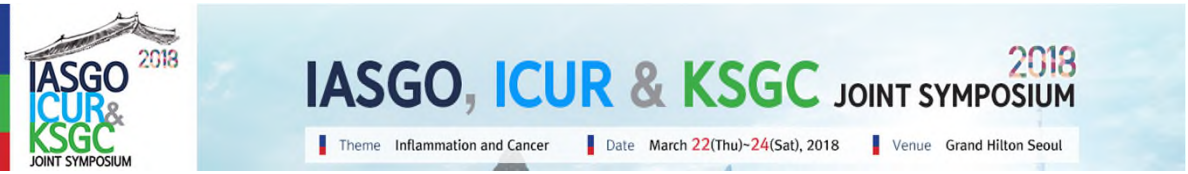

Locally Advanced Pancreatic Cancer

Surgical Perspectives

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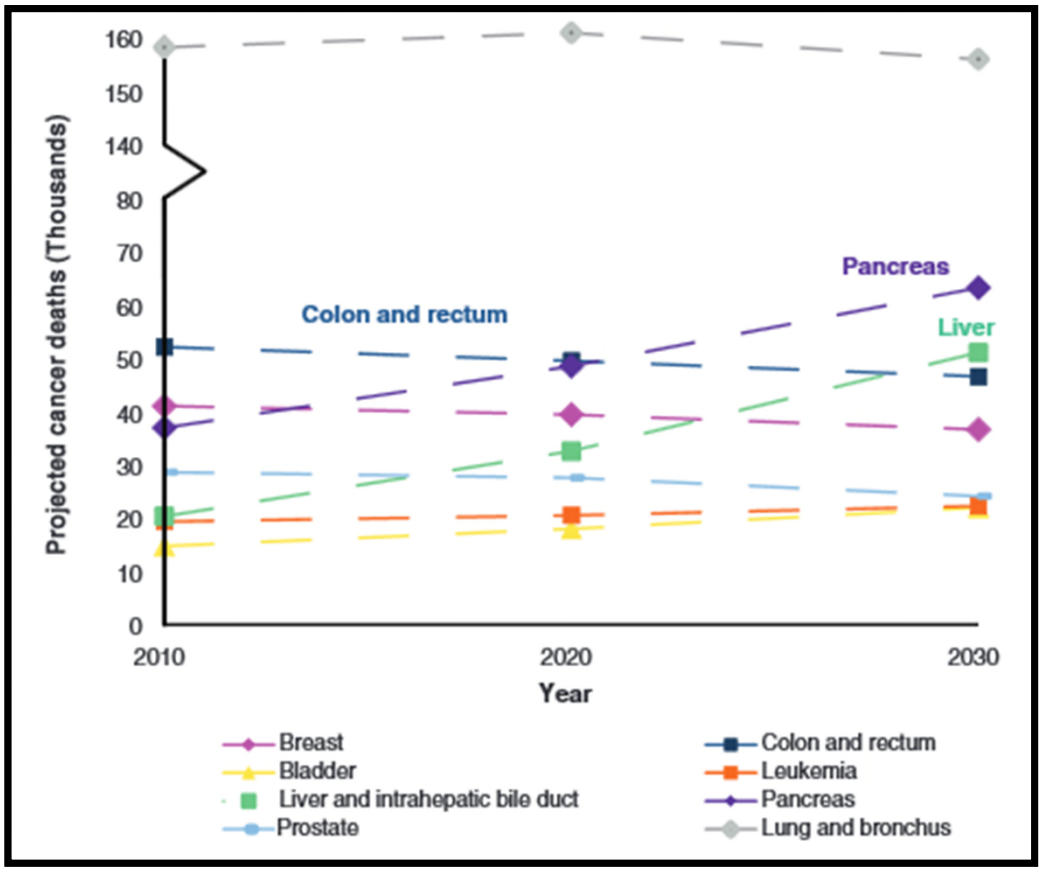
Pancreatobiliary Cancer Center, Severance Hospital, Seoul, Korea

Perspective

Cancer Research

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib[1], Benjamin D. Smith[2], Rhonda Aizenberg[1], Allison B. Rosenzweig[1], Julie M. Fleshman[1], and Lynn M. Matrisian[1]



"Attention has been called to the projected top three cancer killers in 2030: *lung*, ***pancreatic***, and *liver cancer*, through the Recalcitrant Cancer Research Act signed into law by President Obama in January 2013 ."

Cancer Res; 74(11) June 1, 2014

Pancreatic Cancer Surgery:

Oncologic significance

- "Margin-negative pancreatectomy is known to be the most effective monotherapy in treating pancreatic cancer."

- "Postoperative adjuvant chemotherapy should be mandatory for improving oncologic outcome."

