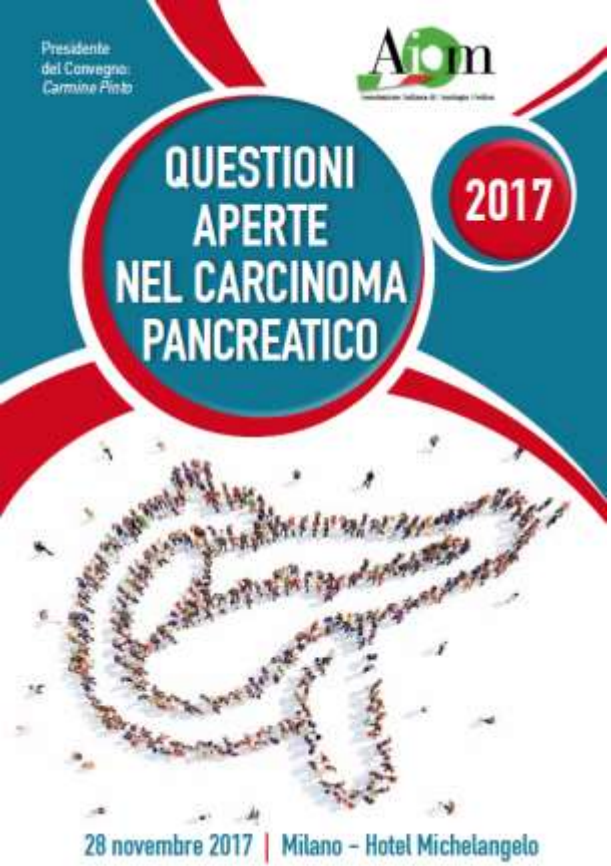


TAVOLA ROTONDA

QUALE EVIDENZA PER I TRATTAMENTI LOCOREGIONALI

Roberto Girelli MD

UNITA' DI CHIRURGIA PANCREATICA
