

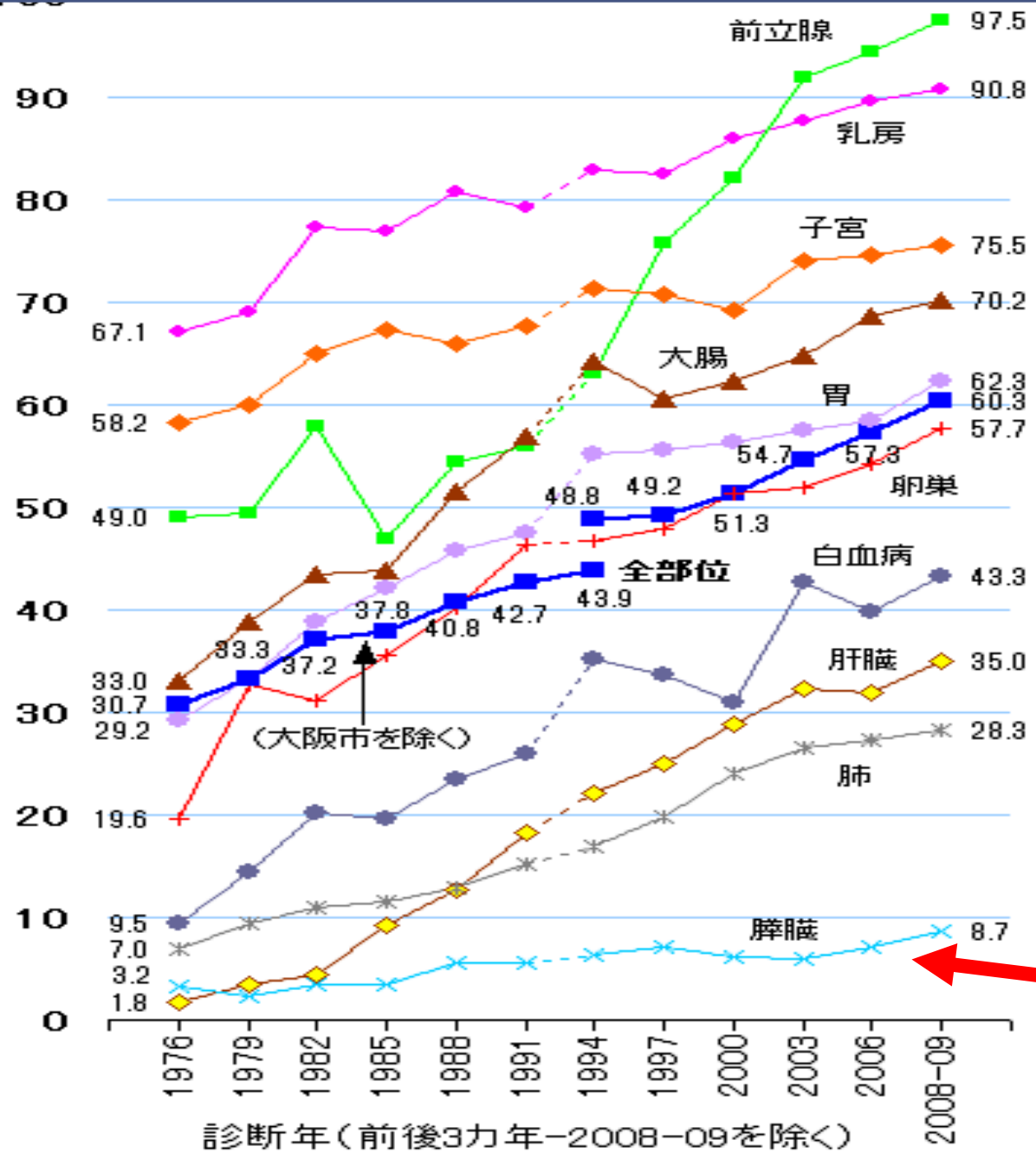
A standing position and future perspective of  
conversion surgery in patients with initially  
unresectable pancreatic ductal adenocarcinoma



Sohei Satoi MD, FACS.

Department of Surgery, Kansai Medical University

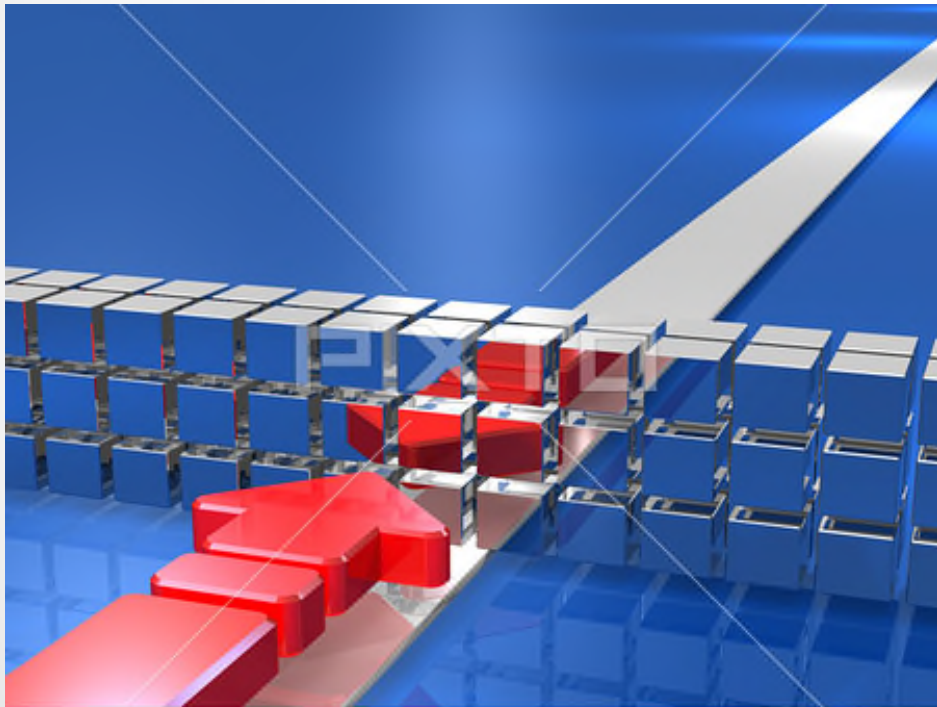
# Cancer Registration in Osaka from 1976 (80<sup>th</sup> 2016 Feb)



5y OS in 2008-09

- Total : 60.3%
- Prostate : 97.5%
- Breast : 90.8%
- Uterus : 76.5%
- Colon : 70.2%
- Stomach : 62.3%
- Ovary : 57.7%
- Leukemia : 43.3%
- Liver : 35.0%
- Lung : 28.3%
- Pancreas : 8.7%

# A Big Wall against PDAC treatments



pixta.jp - 6407828

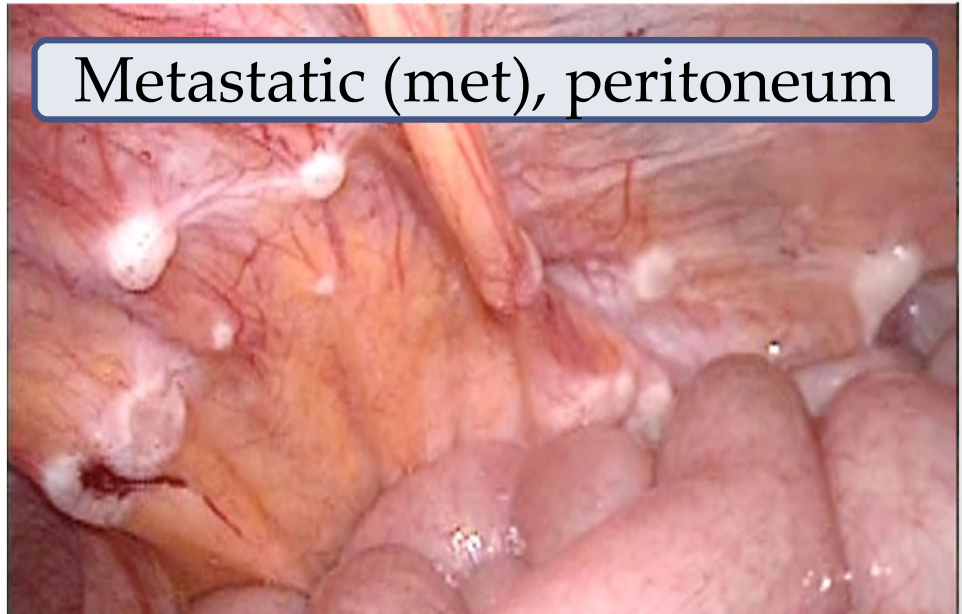
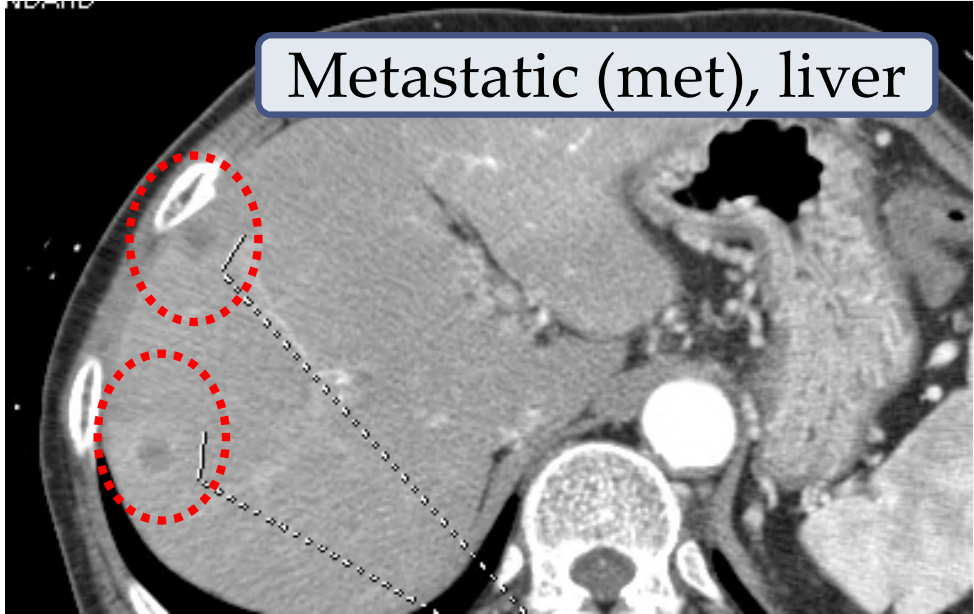
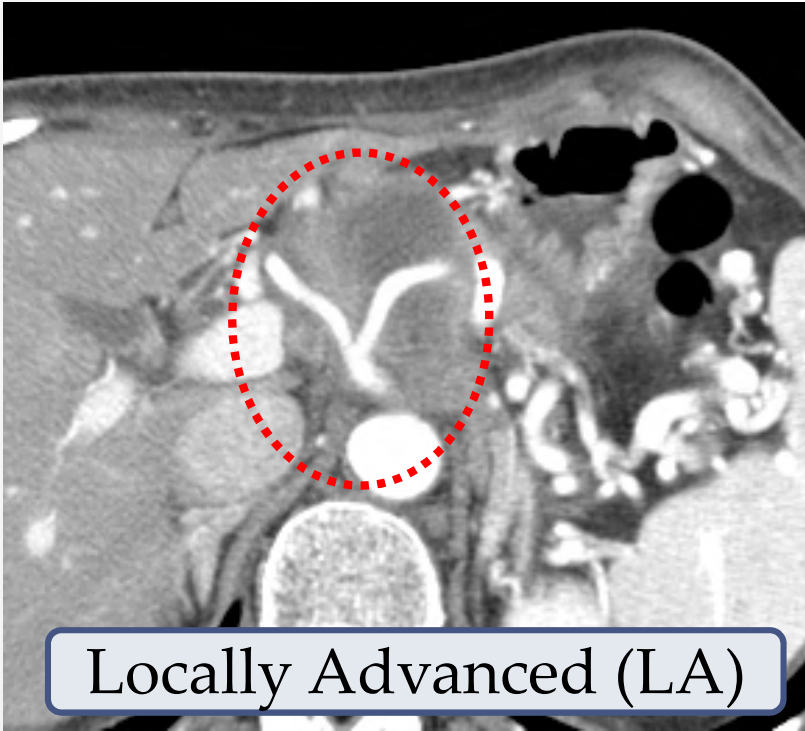
- Anatomical issue  
easy to invade and metastasize