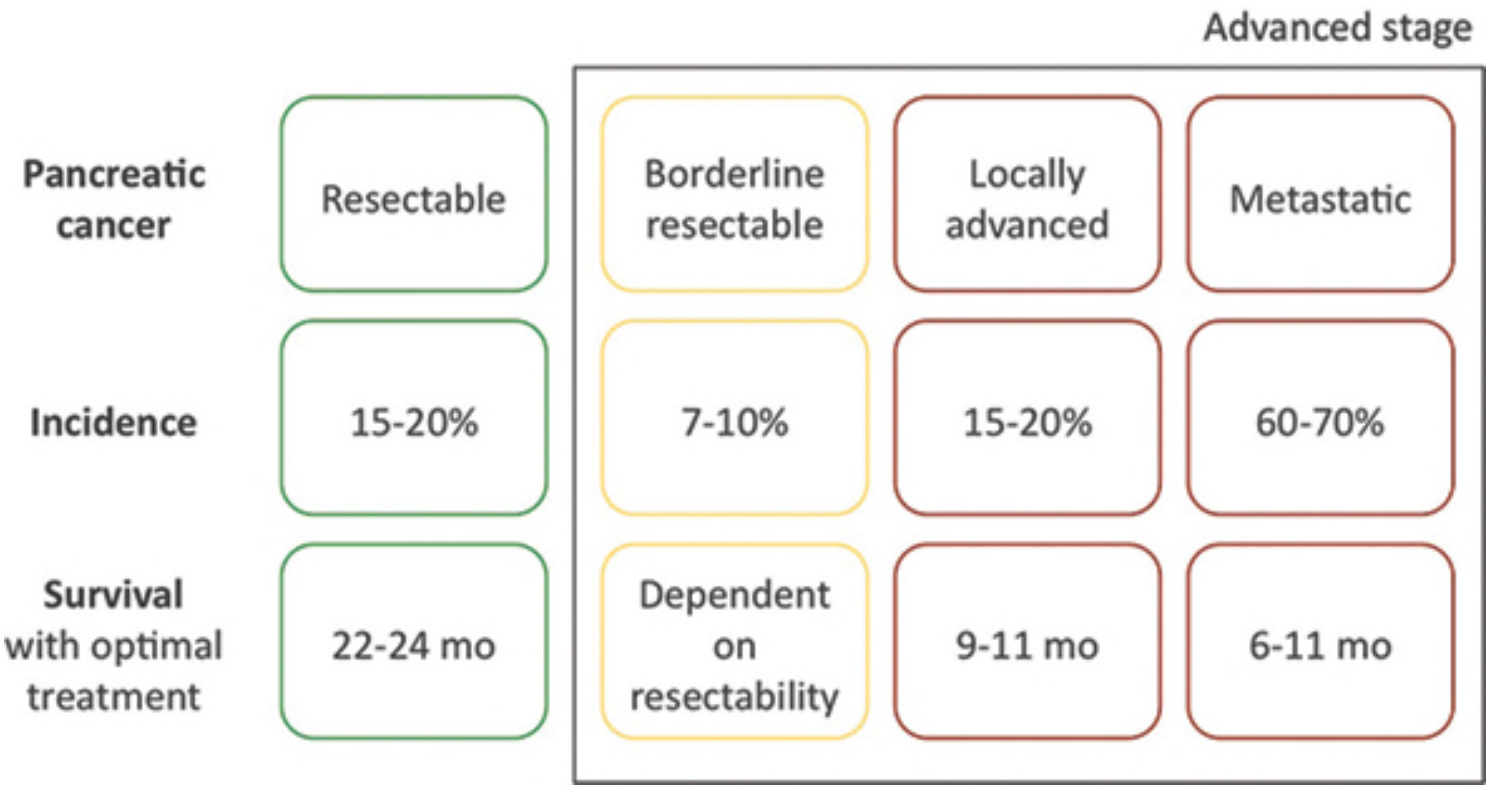
Chapter 10

OPEN ACCESS

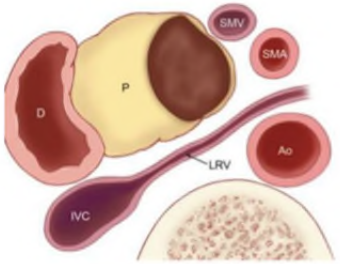
The Role of Vascular Resection in Pancreatic Cancer Treatment

By Nikola Vladov, Ivelin Takorov and Tsonka Lukanova

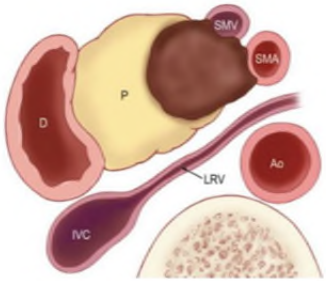
DOI: 10.5772/66910



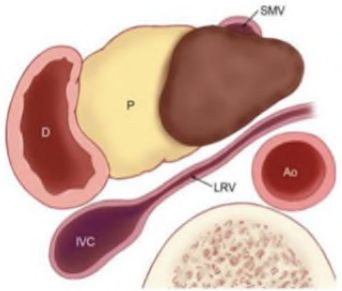
Resectability: 2017 NCCN guideline



Resectable



Borderline Resectable



Locally Advanced

CRITERIA DEFINING RESECTABILITY STATUS[1]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[2]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° • Solid tumor contact with the first jejunal SMA branch Body and tail • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

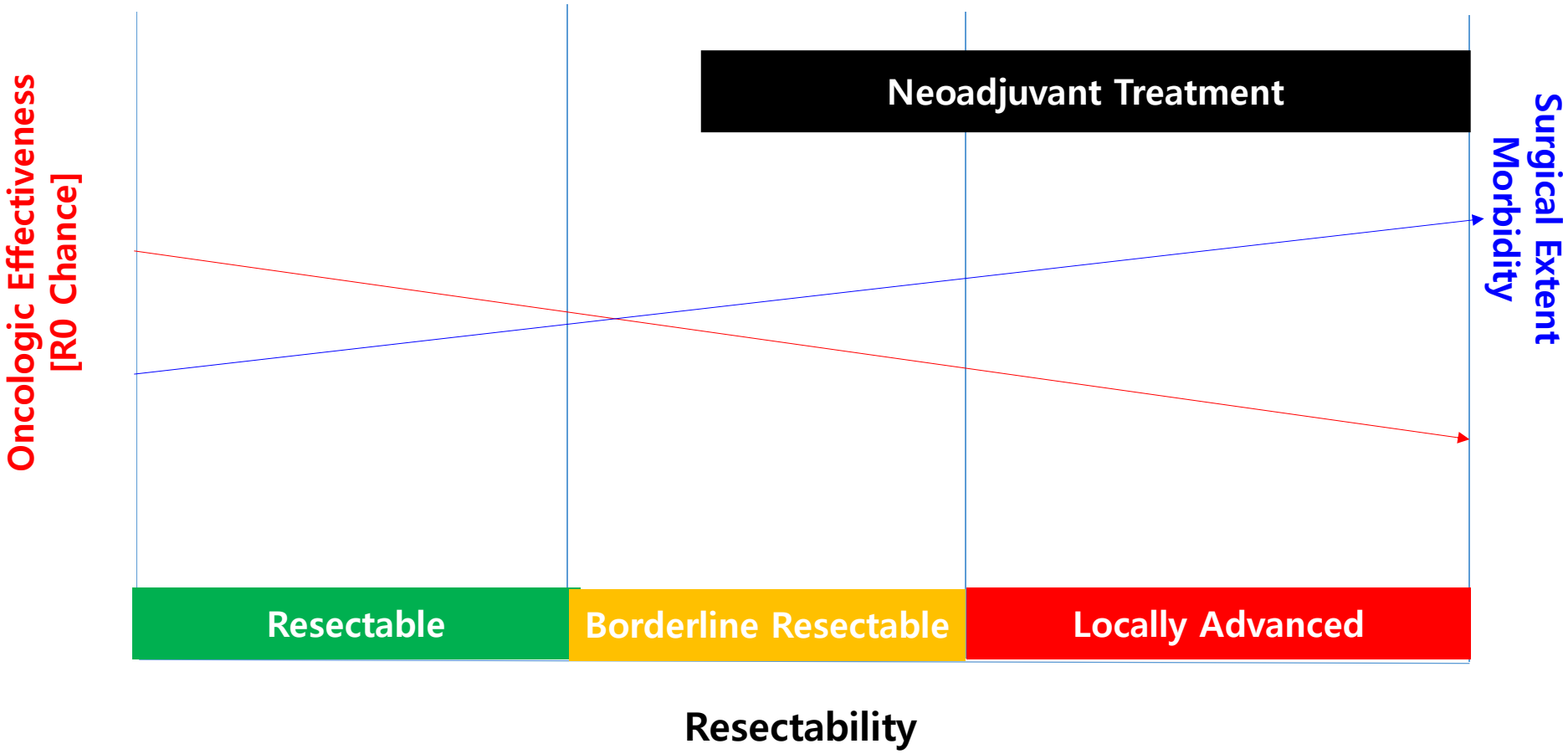
Definition Concept for Resectability
[Surgeon's view]

