

# Are we making progress in surgery of the pancreas?

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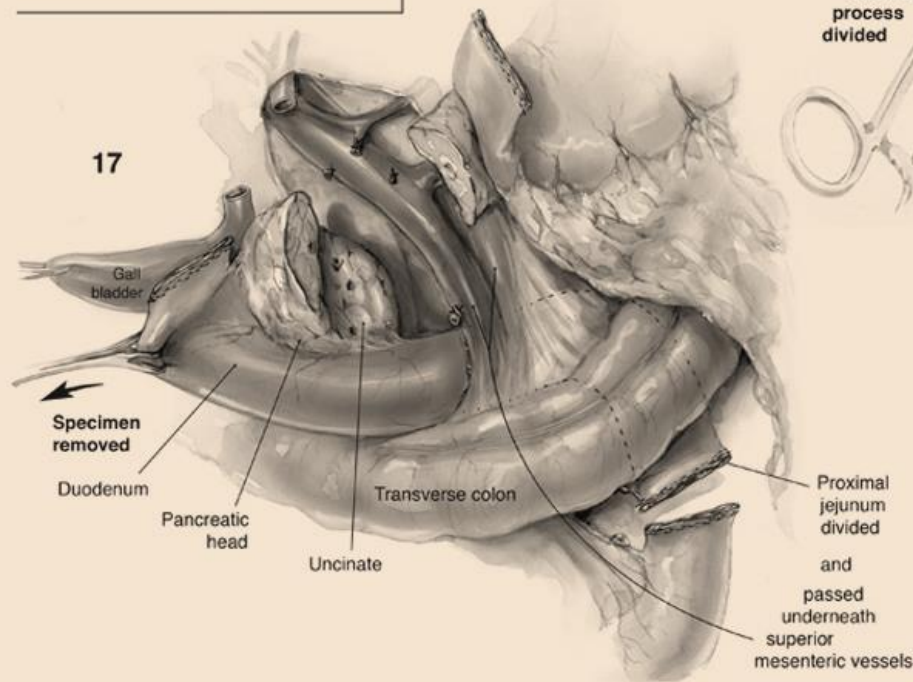
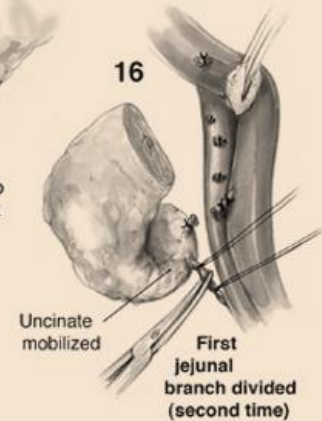
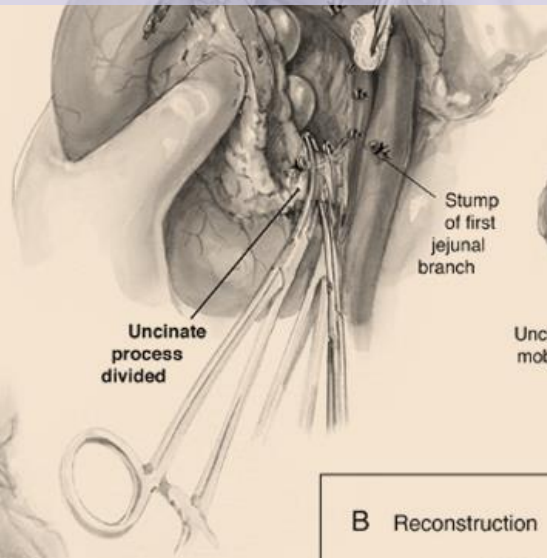
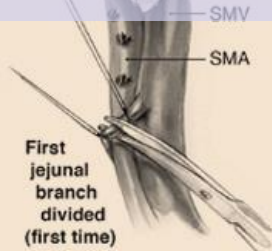
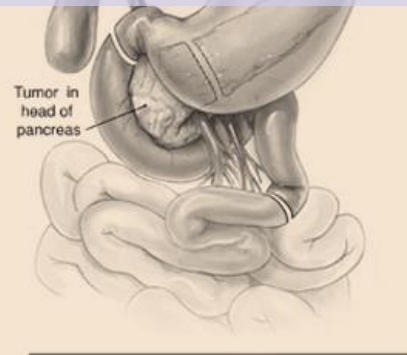


# Conflict of interest

- None, but to be a surgeon
- I will try to limit my talk to surgical aspects in relationship to oncological matter

# A little of history (1)

## Milestone in pancreatic surgery : Whipple Procedure



# A little of history (1)

## Milestone in pancreatic surgery : Whipple Procedure

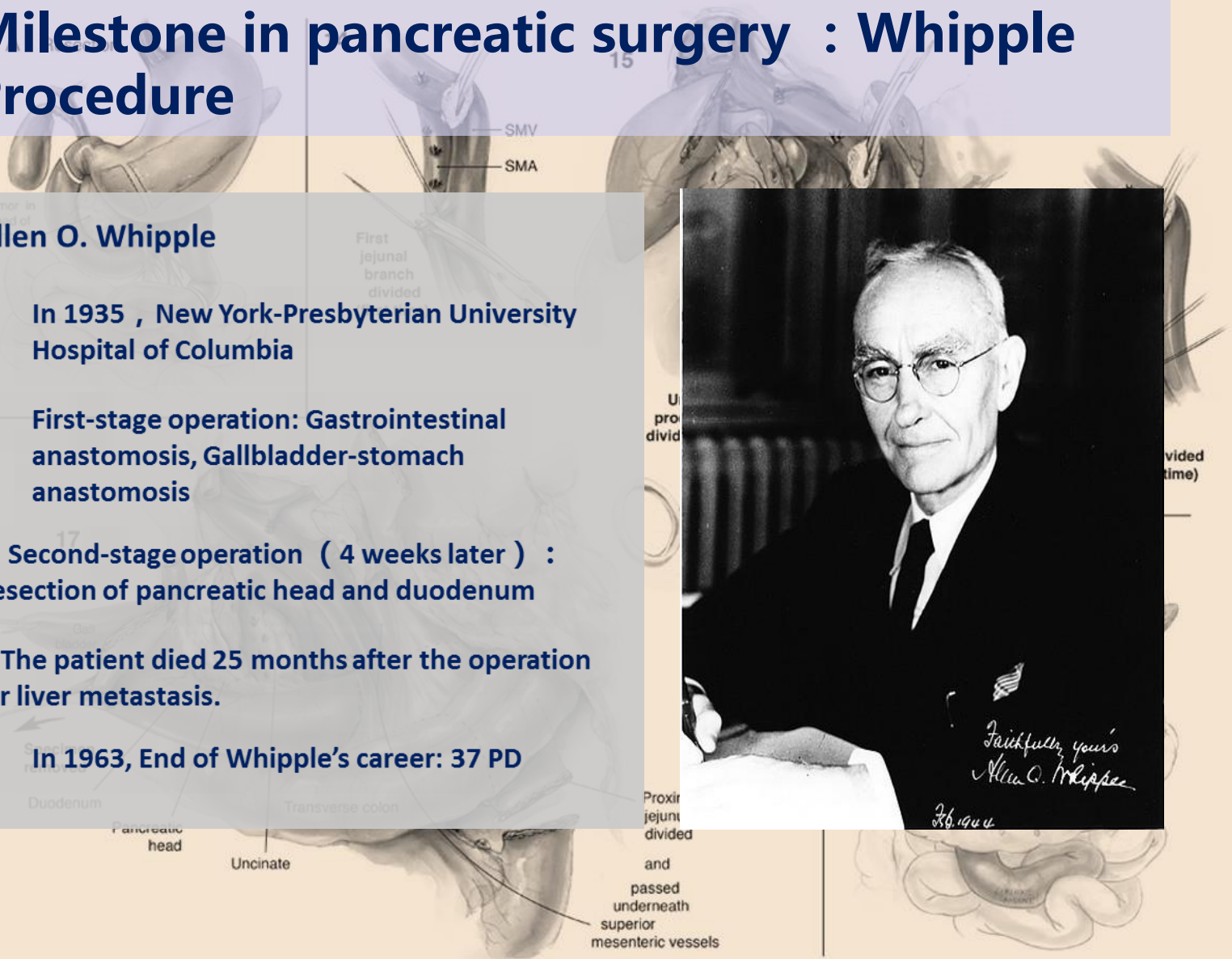
### Allen O. Whipple

- In 1935 , New York-Presbyterian University Hospital of Columbia
- First-stage operation: Gastrointestinal anastomosis, Gallbladder-stomach anastomosis

Second-stage operation ( 4 weeks later ) :  
Resection of pancreatic head and duodenum

The patient died 25 months after the operation  
for liver metastasis.

- In 1963, End of Whipple's career: 37 PD



**A pancreatic surgeon was a pioneer**

# A little of history (2)

## One Thousand Consecutive Pancreaticoduodenectomies

John L. Cameron, MD, Taylor S. Riall, MD, JoAnn Coleman, RN, CRNP, and Kenneth A. Belcher, PA

**Objective:** To trace the evolution of pancreaticoduodenectomy from the decade of the 1960s through the first decade of the new Millennium, through the experience of one surgeon doing 1000 consecutive operations.

**Summary Background Data:** A regional resection of the head of the pancreas was first performed successfully by Kausch in 1909. The operation was popularized by Whipple in 1935, who reported 3 pancreaticoduodenectomies. Because of a hospital mortality of approximately 25%, the operation was performed infrequently until the 1980s. From the 1980s on, experience with this complex alimentary tract operation increased, and high-volume centers developed. This resulted in a significant drop in hospital mortality and allowed institutions and individuals to gain large experiences.

**Methods:** Between March 1969 and May 2003, 1000 consecutive pancreaticoduodenectomies were performed by a single surgeon. A retrospective review of a prospectively maintained database was performed to determine the management and outcome of these patients, as well as to document the evolution of this operative procedure over 5 decades.

**Results:** The median operative time decreased significantly over the decades, being 8.8 hours in the 1970s and 5.5 hours during the 2000s. Postoperative length of stay dropped from a median of 17 days in the 1980s to 9 days in the 2000s. There were only 10 postoperative/hospital deaths, for a mortality of 1%. A total of 405 patients underwent pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas. Overall 5-year survival was 18%; for the lymph node-negative patients, it was 32%; and for node-negative, margin-negative patients, it was 41%.

**Conclusions:** Pancreaticoduodenectomy has become a commonly performed operation in many tertiary care centers. Operative time, blood loss, and length of stay have dropped substantially. The operation has become safe, with a low hospital mortality. It has become an effective operation for pancreatic cancer in those patients in whom their tumor is margin negative and node negative.

(*Ann Surg* 2006;244: 10-15)

The first successful local resection of a periampullary tumor was performed by Dr. William Stewart Halsted in 1898.<sup>1</sup> The patient was a 58-year-old woman with obstructive

jaundice. Halsted resected a segment of the second portion of the duodenum, including the tumor, and anastomosed the duodenum end to end. He then reimplemented the bile and pancreatic ducts. The first successful regional resection for a periampullary tumor was performed by the German surgeon from Berlin, Kausch, in 1909, and reported in 1912.<sup>2</sup> The regional operative procedure for periampullary tumors was popularized by Whipple in a paper published in 1935.<sup>3</sup> In this paper, 3 patients were reported who underwent regional resection performed in 2 stages. Two of the 3 patients survived. Between 1912 and Whipple's report in 1935, a small number of patients in Europe underwent a regional resection of a periampullary tumor successfully. Following Whipple's report, the operative procedure became widely known but was still infrequently performed. By the end of Whipple's career, he had only performed 37 such procedures.<sup>4</sup>

During the 1960s and 1970s, few pancreaticoduodenectomies were performed because of a hospital mortality in the range of 25%. However, during the 1980s and 1990s, experience performing pancreaticoduodenectomy increased, and large volume "centers of excellence" developed. These high-volume centers acquired a substantial experience, and mortality decreased to below 5%.<sup>5-8</sup> In recent years at the Johns Hopkins Hospital, more than 200 pancreaticoduodenectomies have been performed annually. This has allowed individual surgeons to develop significant experiences. Between 1969 and 2003, 1000 consecutive pancreaticoduodenectomies were performed by a single surgeon (J.L.C.) at the Johns Hopkins Hospital. This report reviews that experience and documents the changes that have occurred with this operative procedure over 5 decades.