- Tumor issue  
70-80%: Unresectable  
80% of resected pts: stage III

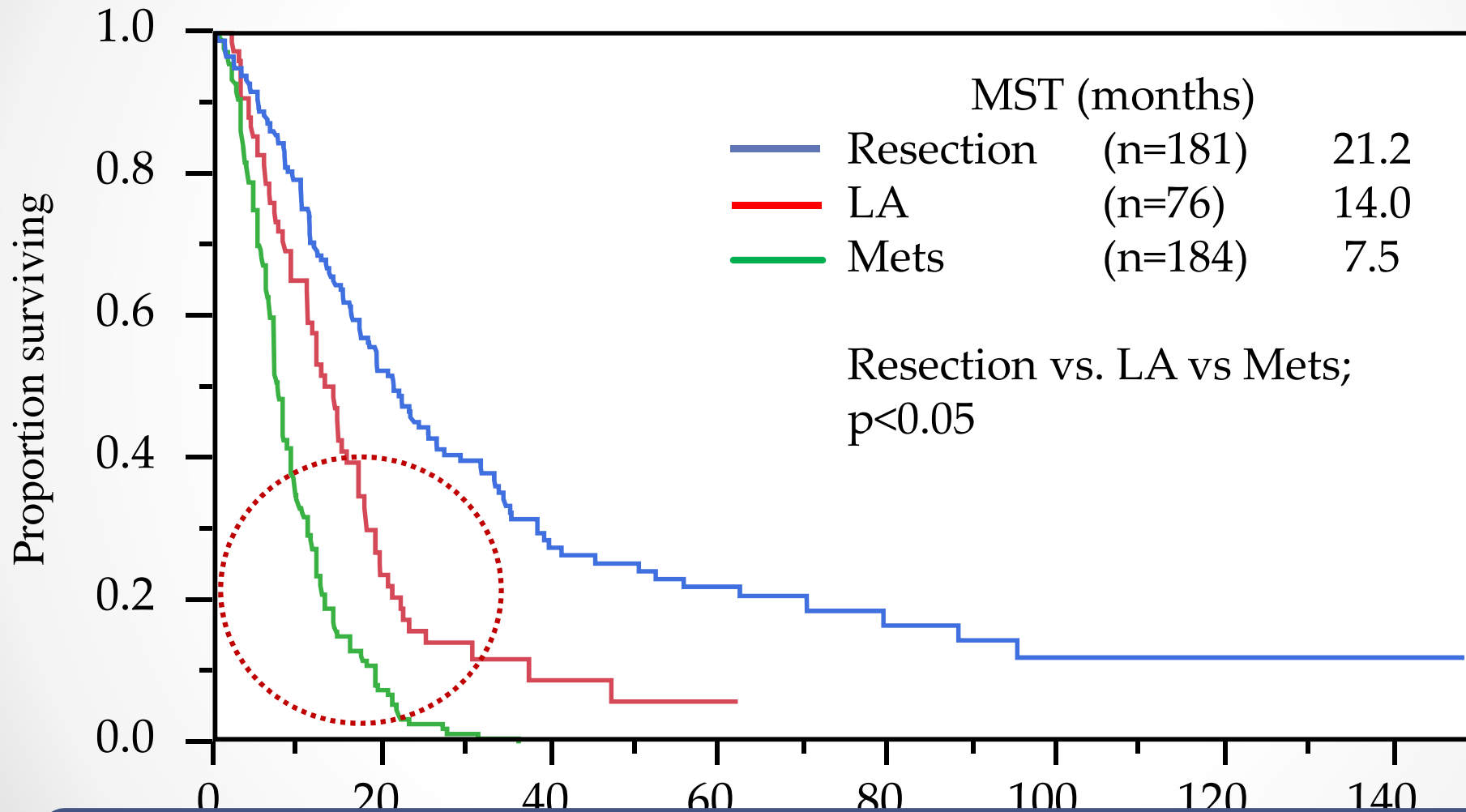
- Treatment issue  
Highly advanced surgery  
High morbidity  
Limitation of CTx use

Implementation of multimodality treatments

# Unresectable (UR)-PDAC



# Pancreatic cancer treatment in KMU (2006-2013 Sep, n=509 (BSC:n=68))



Improvement of prognosis in pts with UR is definitely required

## Recent progress of chemotherapy in patients with UR PDAC

GEM alone: 6-8mo

GEM+erlotinib: 8mo

S-1 alone: 8-9mo

FOLFIRINOX: 12mo

GEM+nab-PTX: 8.5mo

Still palliative but not curative...

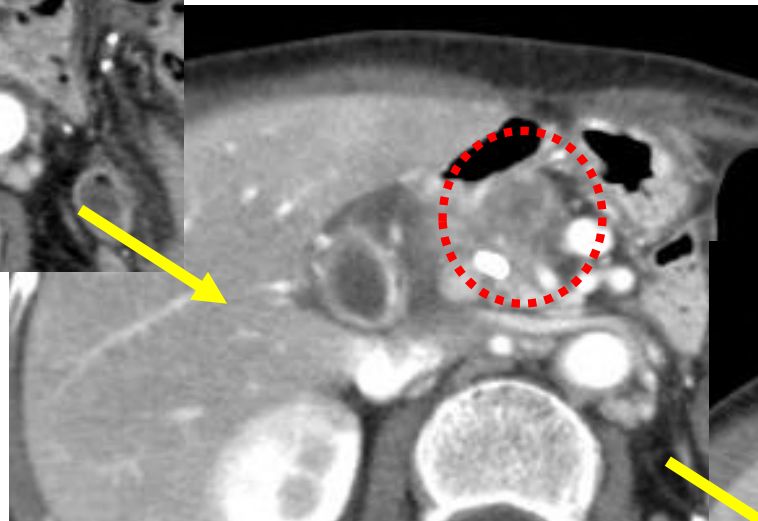
# A Case presentation: CRT/CT using S-1 for 6months

