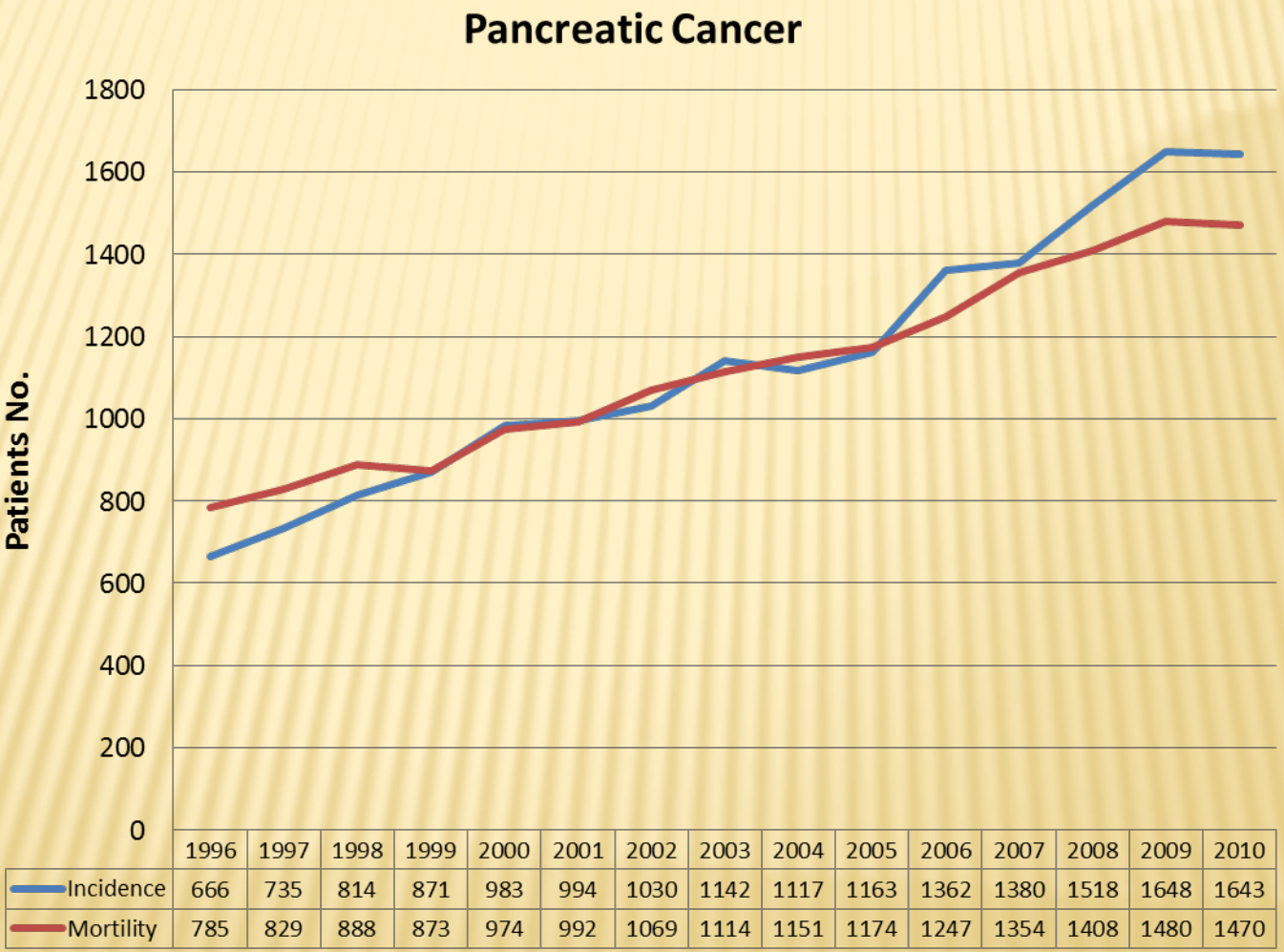

Robert Morreale/Visual Explanations, LLC
Esophagus
Spleen
Kidney
Pancreas
Duodenum
Portal vein
Common bile duct
Accessory pancreatic duct
Duodenal minor papilla
Duodenal major papilla
Pancreatic duct
Duodenum
Inferior vena cava
Aorta
Celiac trunk
Splenic artery
Tail
Body
Neck
Head
Uncinate process
Superior mesenteric artery
Superior mesenteric vein
© 2004 American Society of Clinical Oncology

胰臟癌發生率(照部位)



weight：75g ~ 100g

歷年胰臟癌發生率(藍)和死亡率(紅)



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Incidence	666	735	814	871	983	994	1030	1142	1117	1163	1362	1380	1518	1648	1643
Mortility	785	829	888	873	974	992	1069	1114	1151	1174	1247	1354	1408	1480	1470

AJCC分期

T:原發大小
N:局部淋巴
M:遠端轉移

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	**N1**	M0
Stage III	**T4**	Any N	M0
Stage IV	Any T	Any N	**M1**

按期別之存活率

Table 1. Staging of Pancreatic Cancer.*

Stage	Tumor Grade	Nodal Status	Distant Metastases	Median Survival†	Characteristics
				mo	
IA	T1	N0	M0	24.1	Tumor limited to the pancreas, ≤2 cm in longest dimension
IB	T2	N0	M0	20.6	Tumor limited to the pancreas, >2 cm in longest dimension
IIA	T3	N0	M0	15.4	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
IIB	T1, T2, or T3	N1	M0	12.7	Regional lymph-node metastasis
III	T4	N0 or N1	M0	10.6	Tumor involves the celiac axis or the superior mesenteric artery (unresectable disease)
IV	T1, T2, T3, or T4	N0 or N1	M1	4.5	Distant metastasis

已在胰臟外，但無侵犯腹腔大動脈主分支和腸系膜上動脈

淋巴結陽性

已侵犯腹腔大動脈主分支和腸系膜上動脈

N ENGL J Med 2010.97;15:2403-2413.

按疾病狀態之存活率

- 5-year survival: < 2%

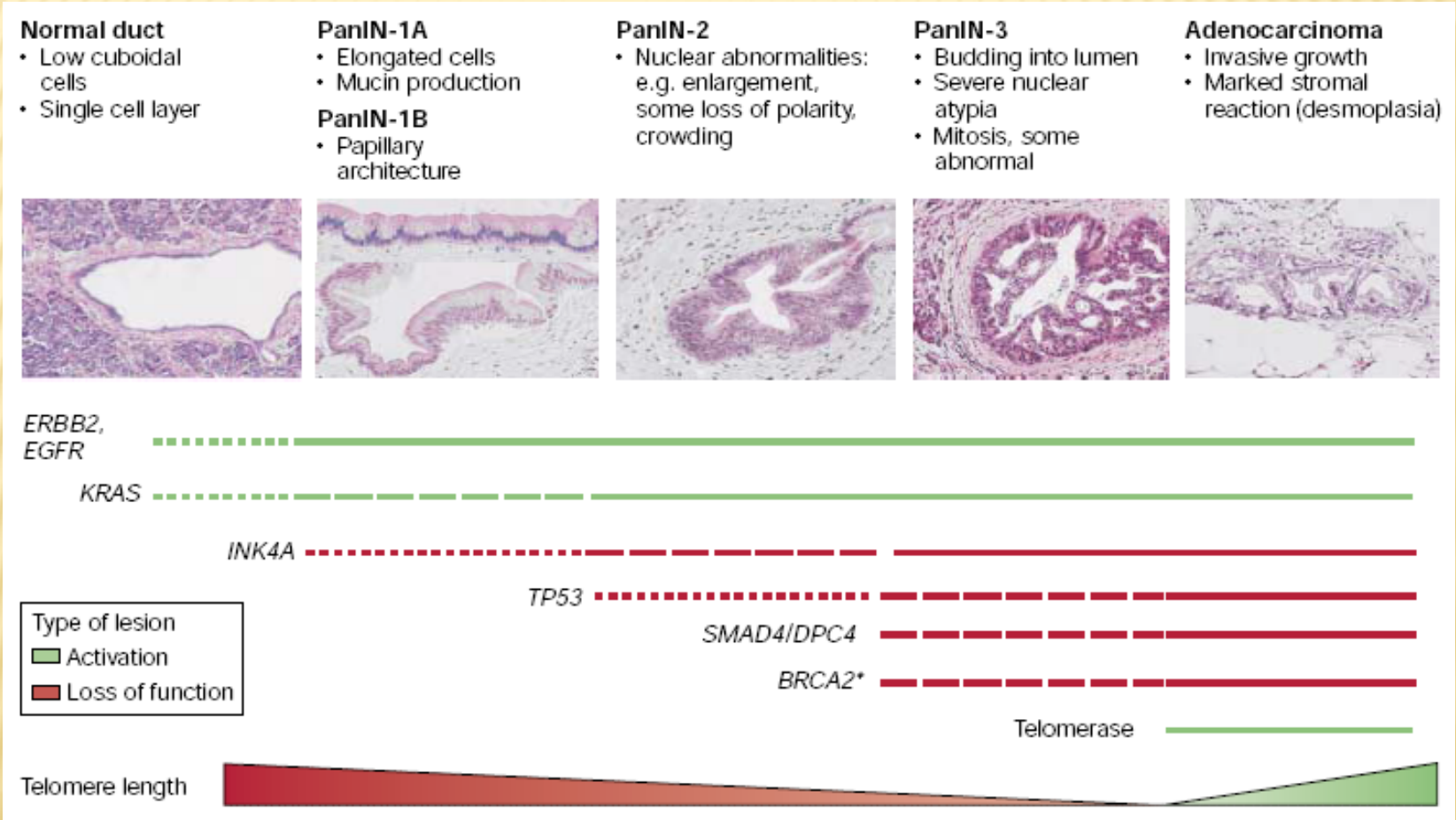
Disease Stage	Percent of Patients at Diagnosis	Median Survival, mos
Metastatic轉移	60	6
Locally advanced局部侵襲嚴重	25	9
Resectable可切除的	15	15

發生常就是死亡

1. Geer RJ, Brennan MF. Am J Surg 1993; 165:68-72.
2. Willett CG, et al. J Clin Oncol. 2005;23:4538-4544.s

胰臟癌前病變演進史

胰臟管腺上皮內癌前病變



Nature Rev.Cancer 2002;2, 897

World J Gastroenterol. 2011 Feb 21;17(7):867-97

病理特性

Classification	Frequency (%)	Survival (5-yr survival after surgical resection)
DIA (incidence per 100 000 patients at risk = 8.37)[69] (Ductal infiltrating adenocarcinoma) 瀰漫性管腺癌	85-90[1]	10% (1996) 18% (2006) 19% (2010)
SPPN (incidence per 100 000 patients at risk = NA)[69]	0.1-3[73]	95%
IPMN (incidence per 100 000 patients at risk = 0.03)[69]		Benign: 95% Malignant: 64%
IPMN with simultaneous DIA: (incidence per 100 000 patients at risk = NA)[69]	5[75]	42% 57% 43%
Pancreatoblastoma (incidence per 100 000 patients at risk = NA)[69]	0.50[79]	50% 80%
Undifferentiated (incidence per 100 000 patients at risk = 0.03)[69]	2-7[81]	3% (3-yr survival) 5 mo (average survival)
Medullary carcinoma (incidence per 100 000 patients at risk = NA)[69]	NA	11% 14 mo (average survival)
Mucinous cystadenocarcinoma (incidence per 100 000 patients at risk = 0.43)[69]	1	56%
Adenosquamous carcinoma (incidence per 100 000 patients at risk = 0.05)[69]	4	5-7 mo (median survival)
Acinar cell carcinoma (incidence per 100 000 patients at risk = 0.02)[69]	2	38 mo after surgical resection (median survival) 14 mo for unresectable disease (median survival)