### Clinical Material

Between March 1969 and May 2003, 1000 consecutive pancreaticoduodenectomies were performed by a single surgeon. One was performed in the decade of the sixties, 2 in the 1970s, 63 in the 1980s, 587 during the 1990s, and 347 during the first 3.5 years of the new millennium. Ages ranged from 15 years to 103 years. Mean age was 63.4 years. Seventy patients were in their 80s, one in the 90s, and one patient was 103 years old. A total of 549 were male, and 451 were female. A total of 652 patients had a periampullary adenocarcinoma (pancreatic 405, ampullary 113, distal cholangiocarcinoma 95, duodenal 39) (Table 1). Eighty-nine patients had chronic pancreatitis, 57 patients had neuroendocrine tumors, and 47 patients had adenomas involving their ampulla or duodenum. The remainder had a variety of neoplasms, many were cystic tumors, and in recent years there has been an increasing number of patients with intraductal papillary mucinous neoplasms

## 1969 -2003

### 1000 PD/a single surgeon

1 - 1960s, 2 - 1970s,  
63 - 1980s, 587 - 1990s,  
347 - 2000~2003

The median operative time  
1970 - 8.8 hours / 2000s- 5.5 hours

Postoperative stay  
1980s - 17 days / 2000s - 9 days

Postoperative mortality 1%

Overall 5-year survival 18%,  
lymph node-negative - 32%,  
Node negative, Margin negative - 41%

From the Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD.

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**March 2012**



**A little of history (2)**

**Pancreatic surgeons as pilots of F1!**

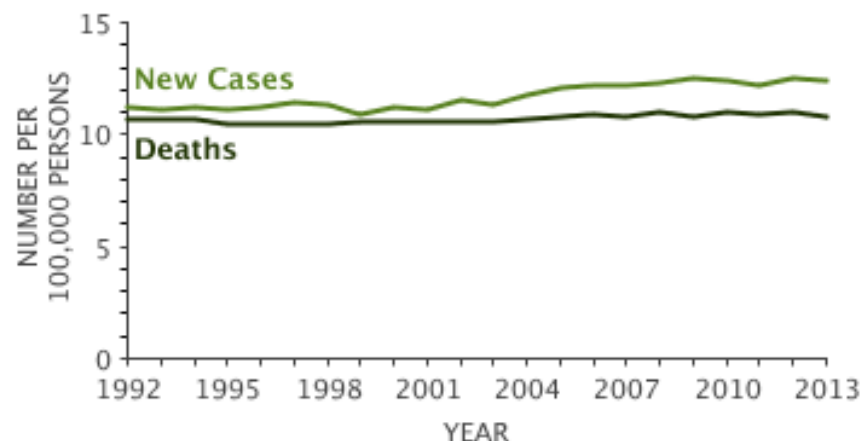




**Woooooh!**

# However....

Estimated New Cases in 2016	53,070
% of All New Cancer Cases	3.1%
Estimated Deaths in 2016	41,780
% of All Cancer Deaths	7.0%



Percent Surviving 5 Years
7.7%
2006-2012

SEER Stat Fact Sheets: Pancreas Cancer.

<http://seer.cancer.gov/statfacts/html/pancreas.html>

# Where is the truth?



# **Many aspects must be considered**

**Depending on:**

- **Technique/technology**
- **Biology**
- **Organizational**

# What we did as surgeons with good results

- Standardized our techniques
- Adopted new devices which became available (i.e. harmonic scalpel, staplers)
- Performed RCTs on technical aspects
- Introduced new approaches (i.e. laparoscopy and robotic)

# **Laparoscopic and robotic approaches in pancreatic surgery:**

## ***a brief summary for oncologists***

- Still demanding the approach to the head
- Easier for the body-tail locations
- Not worldwide accepted/available
- Less blood loss and shorter postoperative stay
- As safe as the open approach in expert centers



# What we did as surgeons with good results

- Standardized our techniques
- Adopted new devices which became available (i.e. harmonic scalpel, staplers)
- Performed RCTs on technical aspects
- Introduced new approaches (i.e. laparoscopy and robotic)
- **Recognized in referral centers the value of less invasive techniques for palliative purposes**

# Palliative Surgical Management of Patients with Unresectable Pancreatic Adenocarcinoma: Trends and Lessons Learned from a Large, Single Institution Experience

Peter J. Kneuert • Steven C. Cunningham • John L. Cameron • Sergio Torrez •  
Nicholas Tapazoglou • Joseph M. Herman • Martin A. Makary • Frederic Eckhauser •  
Jingya Wang • Kenzo Hirose • Barish H. Edil • Michael A. Choti •  
Richard D. Schulick • Christopher L. Wolfgang • Timothy M. Pawlik

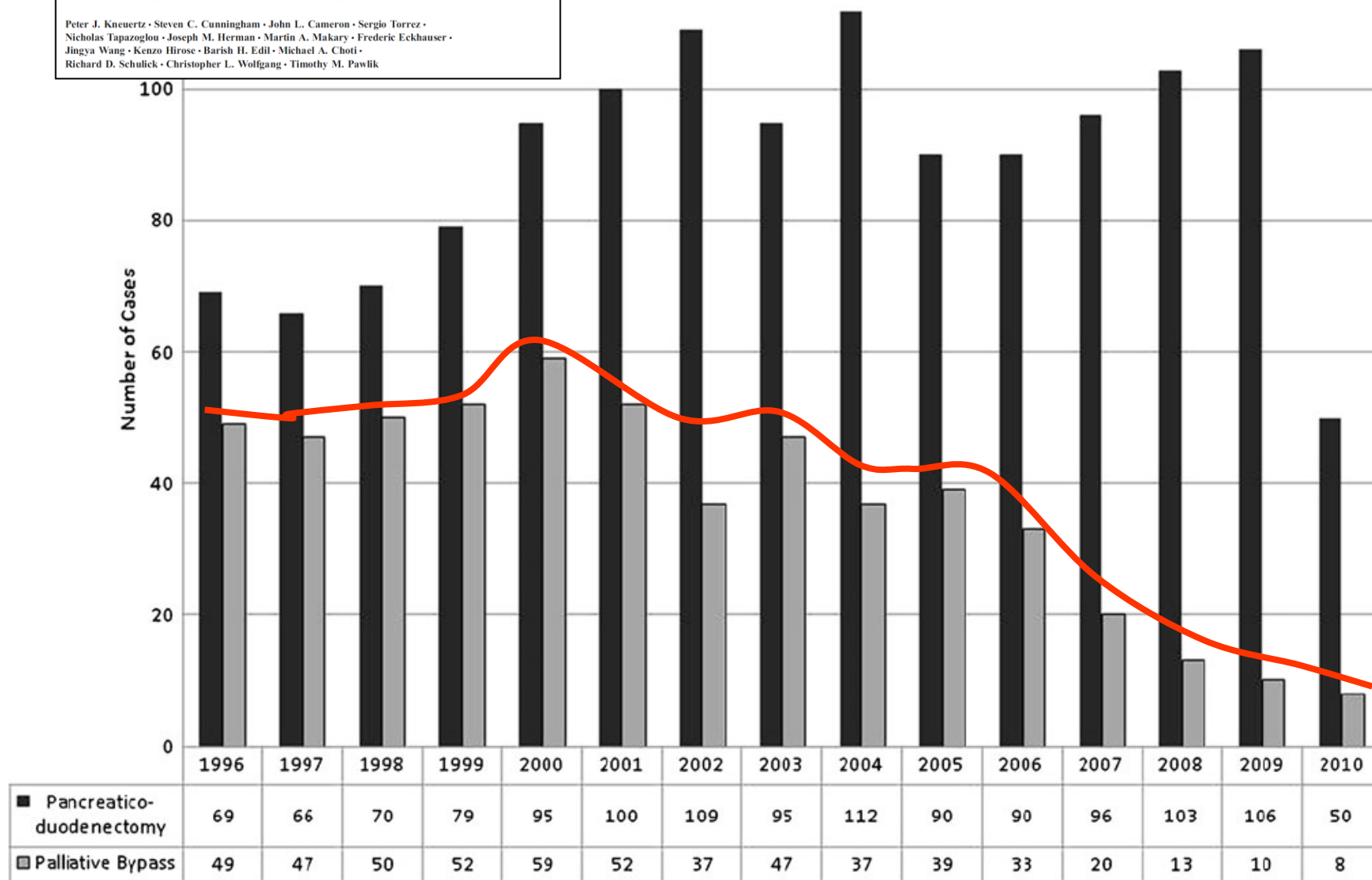


Fig. 1 Annual case volumes of pancreaticoduodenectomy vs. palliative bypass for pancreatic adenocarcinoma between January 1996 and July 2010 at the Johns Hopkins Hospital

# What we did as surgeons with good results

- Standardized our techniques
- Adopted new devices which became available (i.e. harmonic scalpel, staplers)
- Performed RCTs on technical aspects
- Introduced new approaches (i.e. laparoscopy and robotic)
- Recognized in referral centers the value of less invasive techniques for palliative purposes
- **Introduced a standardized perioperative protocols for patients management (i.e. ERAS)**

# What does it mean “good results”?

- In terms of perioperative outcomes

Morbidity	Mortality	Length of Hospital Stay
40-60%	<3%	~10 days

- In terms of oncological outcomes

LN	R1 on classical margins	Adjuvant Tx	Median Survival	5-yr survival
~ 22	~ 20%	~ 60-70%	~ 27 months	~25-30%

from the present Literature

# Many aspects must be considered

Depending on:

- Technique/technology
- **Biology**

# **A lot are the barriers that surgeons have tried to technically overcome**

- Arterial involvement
- Venous involvement
- Minimal metastatic disease
- Invasion of adjacent organs



