Radical Resection for Adenocarcinoma of the Pancreatic Head

is

USELESS

Arek Wiktor, MD

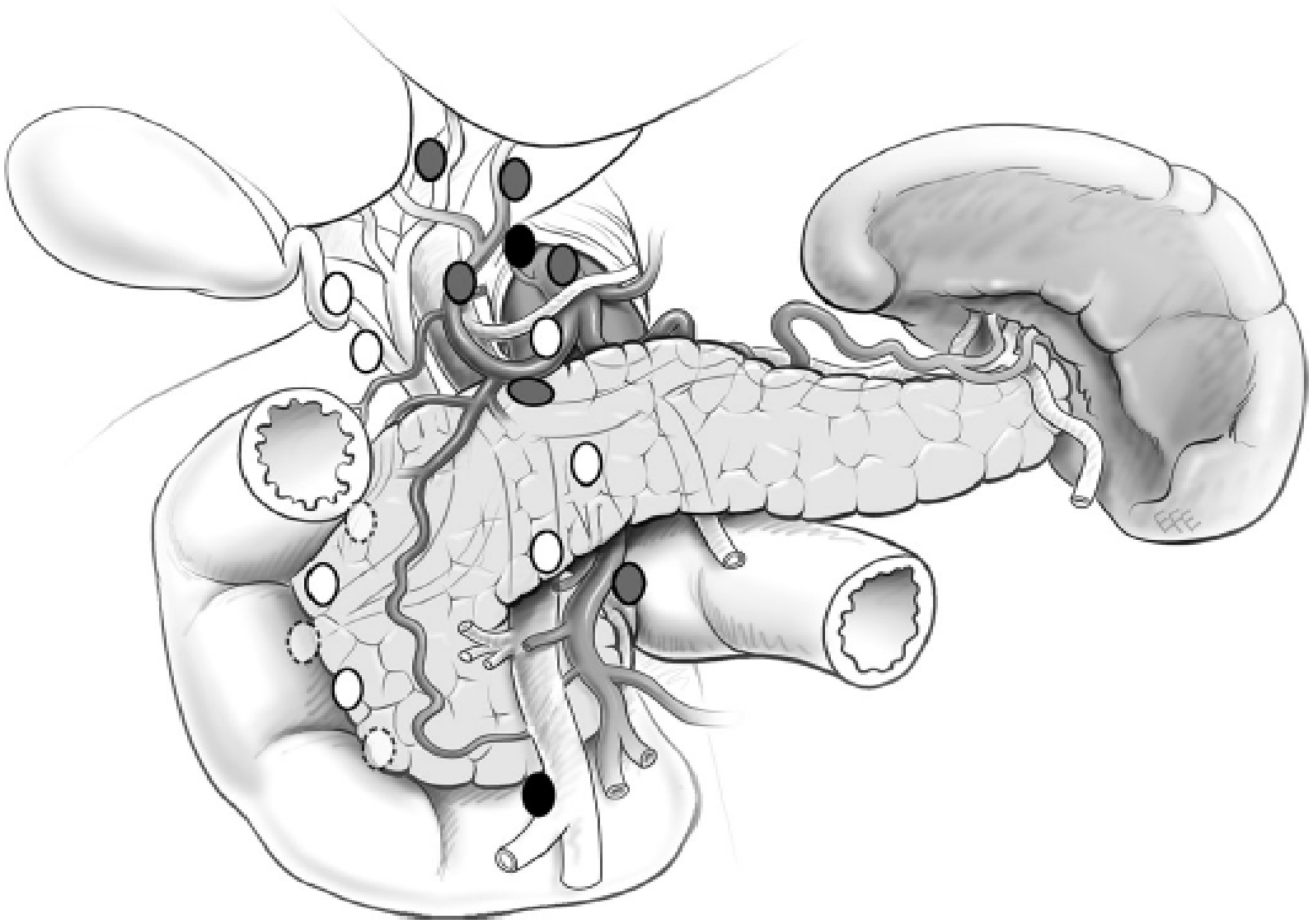
PGY-4

Outline

- How did we get to this point?
- Lymph Node Maps
- The Japanese Experience
- Prospective Randomized Trials
- Cancer Math 101
- Final Thoughts

History

- 1st successful resection: Halsted 1899
- 1st pancreaticoduodenectomy for adenocarcinoma: Dr. Alexander Brunschwig
- 1973- Dr. Joseph Fortner “regional resection” of the pancreas
- LN mapping by Cubilla and Kayahara
- Patterns of failure: recurrence most often are in peripancreatic region and within the liver

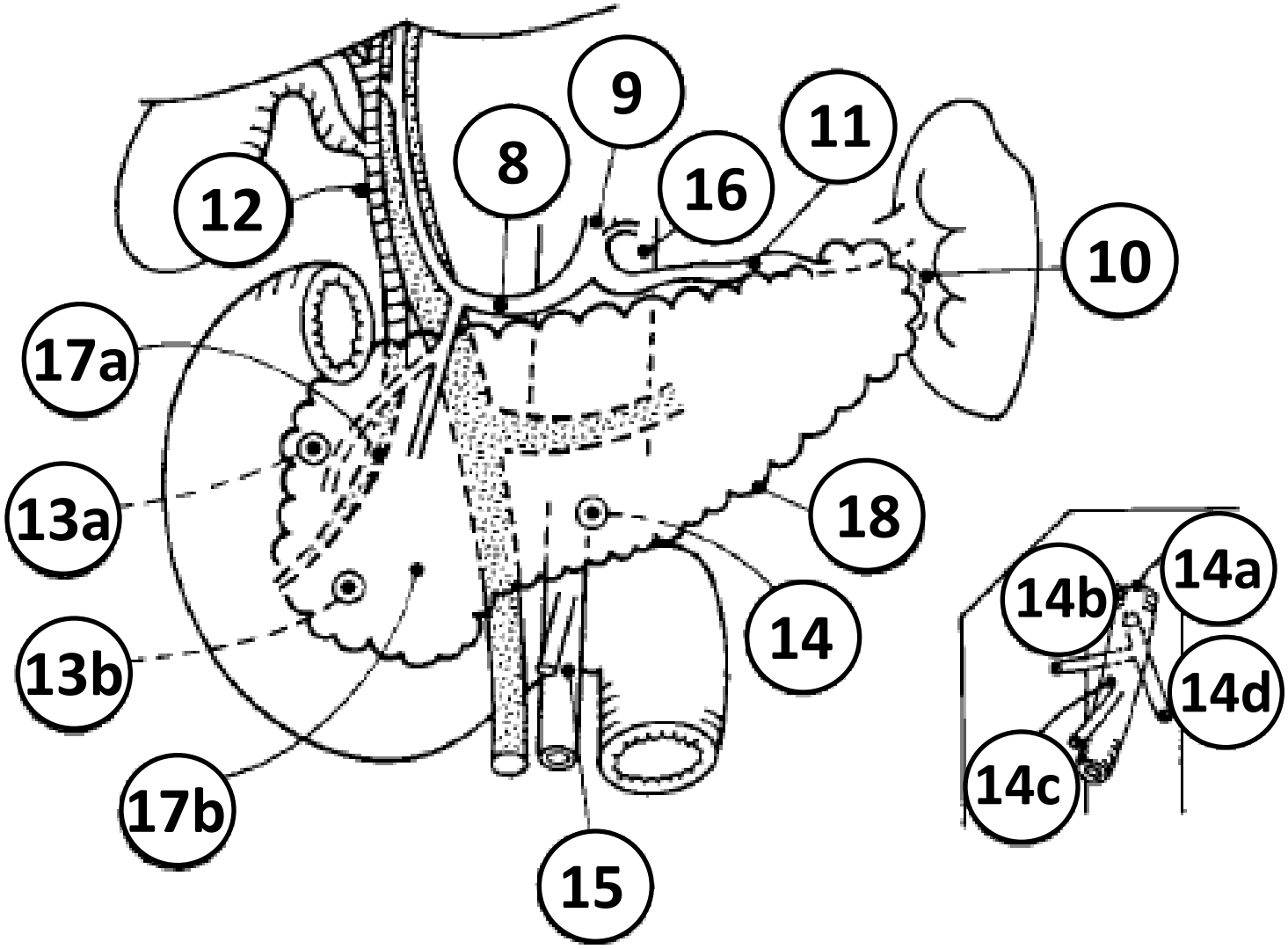


Samra et al. ANZ J Surgery, 2008; 78: 228-236

What is a “Radical” Operation?