SPPN: Solid pseudo-papillary neoplasm; IPMN: Intraductal papillary nucinous neoplasm

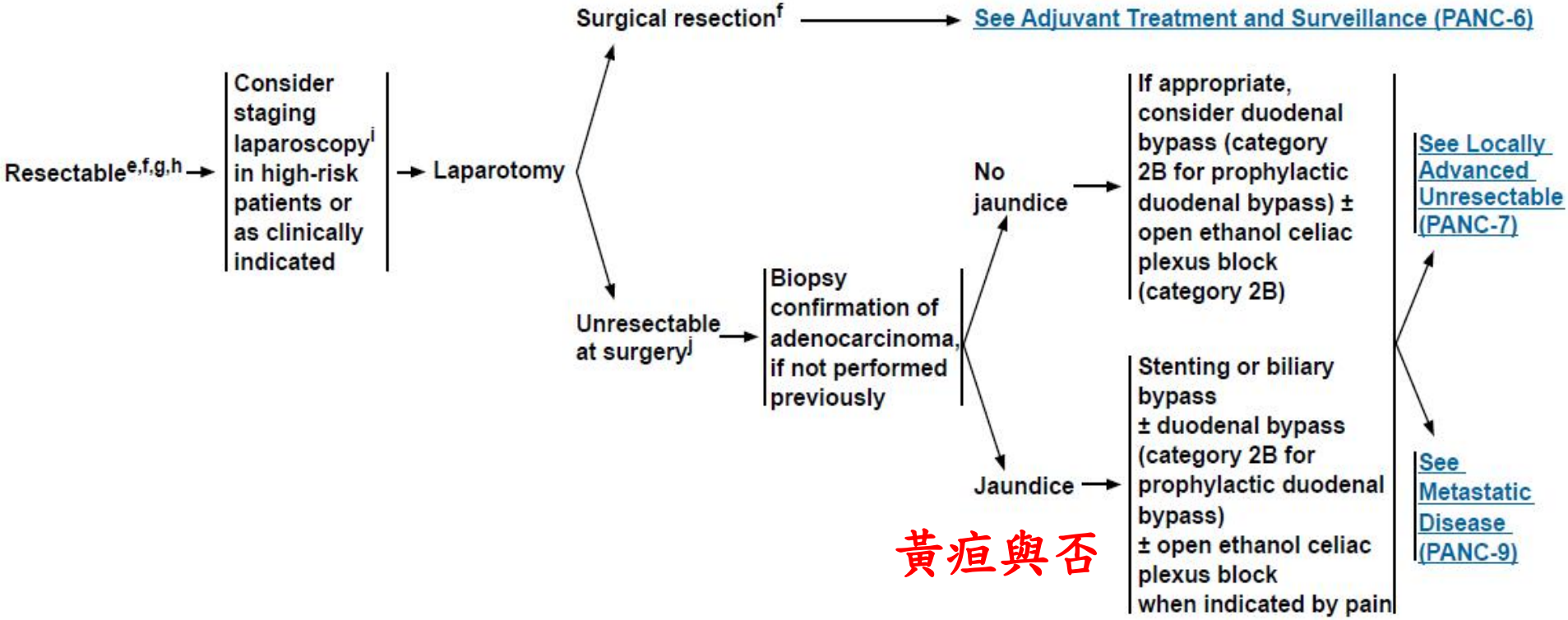
治療挑戰

- 存活率極差
- 大部分發現時不能開刀
- 對大部分治療抗藥性
- 體力營養狀態常快速惡化

術後復發高危險群
胰臟癌病人之
輔助性治療

SURGERY

能開就開



黃疸與否

*膽道支架/膽道繞道
*必要時十二指腸繞道
（預防性待商確）
*必要時神經阻斷

NCCN 2014

ADJUVANT THERAPY(輔助性治療)

JCO 2005;23:4532-4537

CCRT

Study	Primary Included	Treatment	Patient Nos. Total	Patient Nos. Pancreas	Survival for Pancreatic Patients PFS/DFS	Median (months)	2-Year (%)
Kalser et al (1985)[4]	Pancreas	Split course RT 2 Gy for 5 fractions per week for 2 weeks, repeated after 2 weeks (total = 40 Gy) + bolus 500 mg/m^2 FU days 1-3 of each 20-Gy cycle, followed by weekly bolus FU for 2 years	43	21	2-year DFS %: 0.48	20 (P = .03)	43
		Observation		22	2-year DFS %: 0.14	11	18
GITSG 1987[5]	Pancreas	Split course RT 2 Gy for 5 fractions per week for 2 weeks, repeated after 2 weeks (total = 40 Gy) + bolus 500 mg/m^2 FU days 1-3 of each 20-Gy cycle, followed by weekly bolus FU for 2 years	30	30	2-year DFS %: 0.32	18	43
Klinkenbijl et al (1999)[6]	Pancreatic head, peri-ampullary	RT 2 Gy for 5 fractions per week for 2 weeks, repeated after 2 weeks (total = 40 Gy) + FU 25 mg/kg/d continuous infusion with each RT cycle	218	60	PFS (months): 17.4*	17.1 (P = .099)	37
		Observation		54	PFS (months): 16*	12.6	23
Bakkevold et al (1993)[7]	Pancreas, ampulla	FAM: Doxorubicin 40 mg/m^2, mitomycin 6 mg/m^2 and FU 500 mg/m^2, repeated every 3 weeks for 6 cycles	61	23	—	23* (P = .02)	43*
		Observation	30	24	—	11*	32*
Takada et al (2002)[8]	Pancreas, biliary	MF: mitomycin 6 mg/m^2 on day of surgery + FU 310 mg/m^2 for 5 days during postoperative weeks 1 and 3, followed by daily oral FU 100 mg/m^2 from postoperative week 5 until recurrence	508	81	5-year DFS %: 8.6 (P = 0.84)		5-year: 11.5 (P = NS)
		Observation		77	7.8		18.0

Standard in US

Repeated study

EORTC
No 5-FU 2yr

Not significant

C/T

Benefit(+)

Benefit in GB not pancreas

*輔助性同步電化療曾在初期研究有存活提振 但在後續確認性研究中未達成效果

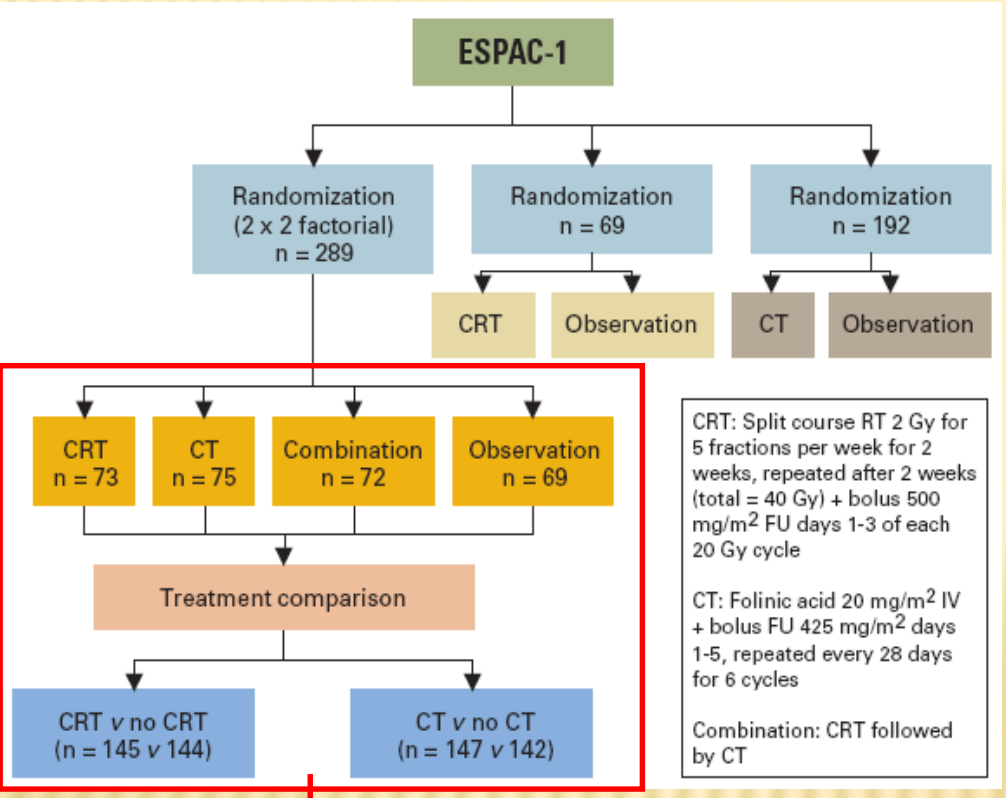
*輔助性化療FAM也曾達到存活提振 但處方太老太毒

ESPAC-1

*有輔助性同步電化療的反存活差
*有輔助性化療傳統bolus 5-FU 的
都有存活率提升 但毒性仍不小

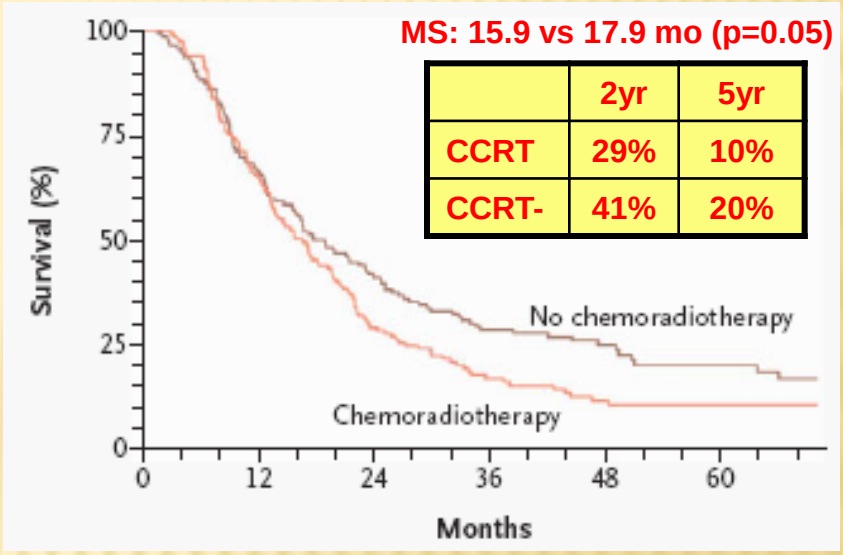
JCO 2005;23:4532-4537
NEJM 2004;350:1200-10