Resectability	Oncologic Outcome	Surgical Extent
Resectable	High chance of R0 resection	Standard surgery: PD(PPPD) / DPS Acceptable morbidity and mortality
Borderline Resectable	High chance of R1 (or possible R2) resection	+Combined resection /Extended dissection /Technically ***"Reconstructable"*** Acceptable morbidity and mortality
Locally Advanced (LAPC, Unresectable)	High chance of R2 resection	"Un-reconstructable" If any, high chance of morbidity and mortality ***No oncologic benefit***

"***Extended pancreatic resection*** can increase morbidity and mortality of pancreatic surgery"

Author, year	N (Total/ Extended)	Morbidity (Extended vs. Standard)	Mortality (Extended vs. Standard)	Comments
Sasson, 2002	116/37 (31.9%)	35% vs. 39%	2.7% vs.1.7%	
Shoup, 2003	57/22 (38.6%)	*9% vs. 0%	All 0%	*Relaparotomy
Adam, 2004	301/41 (13.5%)	65.9% vs.36.9%	NA	
Suzuki, 2004	95/12 (12.6%)	50% vs.44.6%	0%	
Kleeff, 2007	302/109 (36.1%)	34%vs. 23%	5.5% vs.0%	
Nikfarjam, 2009	105/19 (18.1%)	68% vs. 58%	0%	
Harwig, 2009	101/101 (100%)	36.6% vs.25.3%	*6.9%* vs. 3.5%	
Burdelski, 2011	55/55 (100%)	69% vs. 37%	7% vs. 4%	

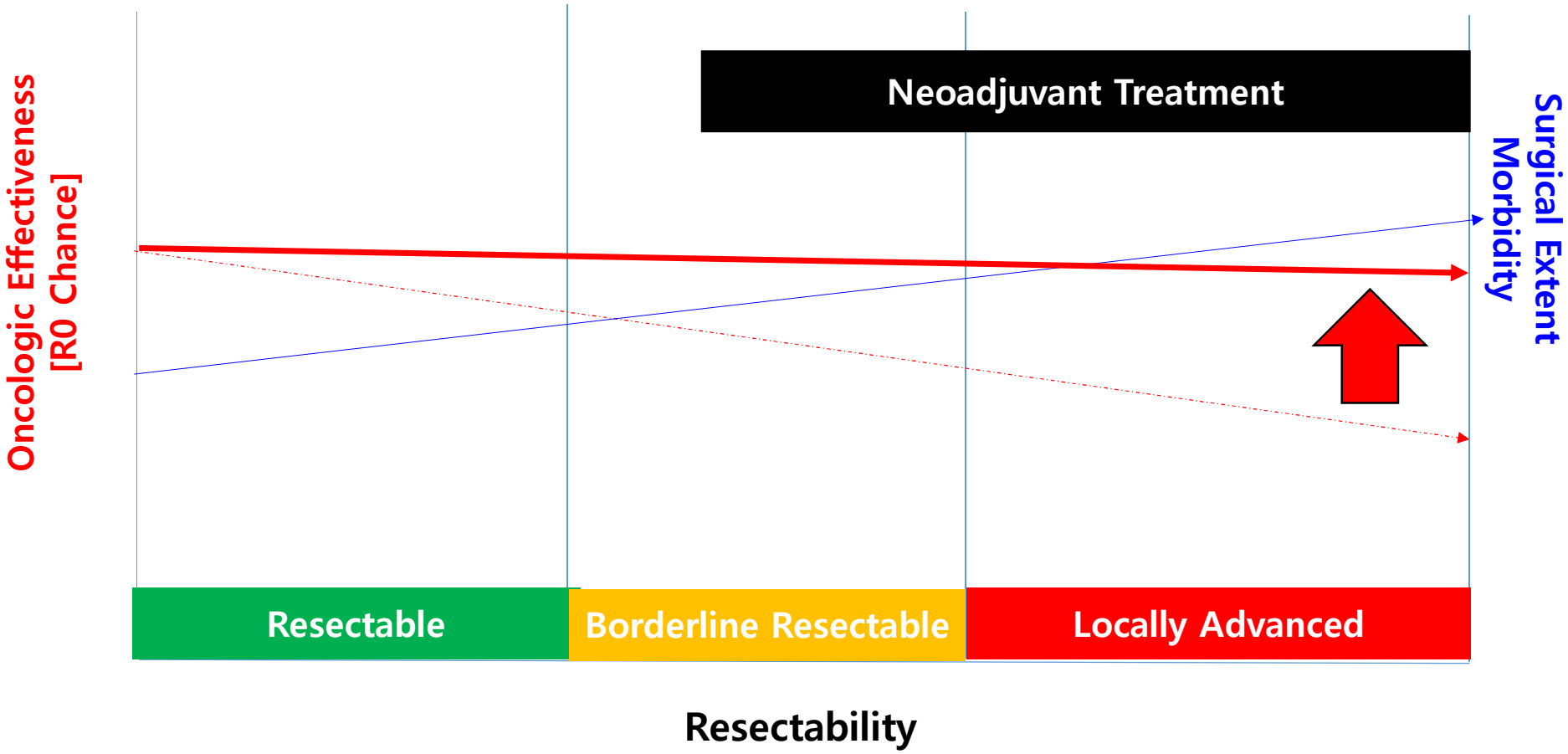
Radical Pancreatectomy: **Benefit ≥ Disadvantage**