- “Extended Pancreaticoduodenectomy”
- “Extended Radical Whipple”
- “Regional Pancreatectomy”
- “Extended Lymphadenectomy
- “En bloc resection”

Lymph Node Stations



Kayahara et al. Cancer 85(3);583-90

Consensus Conference 1998: Castlefranco, Veneto, Italy

http://www.terninrete.it/headlines/articolo_view.asp?ARTICOLO_ID=111990

Standard pancreatoduodenectomy:

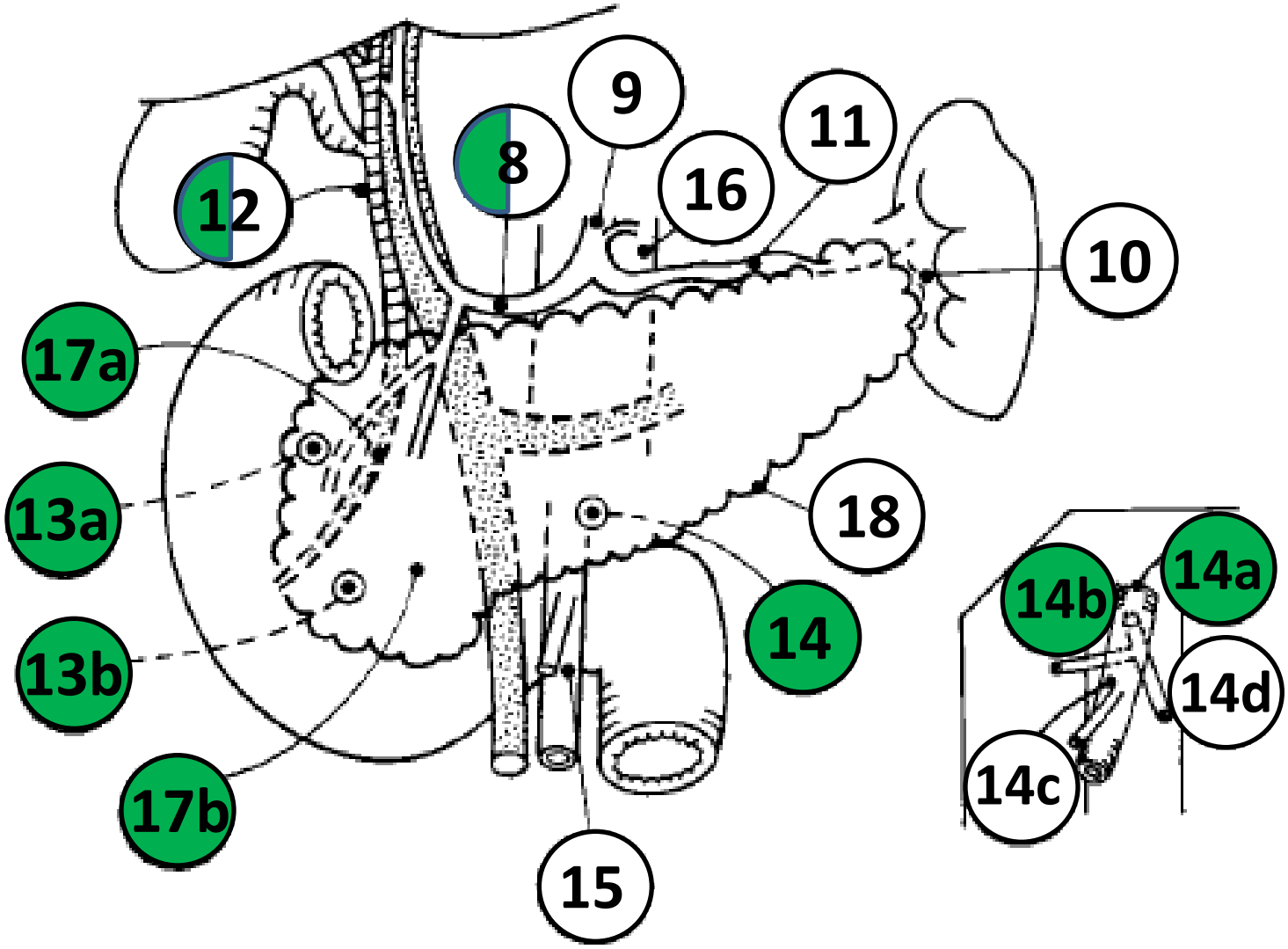
Regional lymphadenectomy around the duodenum and pancreas (stations 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, 17b and 8a)

Radical pancreatoduodenectomy:

Standard operation +

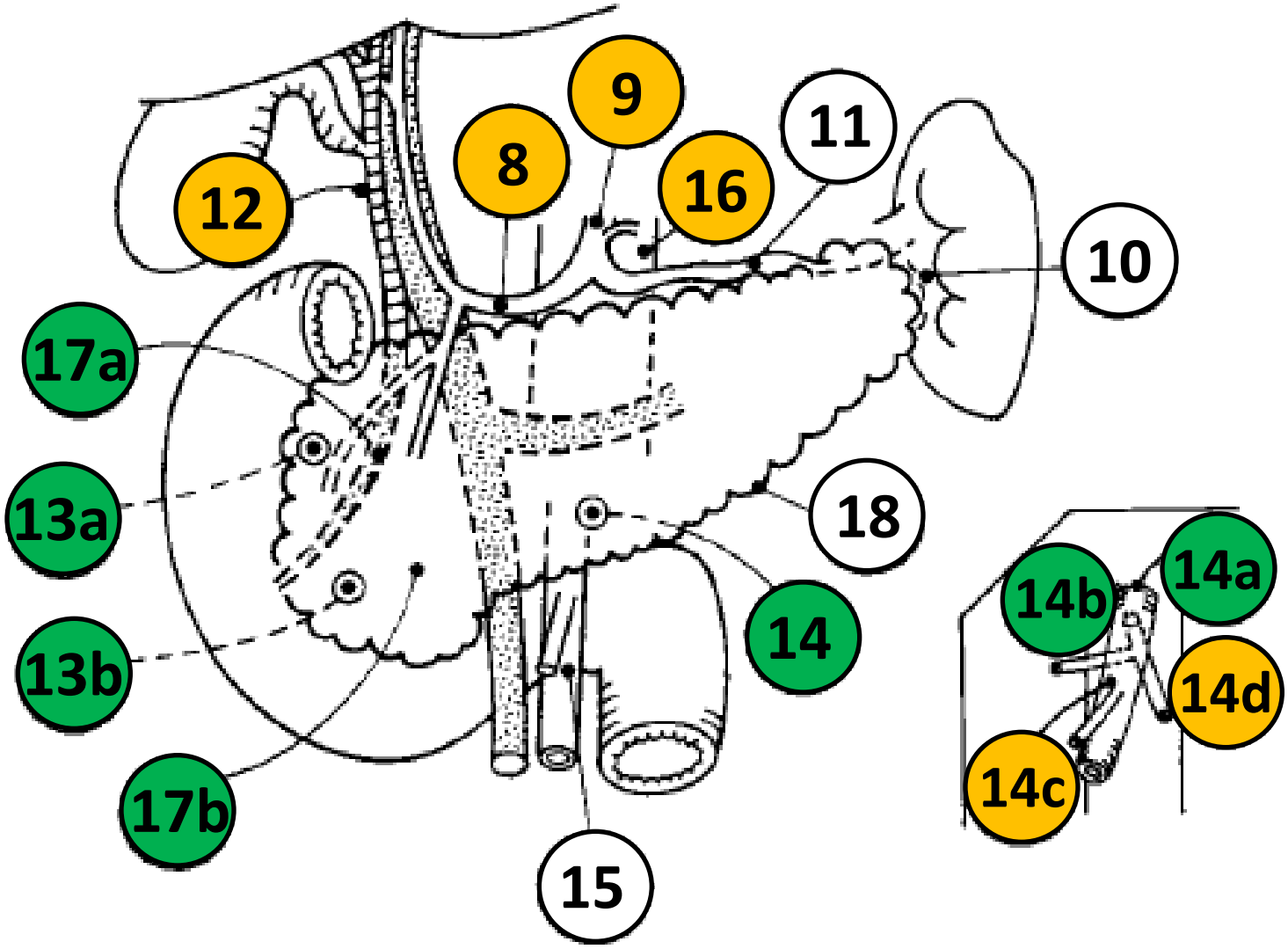
Skeletonization of hepatic arteries, SMA between aorta and inferior pancreaticoduodenal and celiac trunk, dissection of the anterolateral aspect of aorta and vena cava including Gerota's fascia (standard + all station 8, 9, all 12, all 14, 16a2, 16b1

“Standard Resection”



Kayahara et al. Cancer 85(3);583-90

“Extended Resection”



Kayahara et al. Cancer 85(3);583-90

The Japanese Experience

5 yr Survival of 28 - 33.4%!!!