Pre-treatment



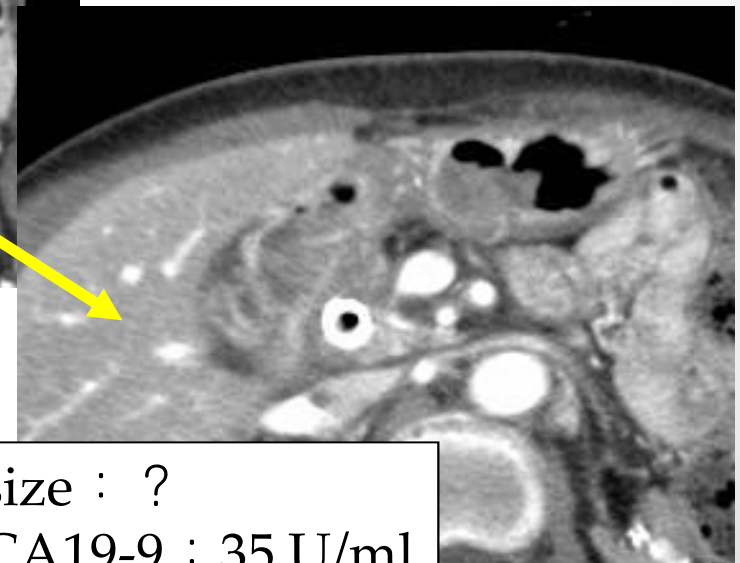
size : 27x24mm  
CA19-9 : 1597 U/ml

After CRT using S-1



size : 22x17mm  
CA19-9 : 604 U/ml

Pre-op

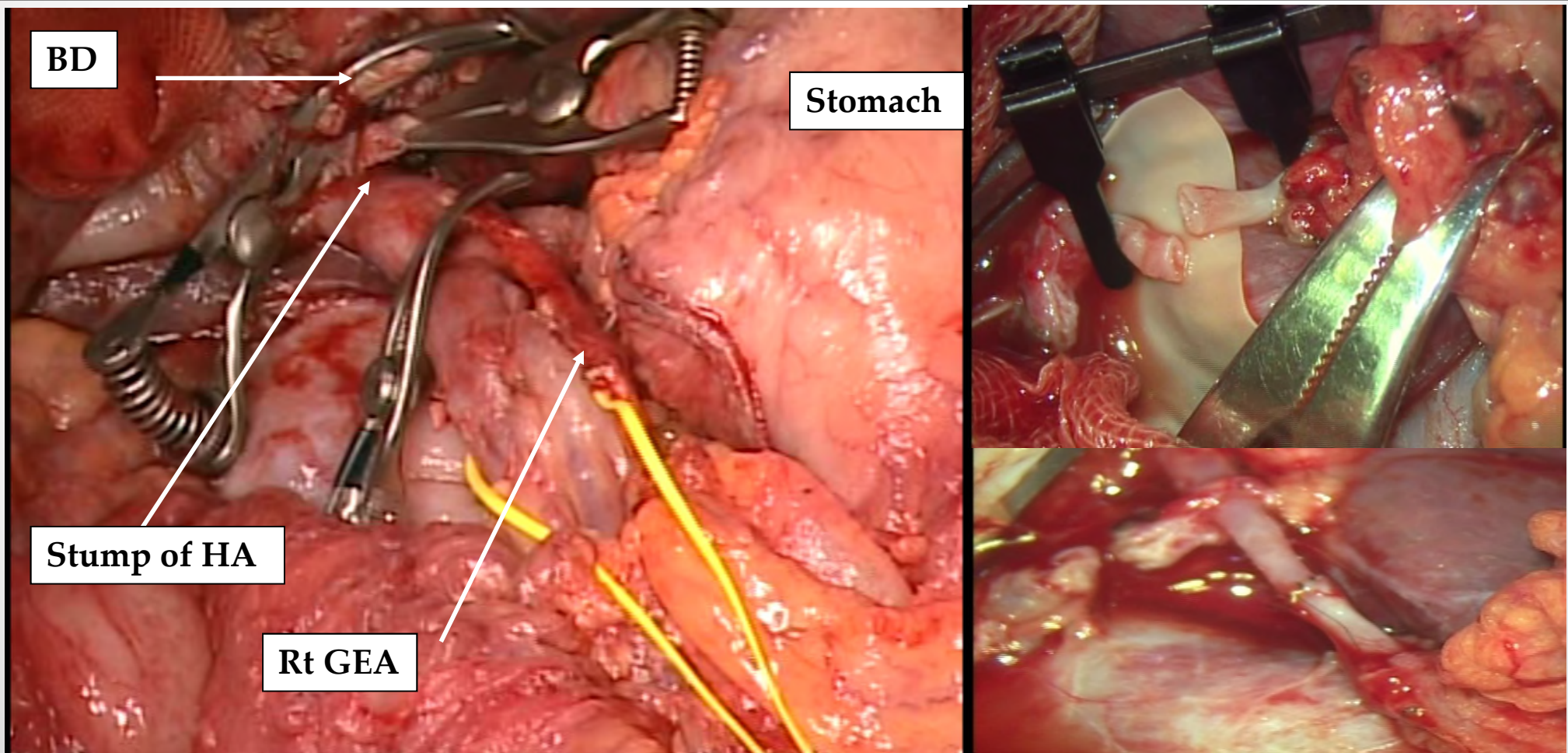


size : ?  
CA19-9 : 35 U/ml

# Conversion surgery at 6months after initial treatment

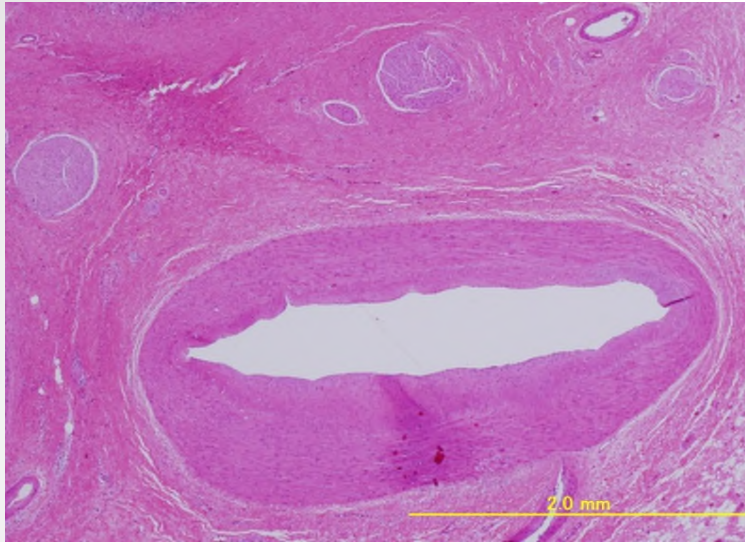
**Total Pancreatectom with PV resection (20mm) and CHA resection (reconstruction using Rt GEA)**

**Op time: 571min, Extent of Blood loss: 1172ml, Blood Tx: RCC 4U**

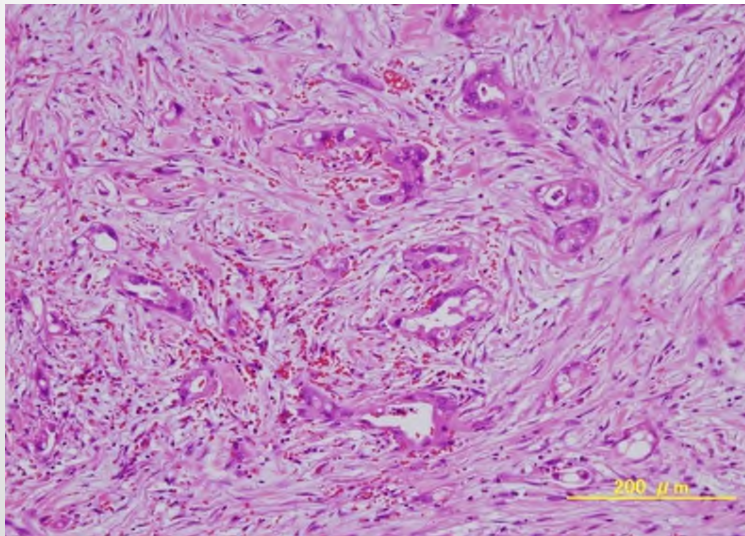




# Pathological findings



**Ph, pTS1, 4x3mm, infiltrative type,  
moderately differentiated tubular adenocarcinoma,  
INF $\gamma$ , Ly1, v1, mpd(-), pCH(-), pDU(-), pS(-), pRP(-),  
pPV(-), pA(-), pPL(-), pBCM(-), pDPM(-), pN0  
EVANS III**



- Stage: T3 to T1
- Tumor size: 4mm
- >90% tumor cell necrosis or degeneration

# Conversion Surgery

“CS” is an additional surgery during multimodality treatment in patients with initially UR-PDAC, but not planned surgery following neoadjuvant therapy in patients with R/BR PDAC.