OSPEDALE P. PEDERZOLI
Peschiera del Garda - Verona

PEDERZOLI

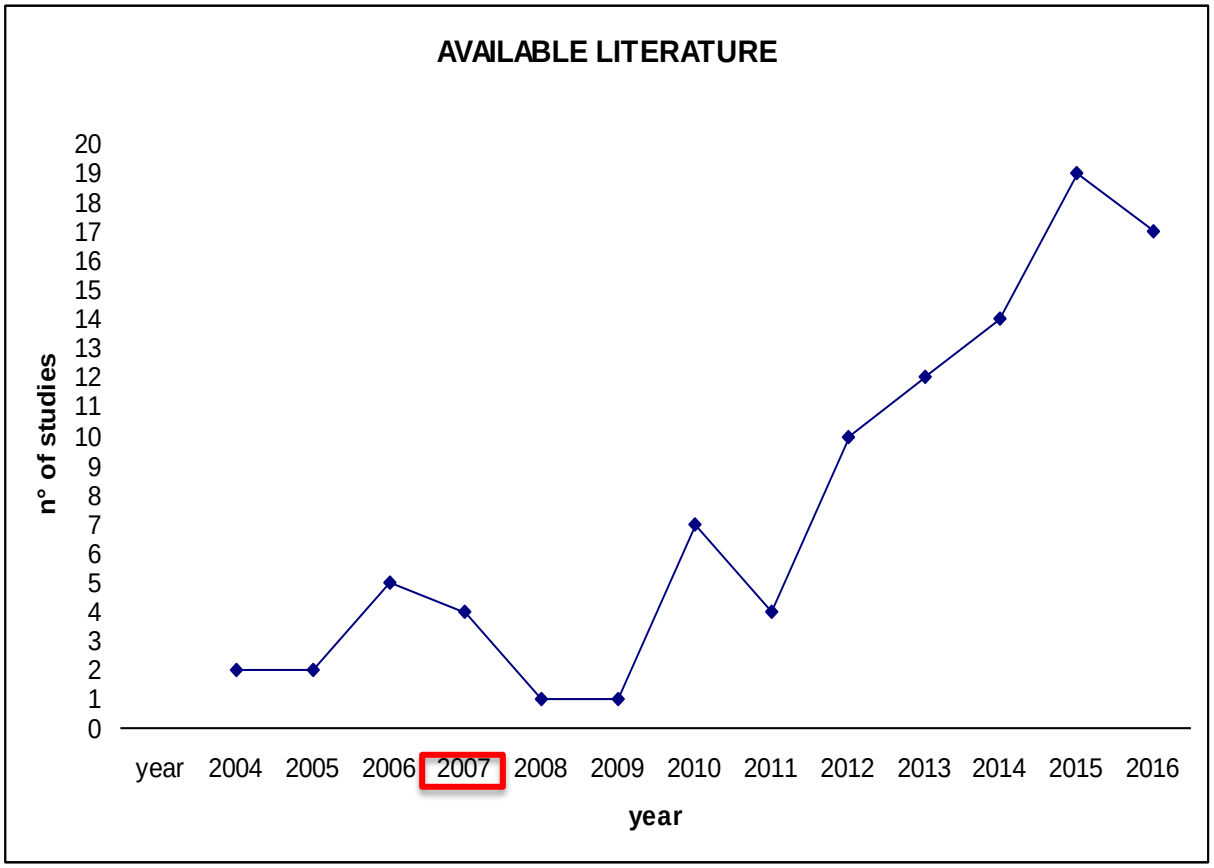
CHIRURGIA PANCREATICA PESCHIERA
"Ospedale P. Pederzoli"