References	No. patients (standard/Extended)	3-year survival (standard, %/extended, %)	5-year survival (standard, %/extended, %)
Ishikawa *et al.*[45]†	59 (37/22)	13/22	13/18
Manabe *et al.*[46]†	74 (42/32)	0/38	0/33
Satake *et al.*[47]†	151 (72/57)	34/39	27/28
Imaizumi *et al.*[8]	316 (67/249)	10/13	8/9
Kawarada *et al.*[48]†	65 (11/54)	9/18	0/13

Samra et al. ANZ J Surgery, 2008; 78: 228-236

The Japanese Experience

5 yr [illegible]al of 28 [illegible]4%!!!

References	No. patien… (standard/Extend…	…ed, %)	5-year survival (standard, %/extended, %)
Ishikawa *et al.*[45]†			13/18
Manabe *et al.*[46]†			0/33
Satake *et al.*[47]†			27/28
Imaizumi *et al.*[8]	…/249)	10/…	8/9
Kawarada *et al.*[48]†	65 (11/54)	9/18	0/13

Samra et al. ANZ J Surgery, 2008; 78: 228-236

Comparison of 4 Randomized Trials

Variable	Pedrazzoli 1998 	Yeo 2002 	Nimura 2004 	Farnell 2005 
Institution	Multi	Single	Multi	Single
Adjuvant Tx		X		X
En bloc	X		X	
Only Adeno Carcinoma	X		X	X
Similar LN stations	X		X	X

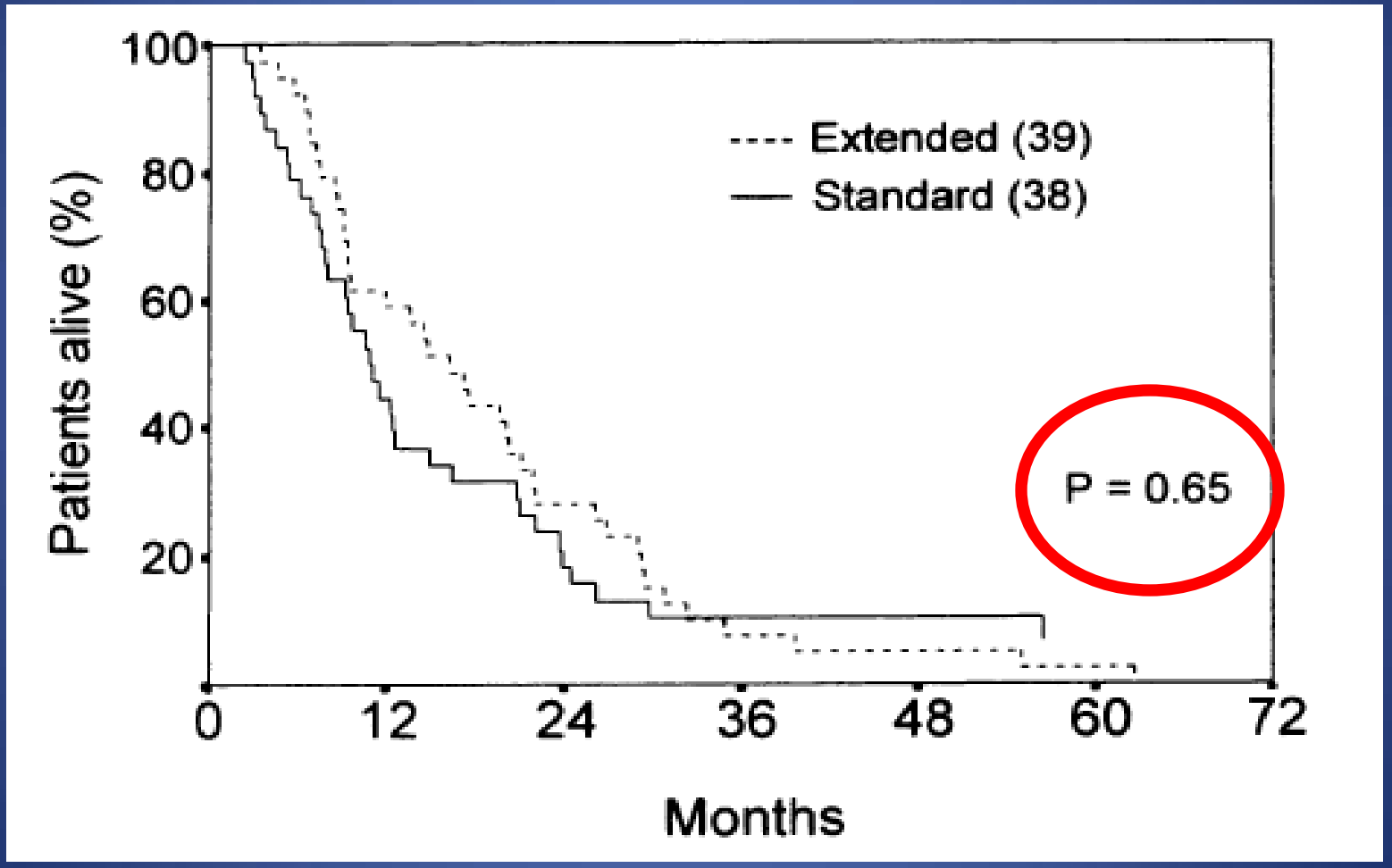
Farnell et al. J Gastrointestinal Surgery 2008;12:651-656

The Italian Experience Pedrazzoli et al. 1998

- 81 patients (40 standard vs 41 extended)
- 1991-1994
- Extended along aorta from diaphragm to IMA
- Pylorus preserved in maj, surgeon preference
- Mean LN harvest 13.3 vs 19.8 ($p<0.03$)
- Operative time 30 min longer
- 4 year survival no difference

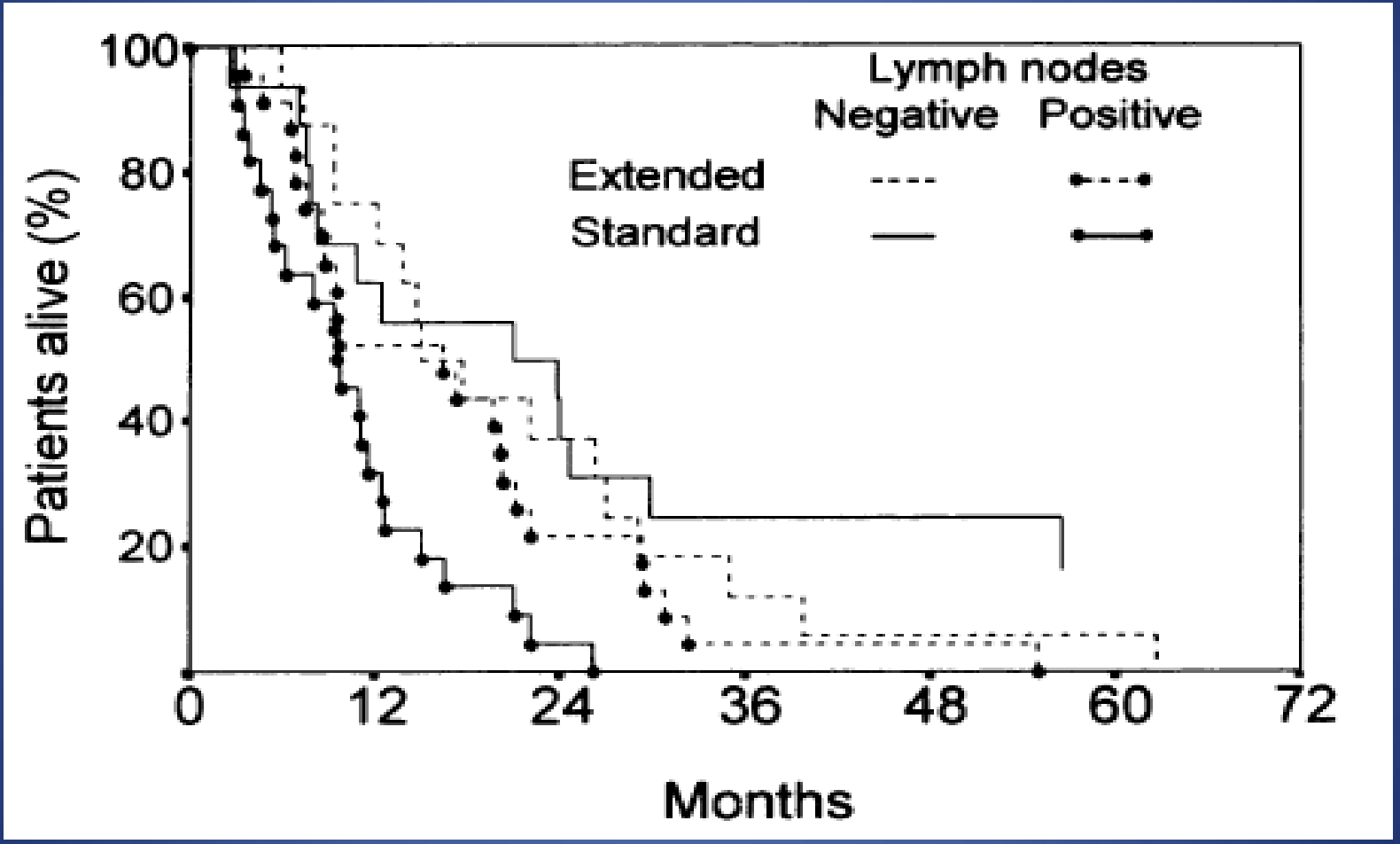
Pedrazzoli et al. Annals of Surgery, 1998; 228: 508-517