# Keeping in mind the list

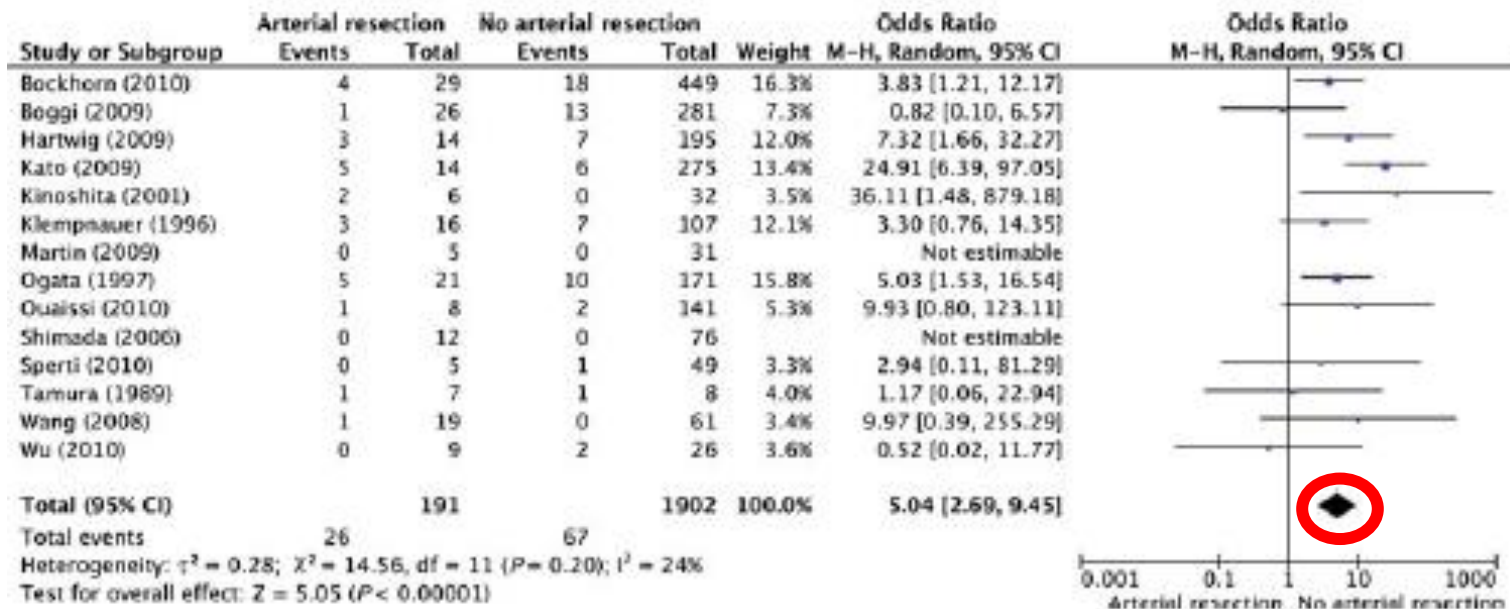
- **Arterial involvement**

# Many studies no one prospective

**TABLE 1.** Characteristics of Identified Studies on Patients Undergoing Pancreatectomy With Concomitant Arterial Resection for Pancreatic Cancer

Reference	Year	Inclusion Period	Sample Size (Total/AR)	Country	Study Type	Follow-up Period (mo)	Risk of Bias
Allendorf <sup>13</sup>	2008	2000–2006	198/11	United States	Retrospec.	—	High
Amano <sup>14</sup>	2009	2005–2009	23/23	Japan	Retrospec.	—	High
Bockhorn <sup>15</sup>	2010	1994–2007	478/29	Germany	Retrospec.	—	Low
Boggi <sup>16</sup>	2009	1987–2004	307/26	Italy	Retrospec.	22	Low
Denecke <sup>17</sup>	2010	2007–2009	6/6	Germany	Retrospec.	—	High
Fortner <sup>18</sup>	1977	1974–1976	18/6	United States	Retrospec.	—	High
Hartwig <sup>19</sup>	2009	2001–2007	216/14	Germany	Retrospec.	15	High
Hirano <sup>20</sup>	2007	1998–2005	23/23	Japan	Retrospec.	27.4	High
Hishinuma <sup>21</sup>	2007	1984–2003	25/7	Japan	Retrospec.	—	High
Kato <sup>22</sup>	2009	1981–2007	176/17	Japan	Retrospec.	20.6	Low
Kinoshita <sup>23</sup>	2001	1965–2001	139/6	Japan	Retrospec.	—	High
Klempnauer <sup>24</sup>	1996	1971–1993	189/16	Germany	Retrospec.	—	High
Martin <sup>25</sup>	2009	1997–2007	36/5	United States	Retrospec.	24	High
Miyakawa <sup>26</sup>	2002	1987–1998	8/8	Japan	Retrospec.	9.5*	High
Miyazaki <sup>27</sup>	2003	1990–2003	80/13	Japan	Retrospec.	—	High
Ogata <sup>28</sup>	1997	1974–1997	192/21	Japan	Retrospec.	—	High
Ouaissi <sup>29</sup>	2010	1977–2008	149/8	Belgium	Retrospec.	17	High
Park <sup>30</sup>	2001	1996–1999	40/15	Korea	Retrospec.	—	High
Settmacher <sup>31</sup>	2004	1989–2003	18/18	Germany	Retrospec.	8*	High
Shimada <sup>32</sup>	2006	1990–2004	88/12	Japan	Retrospec.	20	Low
Sperti <sup>33</sup>	2010	1989–2007	54/5	Italy	Retrospec.	—	High
Stitzenberg <sup>34</sup>	2008	1996–2000	252/12	United States	Retrospec.	17	High
Sugiura <sup>35</sup>	2009	1978–2007	107/25†	Japan	Retrospec.	—	High
Tamura <sup>36</sup>	1992	1980–1991	15/7	Japan	Retrospec.	—	High
Wang <sup>37</sup>	2008	1996–2005	80/19	China	Retrospec.	—	High
Wu <sup>38</sup>	2010	2003–2008	36/9	China	Retrospec.	—	High

# Perioperative mortality



# “Oncological” results: risk of death within 1-yr

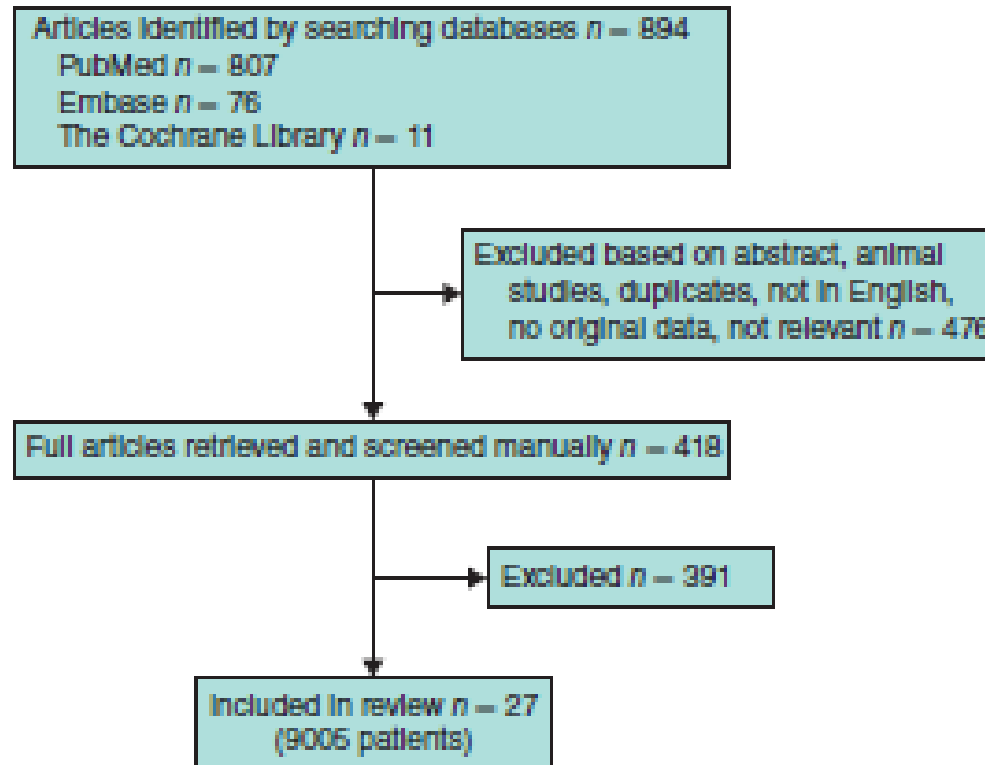
%	Range (%)	OR	95%CI	p
49.1	16-83	0.49	0.31-0.78	0.002



# Keeping in mind the list

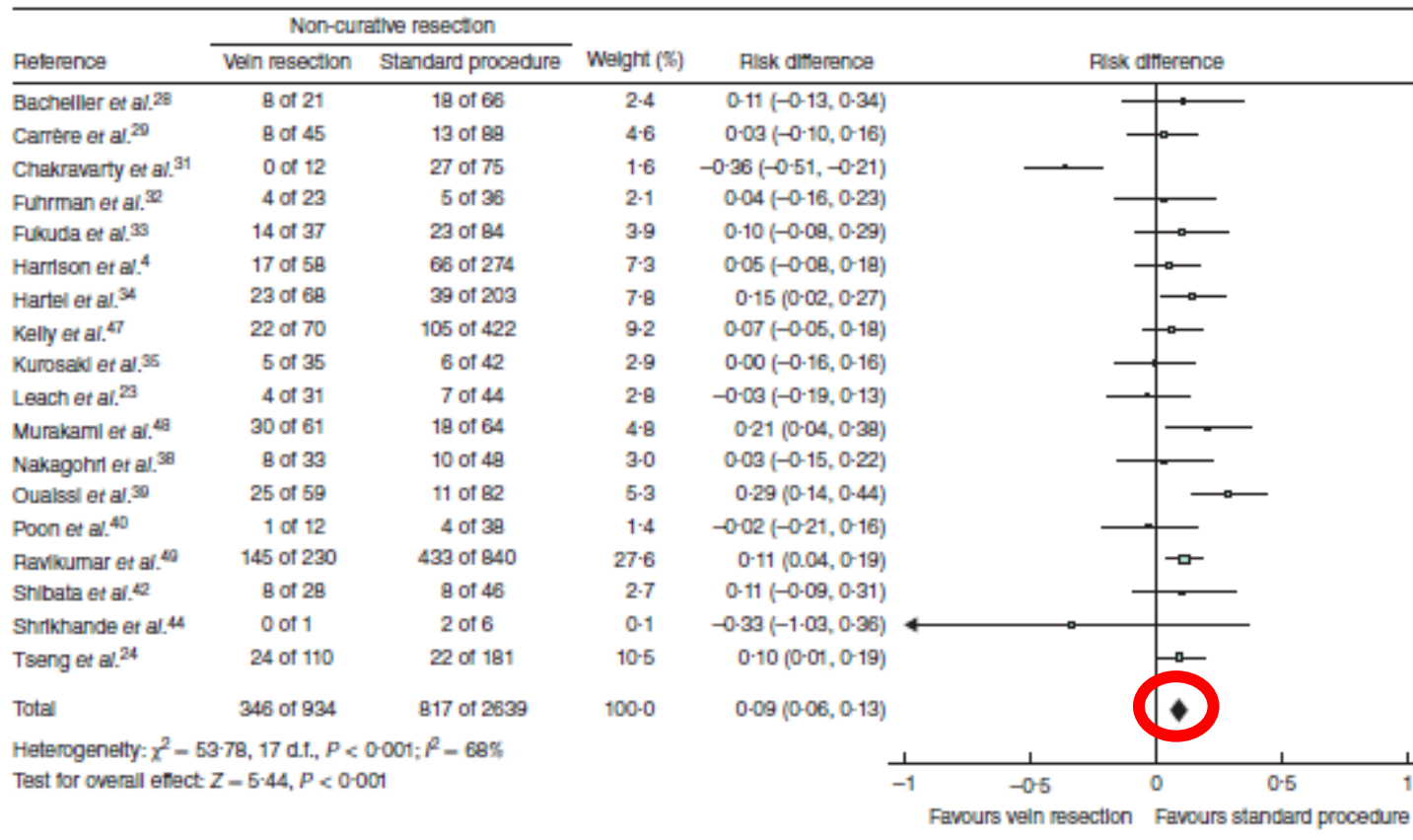
- Arterial involvement
- **Venous involvement**