HR=1.28

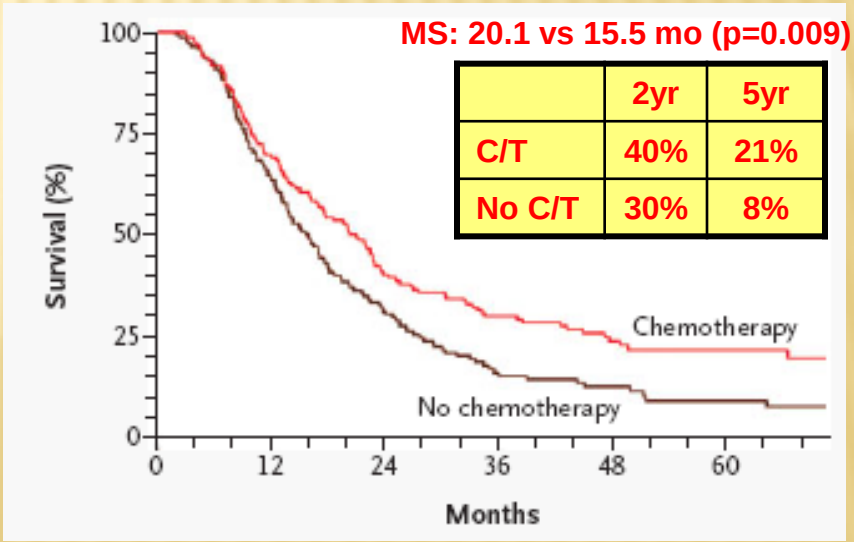


Arm	Median Survival (months)	5-Year Survival (%)
Observation	16.9	11
Chemoradiotherapy	13.9	7
Chemotherapy	21.6	29
Chemoradiotherapy followed by chemotherapy	19.9	13

*最好



	2yr	5yr
CCRT	29%	10%
CCRT-	41%	20%



	2yr	5yr
C/T	40%	21%
No C/T	30%	8%

JAMA. 2007;297:267-277

CONKO-001

輔助性化療健擇
有明顯無病存活期提升
存活率提升邊緣 毒性可接受

N=354

Resected
Adenoca.
T1-4, N0-1
KPS ≥ 50
Ctx (-)
RT (-)

RANDOMIZE

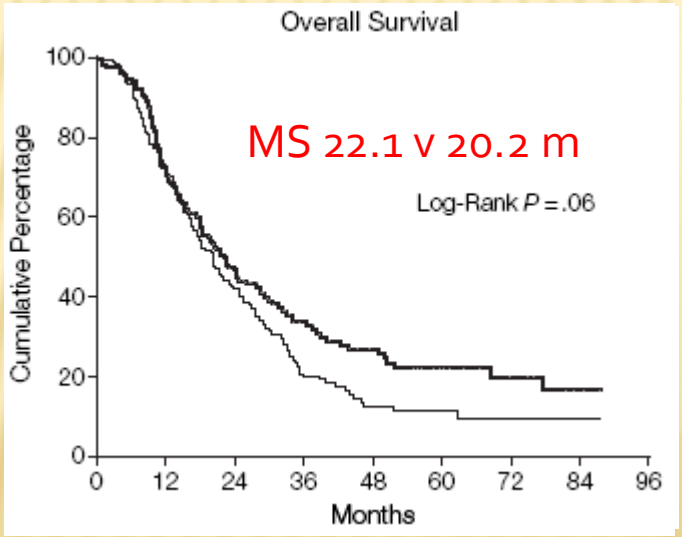
Ctx

Control

G 1000 mg/m^2
D1,8,15; 6 cycles

	G	C
T1	7	7
T2	18	17
T3	14	146
T4	6	5
	8	
N0	52	48
N1	127	127
R0	14	148
R1	5	27
	34	

Survival



≥ Gr 3 toxicity (cycles)

	G	C
Hema		
-Hb	0.6%	0.1%
-WBC	2.4%	0.1%
-PLT	0.8%	0
Non-hema		
-N/V	1.3%	0.2%
-Diarrhea	0.9%	0.4%
-Edema	0.5%	0.1%
-Infection	0.4%	0.3%

Relapse pattern

	G	C
Local	34%	41%
Distant	56%	49%

輔助性化療健擇 和 5-FU
無病存活期和存活率沒有差別
毒性 5-FU 明顯較大

JAMA. 2010;304(10):1073-1081

ESPAC-3

N=1088

Resected
Adenoca.
Non-mets
ECOG ≤2
Ctx (-)
RT (-)

RANDOMIZE

Ctx

5-FU 425 mg/m^2
LV 20 mg/m^2
D1-5; 6 cycles

G 1000 mg/m^2
D1,8,15; 6 cycles

	F	G
I	58	46
II	154	144
III	303	319
IVa	26	16
N0	162	145
N1	387	391
R0	36	348
R1	195	189

DFS and OS
No difference

≥ Gr 3 toxicity

	F	G
Hema		
-WBC	6%	10%
-ANC	22%	22%
-PLT	0%	1.5%
Non-hema		
-N/V	6.5%	4.5%
-Diarrhea	13%	2%
-Stomatitis	10%	0%

Quality of Life

No significant difference

IUAC 1997 staging

JASPAC-01

輔助性TS1(口服愛斯萬) vs G(健擇): 可能更好 (ASCO 2013)

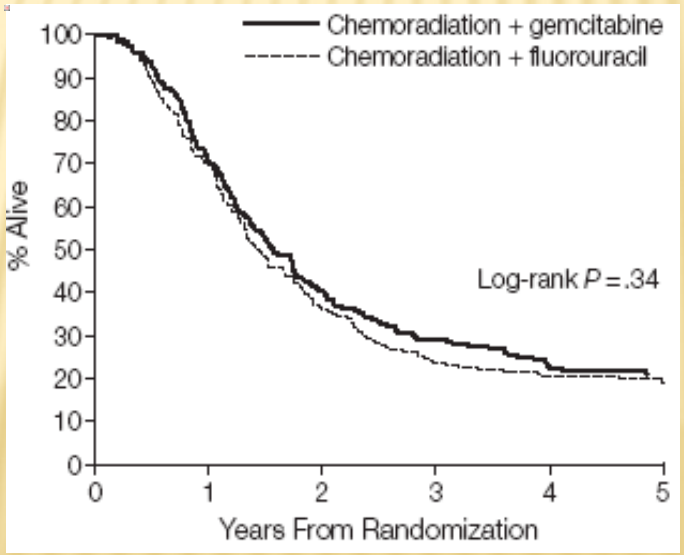
尤其是 low DPD(代謝酵素) and high TS(目標酵素) 的腫瘤

JAMA. 2008;299(9):1019-1026

RTOG 97-04

	F	G
T 1/2	68	43
T 3/4	162	178
N0	82	70
N1	148	151
Margin (-)	102	86
Margin (+)	75	77
unknown	53	58
Head	201	187
nonhead	29	34

Overall survival



Relapse pattern

	F	G
Local	55	43
Regional	15	13
Distant	140	13 8

≥ Gr 3 toxicity

G: 58%

F: 9%

(*P*<.001)

EORTC 40013

N=90

Resected, R0
Adenoca.
Mets
PS 0-2
Ctx (-)
RT (-)

RANDOMIZE

Ctx

G 1000 mg/m^2
D1,8,15; 2 cycles

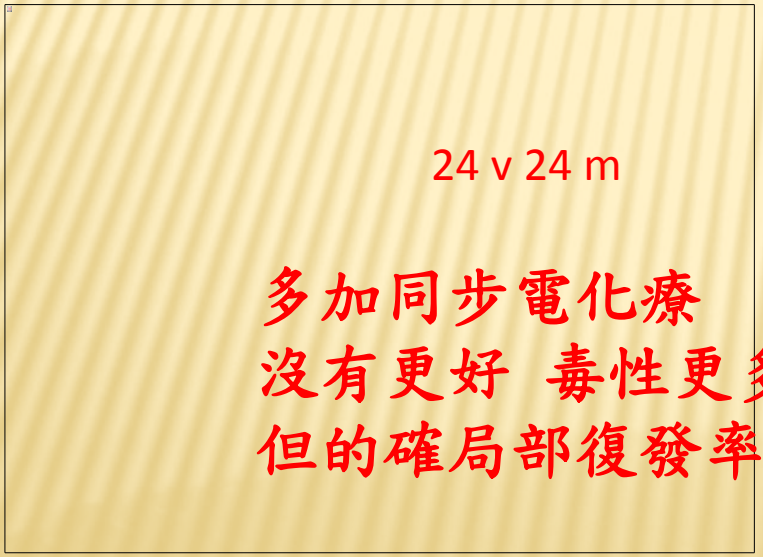
G 1000 mg/m^2
D1,8,15; 4 cycles

CCRT

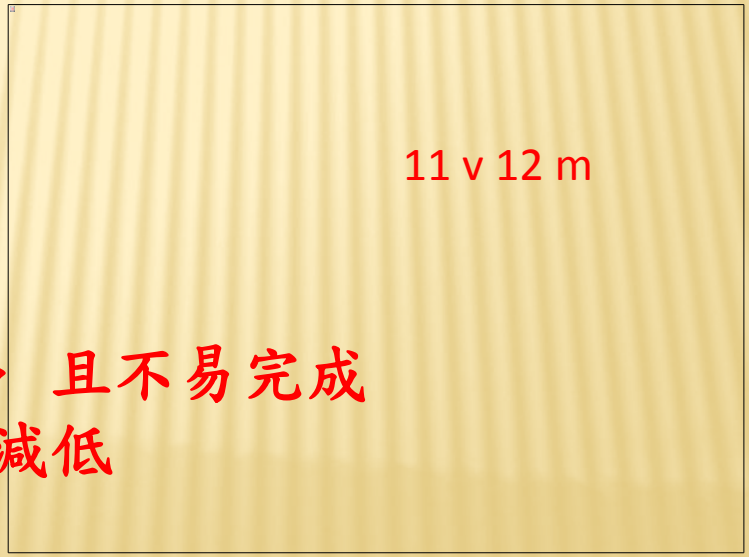
G 300 mg/m^2/wk
RT 50.4 Gy/28 fx

Gr 4 toxicity: 2 (CRT)
Gr 3 toxicity: 3 (CRT)

OS



DFS



多加同步電化療
沒有更好 毒性更多 且不易完成
但的確局部復發率減低

First local recurrence CRT v Ctx (11% v 24%)
Tx completed CRT v Ctx (73.3% v 86.7%)