Actuarial Survival



Pedrazzoli et al. Annals of Surgery, 1998; 228: 508-517

Actuarial Survival, LN Status

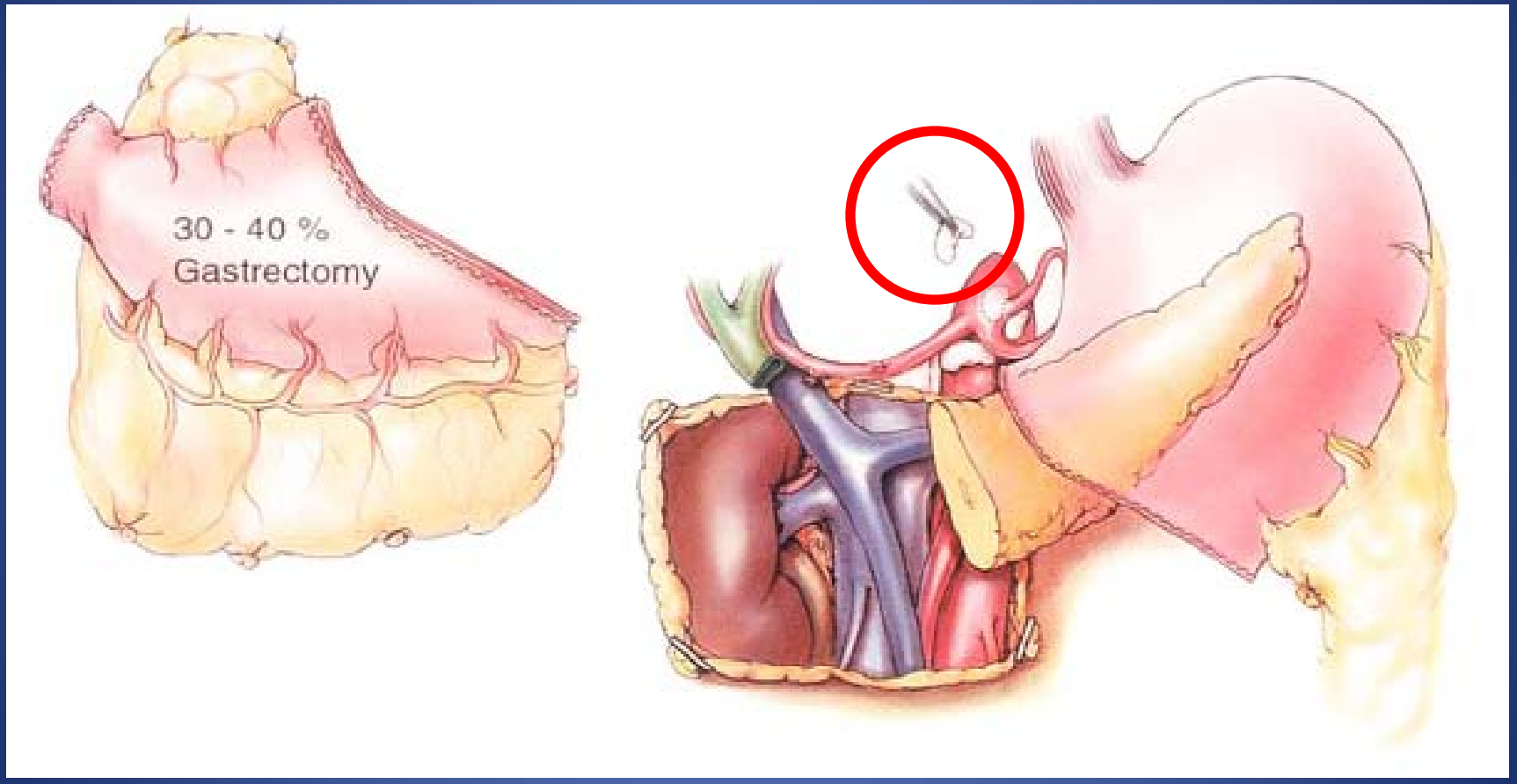


Pedrazzoli et al. Annals of Surgery, 1998; 228: 508-517

The Johns Hopkins Experience Yeo et al. 2002

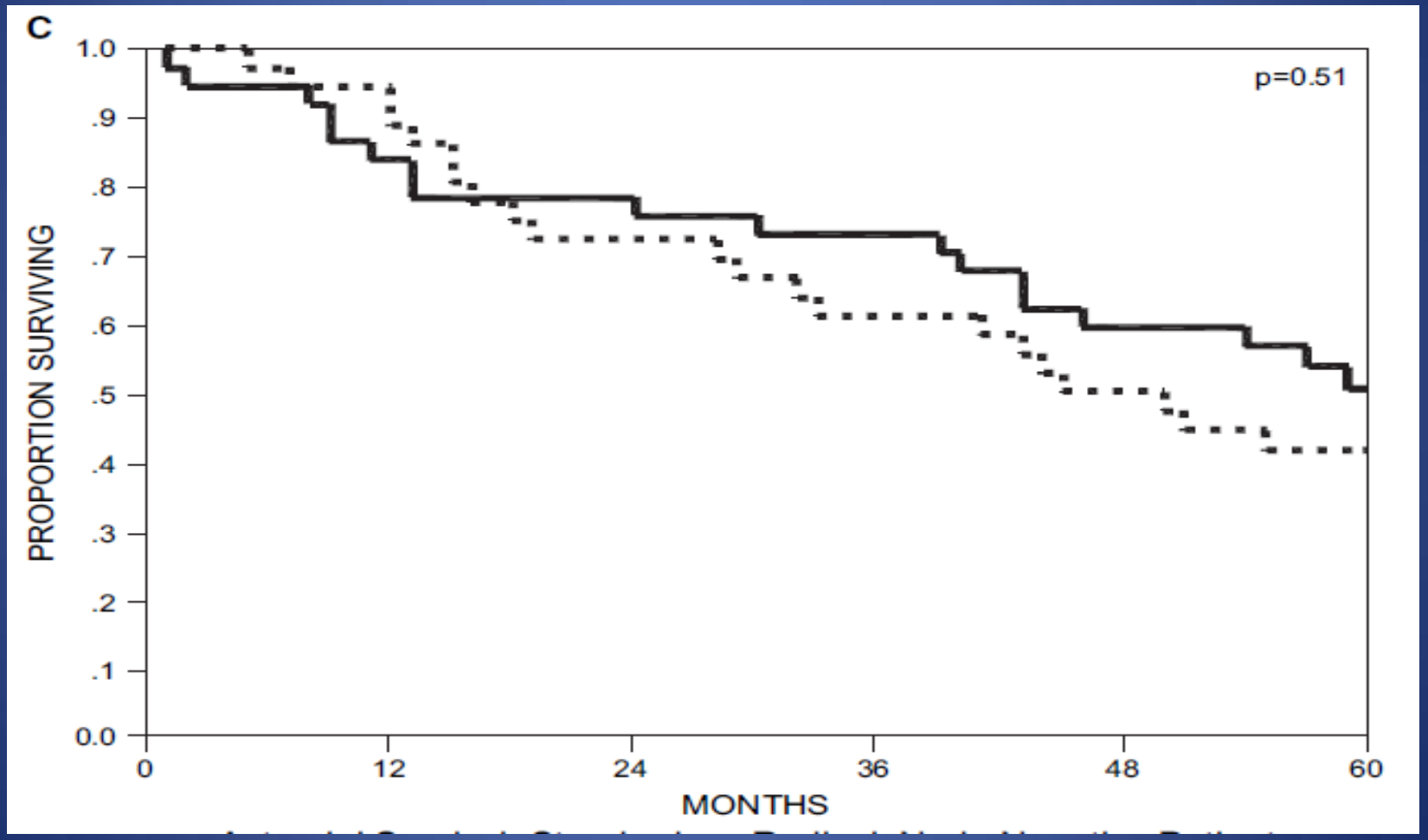
- 294 patients (146 standard vs 148 extended)
- 162 adenocarcinoma (80 standard vs 82 extended)
- Standard – Pylorus preserving
- Extended – Distal gastrectomy
- Mean LN harvest 17 vs 28.5 (p=.001)
- Operative time: 5.9 vs 6.4 (p=0.02)