# The usual PRISMA in this specific issue



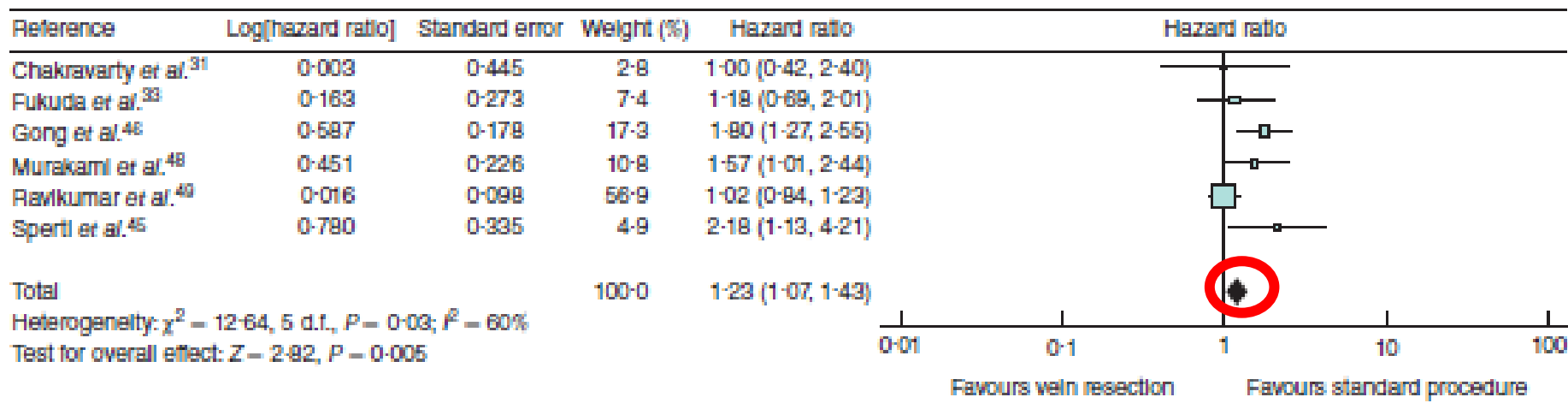


# Comparison for R1/R2 resections



# Risk of death within 1-yr

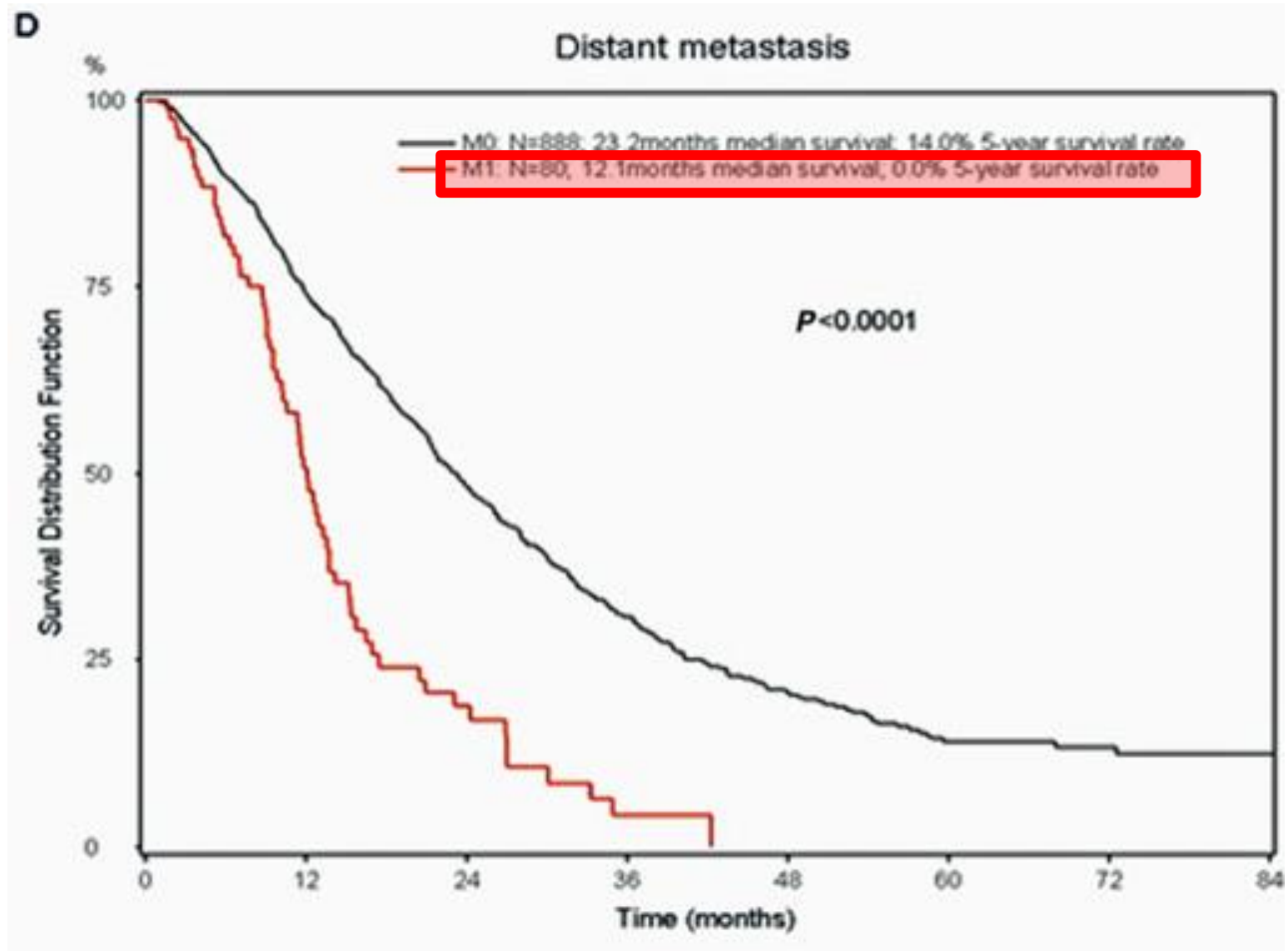
OS (Median)	OR	95%CI	p
14.3 mo	1.23	1.07-1.43	0.005



# Keeping in mind the list

- Arterial involvement
- Venous involvement
- **Minimal metastatic disease**

# Results that comment by themselves



# An outside referral centers even worse!

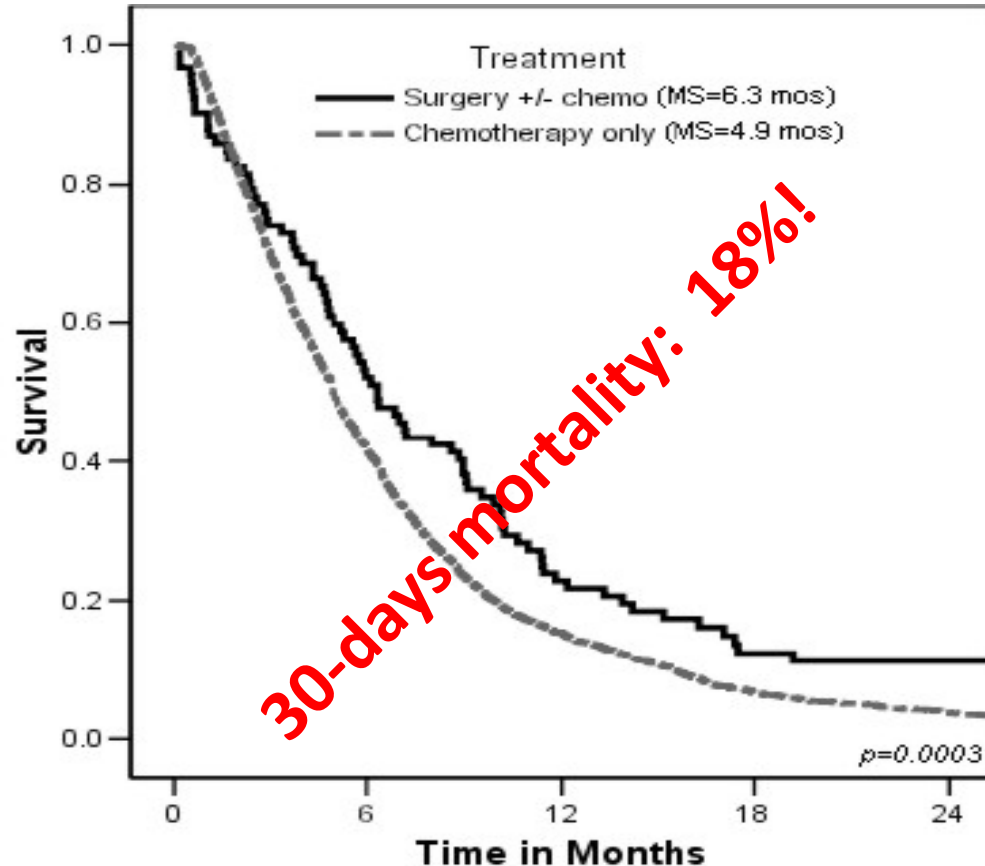


Figure 1. Survival analysis of M1 patients with pancreatic adenocarcinoma who received chemotherapy alone (n=1,683) as compared to patients who underwent pancreatic resection with or without the addition of chemotherapy (n=92). (MS: median survival).

# Keeping in mind the list

- Arterial involvement
- Venous involvement
- Minimal metastatic disease
- **Invasion of adjacent organs**



# Not negligible damages

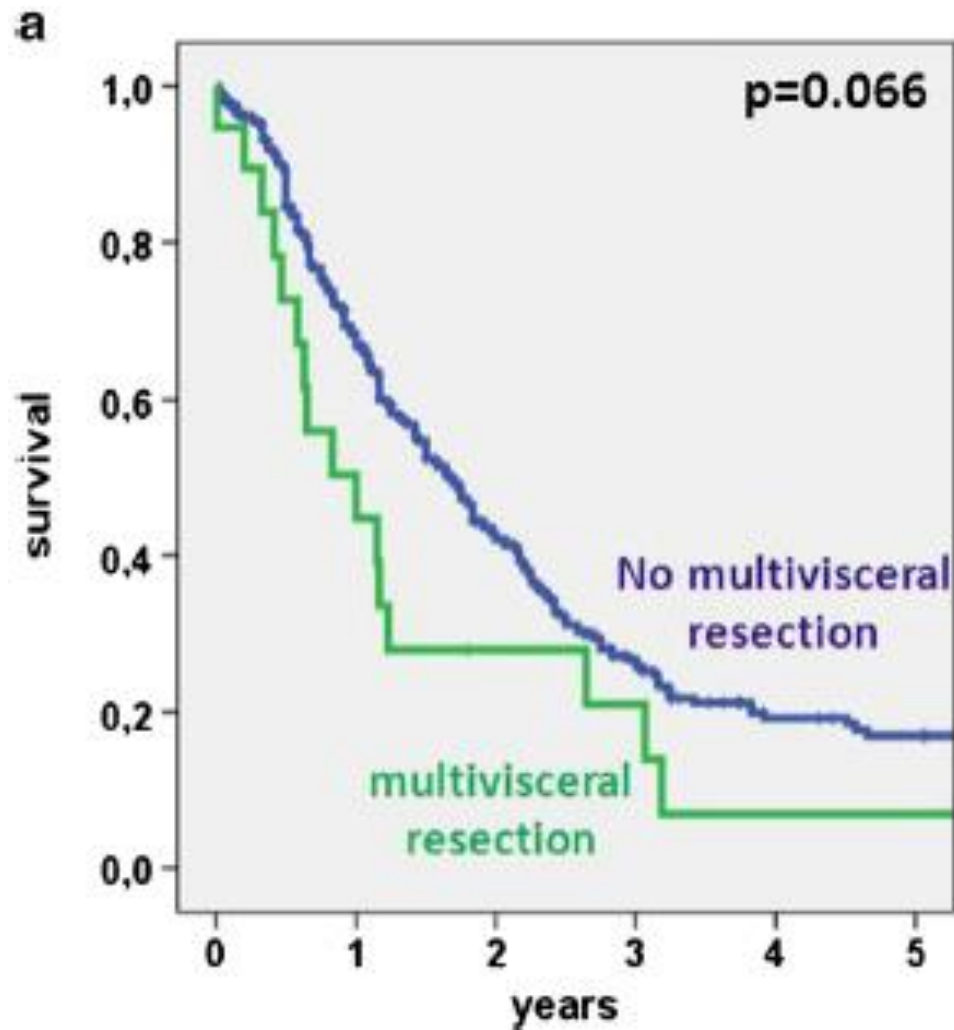
Germany 2009-2013

**TABLE 4. Number and In-hospital Mortality of Pancreatic Surgery Inpatients (Major Pancreatic Resections) According to Concomitant Resections**