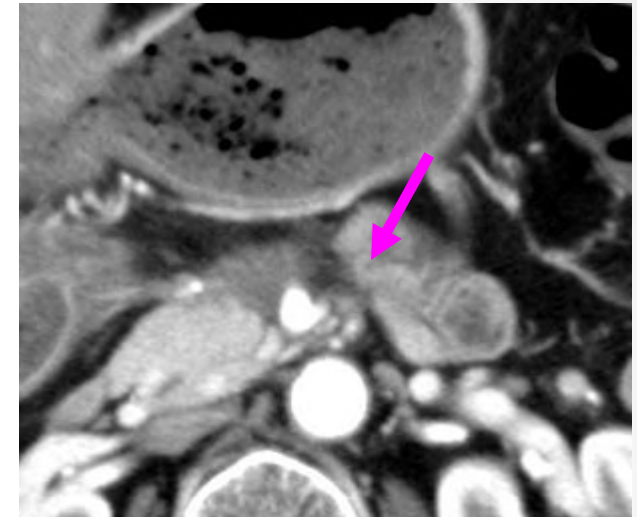
# REQUIREMENTS of conversion surgery

**Tumor**



**SMA7/8 attachment**

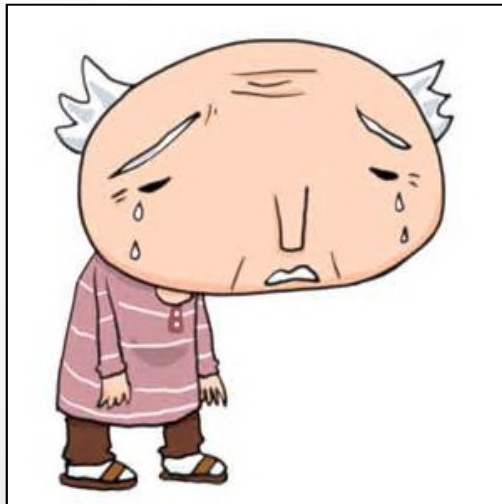
Tumor shrinkage for R0 resection



**SMA1/4 attachment**

Multi-modality therapy

**Host**



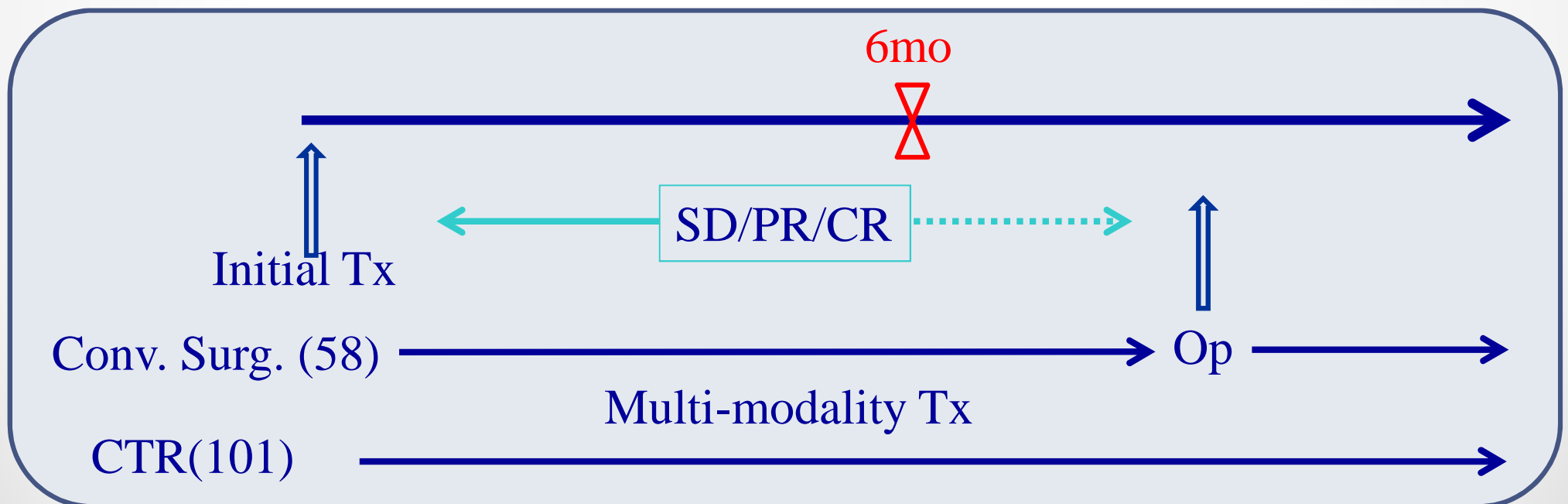
Maintained PS during CTx



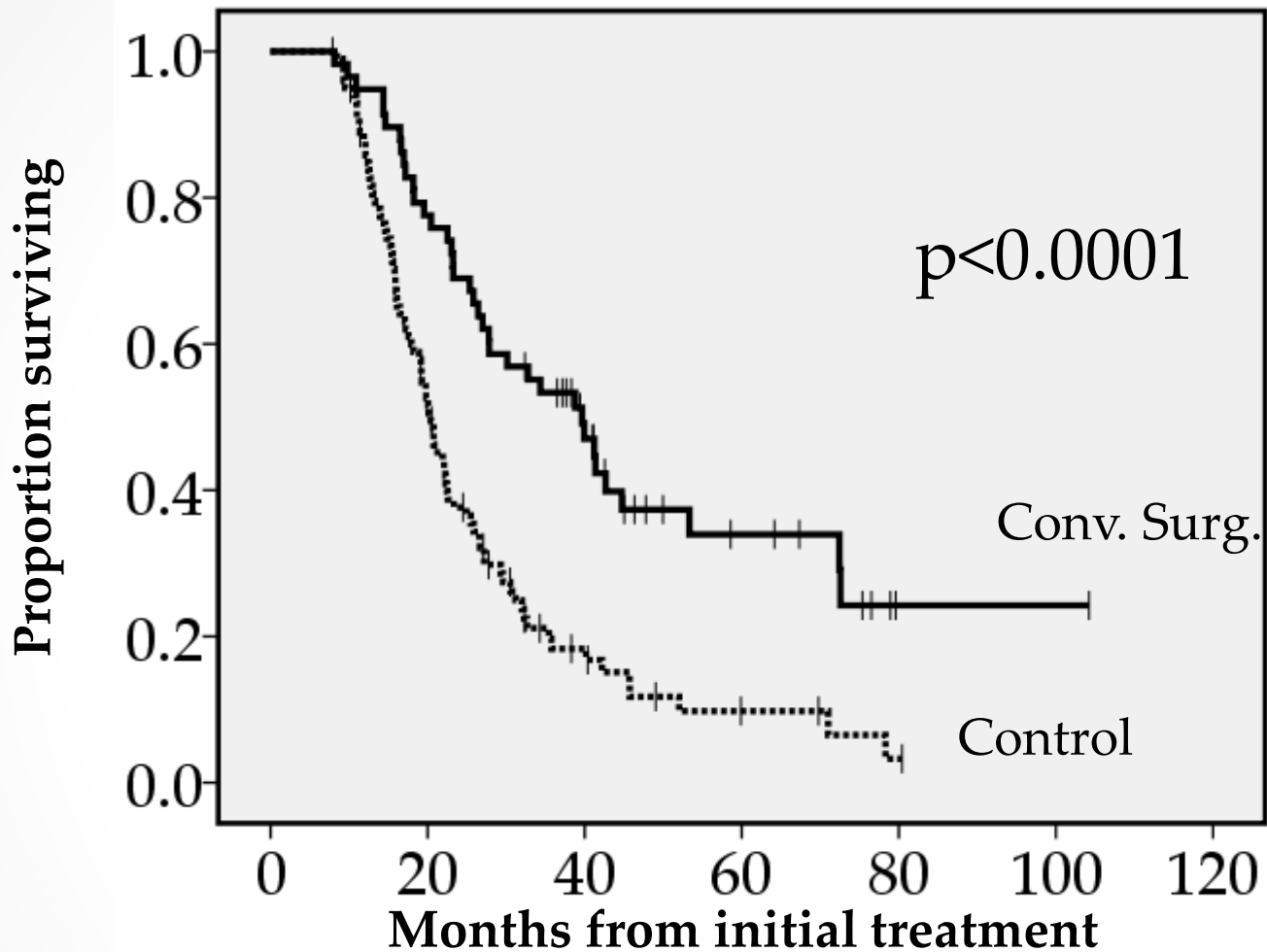
8mo. after initial treatments

**Role of adjuvant surgery for patients with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery**

Satoi S and Yamaue H et al. J Hepatobiliary Pancreat Sci (2013) 20:590–600

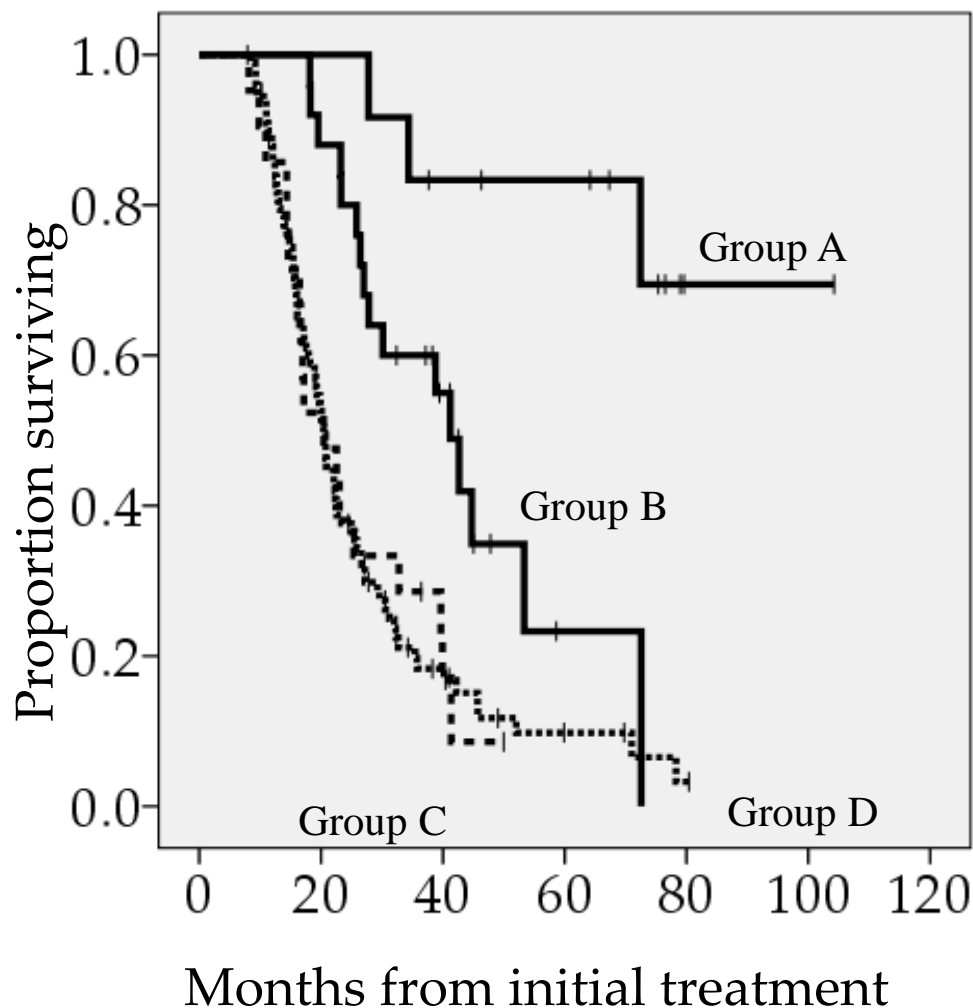


# Survival curves of conversion surgery and control groups from initial treatment



	1y	2y	3y	4y	5y	death	MST	F/U
<u>Conversion surgery (n=58)</u>								
OS (%)	95	69	53	37	34	37/58	39.7	40(8-104)
<u>Control (n=101)</u>								
OS	88	38	18	12	10	83/101	20.8	20(8.5-80)

## Survival curves according to time from initial treatment to surgical resection -Pancreas-01 study of JHBPPS-



	MST (months)
— A: >12mo (12)	not reached
- - B: 8< and ≤12 (25)	41
- - C: 6< and ≤8 (21)	20
... D: control (101)	20

A:  $p < 0.0001$  vs C/D,  $p = 0.003$  vs B  
 B:  $p = 0.002$  vs C,  $p = 0.001$  vs D  
 C:  $p = 0.905$  vs D