“Extended Operation”



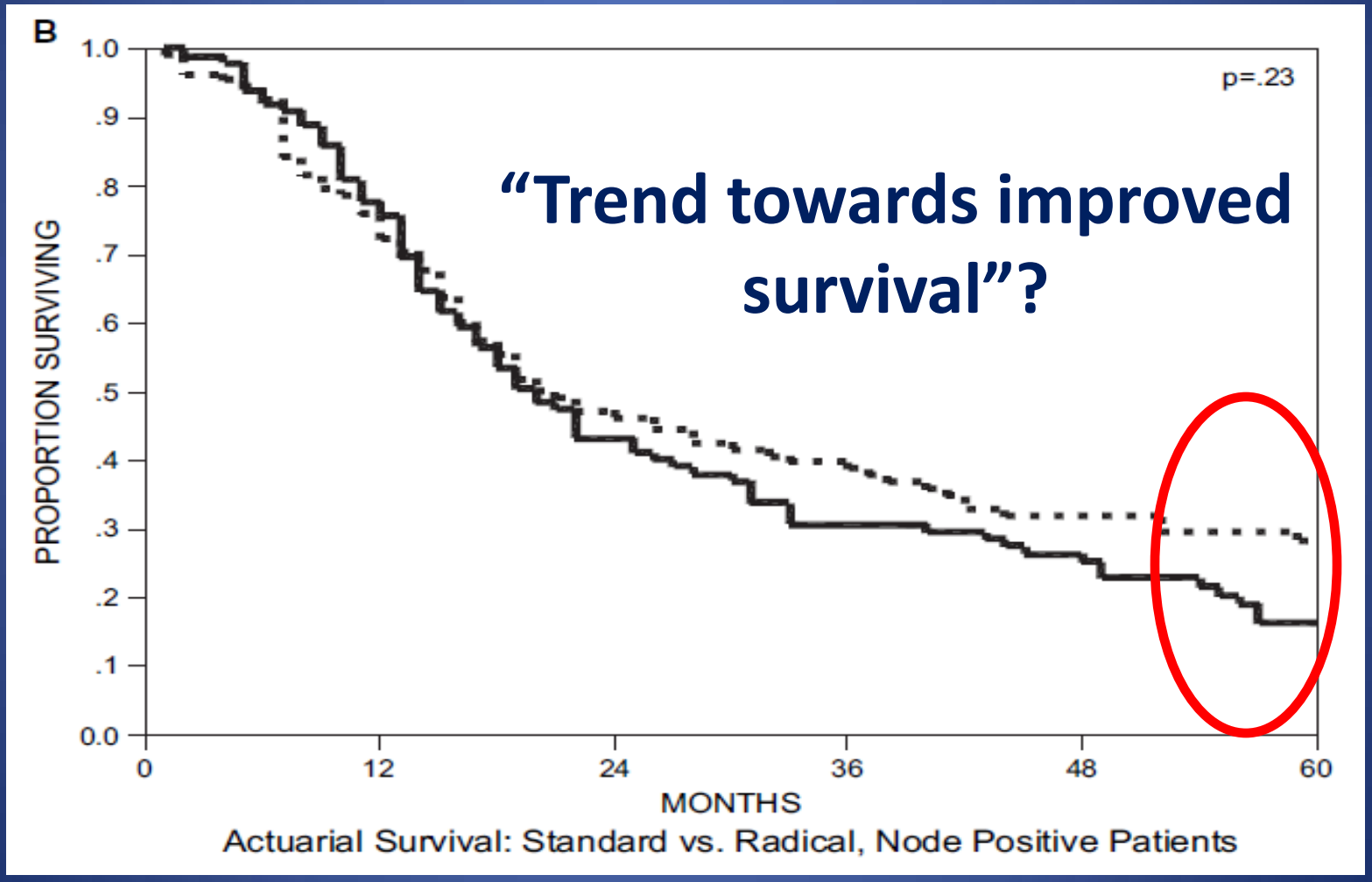
30-40% distal gastrectomy, LN station 3,4,5,6, 9, 16

Actuarial Survival
Standard vs Extended, Node Negative



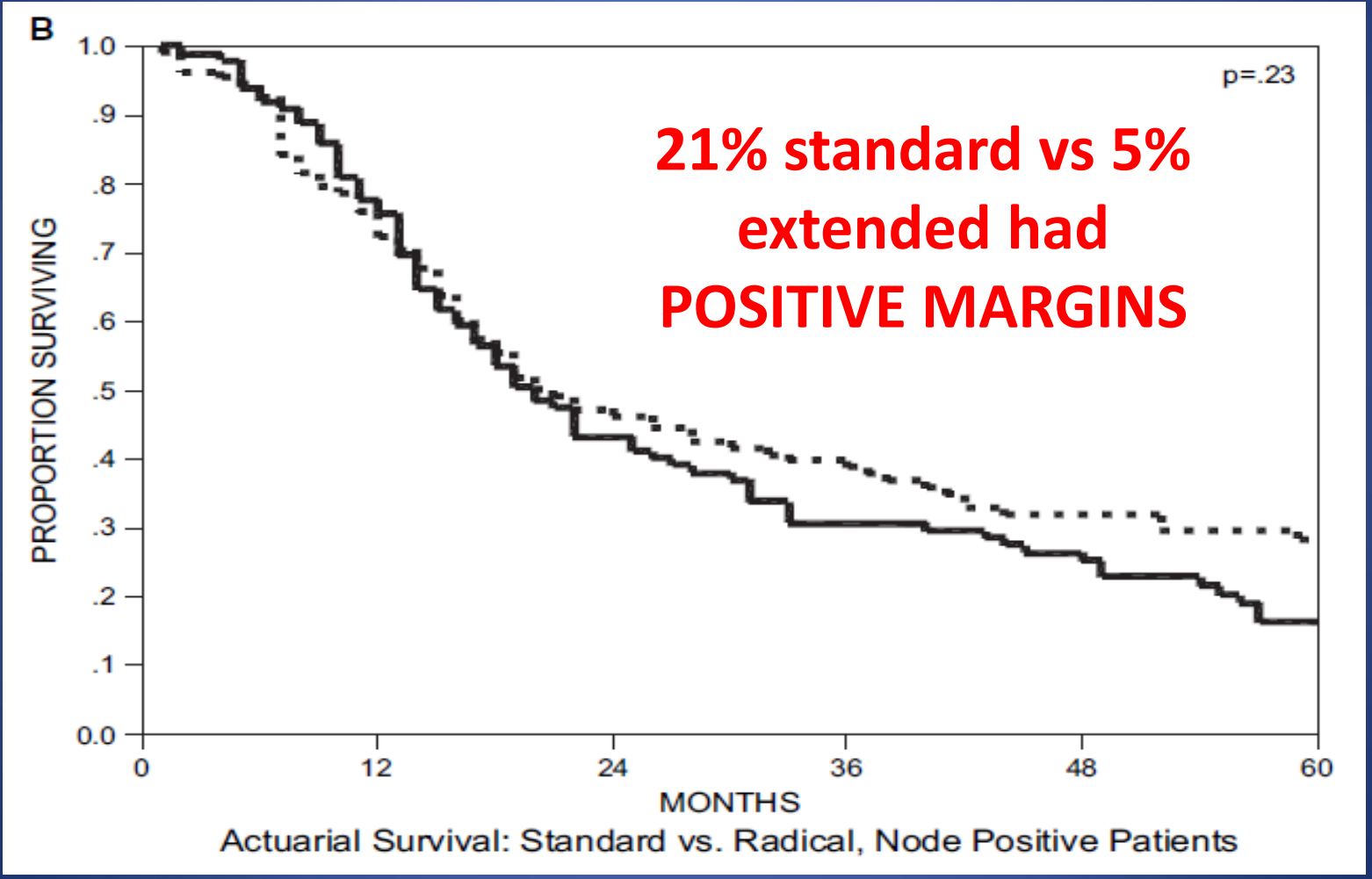
Riall et al. Journal of Gastrointestinal Surgery, 2005; 9:1191- 1206