Ablative methods in PDAC

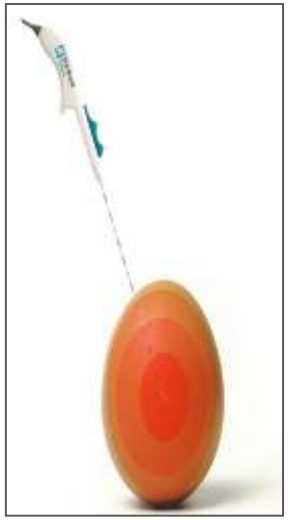
- Thermal tecniques
- Radiofrequency ablation
- Microwave ablation
- Cryoablation
- Laser ablation
- High-intensity focused ultrasound (HIFU)

- Non thermal tecniques
- Irreversible electroporation (IRE)

ABLATIVE THERAPIES IN ADVANCED PANCREATIC CANCER



Only clinical studies or reviews
Full text available, english
Different ablative techinques
LAPC or mPDAC

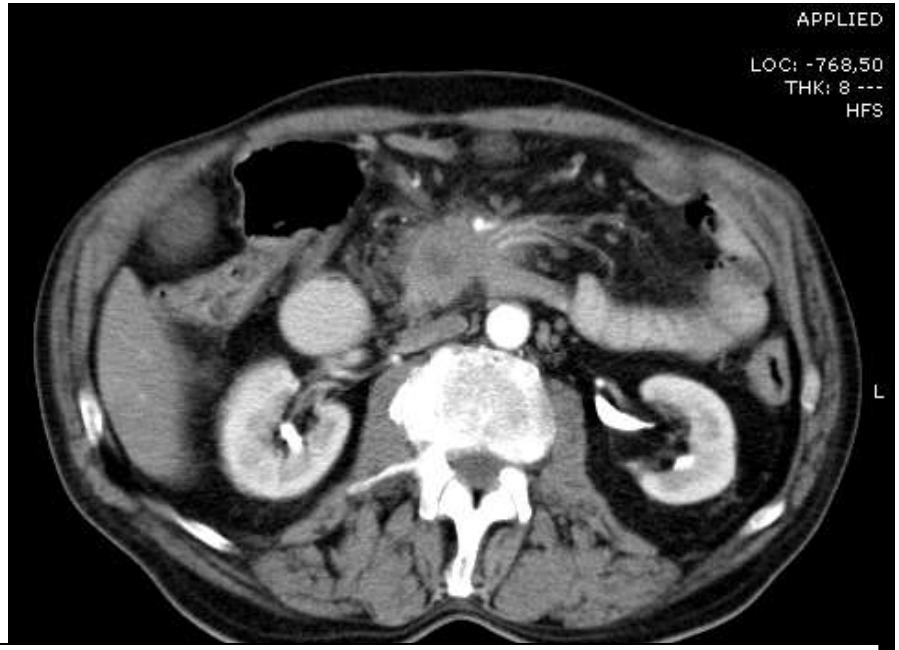


RFA PANCREAS : BASIC PRINCIPLES

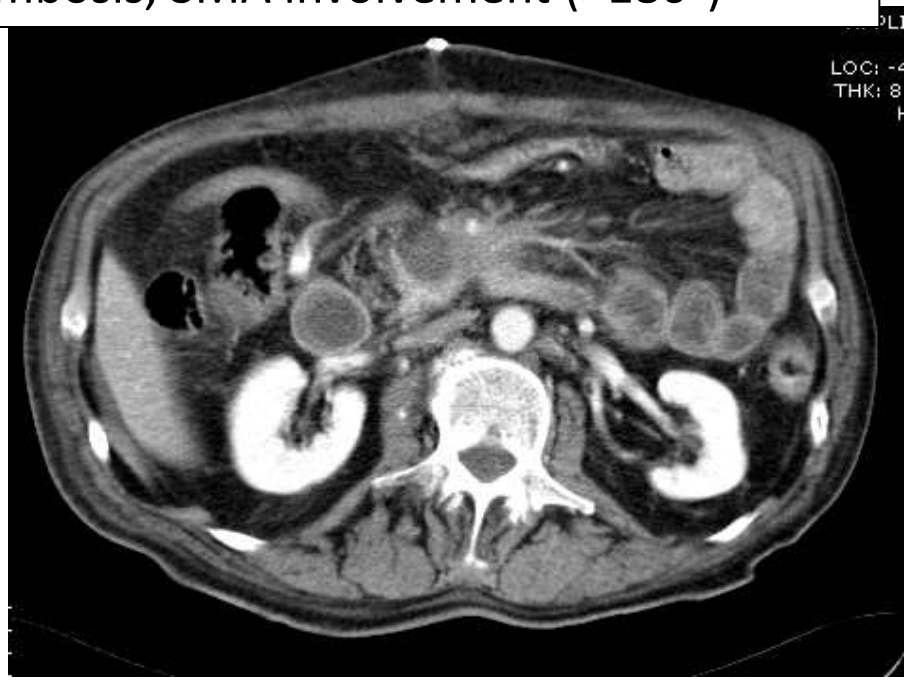
- Histologically proven LAPC (stage III)
- Multimodal treatment setting (CHT/RT)
- Studies approved by ethics committee
- No PRT results available