J Clin Oncol. 2010 Oct 10;28(29):4450-6

T3207 STUDY

第三期隨機臨床試驗:
開刀後 輔助性健擇

之後 同步電化療
或 觀察

術後復發高危險群胰臟癌病人之輔助性治療

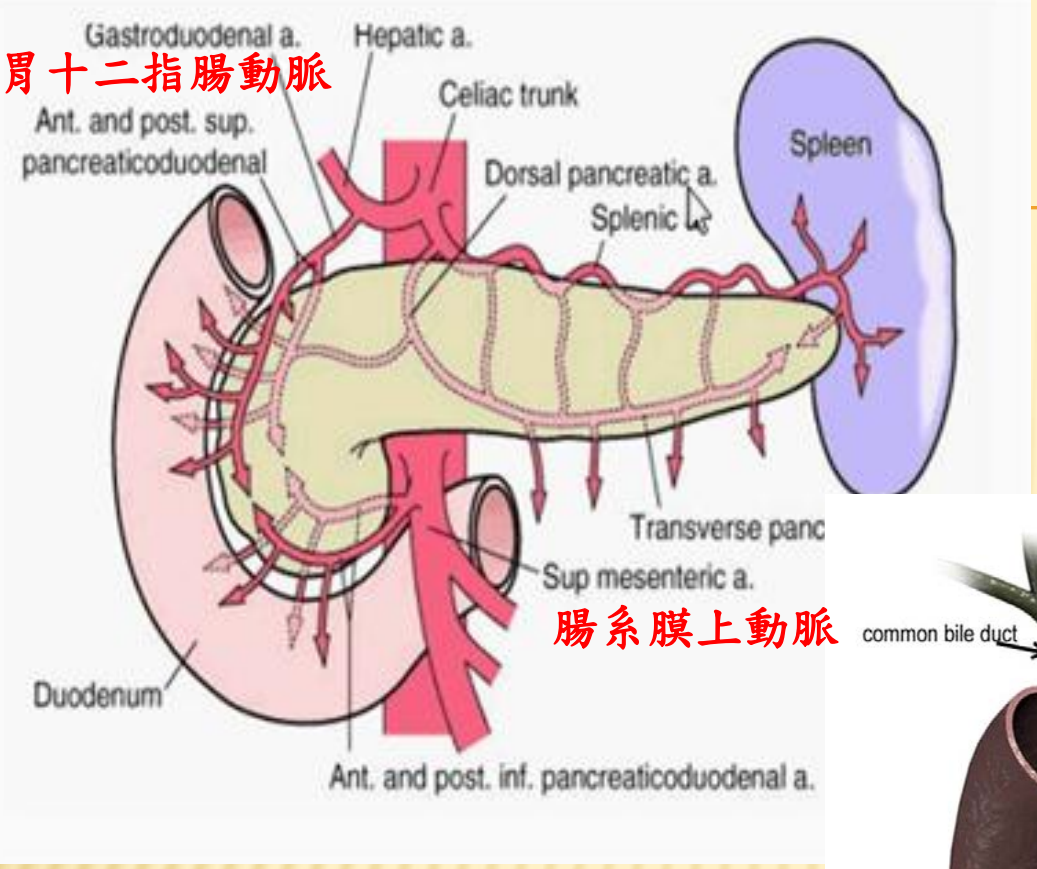
*輔助性 健擇 or 愛斯萬 or 健擇+愛斯萬(研究中)

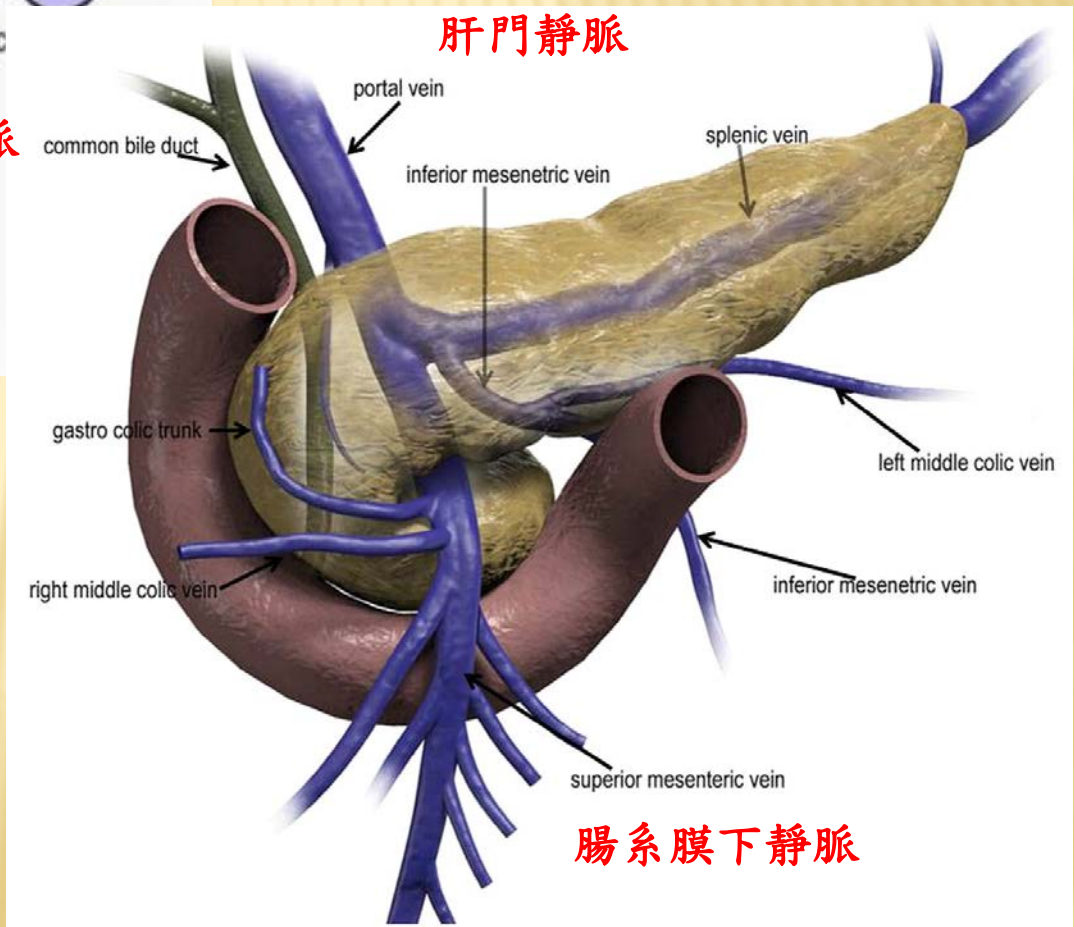
*輔助性化療後 CCRT(同步電療化療)可行
雖局部復發率降低但相對毒性較大

切除可行但不易或局部侵襲嚴重之胰臟癌患者的前導性治療

胰臟癌切除可行但不易的狀況

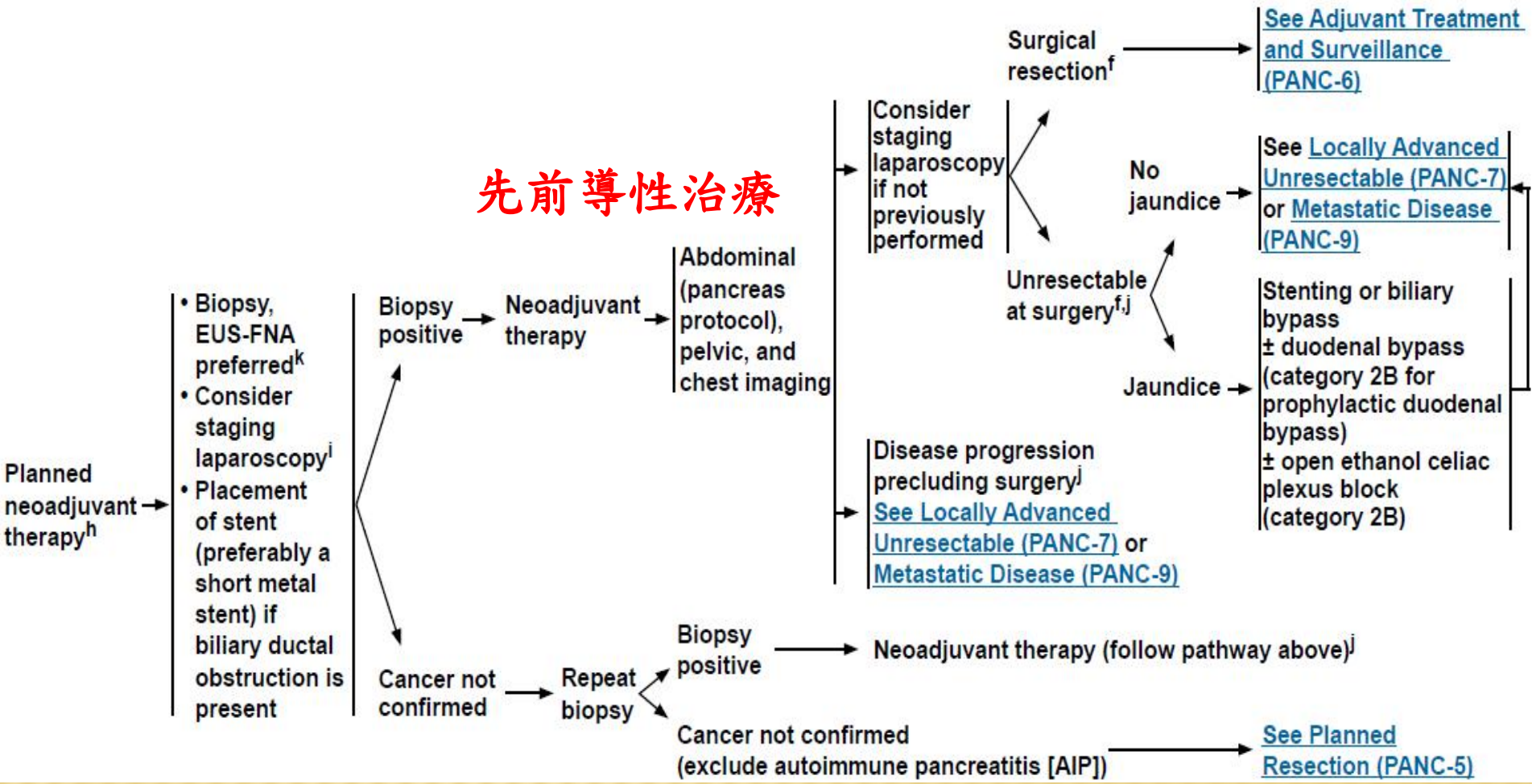
- SMV/PV: tumor abutment, impingement, narrowing the lumen; short-segment venous occlusion allowing for suitable resection/reconstruction（大靜脈影響）
- GDA encasement up to HA with short- segment encasement or abutment of HA, without extension to celiac axis（胃十二指腸動脈侵犯）
- Tumor abutment of SMA, < 180 degrees of circumference（腸系膜上動脈影響 不到180度）


胃十二指腸動脈
Gastroduodenal a.
Hepatic a.
Celiac trunk
Ant. and post. sup. pancreaticoduodenal
Dorsal pancreatic a.
Splenic
Spleen
Transverse panc
Sup mesenteric a.
腸系膜上動脈
Duodenum
Ant. and post. inf. pancreaticoduodenal a.