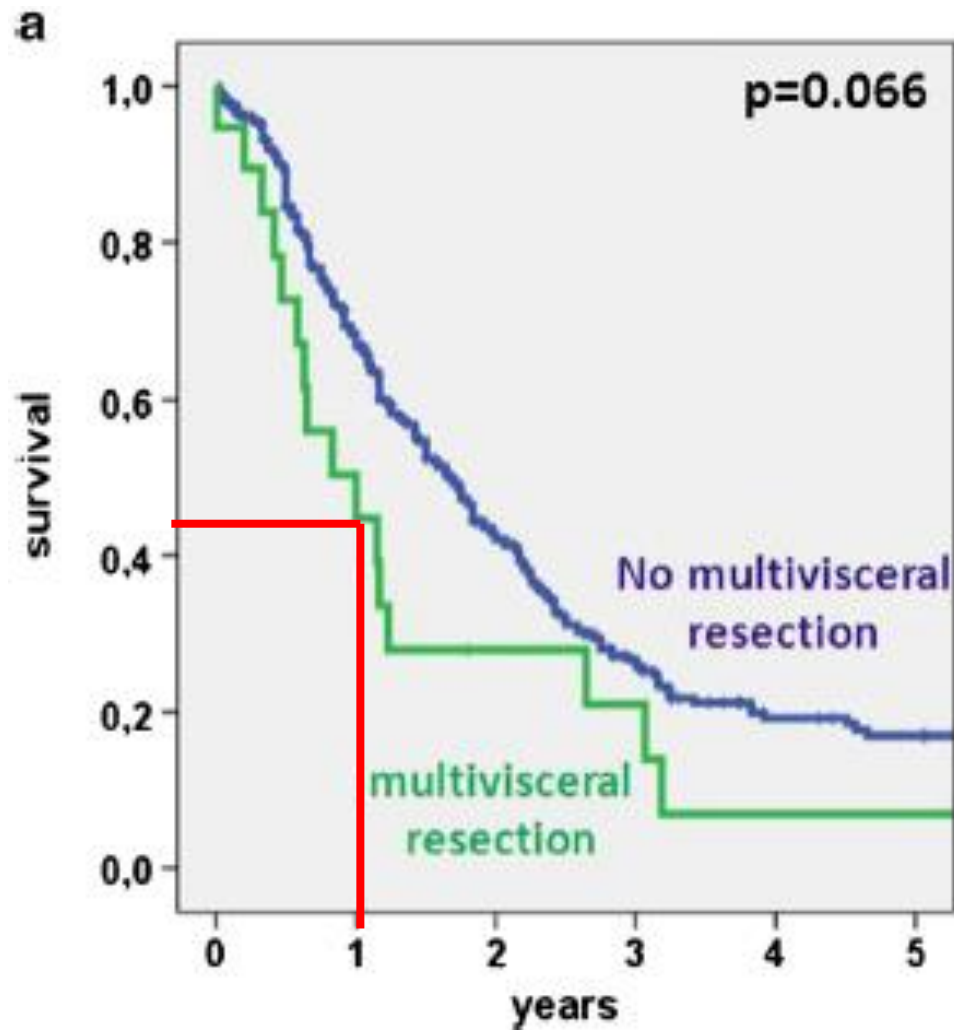
		Spleen	Stomach*	Liver *	Small Intestine*	Large Intestine*	Visceral Arteries	Visceral Veins	Total
All major resection of pancreas	N	11,150	3224	3669	2646	3623	1806	4246	49,959
	Mortality (%)	(12.9)	(19.0)	(11.8)	(24.8)	(24.5)	(28.5)	(12.1)	(9.1)
Total pancreatectomy	N	2729	471	393	534	452	452	992	4783
	Mortality (%)	(24.3)	(39.1)	(25.4)	(41.2)	(49.6)	(43.4)	(21.3)	(22.9)
Proximal pancreatectomy	N	561	709	2015	1264	1109	1030	2728	31,293
	Mortality (%)	(29.1)	(21.4)	(10.1)	(21.5)	(26.8)	(25.0)	(9.6)	(7.7)
Segmental pancreatectomy	N	102	117	97	114	115	23	24	1137
	Mortality (%)	(16.7)	(18.8)	(14.4)	(10.5)	(22.6)	(34.8)	(16.7)	(8.8)
Distal pancreatectomy	N	7758	1927	1164	734	1947	301	502	12,746
	Mortality (%)	(7.7)	(13.1)	(10.0)	(20.7)	(17.5)	(17.6)	(7.8)	(7.3)

\*Includes all standard resection methods.

# With very poor results!



# With very poor results!



# If it was not enough another impressive data!

## n= 2,439

**TABLE 1. Relative Survival of Patients With Pancreatic Cancer by Therapy and Period of Diagnosis in the Netherlands**

Therapy	Year of Diagnosis	N	Relative Survival (% [95%CI])				
			3 Months	6 Months	1 Year	3 Years	5 Years
Resection*	1989–1993	396	82 (78–86)	72 (67–77)	51 (46–56)	24 (20–29)	20 (16–24)
	1994–1998	538	88 (85–90)	77 (74–81)	54 (50–58)	18 (15–21)	12 (9–15)
	1999–2003	608	91 (89–93)	81 (78–84)	60 (56–64)	21 (17–24)	13 (10–16)
	2004–2008	897	93 (91–95)	84 (82–87)	63 (60–66)	23 (20–26)	15 (11–18)

Percentage of patients lost at:

7%

16%

37%

**The pilot is with his bottom on the ground**

# When the barriers might be overtaken?

Depending on:

- Technique/technology
- **Biology**
  - Depending on the disease

# Coming back to the list

- Arterial involvement
- Venous involvement
- Minimal metastatic disease
- Invasion of adjacent organs

# Venous resection: analysis on 1,399 patients!

Ann Surg Oncol (2015) 22:1874–1883

DOI 10.1245/s10434-014-4304-3

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**SURGICAL ONCOLOGY**

OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



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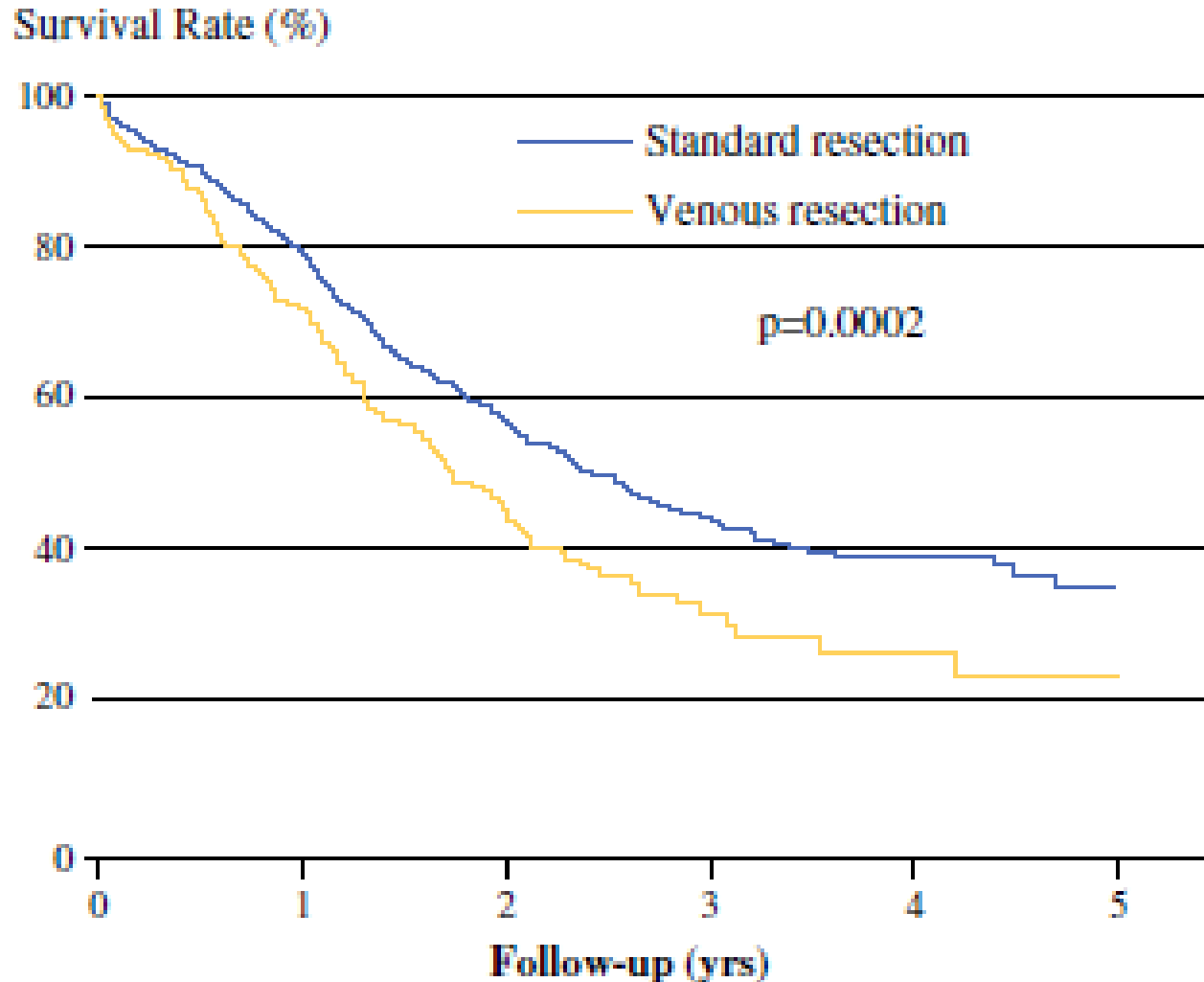
ORIGINAL ARTICLE – PANCREATIC TUMORS

## **Pancreatic Adenocarcinoma with Venous Involvement: Is Up-Front Synchronous Portal-Superior Mesenteric Vein Resection Still Justified? A Survey of the Association Française de Chirurgie**