Neo-adjuvant therapy
Rationales in pancreatic cancer

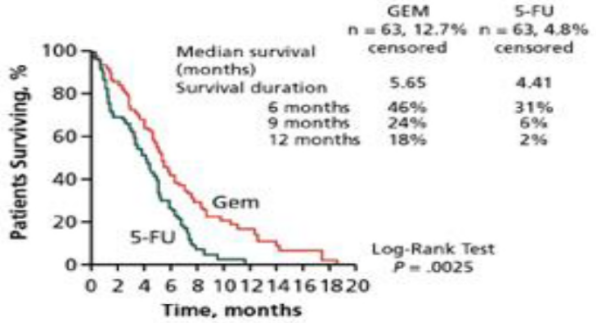
Table 2 Potential advantages of neoadjuvant therapy
Benefits of neoadjuvant therapy
The ability to deliver systemic therapy to all patients
Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of post-treatment, preoperative restaging who thereby avoid the toxicity of surgery
Increased efficacy of radiation therapy; free radical production in a well oxygenated environment
Decreased radiation induced toxicity to adjacent normal tissue as the radiated field is resected at the time of pancreatectomy
Decreased rate of positive resection margins; SMA margin in particular
Decreased rate of pancreatic fistula formation
Potential for the downstaging of borderline resectable tumors to facilitate surgical resection
Disadvantages of neoadjuvant therapy
Potential for complications from pre-treatment endoscopic procedures
Biliary stent related morbidity; stent occlusion during neoadjuvant therapy
Disease progression obviating resectability; loss of a “window” of resectability which may occur (rarely) in the borderline resectable patient
Physicians have to work together during the preoperative phase; discrete handoff from surgeon to medical oncologist to radiation oncologist is not possible in the neoadjuvant setting (as occurs with adjuvant therapy)

Radical Pancreatectomy: **Benefit ≥ Disadvantage**

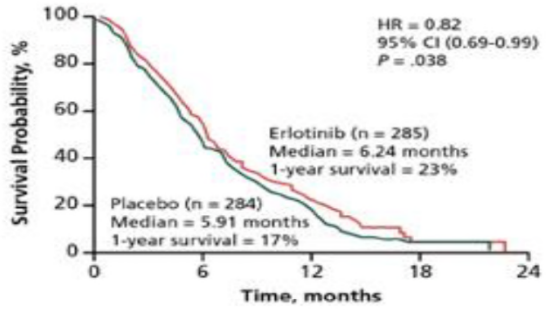


Clinical Trials

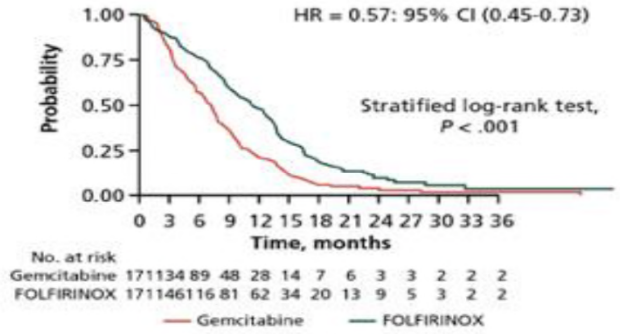
Potent chemotherapeutic agents for pancreatic cancer