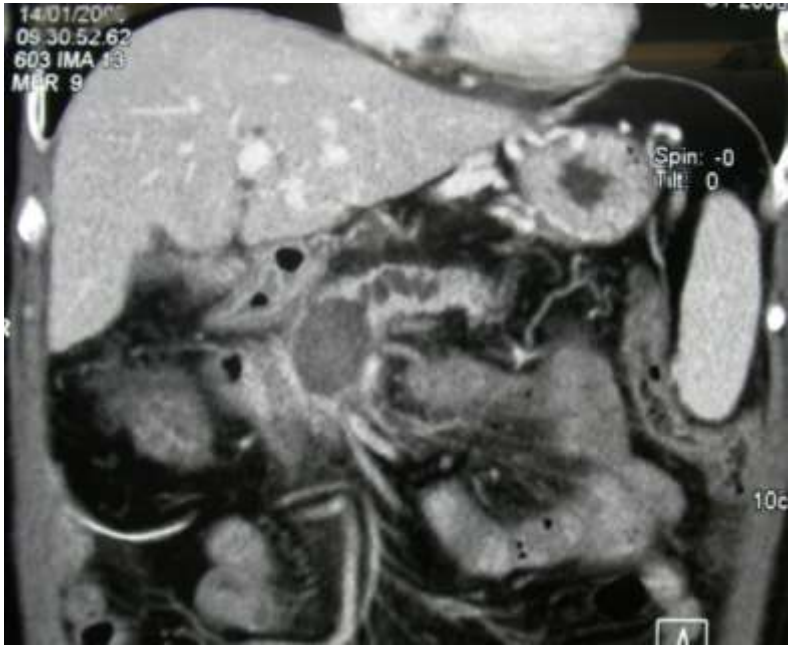
RFA : feb 2007- feb 2017
388 patients

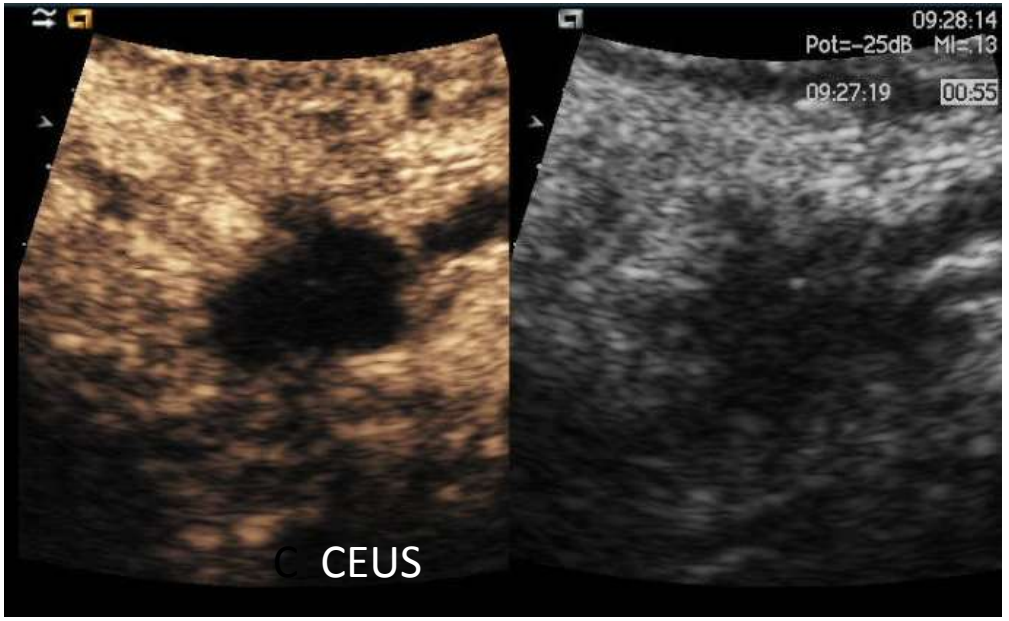
PESCHIERA - VERONA SURGICAL NETWORK	
M/F	230/158
MEDIAN AGE	65 ys
TUMOR SITE head/body tail	268/120
TUMOR SIZE median (IQR)	40mm (30-48)
Mean hospital stay	10.7 days
median follow up	16 ms (3-91)