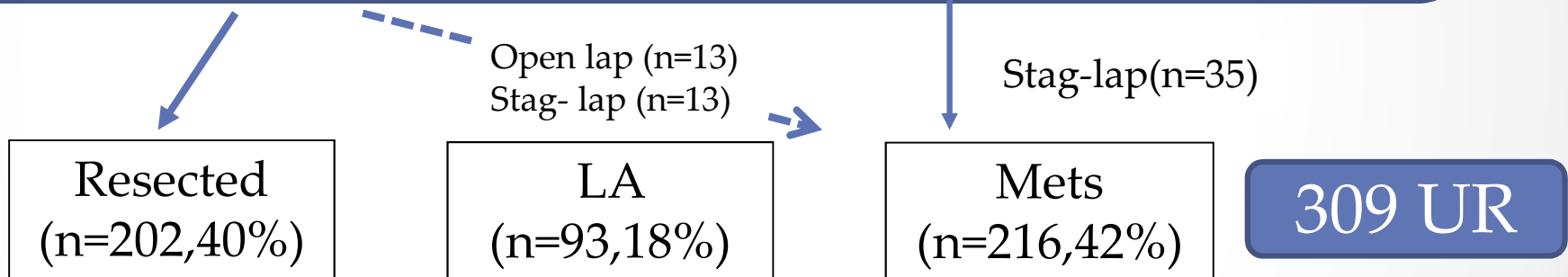
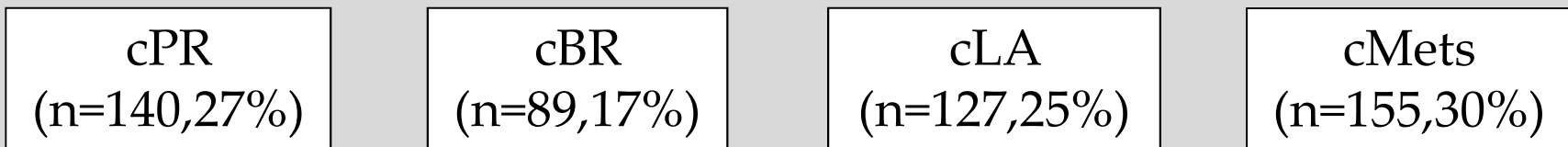
Optimal time for conversion  
surgery may be 8 months

## Review of articles

Institution/year	patients	Regimen	No	RT (%)	resectability (%)	Vascular resection (%)	R0 (%)	NO (%)	MST (mo)
UCLA 2011	LA (stageIII)	multi	41	22	34	6	86	86	52
MSKCC 2012	LA (stageIII)	multi	36	58	36	19	83	83	30
Panc01/2013	LA/mets	multi	58	45	58	69	83	89	40
JH/Pittsburg 2016	mets (stageIV)	FOLFIRINOX GEM-based	23	0	-	13	-	61	34
<b>Interval between initial treatments and conversion surgery &lt; 6months</b>									
Review Lancet2016	LA (stageIII)	FOLFIRINOX	315	57	57	-	74	-	24
Heidelberg 2016	LA/mets	FOLFIRINOX	125	4.8	61	-	41	50	16
		GEM+RT	322	100	47	-	31	58	14.5

# Pancreatic cancer treatments in KMU (2006-2014 Sep, n=579 (incl. BSC:n=68))

ALL patients was assessed with cine-imaging of MDCT



n=39 (42%)      n=39 (18%)

Long PR/SD (more than 8 months), n=78 (25%)

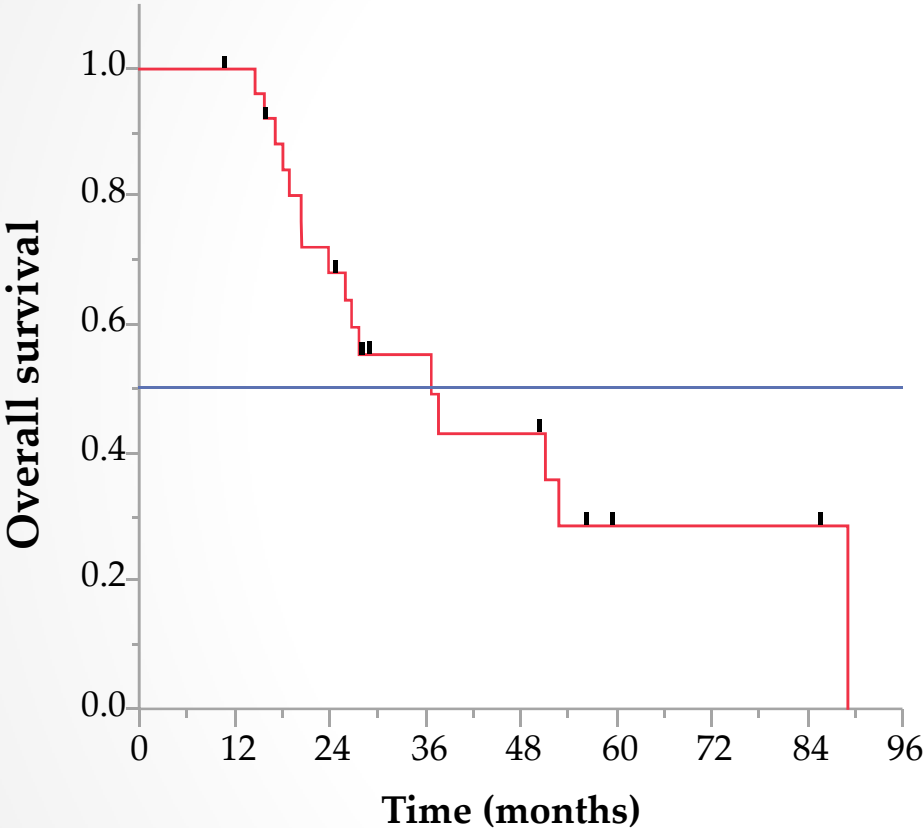
Conversion Surgery, n=22; 7% incl.  
16LA (17%) /6mets (2.8%)

Non-Surgery, n=56



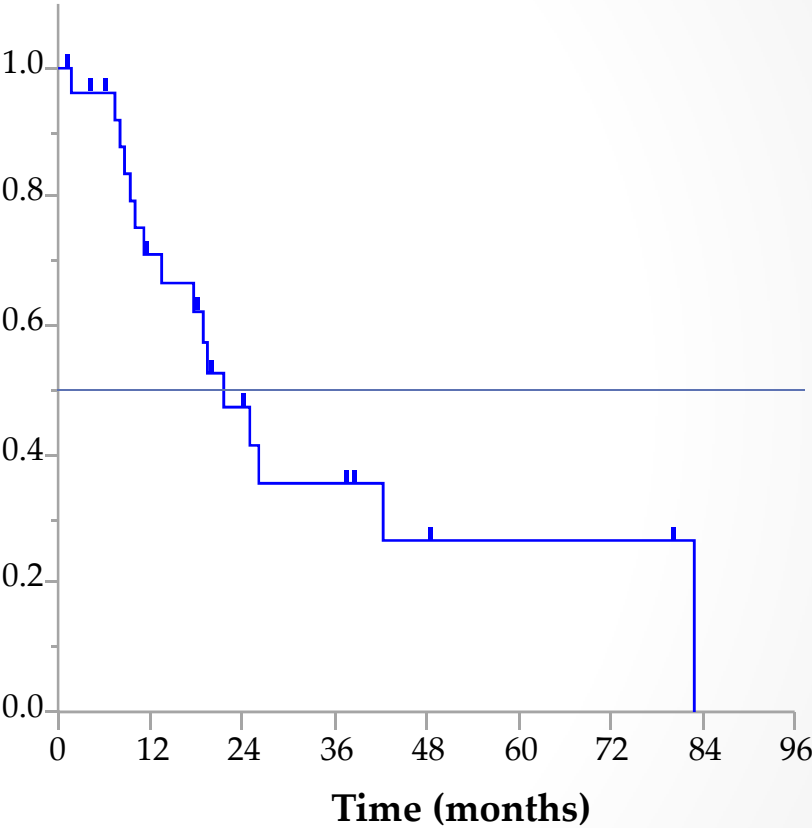
# OS in Conversion surg (n=27, 2006-2017)