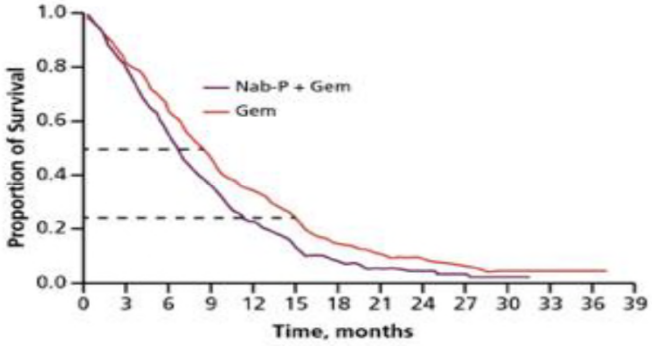
1995
Gemcitabine



2007
Gemcitabine/Erlotinib



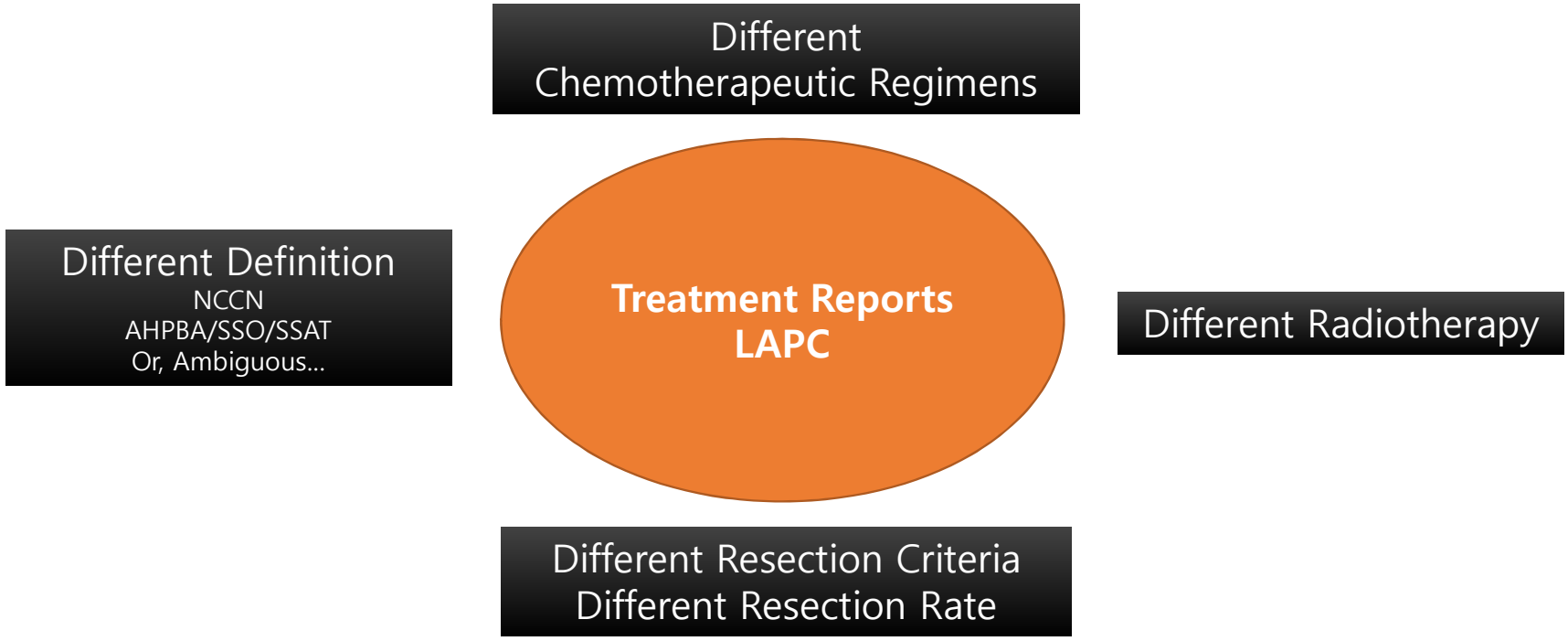
2010
FOLFIRINOX



2013
Gemcitabine/Nab-Paclitaxel

1. Burris HA et al. *J Clin Oncol*. 1997;15:2403-2413. 2. Moore MJ et al. *J Clin Oncol*. 2007;25:1960-1966.
3. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825. 4. Von Hoff DD et al. *N Engl J Med*. 2013;369:1691-1703.

Considering issues in LAPC



Rationale of surgical resection in LAPC

Survival benefit (Oncologic effectiveness) should be estimated in the same tumor conditions.

¡*Survival benefit over* ***non-resected locally advanced pancreatic cancer without disease progression****?*

Systematic Review of Resection Rates and Clinical Outcomes After FOLFIRINOX-Based Treatment in Patients with Locally Advanced Pancreatic Cancer

TABLE 2 Outcomes after FOLFIRINOX-based treatment in patients with LAPC

Author	No. of patients	Treated with radiotherapy	Resection rate	R0 resection rate	Complete pathologic response	Response rate	Median OS (months)	Grade 3–4 toxicity
Blazer et al.[8]	25	15/25 (60)	11/25 (44)	10/11 (91)	0/11 (0)	2/23 (9)[a]	NR	NR
Boone et al.[9]	13[b]	5/10 (50)	2/10 (20)	1/2 (50)	NR	NR	8.9	5/10 (50)
Conroy et al.[10]	11[c]	0 (0)	0/11 (0)	NA	NA	3/11 (27)	15.7	NR
Faris et al.[11]	22	20/22 (91)	5/22 (23)	5/5 (100)	1/5 (20)	8/22 (36)	NRE, 3-year 7 %	NR
Gunturu et al.[12]	16	0 (0)	2/16 (13)	NR	0/2 (0)	8/16 (50)	NRE, 6-month 94 %; 12-month 83 %	NR
Hohla et al.[13]	6	0 (0)	2/6 (33)	NR	NR	NR	NR	NR
Hosein et al.[14]	14	9/14 (64)	6/14 (43)	5/6 (83)	NR	NR	NR	NR
Kraemer et al.[15]	7	0 (0)	1/7 (14)	0/1 (0)	0/1 (0)	NR	NR	NR
Mahaseth et al.[16]	20	10/20 (50)	4/20 (20)	3/4 (75)	NR	NR	NR	NR
Marthey et al.[17]	77	54/77 (70)	28/77 (36)	25/28 (89)	4/28 (14)	22/77 (28)	21.6	20/77 (26)
Mellon et al.[18]	21	21/21 (100)	5/21 (24)	5/5 (100)	0/5 (0)	NR	NR	NR
Moorcraft et al.[19]	13	7/13 (54)	2/13 (15)	2/2 (100)	1/2 (50)	4/13 (31)	18.4	7/13 (54)
Peddi et al.[20]	19	4/19 (21)	4/19 (21)	NR	NR	NR	NRE	5/19 (26)
Sadot et al.[21]	101	63/101 (62)	31/101 (31)	16/29 (55)[d]	0/31 (0)	29/101 (29)	25	14/101 (14)
Overall	365	208/362 (57)	103/362 (28)	72/93 (77)	6/85 (7)	76/263 (29)		51/220 (23)

The median overall survival was reported in five studies and ranged from 8.9 to 25 months; Ann Surg Oncol (2016) 23:4352–4360

FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

	Number of patients	Radiotherapy or chemoradiotherapy	Resection	R0 resection
Boone[22]	10	5 (50%)	2 (20%)	1 (50%)
Conroy[12]	11	NR	0	NA
Faris[21]	22	20 (91%)	5 (23%)	5 (100%)
Gunturu[24]	16	NR	2 (13%)	NR
Hohla[18]	6	2 (33%)	2 (33%)	NR
Hosein[23]	14	9 (64%)	6 (43%)	5 (83%)
Mahaseth[19]	20	10 (50%)	4 (20%)	3 (75%)
Marthey[25]	77	24 (31%)	28 (36%)	25 (89%)
Mellon[28]	21	21 (100%)	5 (24%)	5 (100%)
Moorcraft[26]	8	NR	2 (25%)	NR
Peddi[20]	19	NR	4 (21%)	NR
Sadot[29]	101	63 (62%)	31 (31%)	16 (52%)
Total	325	154 (57%)	91 (28%)	60 (74%)

Data are n (%), unless otherwise specified. Totals were calculated as overall proportions and differ slightly from pooled percentages in Figure 3 that were calculated using random-effects modelling. NA=not applicable. NR=not reported.