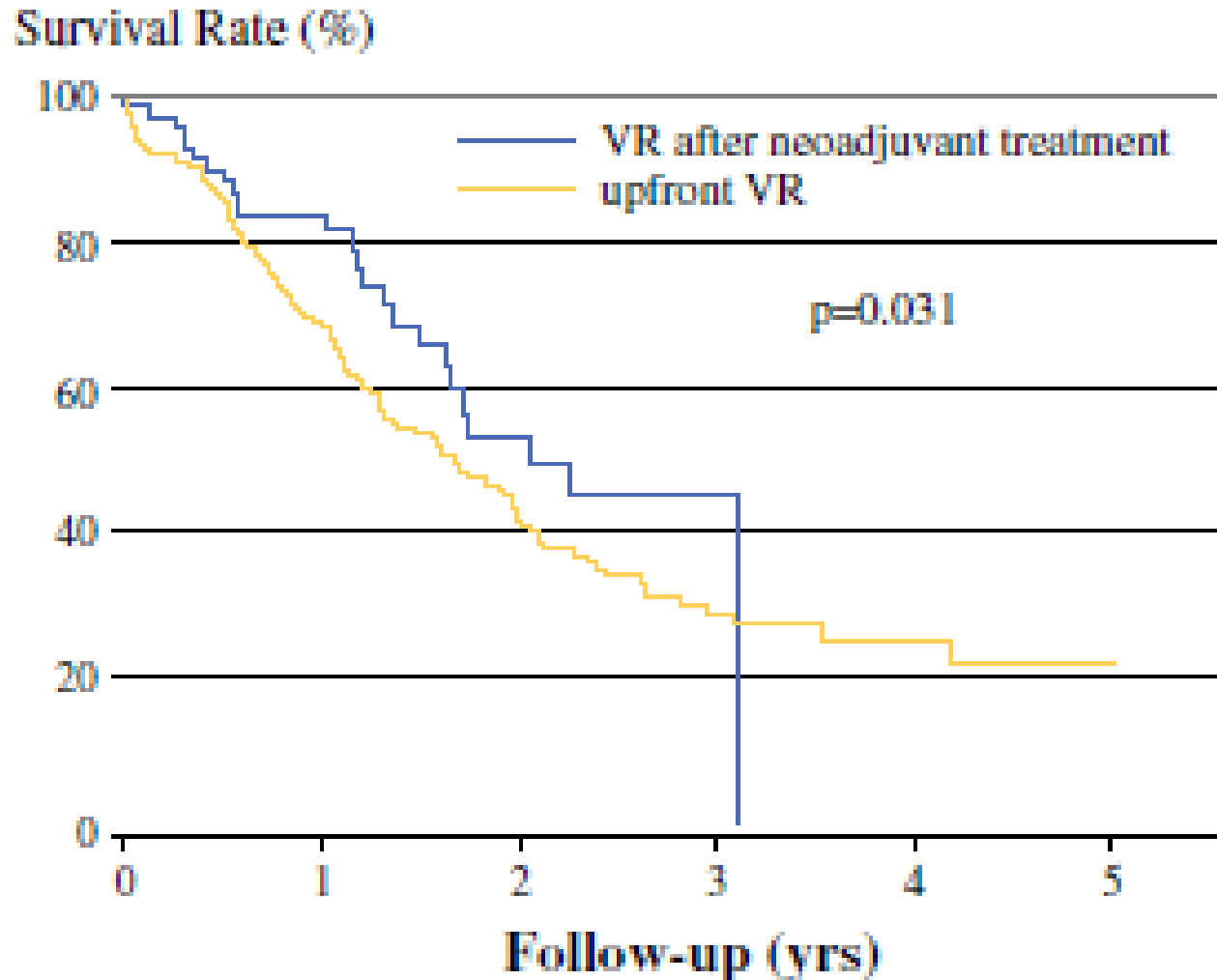
**Jean Robert Delpero, MD<sup>1</sup>, Jean Marie Boher, PhD<sup>2</sup>, Alain Sauvanet, MD<sup>3</sup>, Yves Patrice Le Treut, MD<sup>4</sup>, Antonio Sa-Cunha, MD<sup>5</sup>, Jean Yves Mabrut, MD<sup>6</sup>, Laurence Chiche, MD<sup>7</sup>, Olivier Turrini, MD<sup>1</sup>, Philippe Bachellier, MD<sup>8</sup>, and François Paye, MD<sup>9</sup>**



# A venous resection decreases the OS chances!



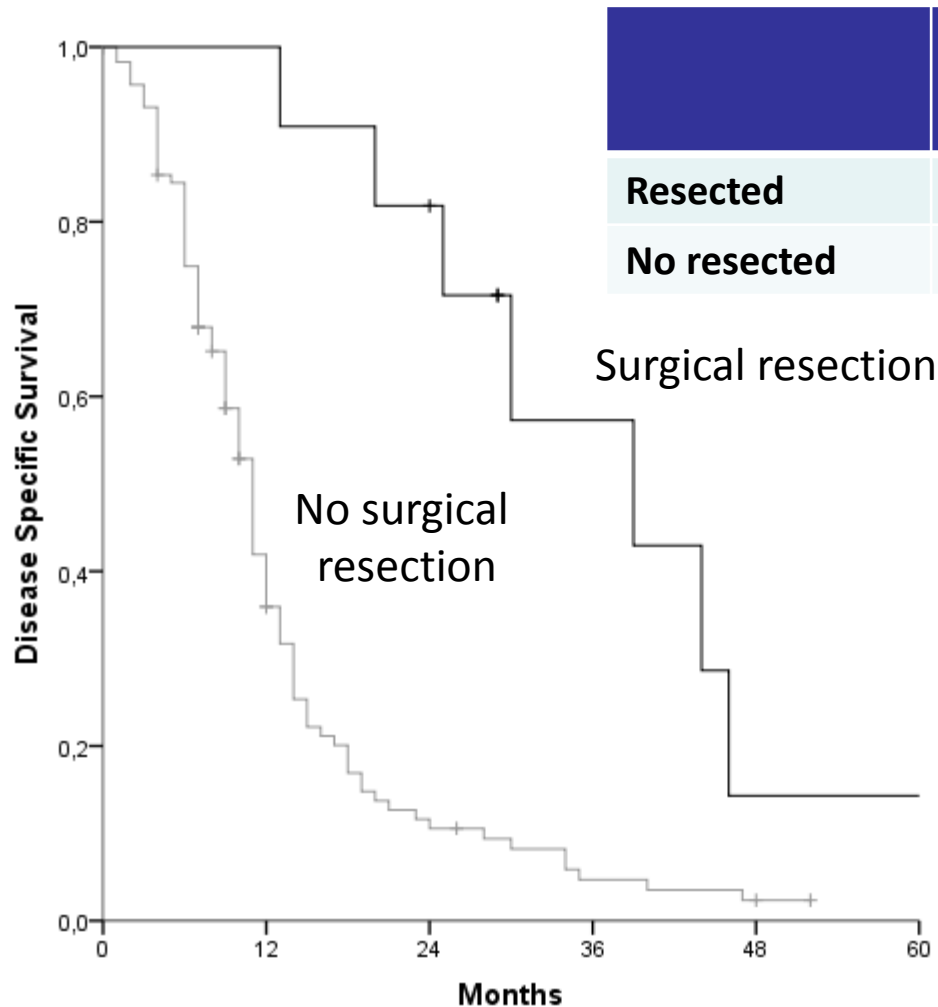
# This is not anymore true after neoadj Tx!



# Coming back to the list

- Arterial involvement
- Venous involvement
- **Minimal metastatic disease**
- Invasion of adjacent organs

# A multicenter Italian experience



Pts. at risk

Resection	11	11	9	4	1	1
No Resection	116	65	8	4	1	0

# But ...

- Surgical resection was carried out in only 11 patients (8.5%)
- The preop work up was very careful (MRI + 18FDG PET-CT)
- **They were operated upon after a median of 12 months (range 6-20) from initial diagnosis and multi-regimen chemo Tx**
- They underwent intraoperative US of the liver that confirmed the presence:
  - no metastases in 7 patients
  - a single metastasis in 3 patients
  - two liver lesions in 1 patient

**In other words more than careful  
morphological and biological selection**

# Keeping in mind the basic principles of oncological surgery



Blake Gady, MD

*How I became foolhardy enough to inflict basic principles in surgical oncology !*

*The technical details of surgical procedures are the Princes and Princesses who frequently try to overthrow the powerful forces of the King or Queen, usually to no long-term avail, although with some temporary apparent victories.*

Techn

is

*77th Annual Meeting of the New England Surgical Society,  
September 27, 1996*

**The surgical eagle can fly only when  
biology allows it**

# Many aspects must be considered

Depending on:

- Technique/technology
- Biology
- **Organizational**

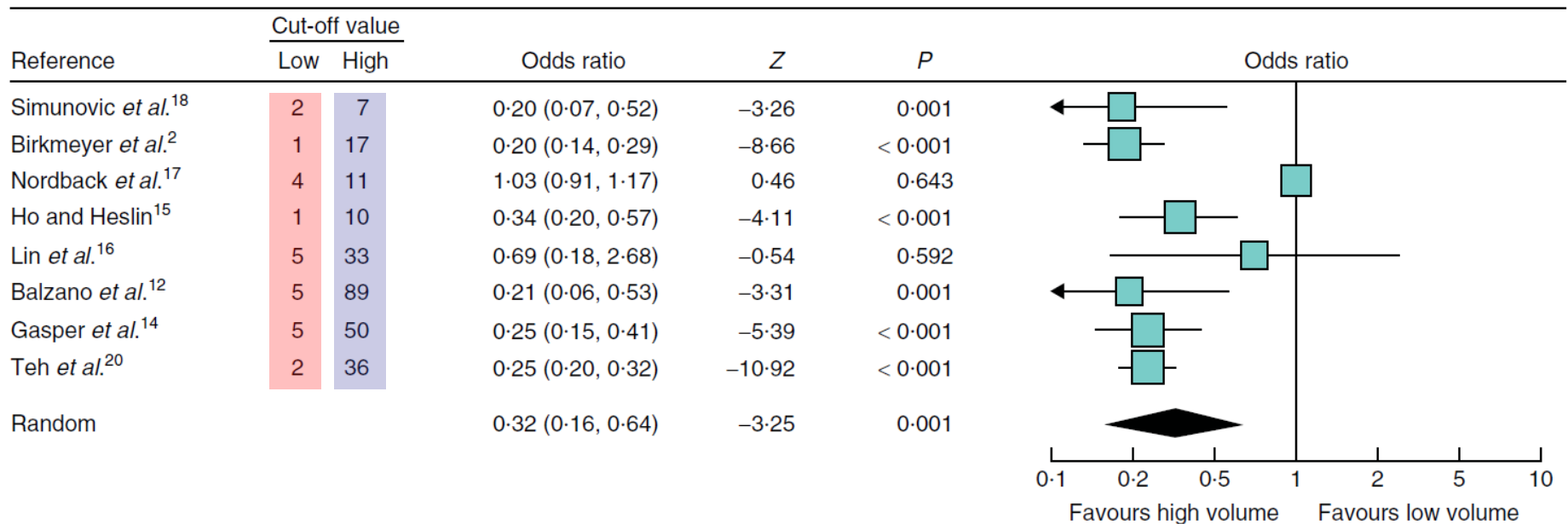


# Systematic review and meta-analysis of the volume–outcome relationship in pancreatic surgery

G. A. Gooiker<sup>1</sup>, W. van Gijn<sup>1</sup>, M. W. J. M. Wouters<sup>1</sup>, P. N. Post<sup>2</sup>, C. J. H. van de Velde<sup>1</sup> and R. A. E. M. Tollenaar<sup>1</sup>, on behalf of the Signalling Committee Cancer of the Dutch Cancer Society