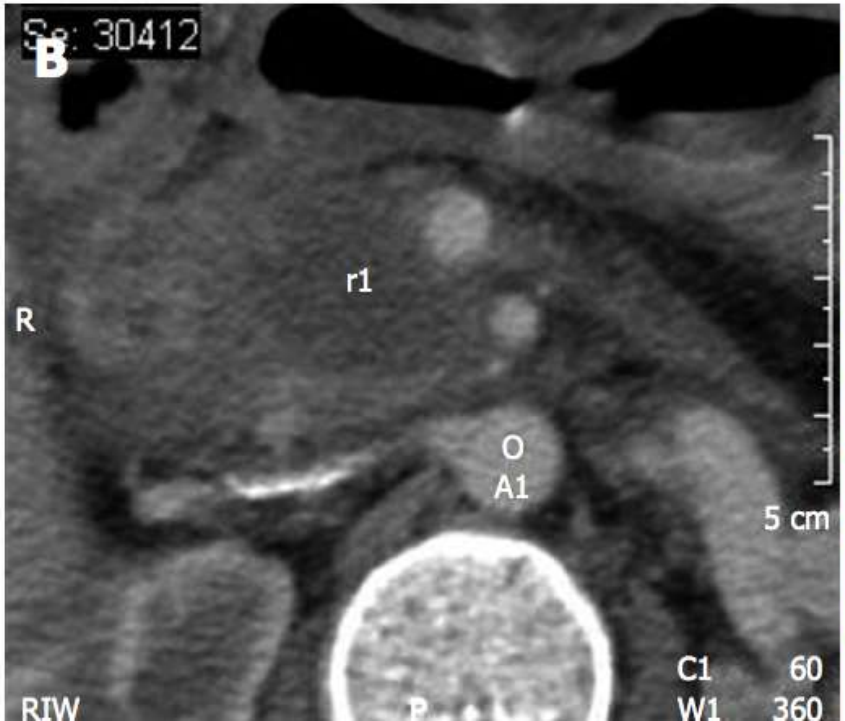


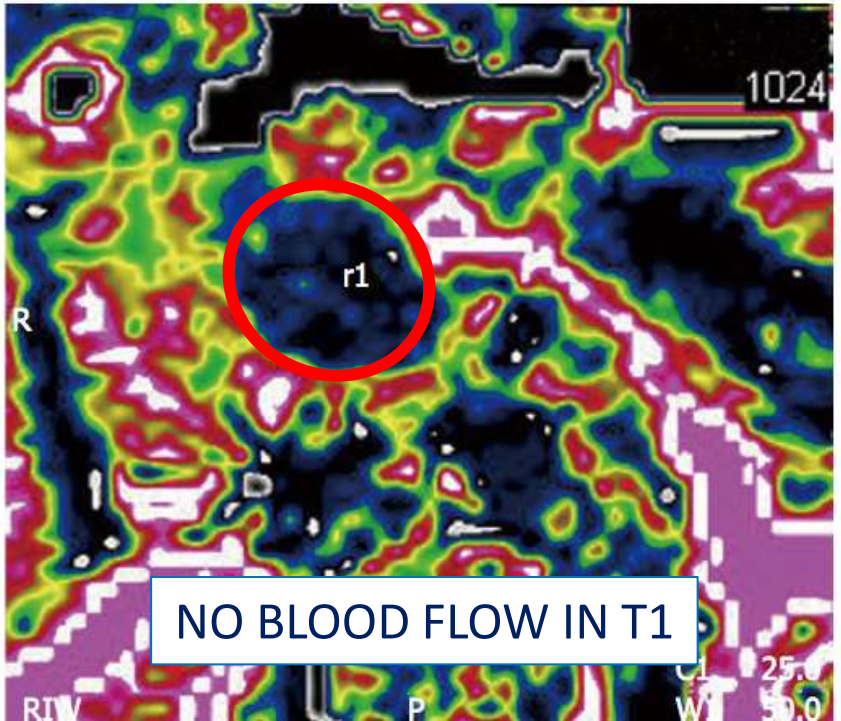
3.5 cm. Size – SMV encasement/ thrombosis, SMA involvement (>180°)






09:28:14
Pot=-25dB MI=.13
09:27:19
00:55
CEUS


B
r1
R
O
A1
5 cm
C1 60
W1 360


1024
r1
R
NO BLOOD FLOW IN T1

Original article

Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer

R. Girelli[1], I. Frigerio[1], R. Salvia[3], E. Barbi[2], P. Tinazzi Martini[2] and C. Bassi[3]

[1]Hepatopancreatobiliary Unit and [2]Department of Radiology, Pederzoli Clinic, Peschiera del Garda–Verona, and [3]Department of Surgery, GB Rossi Hospital, University of Verona, Verona, Italy

Correspondence to: Professor C. Bassi, Surgical and Gastroenterological Department, 'GB Rossi' Borgo Roma Hospital, University of Verona, 37134 – Verona, Italy (e-mail: claudio.bassi@univr.it)