肝門靜脈
portal vein
common bile duct
splenic vein
inferior mesenetric vein
gastro colic trunk
left middle colic vein
right middle colic vein
inferior mesenetric vein
superior mesenteric vein
腸系膜下靜脈

血管供應

胰臟癌切除可行但不易的處理



NCCN 2014

NEOADJUVANT TX FOR (BORDERLINE) RESECTABLE DZ(前導性化療)

111 studies (n = 4,394), 1966-2009

切除機會增加 甚至切乾淨

Group	CR (%)	PR (%)	SD (%)	PD (%)	Explore/All (%)	Resect/All (%)	R0/Resect (%)
All	3.9	29.1	43.9	20.8	69.5	50.7	79.6
可切	3.6	30.6	42.1	20.9	88.1	73.6	82.1
不可切或沒把握但可行的	4.8	30.2	41.6	20.8	46.9	33.2	79.2

PLoS Med. 2010 Apr 20;7(4):e1000267

INDUCTION FOR RESECTABLE PC
(針對可切除之前導性化療)

1. G+TS1(健擇+愛斯萬) induction:
   R0(完全切乾淨) 85.7%;
   2YOS(兩年存活) 45.7%

2. Prep02/JSAP05 study: randomized study 360 patients
   Primary endpoint---OS
   第三期隨機臨床試驗進行中

INDUCTION FOR LOCALLY ADVANCED PC (前導性化療針對局部侵犯嚴重者)

陳立宗院長:

1. GOFL(健擇 歐立普 5-FU) induction:
   good response rate, even to surgery(反應好 直接開刀)
   CCRT for still unresectable---long-term disease-free
   (或之後同步電化療 可長期無病)

2. GOFL induction and CCRT and maintenance GOFL
   (T1204)—前導性化療 同步電化療 維持性化療

3. T2212(randomized phase 2)
   Induction GOFL vs modified FOLFIRINOX
   (歐立普/5-FU/irinotecan) for 3 months followed by CCRT
   Primary endpoint: 9 months PFS 比前導性化療是否強較好

DILEMMA OF LOCALLY ADVANCED PC (局部侵犯嚴重疾病困境)

1. Chemotherapy regimen(化療處方)
2. The role of consolidation CCRT(同步電化療的角色)
3. Induction therapy duration(前導性化療要多久)
4. Radiosensitizer choice(電療時化療或標靶選擇)
5. Maintenance therapy(維持性治療)
6. Targeted Tx(標靶治療)

Neoadjuvant Tx for resectable or locally advanced disease

***Induction G+TS1 for resectable disease**
(可切除者 前導性健擇+愛斯萬)

***Neoadjuvant GOFL and then CCRT and then GOFL maintenance for locally advanced dz(follow T1204)**
(局部侵犯嚴重者 前導性健擇/歐立普/5-FU 有反應者同步電化療 之後維持性化療)

轉移性胰臟癌

胰臟癌藥物治療的困難點

- 高抗藥性
- 藥物副作用
- 易轉移
- 身體(營養)狀況不佳
- 癌症相關併發症

KEY MILESTONE IN THE DEVELOPMENT OF NEW DRUGS FOR ADVANCED PANCREATIC CANCER

Pre-1996	The dark ages. Nothing works
1996 健擇	**Gemcitabine** improves survival compared with 5-FU. Gemcitabine is approved for PC
1996-2005 健擇相關組合	Many agents tested. No drug or drug combination is better than Gemcitabine
2005 健擇+得舒緩	**Erlotinib + Gemcitabine** modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC
2005-2009	More drugs tested. Man
2010 5-FU/歐立普/irinotecan	**FOLFIRINOX** improves survival compared with Gemcitabine
2012	***nab*-Paclitaxel + Gemcitabine** improves survival compared with Gemcitabine

OS 5-7 m

Gem+ X

OS= 6.24 m, +0.3m

愛斯萬 2006:S-1 was approved in Japan

OS= 11.1 m vs 6.8 m

白蛋白紫杉醇+健擇

Presented By Hedy Lee Kindler, MD at 2013 ASCO Annual Meeting

藥物選擇-

腫瘤反應率

Agent	RR
5-FU Capecitabine S-1 UFT	0-20% 7.3% 22.6% 0%
Pemetrexed Raltitrexed	5.7% 0-5%
Paclitaxel Docetaxel	5.5% 0-15%
Irinotecan	9%
Oxaliplatin Cisplatin	0% 24%

CBR: clinical beneficial response
=>Karnofsky PS + pain + weight gain (P=0.0022)

	Gemzar	5-FU
RR	5.4%	0%
CBR	23.8%	4.8%
MS	5.65mo	4.41mo
1yr-Sur	18%	2%

All parameters were significant !!

健擇所有臨床指標都較好

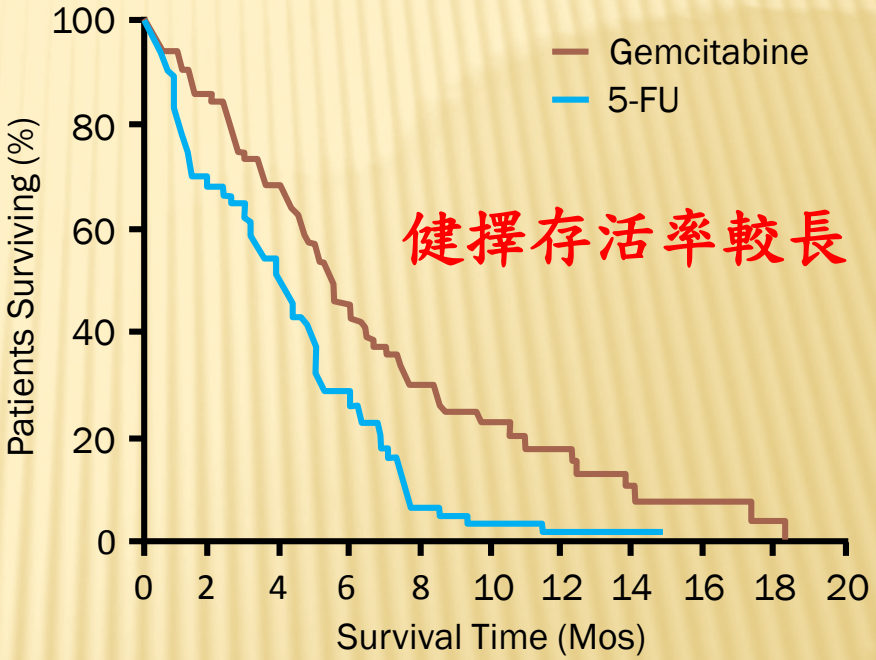
J Clin Oncol 1997;15:2403

Principles & Practice of Oncology, 7th edition

Int J Radiat Oncol Biol Phys 56(4) suppl 24-30, 2003

METASTATIC PANCREATIC CANCER: THE BASIS OF GEMCITABINE AS THE MAINSTAY OF TREATMENT

- Pivotal study defining role for gemcitabine as first-line treatment for patients with advanced pancreatic cancer
  - Median survival (vs bolus 5-FU): 5.65 vs 4.41 mos. (*P* = .0025)
  - 1-year survival: 18% vs 2%
  - Clinical benefit*: 23.8% vs 4.8% (*P* = .0022)
  - Response rate: 5.4% vs 0% (*P* = NS)



*A composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least 1 parameter without worsening in any others.

Burris HA, et al. J Clin Oncol. 1997;15:2403-2413.

GEMCITABINE COMBINATION IN TAIWAN

GOFL since 2002: (國衛院陳立宗院長)

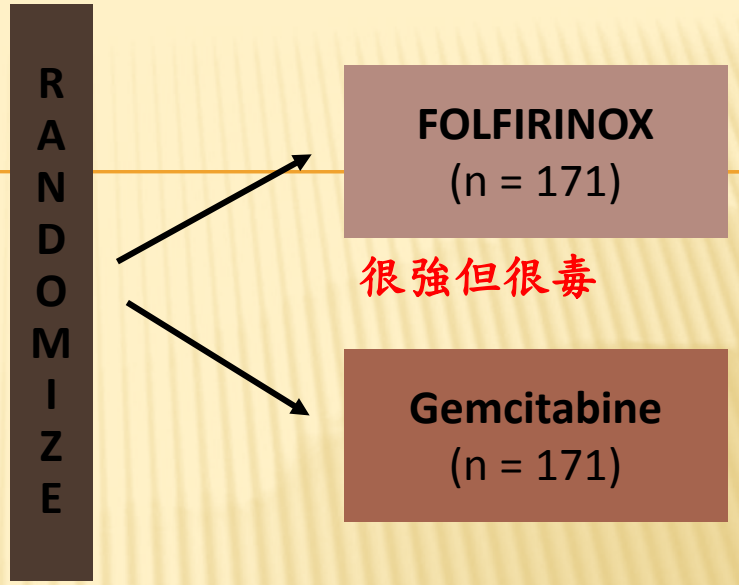
Good salvage response rates but high KPS demanded (反應好 但要體力好)

ERLOTINIB (得舒緩)

- 作用機轉: 表皮生長因子受體抑制劑
- 適應症: 肺癌、(胰臟癌)
- 副作用:
  - 50%左右患者可發生丘疹、斑疹、膿皰樣皮炎，多在服藥第一周出現，4周後可逐漸減輕。少數可能非常嚴重需停藥或減少藥量
  - 皮膚乾燥、瘙癢
  - 噁心、嘔吐、腹瀉
  - 肝功能異常
  - 間質性肺炎

PRODIGE 4/ACCORD 11

- ECOG: 0(40%), 1 (60%)
- DI: G (100%); F(82%), I (81%), O (78%)
- 2nd line:
  - F group: G alone (82.5%), G-com (12.5%)
  - G group:
    - FOLFOX (49.4%), GO (17.6%), PFL (16.5%)
    - **FOLFIRINOX: 4.7%**
- G-CSF:
  - **F group: 42.5%**
  - G group: 5.3%
- QoL score: F > G

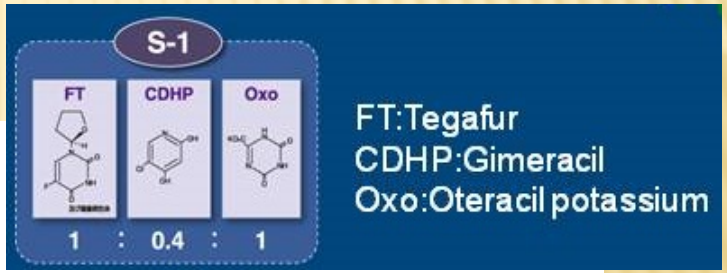


Event *Gr 3-4*	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

N Engl J Med 2011;364:1817-25

BIOCHEMICAL ACTION OF S-1

- S-1 (tegafur, CDHP, Oxo) is an oral “DPD inhibitory fluoropyrimidine (DIF)”



Randomized Phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (Gem) in unresectable advanced pancreatic cancer in Japan and Taiwan

GEST study group

Hideki Ueno [1], Tatsuya Ioka , Masafumi Ikeda , Shinichi Ohkawac, Hiroaki Yanagimoto, Narikazu Boku, Akira Fukutomi, Kazuya Sugimori, Hideo Baba, Kenji Yamao, Tomotaka Shimamura, Masayuki Sho, Masayuki Kitano, Ann-Lii Cheng [2], Kazuhiro Mizumoto, Jen-Shi Chen[3], Junji Furuse, Akihiro Funakoshi ,Takashi Hatori, Taketo Yamaguchi, Shinichi Egawa, Atsushi Sato, Yasuo Ohashi, Takuji Okusaka [1]*,and Masao Tanaka