*British Journal of Surgery* 2011; **98**: 485–494

## Relationship between volume-perioperative mortality



14 studies: 9 USA, 2 Canada,  
1 Finland, 1 Italy, 1 Taiwan

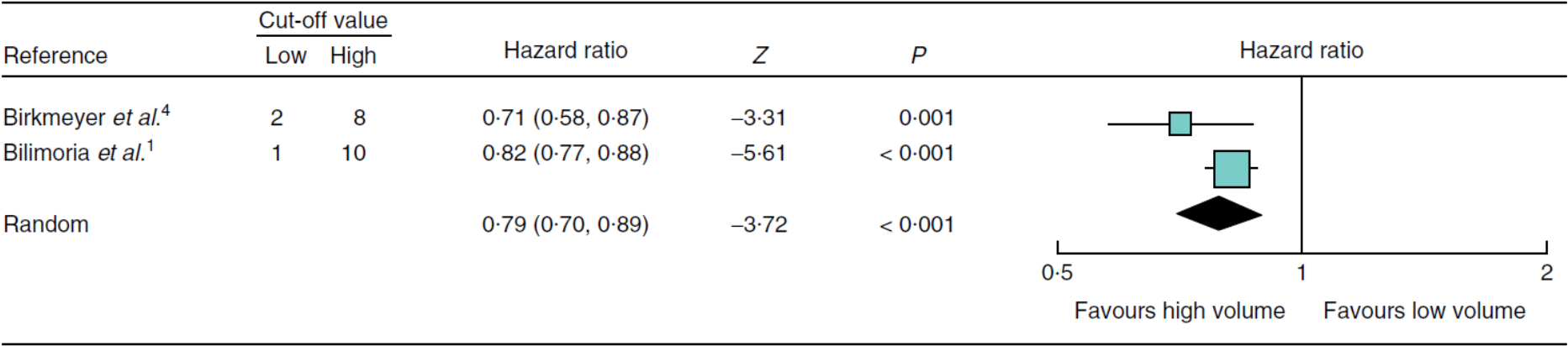
Forest plots of included studies on hospital volume and postoperative mortality

# Systematic review and meta-analysis of the volume–outcome relationship in pancreatic surgery

G. A. Gooiker<sup>1</sup>, W. van Gijn<sup>1</sup>, M. W. J. M. Wouters<sup>1</sup>, P. N. Post<sup>2</sup>, C. J. H. van de Velde<sup>1</sup> and R. A. E. M. Tollenaar<sup>1</sup>, on behalf of the Signalling Committee Cancer of the Dutch Cancer Society

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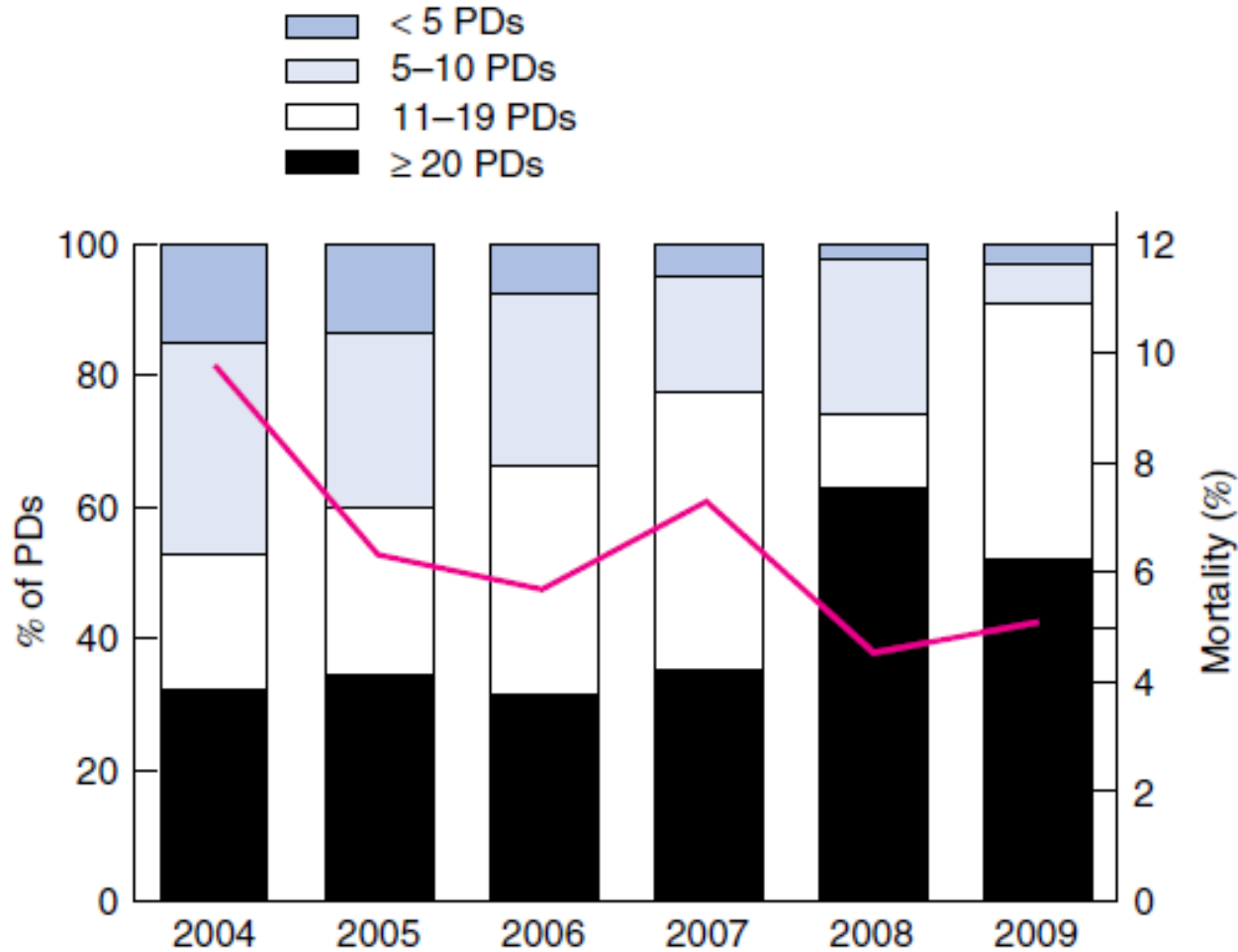
## Relationship between volume – survival



2 USA studies

Forest plots of included studies on hospital volume and 5-year survival

# The virtuous Dutch



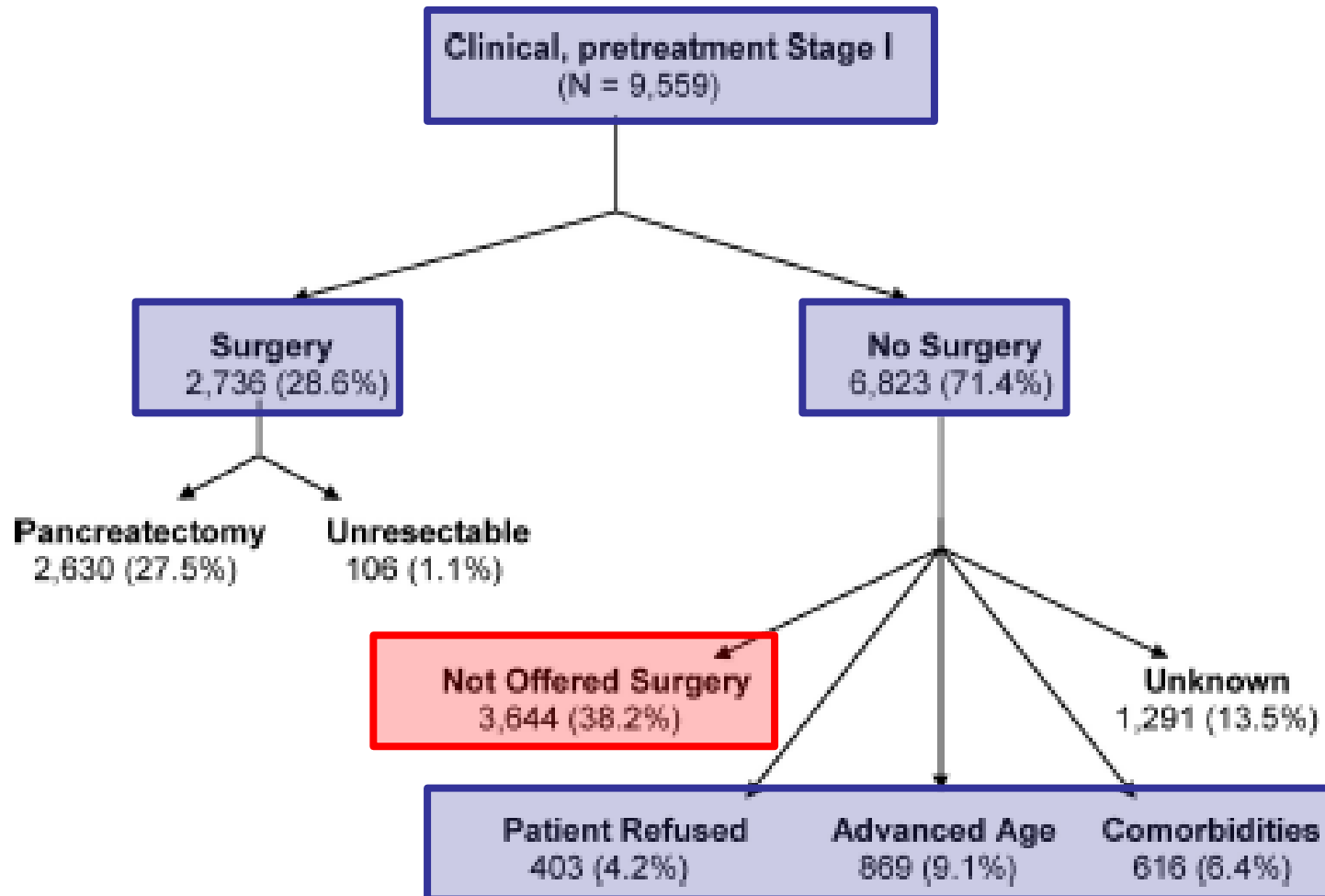
**Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality**

R. F. de Wilde<sup>1</sup>, M. G. H. Besselink<sup>1</sup>, I. van der Tweel<sup>2</sup>, I. H. J. T. de Hingh<sup>3</sup>, C. H. J. van Eijck<sup>4</sup>, C. H. C. Dejong<sup>5</sup>, R. J. Porte<sup>6</sup>, D. J. Gouma<sup>7</sup>, O. R. C. Busch<sup>7</sup> and I. Q. Molenaar<sup>1</sup>, for the Dutch Pancreatic Cancer Group

*British Journal of Surgery* 2012; 99: 404–410

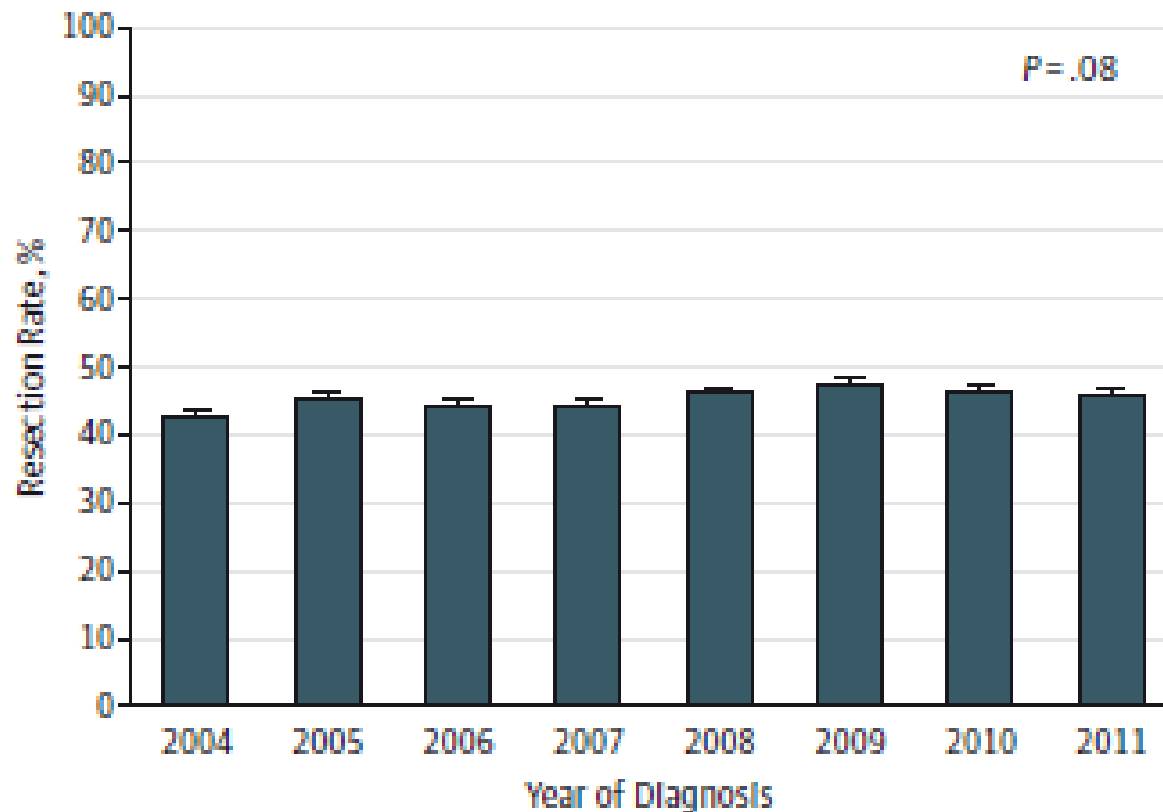
# More difficult to apply in larger countries!