From Initial Treatment



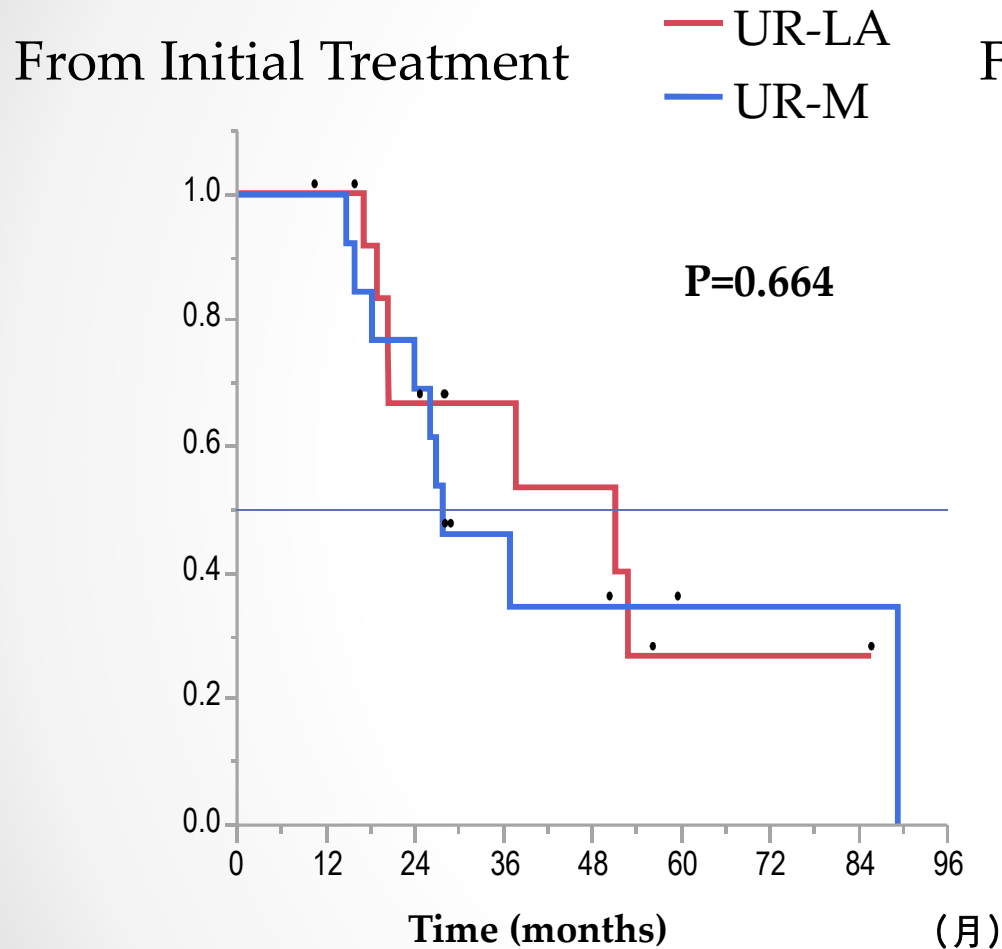
**MST: 36.9 months**

From Conversion Surgery

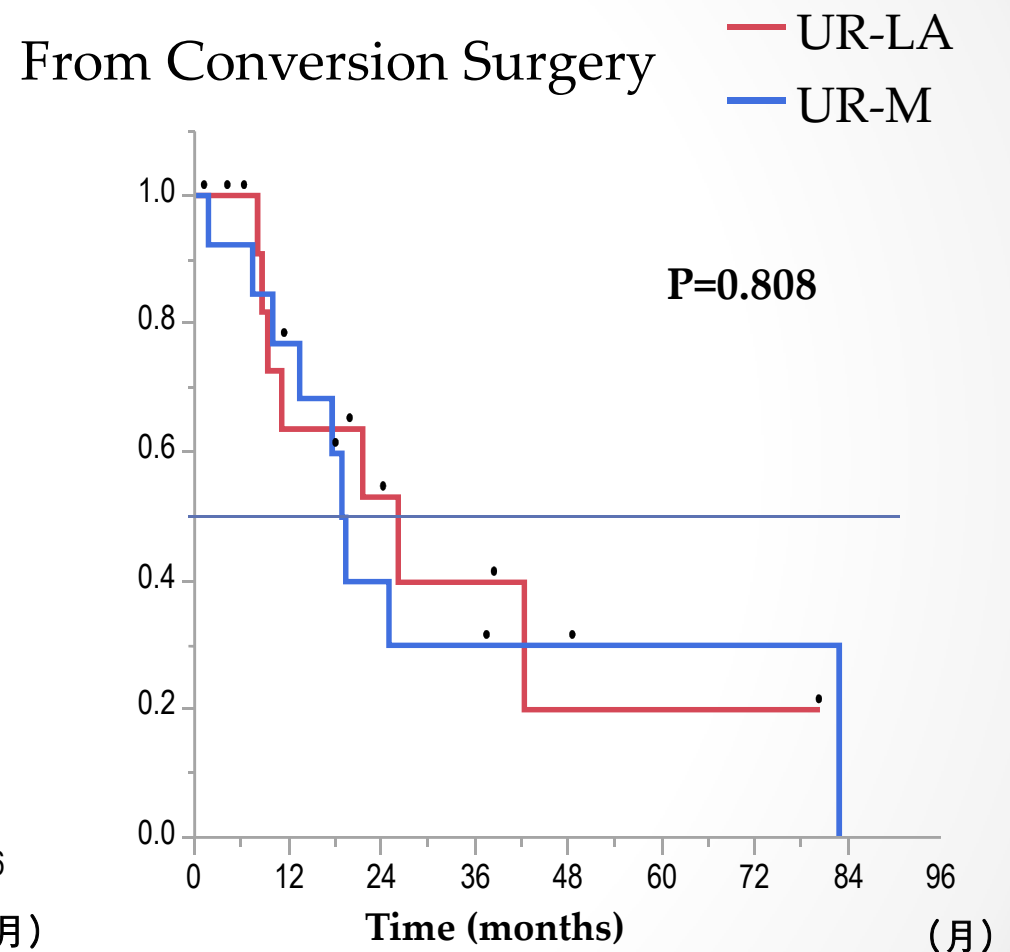


**MST: 21.6 months**

# UR-LA (n=13) vs UR-M(Met/CY) (n=14)



	MST(months)
UR-LA	51.2
UR-M	27.8

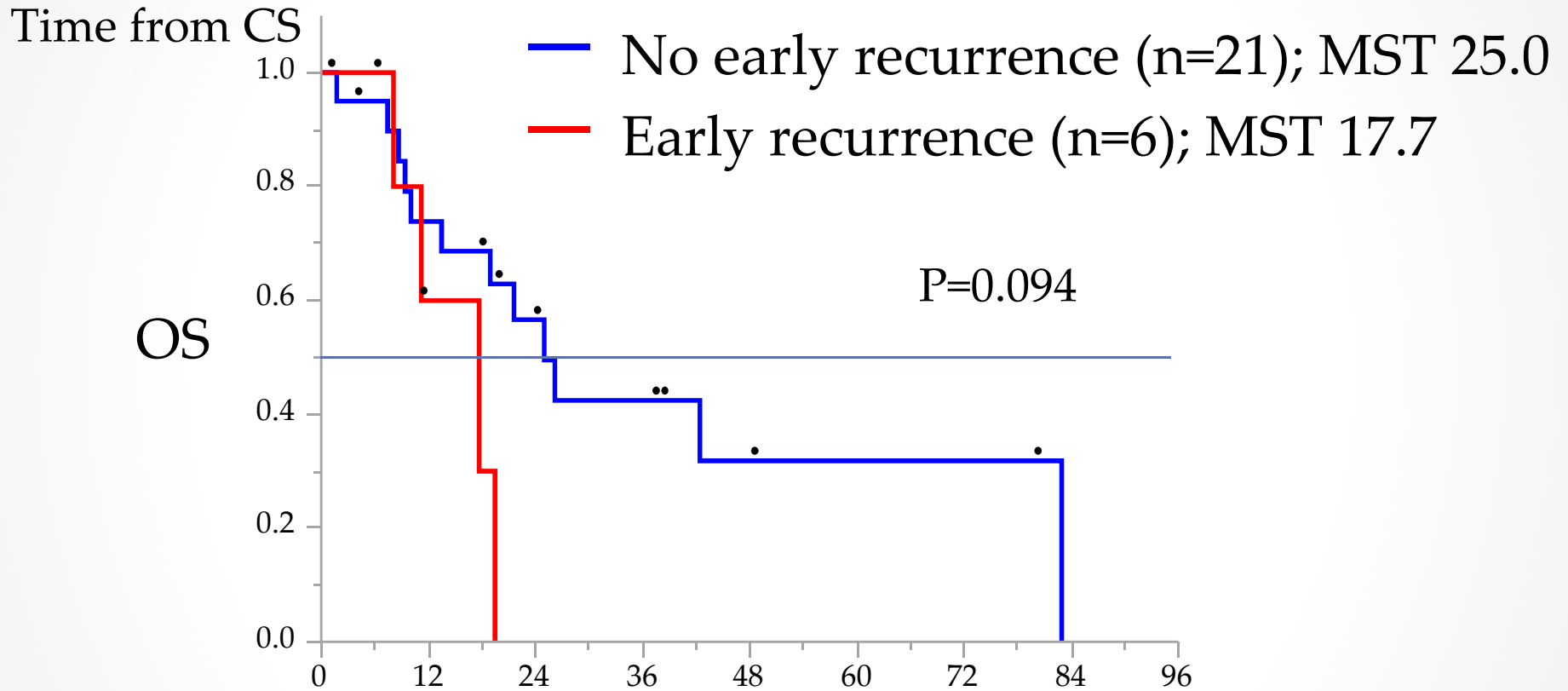


	MST(months)
UR-LA	26.2
UR-M	18.9

# Early recurrence (within 6mo): 6/27 (22%)

localization :size (mm)	Reason for UR	Initial Tx	Time to surg	CA19-9	Op	Evans	T (JPS6th)	N (JPS6th)	Time to recur	Site of recur.
Pb:37	LA (CHA/SMA)	GS+RT	11	126 →48	TP	I	4	0	3	L
Pbt:35	LA (CA/SMA)	GS	6	1325 →105	DP	II a	4	0	3	P
Pbt:43	Peritoneum	S1+PTXiv/ip	8	1464 →69	DP	II a	4	1	5	L
Pbt:74	Peritoneum	GS+PTXip	8	9 →8	DP	II a	3	1	6	P
Pbt:45	Liver mets	GEM+nabP	17	571 →7	DP	IV	0	0	6	L
Pbt:35	LA(CHA/CA/S MA)	GEM+nabP	18	8 →8	DP-CAR	II b	3	0	5	Local

# OS between Early recurrence and not



23 PDAC pts with mets (L;16, Lung; 6, P; 2) between 2006-13  
MST; 34.1 months

Early recurrence within 6 months: 7/23 (30.4%)

## Surgical indication of “conversion surgery”

- Tumor remission downsized to BR or R, (UR)
- Decreased tumor marker
- Maintained performance status
- At least 8 months between an initial treatment and planned surgery\*

# 膵癌術前治療研究会 (PREP)

Study group of **PRE**-operative therapy  
for **P**ancreatic cancer (**PREP**) since 2010