Table 4: **Proportion of patients who underwent radiotherapy or chemoradiotherapy, resection, and R0 resection**

	Number of patients	Median follow-up* (months; IQR)	Median overall survival (months; 95% CI)	Median progression-free survival (months; 95% CI)
Conroy[12]	11	26·6 (26·0–33·4)	15·7 (10·7–20·7)	7·6 (3·6–12·0)
Faris[21]	22	54·0 (32·7–55·3)	24·7 (19·0–30·3)	11·8 (8·6–15·1)
Gunturu[24]	16	33·1 (11·4–49·3)	25·3 (9·2–41·4)	17·3 (13·5–21·2)
Hohla[18]	6	Not calculable	10·0 (4·0–16·0)	3·0 (not calculable†)
Hosein[23]	14	36·1 (32·9–38·8)	32·7 (23·1–42·3)	17·3 (5·9–28·7)
Mahaseth[19]	20	4·0 (4·0–4·0)	21·2 (12·4–30·1)	11·0 (5·4–16·6)
Marthey[25]	77	11·3 (7·8–17·6)	21·1 (12·3–29·9)	18·5 (12·9–24·1)
Mellon[28]	21	10·5 (7·3–20·1)	24·0 (not calculable†)	20·4 (6·5–34·3)
Moorcraft[26]	8	15·9 (15·4–16·3)	18·4 (11·6–25·2)	12·8 (not calculable†)
Peddi[20]	19	11·4 (8·2–16·2)	Not reached	12·4 (7·2–17·6)
Sadot[29]	101	12·0 (8·0–18·0)	26·0 (19·3–32·7)	16·0 (13·3–18·7)
Pooled patient-level data	315	12·3 (8·0–20·5)	24·2 (21·7–26·8)	15·0 (13·7–16·3)

*Of patients alive at last follow-up. †Because of small number of events.

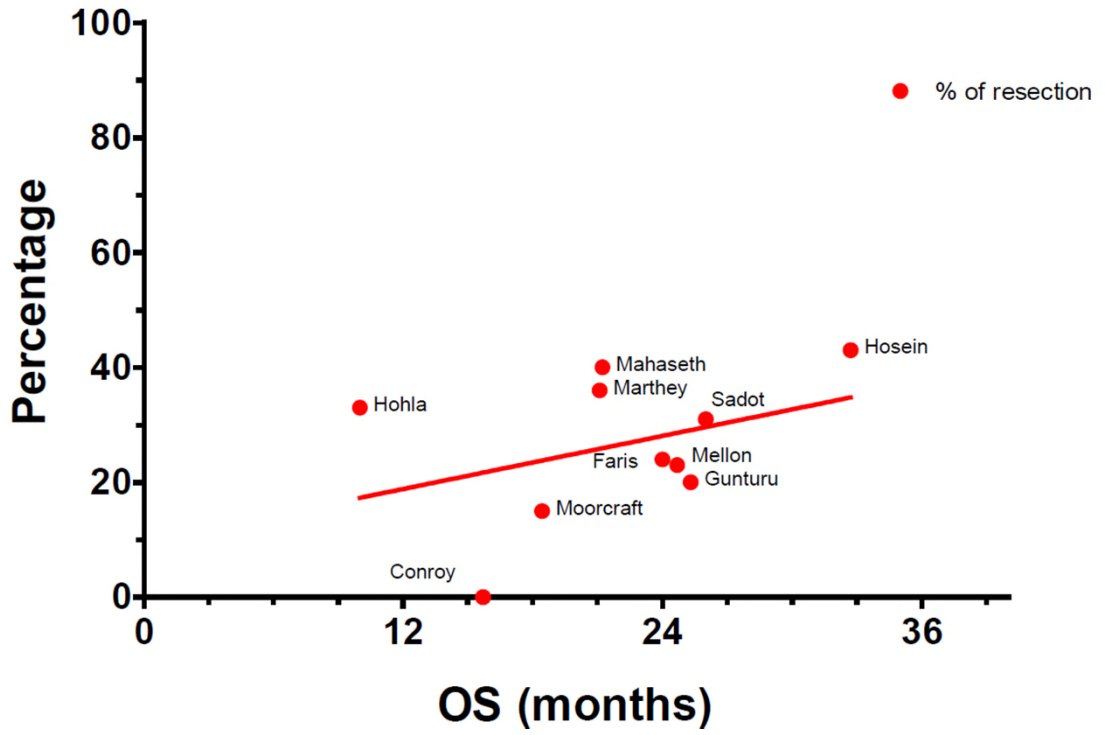
Table 2: **Median overall and progression-free survival**

Lancet Oncol 2016; 17: 801–10

Resection vs. Non-resection without progression
Resection is benefit?

"There was no significant correlation across studies between the proportion of patients undergoing resection and overall survival."

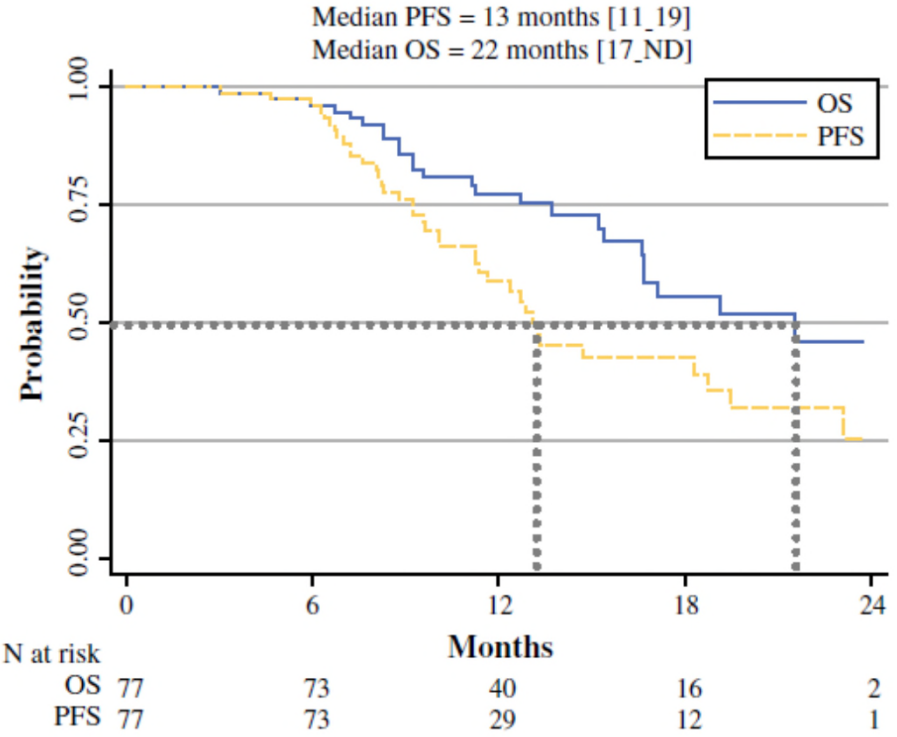
Figure 4 Percentage of resection and median OS across studies (p=0·39).



Resection vs. Non-resection without progression

Resection is benefit?