1 Corresponding author : Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, Japan

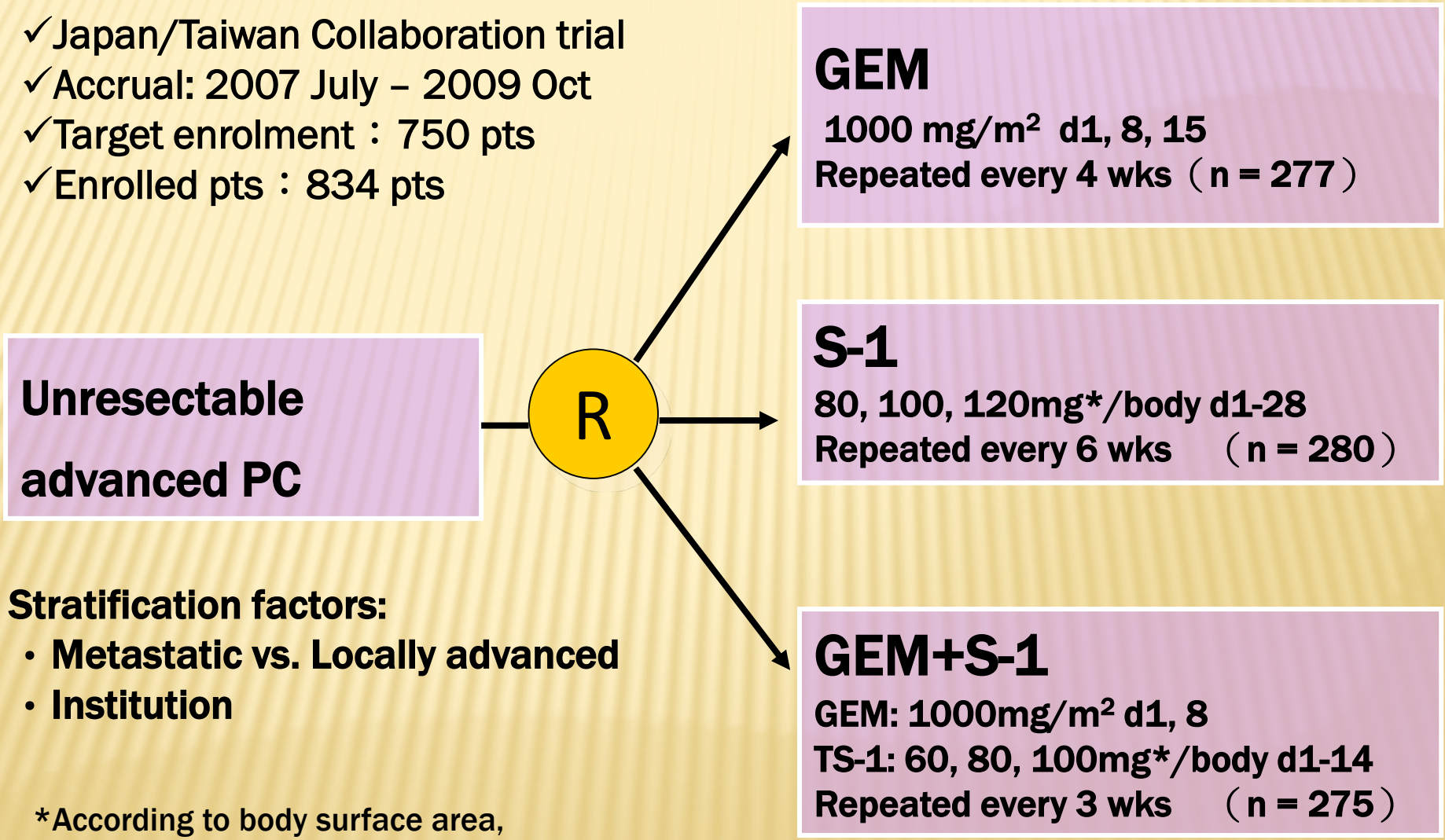
2 Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

3 Department of Oncology, Linkou Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Study Design

- ✓Japan/Taiwan Collaboration trial
- ✓Accrual: 2007 July – 2009 Oct
- ✓Target enrolment：750 pts
- ✓Enrolled pts：834 pts



Stratification factors:

- **Metastatic vs. Locally advanced**
- **Institution**

*According to body surface area,
BSA < 1.25 m^2, 1.25=<BSA <1.5, BSA >=1.5

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Study Objectives

Compared to Gem
- ✓ Superiority: Gem + S-1 (GS)
- ✓ Non-inferiority : S-1

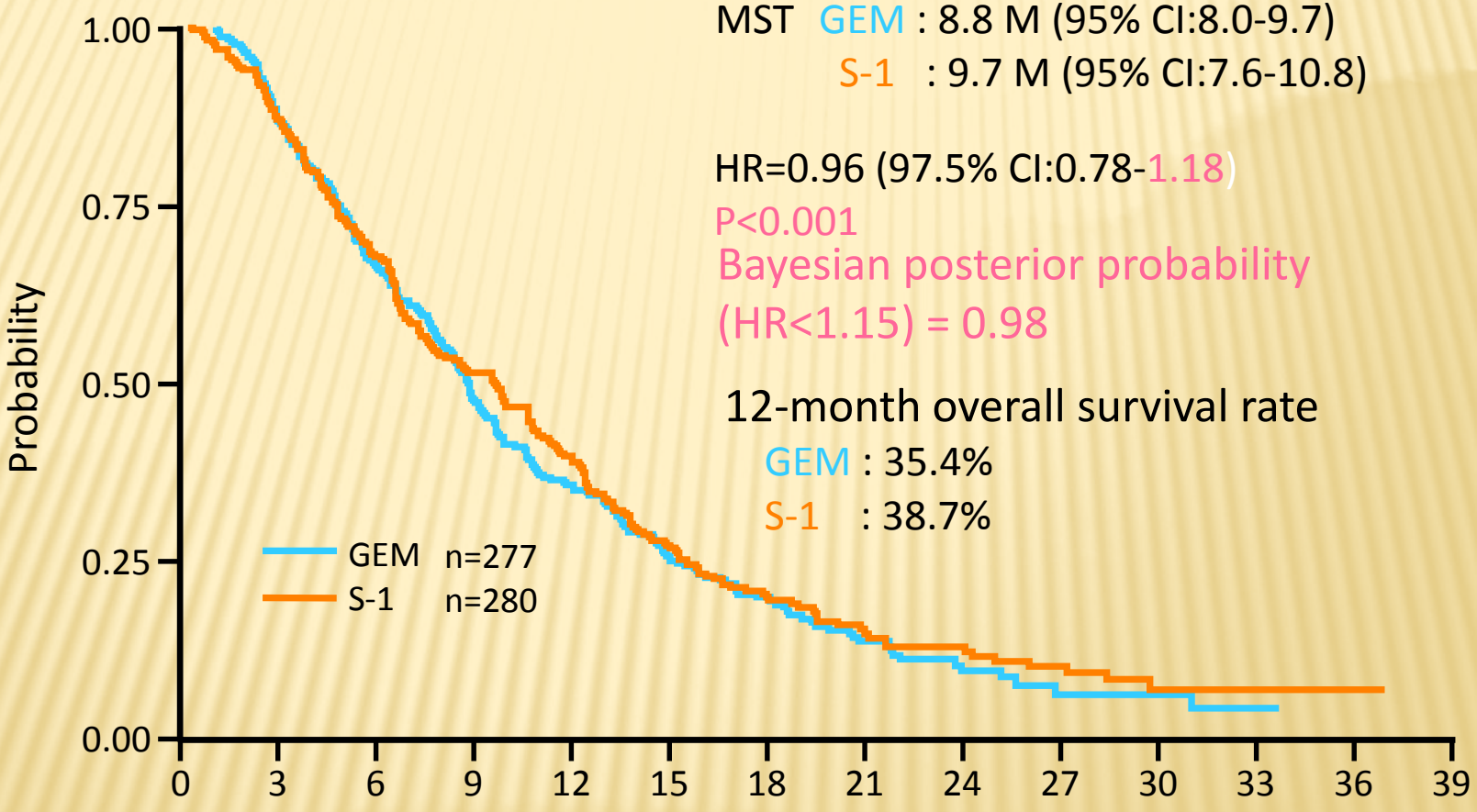
- Primary endpoint:
  - Overall survival (OS) 比存活率

- Secondary endpoint:
  - Progression-free survival (PFS)
  - Response rate (RR)
  - Toxicity
  - QOL (EQ-5D)

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Overall Survival (Noninferiority:GEM vs. TS-1)

愛斯萬 健擇存活一樣好



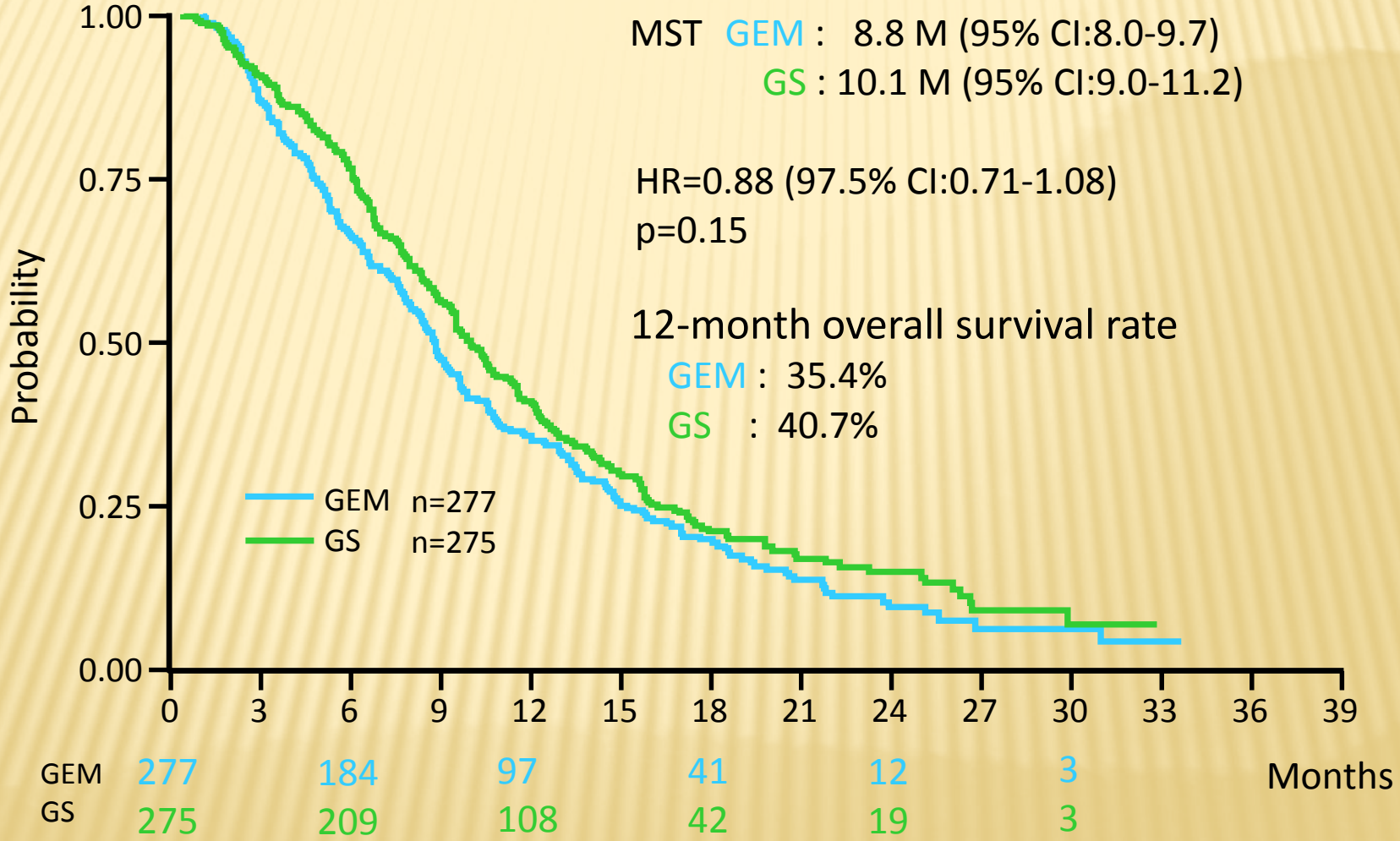
MST GEM : 8.8 M (95% CI:8.0-9.7)
S-1 : 9.7 M (95% CI:7.6-10.8)