## *USA (1995-2004)*



# The reality has not been changed over the years

Figure 1. Rate of Surgical Resection for Patients With T1 Through T3 Pancreatic Adenocarcinomas Diagnosed Between 2004 and 2011



# An even cruel reality

The chance to be resected depends on:

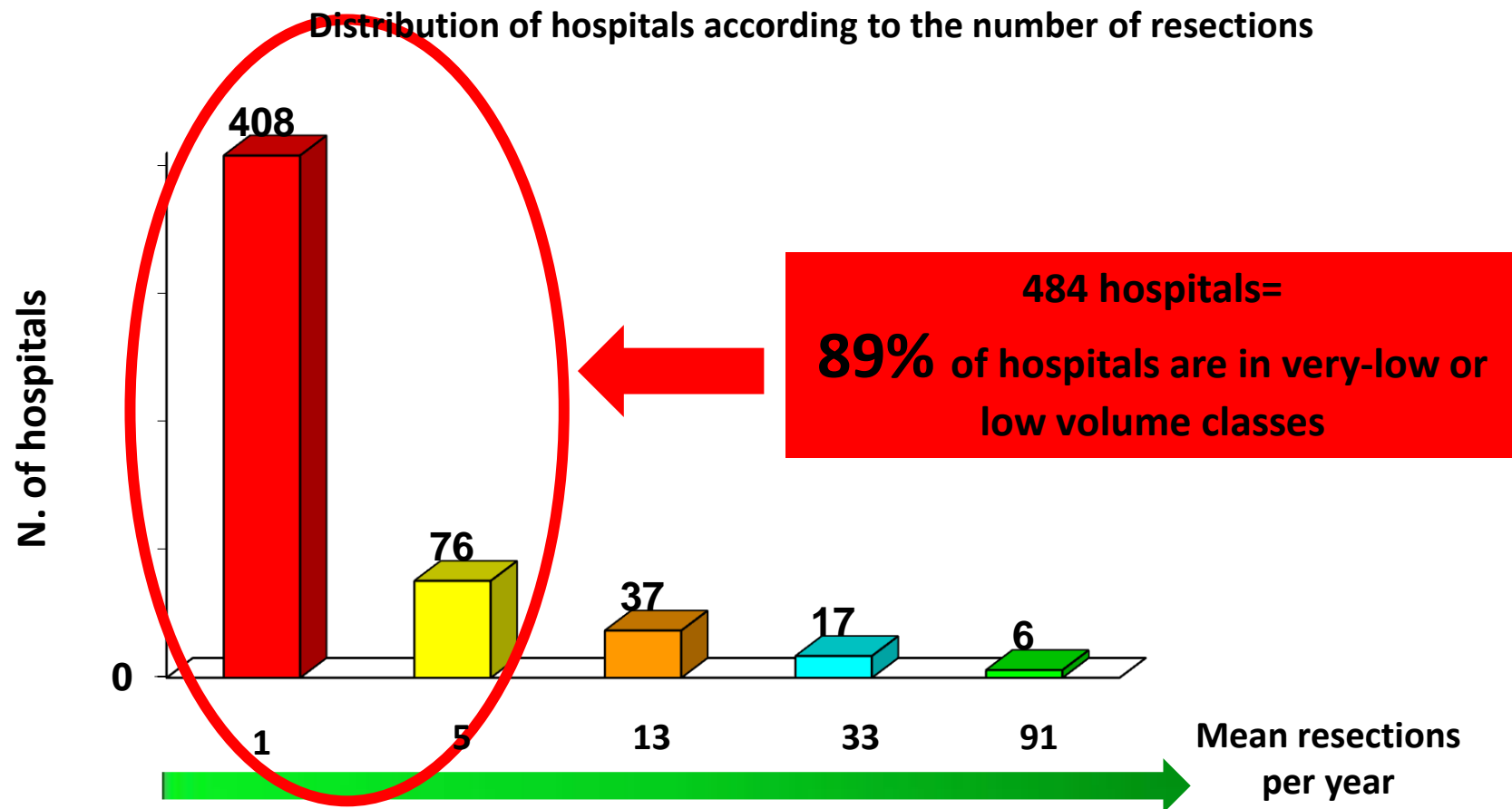
**Table 2. Socioeconomic and Tumor Characteristics Associated With Surgical Resection for Patients With Localized, Resectable Pancreatic Cancer**

Variable	Underwent Resection, %	Univariate		Multivariate <sup>a</sup>	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Age, y <sup>b</sup>	...	0.95 (0.94-0.95)	<.001	0.95 (0.94-0.95)	<.001
Race					
White	46.1	1.16 (1.08-1.26)	<.001	1 [Reference]	...
African American	40.6	0.80 (0.73-0.88)	<.001	0.76 (0.65-0.88)	<.001
American Indian	37.0	0.71 (0.47-1.06)	.09	0.65 (0.36-1.17)	.15
Asian/Pacific Islander	45.6	1.01 (0.90-1.14)	.84	1.01 (0.85-1.21)	.89
Ethnicity					
Non-Hispanic	45.7	1 [Reference]	...	1 [Reference]	...
Hispanic	41.1	0.83 (0.74-0.93)	<.001	0.72 (0.60-0.85)	<.001
Marital status					
Single	37.6	1 [Reference]	...	1 [Reference]	...
Married	51.7	1.78 (1.67-1.89)	<.001	1.42 (1.30-1.57)	<.001
Insurance status					
Not insured	47.8	1 [Reference]	...	1 [Reference]	...
Insured	46.3	0.94 (0.75-1.19)	.62	1.63 (1.22-2.18)	.001

modified from Shapiro M, et al JAMA Surg. 2016;151(4):338-345

# Surgery for PDAC in Italy (2010-2012)

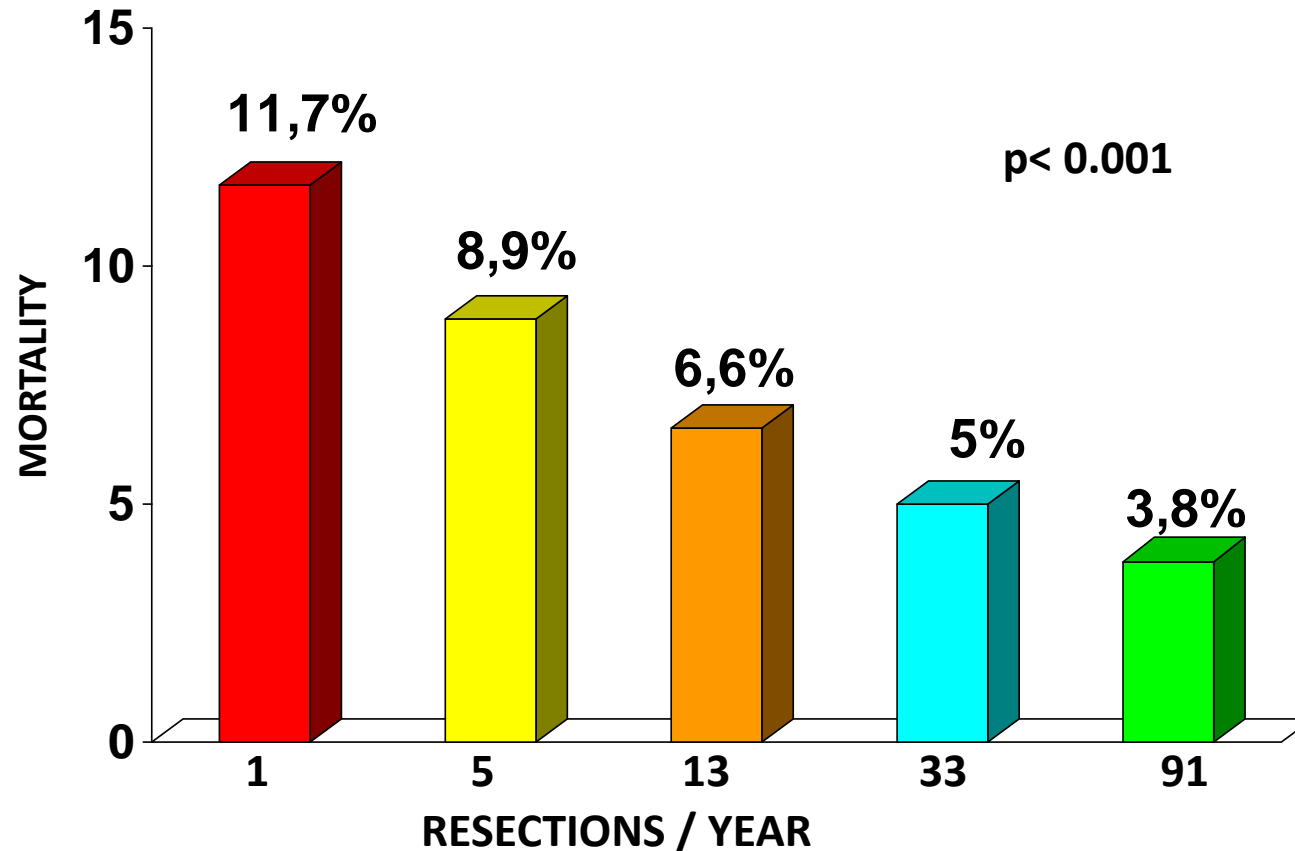
In the period 2010-2012, **544** Italian hospitals performed **10.936** operations for pancreatic cancer



# Results: mortality for cancer resections

6570 RESECTIONS (2010-2012)

Overall mortality : 6.7%





# The weakness of the system in many countries

## The lottery of cure



# Acceptable any more?

# Are we making progress in surgery of the pancreas?

- **Technique/technology**



- **Biology**



- **Organizational**



# Most of the results are still depending on how the pancreatic surgeon is

## Optimal when

1. biologically oriented
2. technically skill

## Uncertain toward worse when

1. technically skill
2. biologically **dis**oriented

## Disastrous when

1. technically **un**skilled
2. biologically **dis**oriented

**Despite the progresses there is still a  
long way to go...**



# Thank you

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