Actuarial Survival
Standard vs Extended, Node Positive



Riall et al. Journal of Gastrointestinal Surgery, 2005; 9:1191- 1206

Actuarial Survival
Standard vs Extended, Node Positive

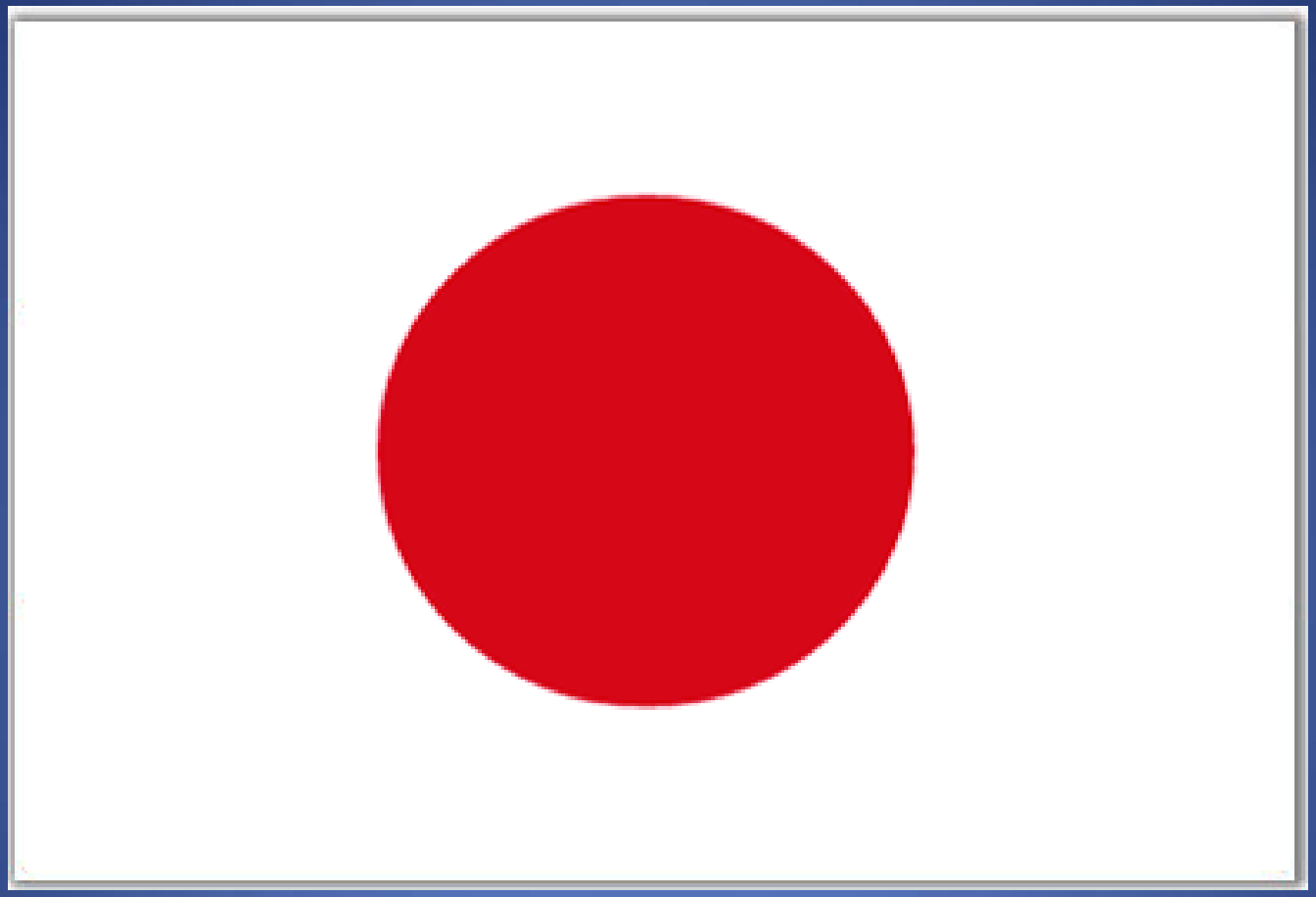


Riall et al. Journal of Gastrointestinal Surgery, 2005; 9:1191- 1206

Postoperative Complications

Variable	Standard	Extended	P value
Any Complication	42 (29%)	**64 (43%)**	**0.01**
Delayed Gastric Emptying	9(6%)	**24 (16%)**	**0.006**
Pancreatic Fistula	9 (6%)	**19(13%)**	**.05**
Wound Infection	7 (5%)	16 (11%)	0.06
LOS	11.3	**14.3**	**0.003**

Overall Morbidity 29 vs 43% (p<0.01)



?

6 REGIONAL VERSUS EXTENDED LYMPH NODE DISSECTION IN RADICAL PANCREATODUODENECTOMY FOR PANCREATIC CANCER: A MULTICENTER, RANDOMIZED CONTROLLED TRIAL

Yuji Nimura, Masato Nagino, Hiroyuki Kato, Shuichi Miyagawa, Akihiro Yamaguchi, Taira Kinoshita, Sonshin Takao, Tadahiro Takada, Koji Miyazaki, Shuichi Ishiyama, Hiroshi Shimada, Yoshifumi Kawarada, Hiroshi Takeda, Koro Sagota and Kenzo Yasui, Nagoya University Hospital, Nagoya, Japan, Nagoya University Hospital, Hokkaido University Hospital, Fujita Health University Hospital, Ogaki Municipal Hospital, National Cancer Center Hospital East, Kagoshima University Hospital, Teikyo University Hospital, Saga Medical University Hospital, National Sendai Hospital, Yokohama City University Hospital, Mie University Hospital, National Osaka Hospital, Kagoshima Medical Association Hospital and Aichi Cancer Center Hospital

PURPOSE: The purpose of this study was to evaluate, in a multicenter randomized controlled trial (RCT), whether an extended lymph node dissection in radical pancreatoduodenectomy prolongs the survival of patients with pancreatic cancer. METHODS: From March 2000 to May 2003, 112 patients with carcinoma of the head of the pancreas were enrolled. After intraoperative investigation, patients were randomized to regional or extended (regional plus para-aortic) lymphadenectomy in radical pancreatoduodenectomy. None of the patients received any adjuvant therapy. All pathology specimens were reviewed and categorized, and morbidity, mortality, survival and quality of life were analysed. RESULTS: Of the 112 patients randomized, 11 were subsequently excluded because of the final pathology (7 chronic pancreatitis and 4 bile duct cancer), and the remaining 101 patients were analysed (51 regional vs 50 extended). There was no significant difference between the 2 groups with regard to age, gender and BMI. Although the mean operative time (426 minutes vs 547 minutes), intraoperative blood loss (1118 ml vs 1680 ml), number of retrieved lymph nodes (13 vs 40) and incidence of postoperative diarrhea (0 vs 24) differed in the 2 groups, there was no significant difference with respect to transfusion requirements, type of resection, overall morbidity excluding diarrhea, postoperative length of hospital stay (44 vs 42), mortality (0 vs 1), histological stage of the disease and QOL at 1 year after surgery. The 1-, 2- and 3-year survival rates for all 101 patients (78.7, 43.2, 32.4 vs 51.3, 39.9, 16.0%) and those with negative or positive node disease and disease-free survival (42.3, 17.8, 6.7 vs 48.8, 16.0, 12.0%) showed no significant difference between the 2 groups. CONCLUSIONS: In this multicenter RCT, radical pancreatoduodenectomy with extended lymph node dissection did not provide any survival benefit in the treatment of patients with resectable pancreatic cancer.

Nimura et al. HPB Off J Int Hepato Pancreato Biliary Assoc 2004;6(suppl 1):2, Abstract.