HR=0.96 (97.5% CI:0.78-1.18)
P<0.001
Bayesian posterior probability (HR<1.15) = 0.98

12-month overall survival rate
GEM : 35.4%
S-1 : 38.7%

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Overall Survival
(Superiority ：GEM vs. GS)　健擇+愛斯萬 稍好但不顯著



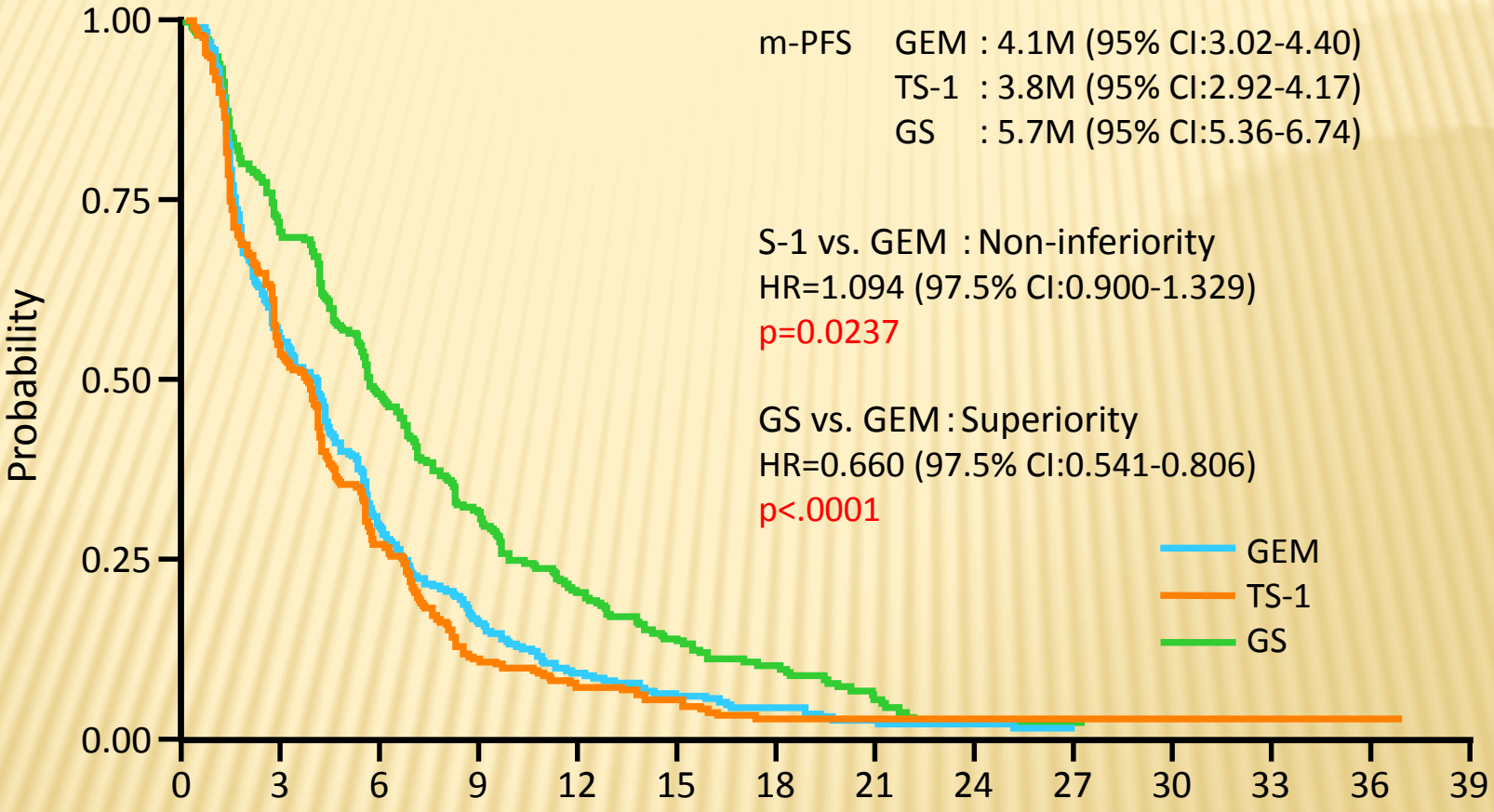
MST GEM： 8.8 M (95% CI:8.0-9.7)
GS : 10.1 M (95% CI:9.0-11.2)

HR=0.88 (97.5% CI:0.71-1.08)
p=0.15

12-month overall survival rate
GEM： 35.4%
GS ： 40.7%

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Progression-free survival　健擇+愛斯萬 顯著減緩惡化



m-PFS　GEM : 4.1M (95% CI:3.02-4.40)
TS-1 : 3.8M (95% CI:2.92-4.17)
GS : 5.7M (95% CI:5.36-6.74)

S-1 vs. GEM : Non-inferiority
HR=1.094 (97.5% CI:0.900-1.329)
p=0.0237

GS vs. GEM : Superiority
HR=0.660 (97.5% CI:0.541-0.806)
p<.0001

At risk							
GEM	277	82	25	10	3	0	0
S-1	280	73	19	6	3	2	1
GS	275	130	55	21	3	0	0

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Response rate

	GEM n=241	S-1 n=248	GS n=242
CR	1	0	2
PR	31	52	69
RR	13%	21%	29%

反應較好

GEM vs. S-1：p=0.0242, GEM vs. GS: p<.0001

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Post-Study Treatment

會交叉使用

	GEM n=277	TS-1 n=280	GS n=275
GEM-based *	16 %	51 %	27 %
S-1-based *	40 %	9 %	11 %
GS	11 %	8 %	20 %
Other	3 %	3 %	11 %
BSC	27 %	25 %	29 %
Unknown	4 %	4 %	4 %

* Except for GS

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

Toxicities: Laboratory Data(毒性可調控)

AE term	GEM (n=273)		S-1 (n=272)		GS (n=267)	
	Any(%)	Gr.3≦ (%)	Any(%)	Gr.3≦ (%)	Any(%)	Gr.3≦ (%)
Hemoglobin	80	14	68	10	85	17
Leukocytes	76	19	43	4	88	38
Neutrophils	68	41	34	9	83	62
Platelets	78	11	46	2	81	17
ALT	58	15	42	6	60	11
AST	60	15	49	8	61	12
Bilirubin	26	10	53	14	39	9
Creatinine	18	1	19	1	16	0.4

Treatment-related death GEM 3, S-1 1 , GS 4 (total 8: 0.99%) Except for no treatment

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

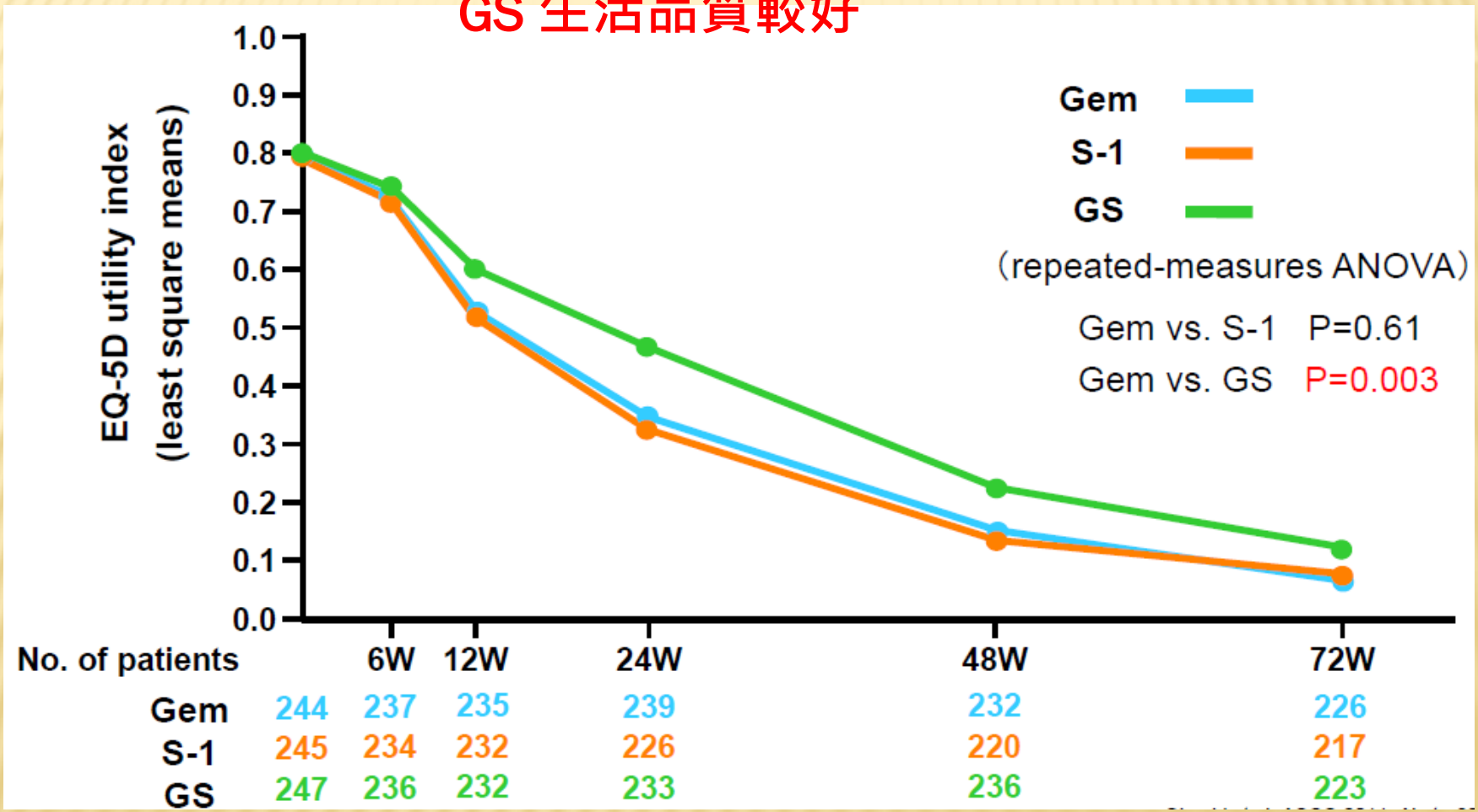
Toxicities (Symptom)