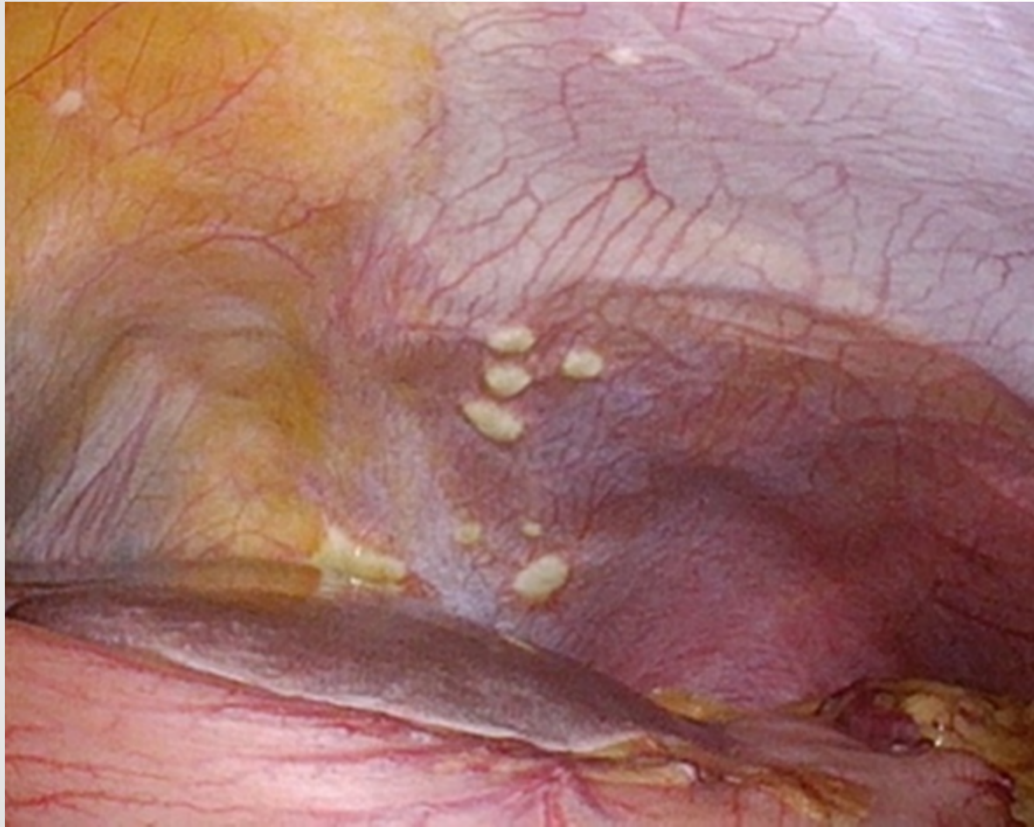
<http://www.surg1.med.tohoku.ac.jp/society/index.html>

Organizer Univ. of Tohoku **Michiaki Unno**



- PREP-01: GS NAC phase II study
- PREP-02: GS NAC vs Surgery first (PhaseII/III)
- PREP-03: S1+RT for BR
- PREP-04: Prospective cohort study of conversion surgery

# UR-M-PDAC



Metastatic (met)

## Clinical Issues on PDAC Patients with Peritoneal Carcinomatosis

- Difficulty of accurate diagnosis
- High frequency of ascites during CTx.
- No effective systemic CTx.



Satoi S World J Surg Oncol. 2016

Intra-peritoneal (i.p.) chemotherapy  
high drug concentration in the peritoneal cavity which  
can directly contact the tumor nodules.



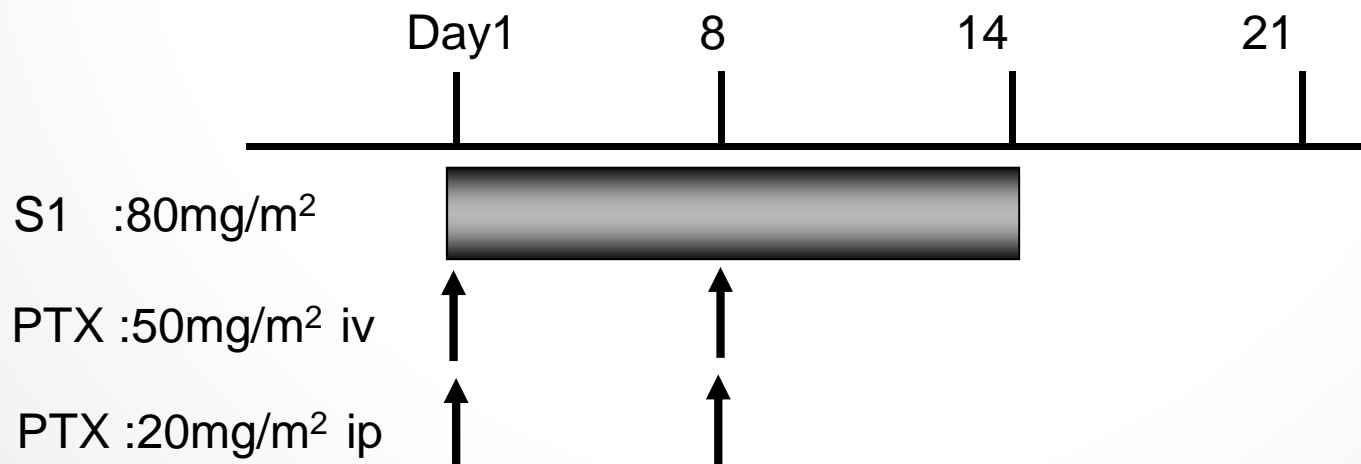
# S1+ iv/ip PTX therapy for patients with peritoneal mets

## Eligibility criteria :

1. pathologically evidenced PDAC
2. laparoscopically diagnosed positive cytology or peritoneal dissemination in patients with radiographically defined locally advanced PDCA
3. open laparotomy-diagnosed peritoneal dissemination in patients with R/BR status

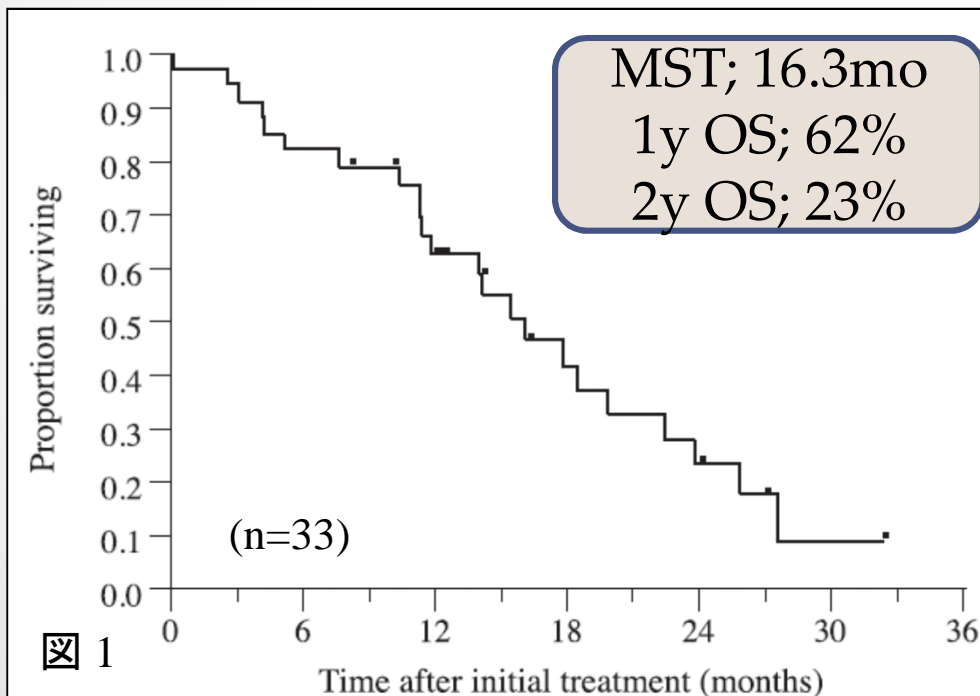
## Exclusion criteria

1. no other sites of occult distant organ metastasis such as liver, lung and so on.
2. Patients with R/BR who had positive cytology on laparotomy

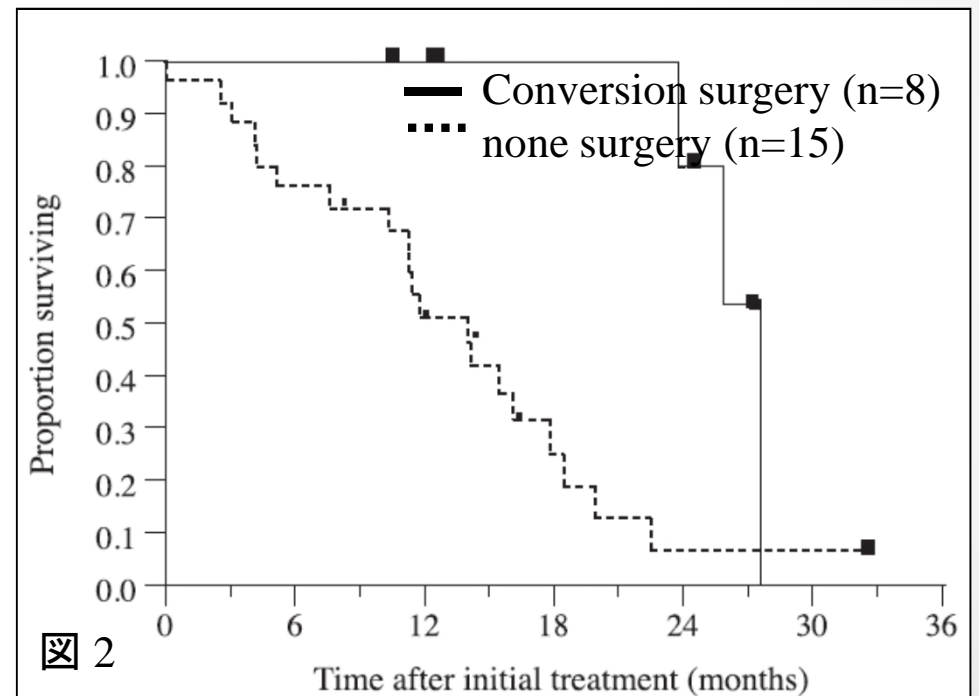


# Multicenter Phase II Study of Intravenous and Intraperitoneal Paclitaxel With S-1 for Pancreatic Ductal Adenocarcinoma Patients With Peritoneal Metastasis

OS in 33 PDAC patients with peritoneal mets



OS in conv. surg (n=8) vs. none (n=25)