FOLFIRINOX for Locally Advanced Pancreatic Adenocarcinoma: Results of an AGEO Multicenter Prospective Observational Cohort



N=77
Resection rate= 28/77 (36%)
R0 rate= 25/28 (89%)

Mortality=7%, Morbidity=43%

OS= 24.9 months [95% CI: 21.1-ND]

Ann Surg Oncol (2015) 22:295–301

Resection vs. Non-resection without progression
Resection is benefit?

FOLFIRINOX induction therapy for stage III pancreatic adenocarcinoma

N=101

Resection rate= 32/101 (31%)
R0 rate= 16/29 (55%)

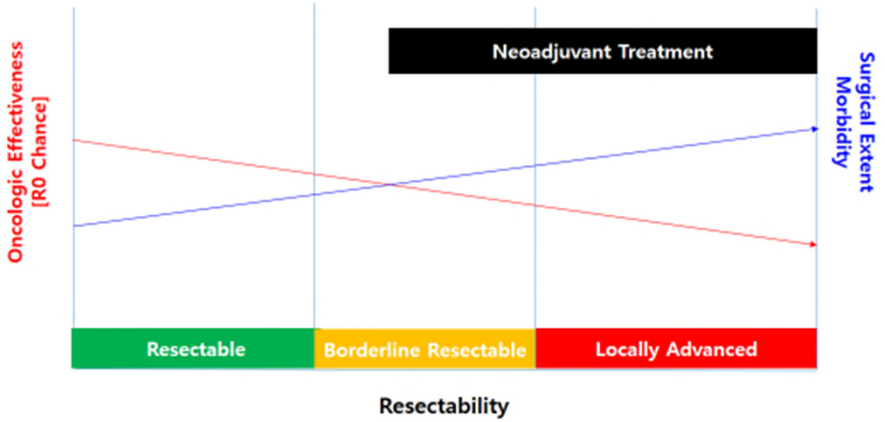
Mortality=?%, Morbidity=?%

R0-OS= "NOT REACHED MEDIAN SURVIVAL"

Non-resection with progression-OS=11months (95% CI:9-13)

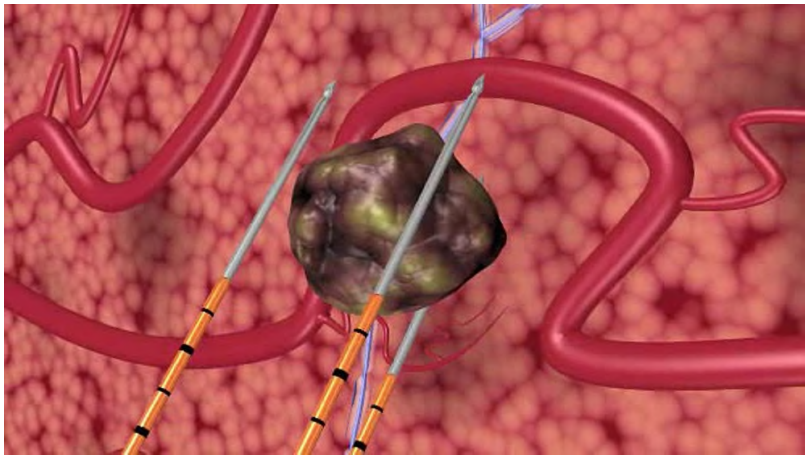
***Non-resection with progression free-OS= *26 months* (CI:18-33)**

Radical Pancreatectomy: **Benefit ≥ Disadvantage**

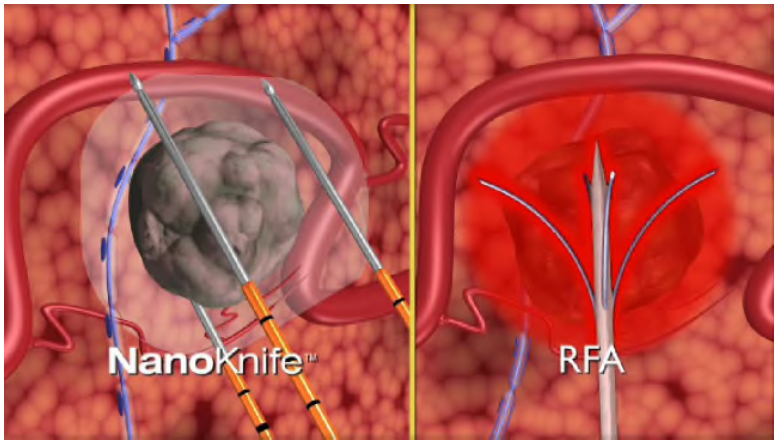


Ann Surg Oncol. 2015 October ; 22(11): 3512–3521

Potential role of local ablation therapy
IRE: Irreversible electroporation



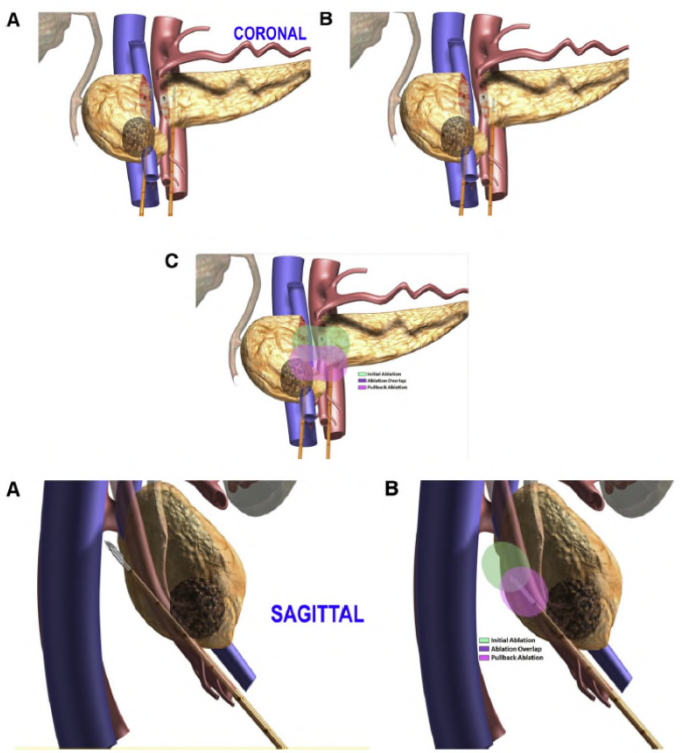
- Electrodes around the tumor
- Pulsed & direct electric current (2000V/cm)
- Cell membrane pore, apoptosis, and death



- Without causing significant heating of the tissues, sparing extracellular matrix and protein

Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation

David Kwon, MD, FACS,[a] Kelli McFarland, MD, FACS,[a] Vic Velanovich, MD, FACS,[b] *and* Robert C. G. Martin, II, MD, PhD, FACS,[c] *Detroit, MI, Tampa, FL, and Louisville, KY*



N=48 (LAPC:11 (PD)+10 (DP))

Preoperative Neo-CT/RT 100%
R0 resection rate 66.7%

Morbidity 38%
Mortality N/A

Median OS-22 months [95% CI: 17.9-24.9]

Surgery 2014;156:910–22.