AE term	GEM (n=273)		S-1 (n=272)		GS (n=267)	
	Any(%)	Gr.3≦(%)	Any(%)	Gr.3≦(%)	Any(%)	Gr.3≦(%)
Fatigue	45	4	53	7	66	5
Alopecia	11	-	3	-	18	-
Rash	28	1	19	1	41	4
Anorexia	58	7	66	11	65	9
Diarrhea	21	1	39	6	38	5
Mucositis (clinical exam)- Oral cavity	14	0	25	1	34	2
Nausea	43	2	54	2	55	5
Vomiting	27	1	32	2	34	5
Febrile neutropenia	0.4	0.4	0.4	0.4	2	2
Pneumonitis	3	2	0.4	0	2	1

Ueno et al, J Clin Oncol. 2013 May 1;31(13):1640-8

EQ-5D UTILITY COMPARISON BETWEEN 3 ARMS

GS 生活品質較好



Ohashi et al, ASCO 2011 abstract 9070

SELECTION CRITERIA FOR APPROPRIATE TS-1 ADMINISTRATION

ULN : (facility) Upper limit of normal

	Item	Appropriate criteria	Careful administration ※	Drug withdrawal
	PS(ECOG) or KPS	PS 0-2 KPS 100 - 50%	PS 3 KPS 40 - 30%	PS 4 KPS ≦20%
Bone Marrow function	Hemoglobin	≧ 9.0 g/dL	8.0 - 9.0 g/dL	＜ 8.0 g/dL
	WBC	3,500 ～ 12,000/mm^3	2,000 ＜WBC＜ 3,500/mm^3 ≧ 12,000/mm^3	＜ 2,000/mm^3
	Neutrophil count	≧2,000/mm^3	1,000＜Neutrophil＜ 2,000/mm^3	＜ 1,000/mm^3
	Pletelet count	≧ 100,000/mm^3	75,000 ～ 100,000/mm^3	＜ 75,000/mm^3
Hepatic function	Total Bilirubin	Below ULN × 2	Below ULN × 2＜T.Bill ＜3mg/dL	≧ 3mg/dL
	AST(GOT) ALT(GPT)	Below ULN × 2	ULN × 2<AST・ALT<150IU/L	≧ 150 IU/L
Renal function	Creatinine	Below ULN	ULN<Creatinine<1.5mg/dL ※※	≧ 1.5mg/dL

Estimated Ccr (mL/min)	≧80	80＞Ccr≧60	60＞Ccr≧30	30＞
Initial dose	Start administration	1 step dose down	1 step and further dose down	Disapprove for administration

※: It is desirable to postpone S-1 administration until the patient recovers to a level that fulfills the selection criteria for appropriate S-1 admninistration

※※: Whenever creatinine value is less than 1.5mg/dL,initial dose should be decided by estimated Ccr.

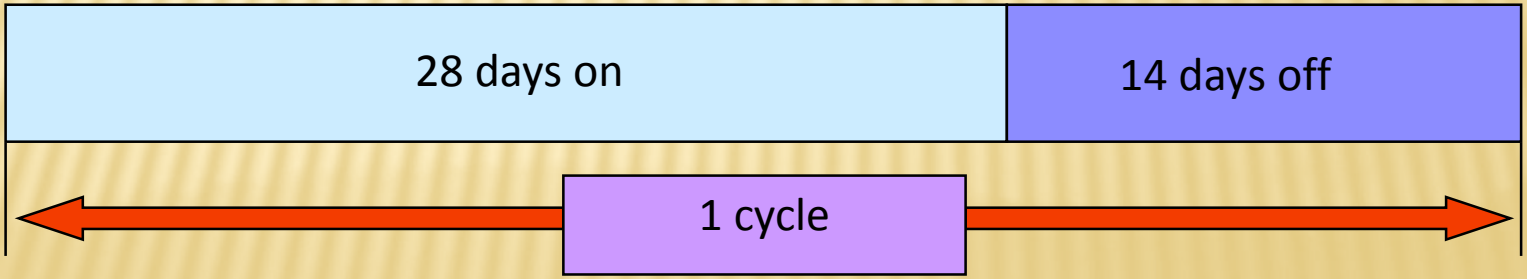
Ccr Estimation (Cockcroft-Gault equation) = [(140-age) x body weight (kg)] / [72 x Serum Creatinine (mg/dL)]
(obtained value x 0.85 for female)

Dose and Administration

- TS-1 is administered twice daily, after breakfast and after the evening meal:

BSA	Initial Dose (equal to dose of Tegafur)	Dose/Day
<1.25 m^2	40 mg/ time	80 mg/day
1.25 m^2 ～1.5 m^2	50 mg/ time	100 mg/day
≥ 1.5 m^2	60 mg/ time	120 mg/day

- 1 cycle:28 consecutive days, followed by a 14-day rest



Major Side Effects: （腹瀉 手足症 嘴破）
Time of Occurrence and Discovery

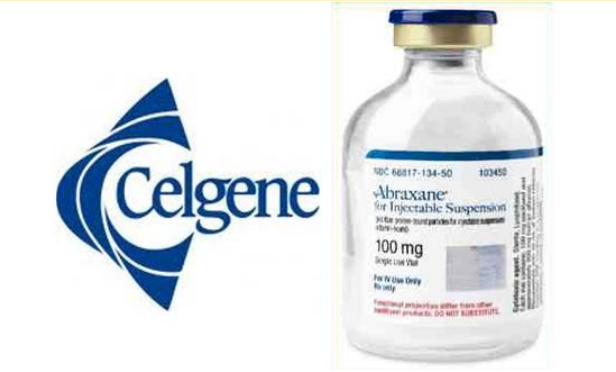
Abnormal clinical laboratory findings	Number of incidence	Nadir : (median)	Period of up to nadir value : median day (range)	Number of recovery	Period of up to recovery : median day (range)
Leukopenia	92	2,560/mm^3 (300-2,990/mm^3)	27 (4-43)	85	7 (1-93)
Decreased hemoglobin	29	7.3 g/dL (3.5-7.9 g/dL)	25 (5-43)	24	5.5 (1-21)
Thrombocytopenia	28	6.7*10^4/mm^3 (1.0-7.4/mm^3)	24 (9-51)	25	6 (1-46)

Abnormal clinical laboratory findings	Number of incidence	Period of up to occurrence:day median (range)	Number of recovery	Period of up to improvement Occurrence day : median (range)
Diarrhea	100	24.5 (2-189)	95	9 (1-62)
Rash	67	21 (2-248)	63	14 (2-254)
Stomatitis	100	24 (3-262)	94	13.5 (2-99)

SLOG(T1210 STUDY)

Gemcitabine, oxaliplatin, TS1, LV
(健擇 歐立普 愛斯萬 LV)

ABRAXANE
(奈米顆粒白蛋白 PACLITAXEL)



- 該藥物屬太平洋紫杉醇與白蛋白的結合
- 適應症:乳癌、非小細胞肺癌
- 晚期胰臟癌第三期臨床試驗(861位病患)
- Abraxane 加上 Gemcitabine 有統計上重大的改善
  - 整體存活: [(中位存活期為 8.5 與 6.7 月) (HR 0.72， P=0.000015)]。
  - 一年存活率: 35%(合用)與22%(Gemcitabine)
  - RR: 23% v 7%

GEMCITABINE-REFRACTORY DZ(健擇失敗後)

Liposomal(微脂體)-CPT11:

1. Phase I: PEP0201 study

2. Phase II: PEP0208 study

3. Phase III: NAPOLI study---Lipo-CPT11 vs HDFL
Lipo-CPT11 加上 5-FU/LV更好

NAPOLI STUDY

轉移性

G+TS1(健保 毒性可)

G+albumin-Taxol:cost　(毒性和價格較高)
FOLFIRINOX:toxicity

Refractory status(二線): Lipo-CPT11 + 5-FU/LV

膽管癌

解剖位置

1.膽道(肝內-6% 肝門-67% 肝外-27%)
和 膽囊(較多)
年老較多

2.除非choledochal cyst 或
自體免疫性硬化性膽管炎
否則很少年輕人患癌

病因和病理

1.肝吸蟲 很少了

2.慢性發炎 膽結石

3.抽菸 糖尿病 C肝

4.單發息肉(肥胖 運動)

5.Adenocarcinoma為主

症狀和診斷

1.腹痛 黃疸 體重減輕

2.ALP Bil(T/D) GOT/GPT CA19-9

3.超音波 CT MRI/MRCP

4.PES ERCP Liver biopsy

預後

1.肝內(多發 往外侵襲 淋巴結陽性都不好)
膽囊 淋巴結陽性需輔助性治療
肝外(往周邊侵襲不好)
淋巴結陽性也可能需輔助性治療

2.膽道阻塞 早期引流支架

治療(膽囊)

1. 手術

輔助性化療(淋巴結陽性---
健擇+愛斯萬)

輔助性電化療(不乾淨
淋巴結陽性或多?)

2. 前導性健擇+愛斯萬 再開 若困難開
若不能開 前導性化療後 同步電化療

治療(肝內)

1. 手術
   輔助性化療(T3/N1以上)
   輔助性電化療(不乾淨 or T3/N1以上?)

2. 前導性健擇+愛斯萬 再開 若困難開
   若不能開 前導性化療後 同步電化療

3. TAE or RFA for 可行病灶

治療(肝門肝外)

1. 手術

輔助性化療(淋巴結陽性)

輔助性電化療(不乾淨 or 淋巴結陽性或多?)

2. 前導性健擇+愛斯萬 再開 若困難開 若不能開 前導性化療後 同步電化療

3. 引流 支架 光動力治療

輔助性化療

健擇 or 愛斯萬 or 健擇+愛斯萬

前導性化療

*健擇 + 愛斯萬

*Erbitux(表皮生長因子接受體抗體) and GEMOX(健擇 + 歐立普)

(若MET/ROS/RET 過度表現---反應差)

陳立宗教授研究:

Induction Erbitux and GEMOX---
Erbitux and oxaliplatin(CCRT)

轉移性化療

*G; G-HDFL;
GP(健擇 + 白金---
第三期隨機臨床試驗有明顯存活提振)
GEMOX; GOFL

*Erbitux and GEMOX

*TS1 combination(G+TS1; SLOG)