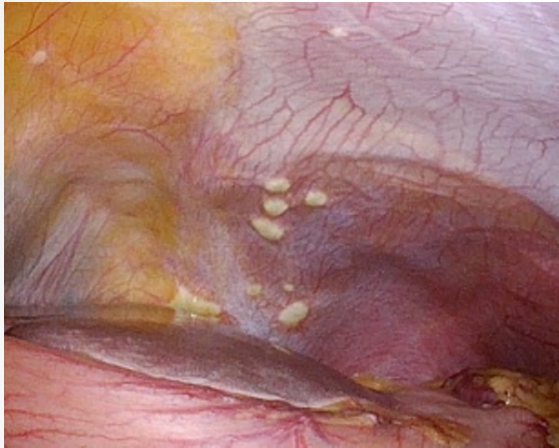
PR: 36%  
Negative CY; 55%

Satoi S, Fujii T, et al. Ann Surg 2017

# The first and second-look staging laparoscopy

Pre

lt sub-phrenic



Sampling: adenoca.

rt sub-phrenic



Sampling: adenoca.

rt sub-phrenic



Multiple peritoneal nodules

2nd look staging-lap

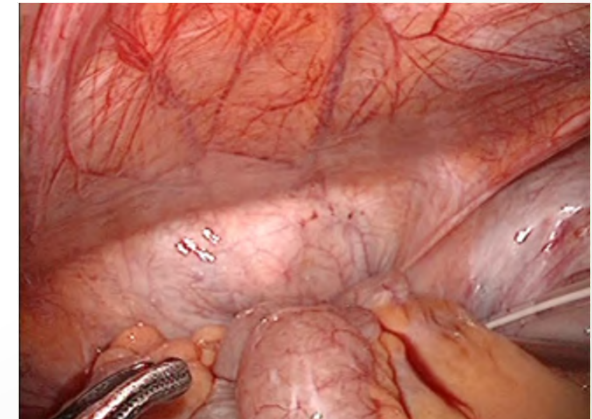
lt sub-phrenic



rt sub-phrenic



Douglas' pouch



## Review of articles (UR-M)

Intsituation /year	subje ctives	Regime n	No	Resectab ility (%)	R0 (%)	N0 (%)	Time from intial Tx to surgery (m)	MST(m ) from surgery	MST(m) from initial Tx
Wright 2016 <sup>15</sup>	M	FFX/ GEM	1147	2.0	91	61	9.7	18.2	34.1
Satoi/Fujii 2017 <sup>16</sup>	PM	S-1+iv/ip PTX	33	24	75	50	9.5	-	26
Frigerio 2017 <sup>17</sup>	M	FFX/ GEM	24/535	4.5	88	63	10	13	56
KMU	UR- LA	various	13	(17)	92	85	11.2	26.2	51.2
	UR-M	various	14	(2.8)	86	36	9.9	18.9	27.8

PM, peritoneal metastasis

# Treatment Algorithm of UR-LA PDAC

UR-LA on CT/MRI

Staging lap.

UR-LA (40%)

GnP  
FOLFIRINOX  
(+RTx)

17%

Peritoneal mets  
(40%)

S-1+iv/ip PTX

24%

Liver mets (20%)

GnP  
FOLFIRINOX  
etc.

2.8%

Conversion surgery

## Take Home Messages

- Conversion surgery can be the important key to open the door for improving long-term survival in patients with UR-PDAC.
- Staging lap is necessary for patient selection in patients with LA-PDAC.
- S-1+ iv/ip PTX therapy may be promising option in pts with peritoneal mets in terms of improved OS and high rate of conversion surgery.
- An appropriate regimen of chemotherapy and measure of tumor remission, surgical indication, optimal time of conversion surgery, and extent of surgical resection are still under investigation

## Conclusion

Conversion surgery can be the important key to open the door for improving long-term survival in patients with unresectable PDAC. Sustainable efforts are warranted to conduct a decently designed clinical trials to confirm efficacy of conversion surgery in the subset of patients with initially UR-PDAC.

Many Thanks for your kind attention  
Please come, see and enjoy our pancreatic surgery in KMU!!!

## Kansai Medical University and Hospital

### 枚方新キャンパス

関西医科大学は分散している牧野・滝井学舎を統合し、「エコ&グリーン」を基本コンセプトとして平成25年4月附属枚方病院の隣接地で生まれ変わります。

もっと詳しくはこちら



[satoi@hirakata.kmu.ac.jp](mailto:satoi@hirakata.kmu.ac.jp)





# Clinical Characteristics of Patients Who Underwent Conversion Surgery

	Age/ Gender	Locatio n/Size	Reason for UR	CA19-9 (IU/L)	Time to surgery (months)	Type of surgery	R	Evans	TNM staging		
									T	N	M
1	69/M	Pbt/43	LA/P	1464→69	8	RAMPS	0	Ila	3	1	0
2	60/F	Pb/35	LA/CY+	150→16	9	DPCAR(PV)	0	Ila	3	1	0
3	75/M	Pt/44	LA/P	598→74	10	RAMPS	1	Ila	3	1	0
4	50/F	Pb/25	LA/P	1164→17	12	mDPCAR(PV)	0	I <b>lb</b>	3	1	0
5	74/F	Ph/48	LA/CY+	3400→13	13	TP(PV)	0	I <b>lb</b>	3	0	0
6	73/M	Pt/22	PR/P	106→70	10	DP	1	Ila	3	1	0
7	73/F	Ph/34	LA/CY+	175→21	8	PD(PV)	0	Ila	3	0	0
8	67/M	Pt/26	PR/P	26→24	8.5	Lap-DP	0	Ila	3	1	0

# Locally Advanced Pancreatic Cancer

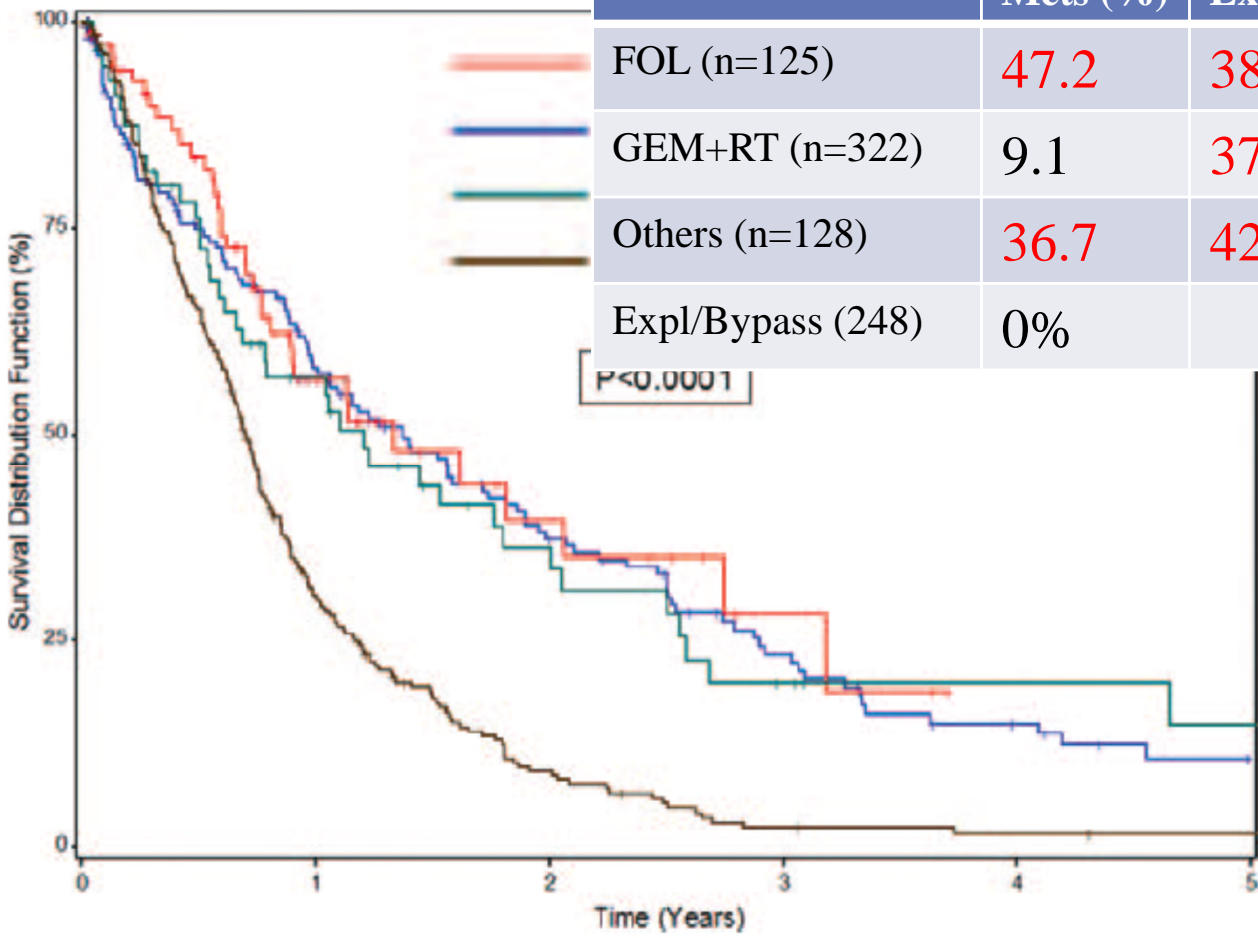
## Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients

Thilo Hackert, MD,\* Milena Sachsenmaier,\* Ulf Hinz, MSc,\* Lutz Schneider, MD,\*  
 Christoph W. Michalski, MD,\* Christoph Springfield, MD,† Oliver Strobel, MD,\* Dirk Jäger, MD,†  
 Alexis Ulrich, MD,\* and Markus W. Büchler, MD\*

Ann Surg 2016;264:457–463

OS after resection

575 pts (2001-2015)	Reason for UR: Mets (%)	UR confirmation; Exploration	Resectability	R2 rate	MST (mo)	3-y OS (%)
FOL (n=125)	47.2	38%	61%	0	16.0	28.1
GEM+RT (n=322)	9.1	37%	47%	8.0	16.5	23.2
Others (n=128)	36.7	42%	52%	6.0	14.5	19.7
Expl/Bypass (248)	0%		0%	6.5	6.5	2.4



Folfirinox seems to be the most effective protocol resulting in a significantly better secondary resection rate and overall survival than other treatments.