Ann Surg Oncol (2016) 23:1736–1743
DOI 10.1245/s10434-015-5034-x

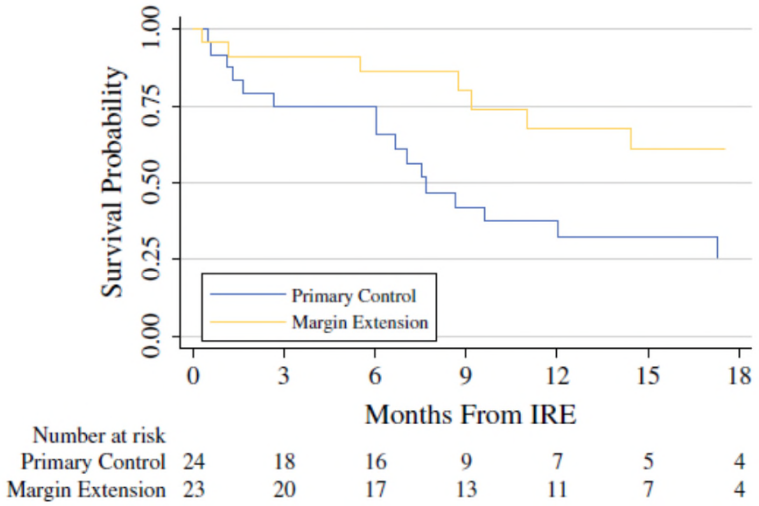
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Single-Institution Experience with Irreversible Electroporation for T4 Pancreatic Cancer: First 50 Patients

TABLE 1 Patient, tumor, and irreversible electroporation (IRE) characteristics

	All ($n = 53$)	Primary treatment ($n = 29$)	Margin extension ($n = 24$)
Median age: years (IQR)	66.5 (60.2–72.0)	68.6 (63.4–73.8)	62.4 (56.1–68.6)
Male gender: *n* (%)	31 (58.5)	15 (51.7)	16 (66.7)
Location: *n* (%)			
Head	32 (60.4)	17 (58.6)	15 (62.5)
Neck/body	21 (39.6)	12 (41.4)	9 (37.5)
Median tumor size: cm (IQR)	3.0 (1.7–5.0)	2.7 (2.4–4.0)	3.2 (2.0–4.5)
Chemotherapy before IRE: *n* (%)			
GTX/GAX	29 (63.0)	14 (58.3)	15 (68.2)
FOLFIRINOX	7 (15.2)	3 (12.5)	4 (18.2)
Other	10 (21.8)	7 (29.2)	3 (13.6)
Radiation therapy before IRE: *n* (%)			
Intensity-modulated	5 (12.8)	3 (16.7)	2 (9.5)
Stereotactic body	34 (87.2)	15 (83.3)	19 (90.5)
Operation: *n* (%)			
Whipple/IRE			15 (63)
Portal reconstruction			10
Distal/IRE			7 (29)
Portal reconstruction			1
Appleby/IRE			2 (8)
Portal reconstruction			1



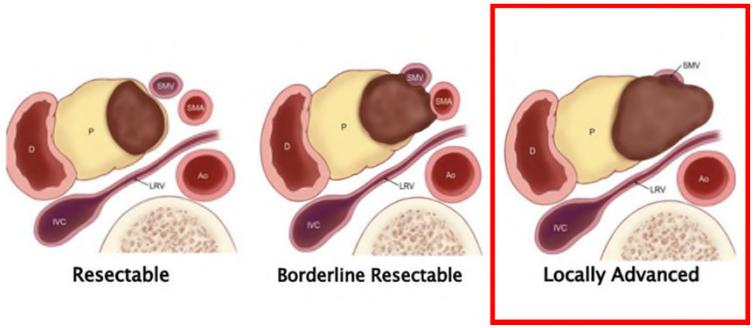
IRE vs. FOLFIRINOX without progression
IRE is benefit?

"The mortality rate after IRE was **higher** than reported in other series"

30-day mortality: 7.6%
90-day mortality: 11.4%

IRE	5	No details; presented to an outside hospital	Yes
IRE	5[a]	Duodenal and bile duct necrosis; interventional radiology attempt at transhepatic drain insertion; hemorrhage requiring transfusion; operative reexploration; comfort care in support of advanced directives	No
IRE	5	Interventional radiology drain placement for deep surgical-site infection; reoperation for retroperitoneal fluid collection; hemorrhage requiring transfusion; interventional radiology placement of inferior vena cava stent for symptomatic stenosis; respiratory failure and intubation; multisystem organ failure	No
Whipple, portal vein, & IRE	5	Early postoperative anemia, transfusion; cardiopulmonary arrest at home, no postmortem	No
IRE	5[a,b]	Upper gastrointestinal bleed requiring endoscopy and transfusion; duodenal-cutaneous fistula; portal vein thrombosis that could not be anticoagulated; failure to thrive	Yes
IRE	5[a,b]	Intraperitoneal hemorrhage requiring transfusion; angiogram embolization of gastroduodenal artery; multisystem organ failure	Yes

Conclusions



- Margin-negative resection is crucial for treating resectable pancreatic cancer.
- Currently, new emerging potential chemotherapeutic regimens are under tested. (FOLFIRINOX…)
- Extended pancreatectomy following neo-Tx will be choice for treating LAPC (if any).

- Natural course of non-disease progression after potent chemotherapy "FOLFIRINOX' also need to be investigated to estimate the oncologic role of surgical resection in treating LAPC.

- Surgical approach and modality in treating LAPC need to be determined with following considerations;

Oncologic benefit over observation following potent chemotherapeutic agents?
Potential surgery-related morbidity and mortality?
Improving quality of Life?
Increasing medical cost?
Intension-to-treat analysis