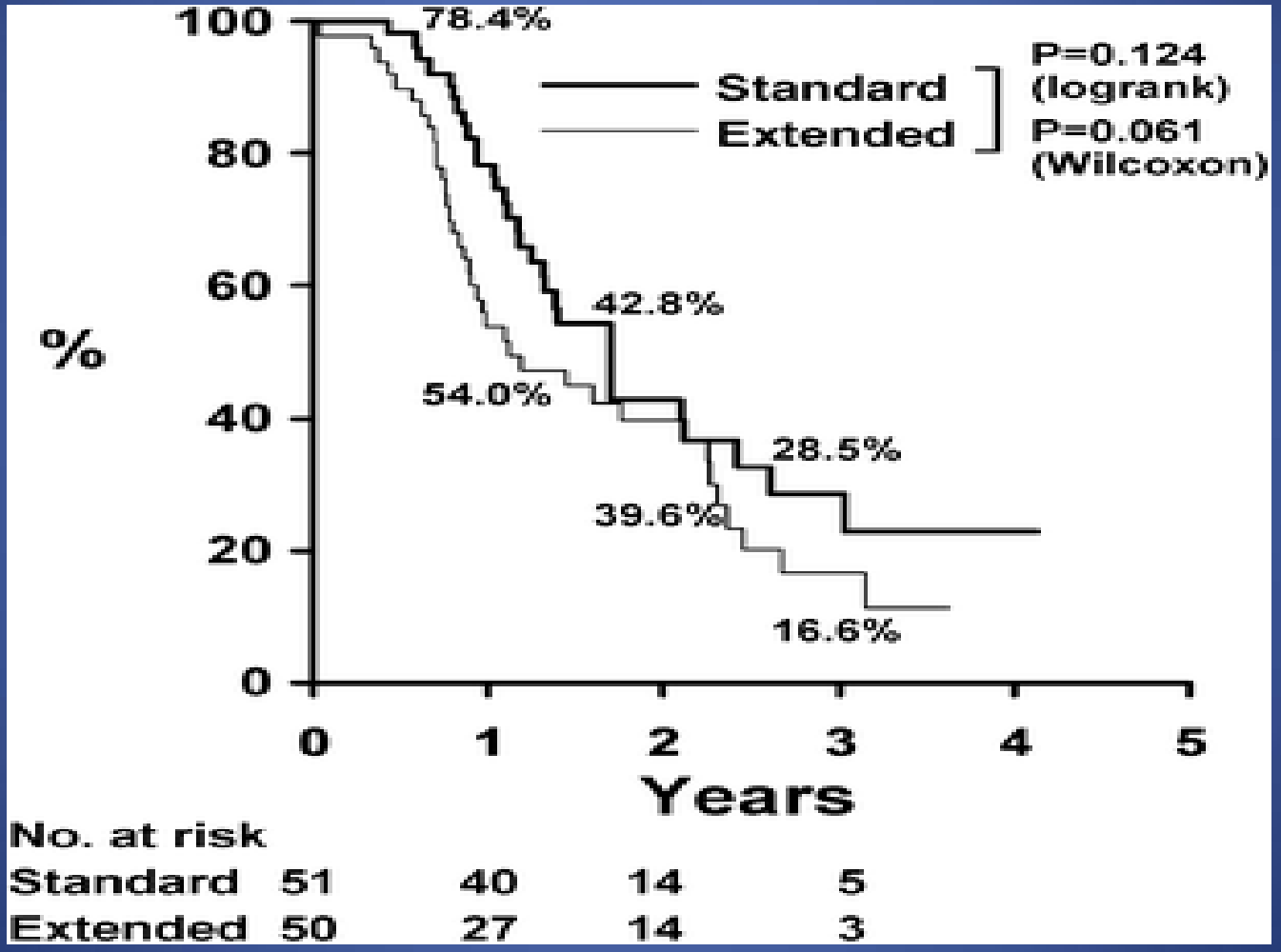
Multicenter randomized trail Nimura et al. 2004

- 101 patients (51 standard vs 50 extended)
- LN harvest - standard 13 vs extended 40
- 1, 2, 3 – year survival the same in both groups

“extended lymph node dissection did not provide any survival benefit in the treatment of patients with resectable pancreatic cancer”

Nimura et al. HPB Off J Int Hepato Pancreato Biliary Assoc 2004;6(suppl 1):2, Abstract.

Actuarial Survival



Survival curve provided by Yuji Nimura, M.D., President, Aichi Cancer Center, Nagoya, Japan

The Mayo Clinic Experience Farnell et al. 2005

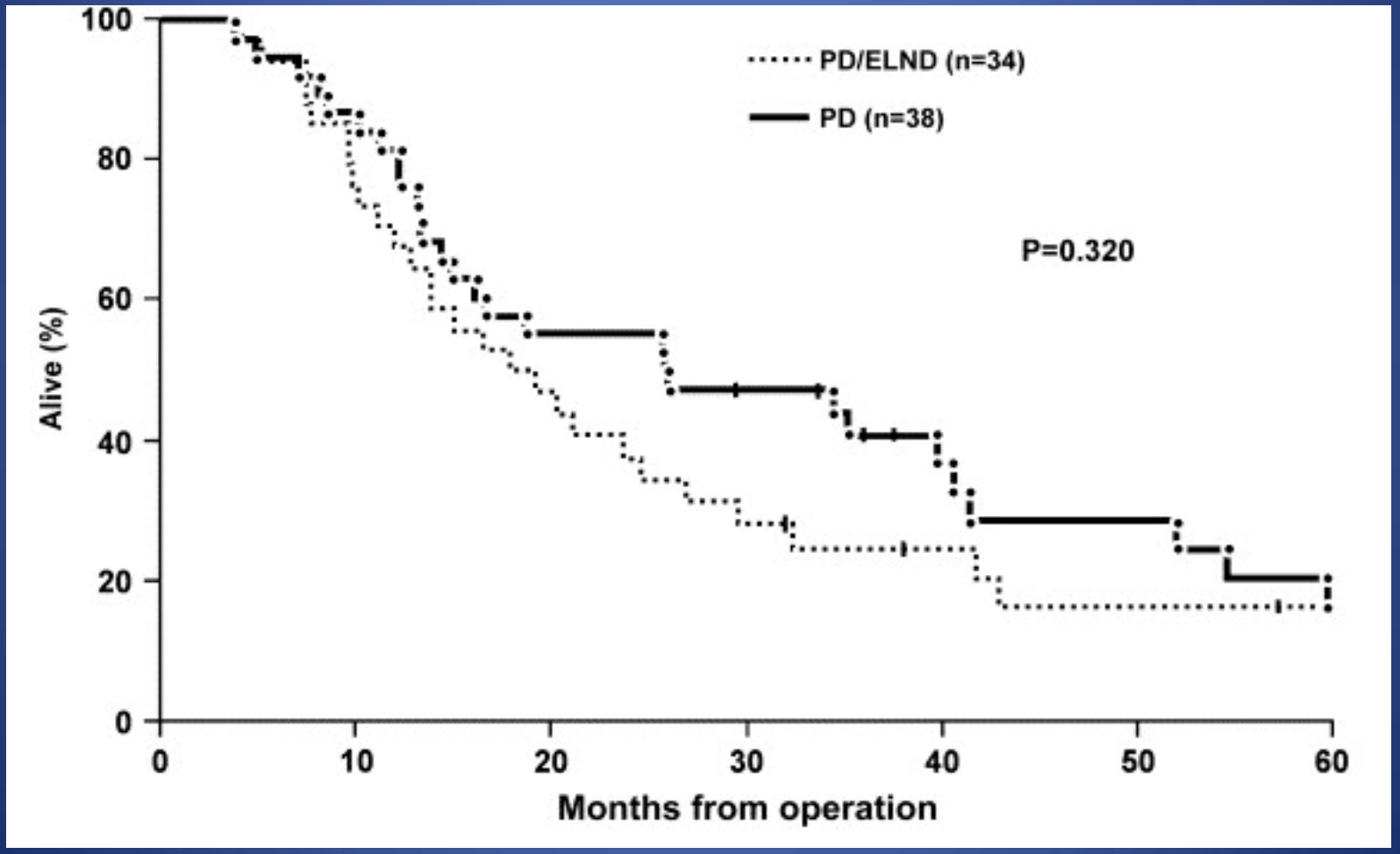
- 79 patients (40 standard, 39 ELN)
- Non-pylorus preserving
- 75% patients received adjuvant chemotherapy

Variable	Standard	Extended	P value
Operative Time	6.2 hrs	**7.6 hrs**	< .001
Transfusion (1)	5%	**23%**	.01
Lymph Nodes	15	**36**	< .001

Farnell et al. Surgery; 2005138:618-630

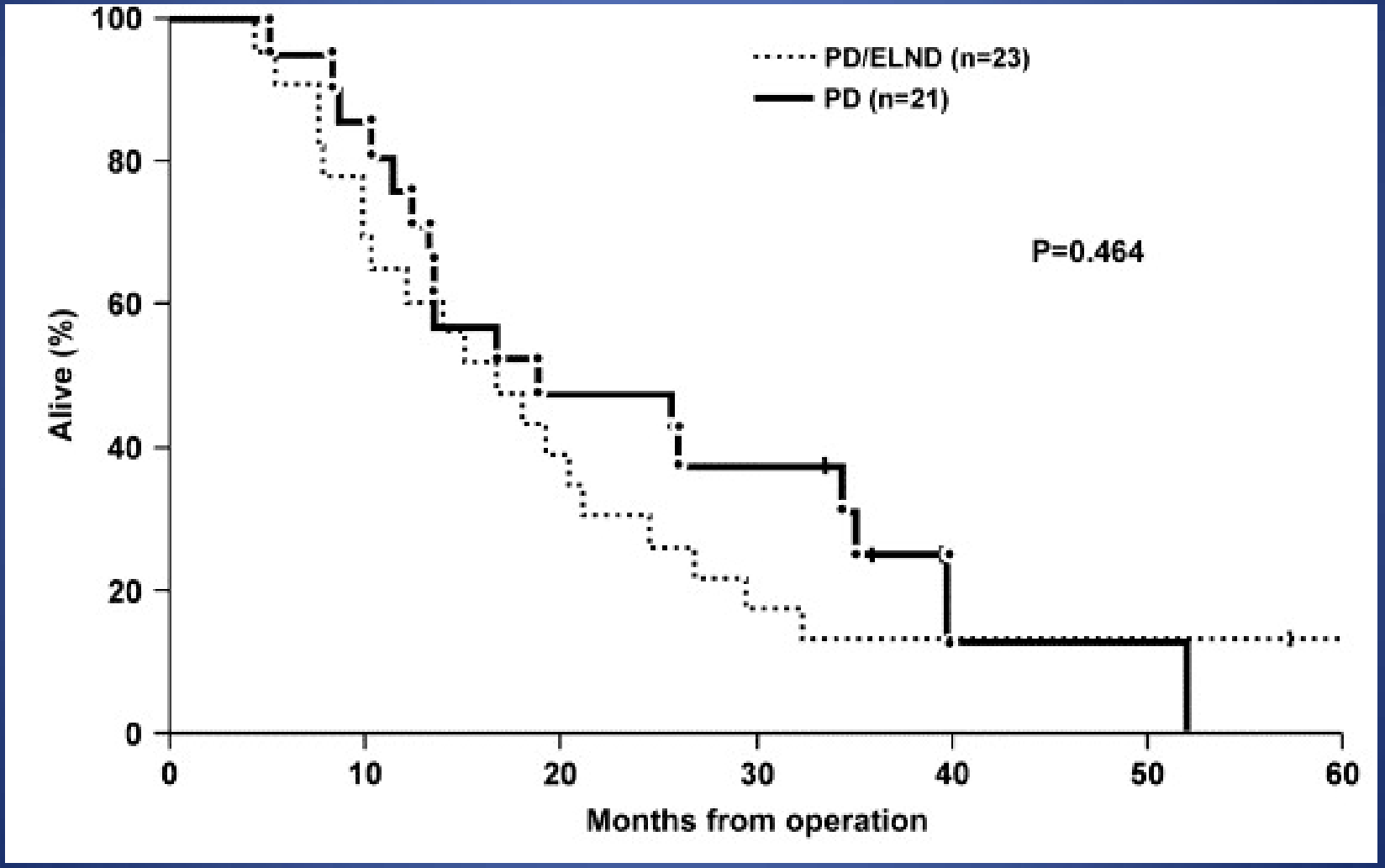
MAYO CLINIC

Overall Survival



Farnell et al. Surgery; 2005138:618-630

Positive Lymph Node Survival



Farnell et al. Surgery; 2005138:618-630

Quality of Life at 4 months

Variable	Standard	Extended	P value
Physical Well-being	0	-14.3	.37
Emotional Well-being	10	0	.30
Bowel Control	0	-25	**.038**
Diarrhea	25	-50	**.002**
Appearance	0	-50	**.005**
Additional Concerns	5.6	-22.2	**.002**

53% of extended patients had "no control" or "little control" of bowels vs 9% in standard

Farnell et al. Surgery; 2005138:618-630

The Mayo Clinic Experience

After interim analysis, the trial was terminated on July 31, 2003

Farnell et al. Surgery; 2005138:618-630

The Mayo Clinic Experience

"Quality-of-life issues in our patients 4 months postoperatively, lack of improvement in survival, and the aforementioned published prospective randomized trials should put to rest the controversy that more radical operation confers improved survival."

Farnell et al. Surgery; 2005138:618-630

Cancer Math 101

Feasibility of a Randomized Trial of Extended Lymphadenectomy for Pancreatic Cancer

Timothy M. Pawlik, MD, MPH; Eddie K. Abdalla, MD; Carlton C. Barnett, MD; Syed A. Ahmad, MD; Karen R. Cleary, MD; Jean-Nicolas Vauthey, MD; Jeffrey E. Lee, MD; Douglas B. Evans, MD; Peter W. T. Pisters, MD

- 1998-2002
- 304 patients underwent pancreticoduodenectomy for adenocarinoma
- 158 patients with 2nd-echelon nodes
- Median survival 26.5 mo vs 24.7 mo p=0.91

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Assumptions

1) Only patients who have pathologically involved second echelon lymph nodes can benefit from extended lymphadenectomy.
2) R0 resection is required for extended lymphadenectomy to confer a possible survival benefit.
3) Only patients who have involved second-echelon lymph nodes and are M0 may derive a potential survival benefit from the removal of additional pathologically positive lymph nodes.

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Fraction who may derive benefit

= *FN2 x FN0 × FTM0*

LN Status	Patients (%)	R0 Resection (%)
Negative 1st Negative 2nd	76 (48.1)	89.5%
Positive 1st Negative 2nd	65 (41.1)	84.6%
Positive 1st **Positive 2nd**	17 (10.8)	47.1% p<.001

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Fraction who may derive benefit

= FN2 x FN0 × FTM0

LN Status	Patients (%)	R0 Resection (%)
Negative 1st Negative 2nd	76 (48.1)	89.5%
Positive 1st Negative 2nd	65 (41.1)	84.6%
Positive 1st **Positive 2nd**	17 (10.8)	47.1% p<.001

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Fraction who may derive benefit

= *FN2 x FN0 × FTM0*

LN Status	Patients (%)	R0 Resection (%)
Negative 1st Negative 2nd	76 (48.1)	89.5%
Positive 1st Negative 2nd	65 (41.1)	84.6%
Positive 1st **Positive 2nd**	17 (10.8)	47.1% p<.001

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Fraction who may derive benefit

= *FN2 x FN0 x FTM0*

LN Status	Patients (%)	R0 Resection (%)
Negative 1st Negative 2nd	76 (48.1)	89.5%
Positive 1st Negative 2nd	65 (41.1)	84.6%
Positive 1st **Positive 2nd**	**17 (10.8)**	47.1% p<.001

4/17 (23.5%) Alive

1/17 (5.9 %) ALIVE without recurrent disease

Fraction who may derive benefit

= FN2 x FN0 × FTM0

= 10.8% x 47.1% x 5.9%

= 0.3%

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

Feasibility of Randomized Trial

- 3/1000
- 5yr survival standard: 27.3%
- 5 yr survival extended: 27.52%
- 202,000 patients in each arm
- 1010 year accrural period

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

400 patients
4 Randomized Trials
What Have We Learned?

Pawlik et al. Archives of Surgery, 2005; 140:v584-591

What Have We Learned?

- Extended lymphadenectomy adds 1 hour to operative time
- Significantly more LN are taken
- Less bowel control and more diarrhea

Does NOT increase survival

Final Thoughts

- Systemic disease
- Local therapy yields minimal improvement
- Less radical surgery as in breast and gastric cancer
- Early detection and ? chemoprevention
- Gene expression and protein biochip technology
- Better adjuvant / neo-adjuvant therapies
- Immunotherapy

Final Thoughts

- Systemic disease
- Local therapy yields minimal improvement
- Less radical surgery as in breast and gastric cancer
- **Early detection and ? chemoprevention**
- **Gene expression and protein biochip technology**
- **Better adjuvant / neo-adjuvant therapies**
- **Immunotherapy**

Thank You