British Journal of Surgery 2010; **97**: 220–225

	Applied t°	% complications	PV thrombosis
Paz 1 - 25	105°C	20% (5/25)	4 cases
Paz 26 - 50	90°C	8% (2/25)	0

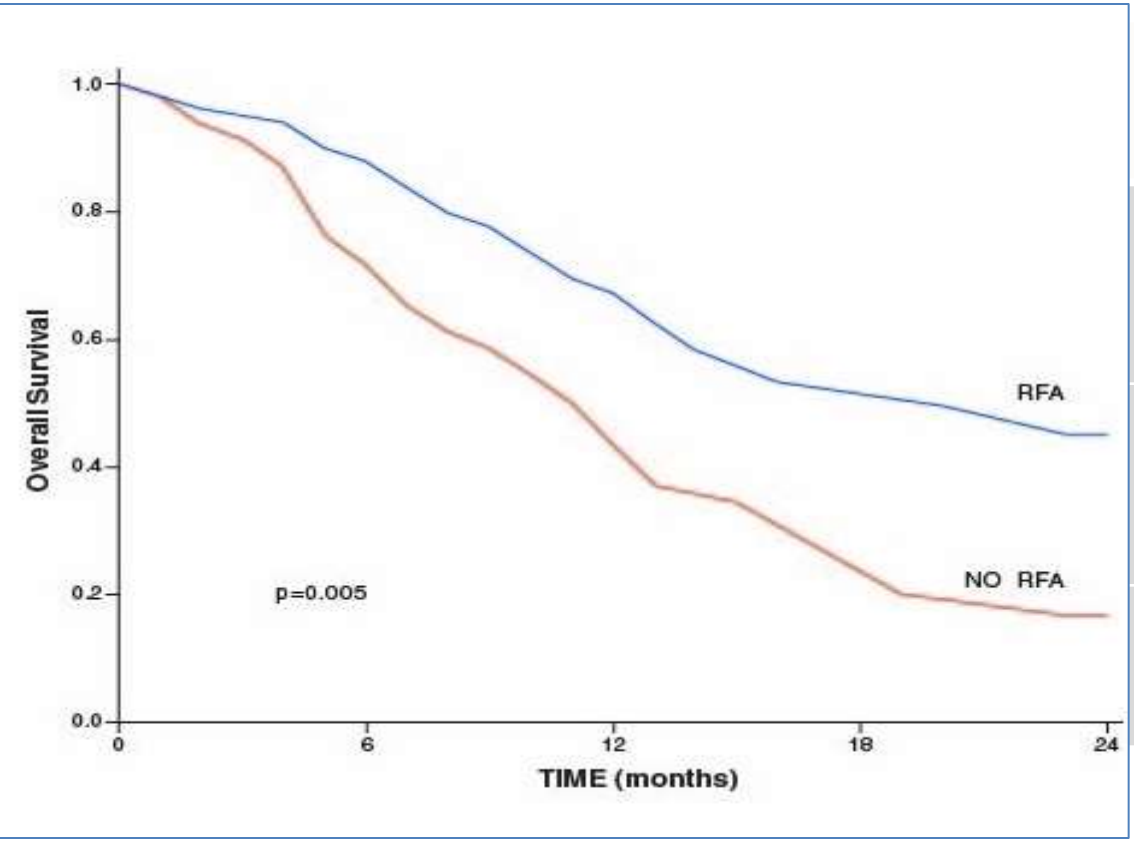
Langenbecks Arch Surg
DOI 10.1007/s00423-012-1011-z

ORIGINAL ARTICLE

Results of 100 pancreatic radiofrequency ablations in the context of a multimodal strategy for stage III ductal adenocarcinoma

Roberto Girelli & Isabella Frigerio & Alessandro Giardino & Paolo Regi & Stefano Gobbo & Giuseppe Malleo & Roberto Salvia & Claudio Bassi

**GESCOR Huguet et al, J Clin Oncol 2007.*

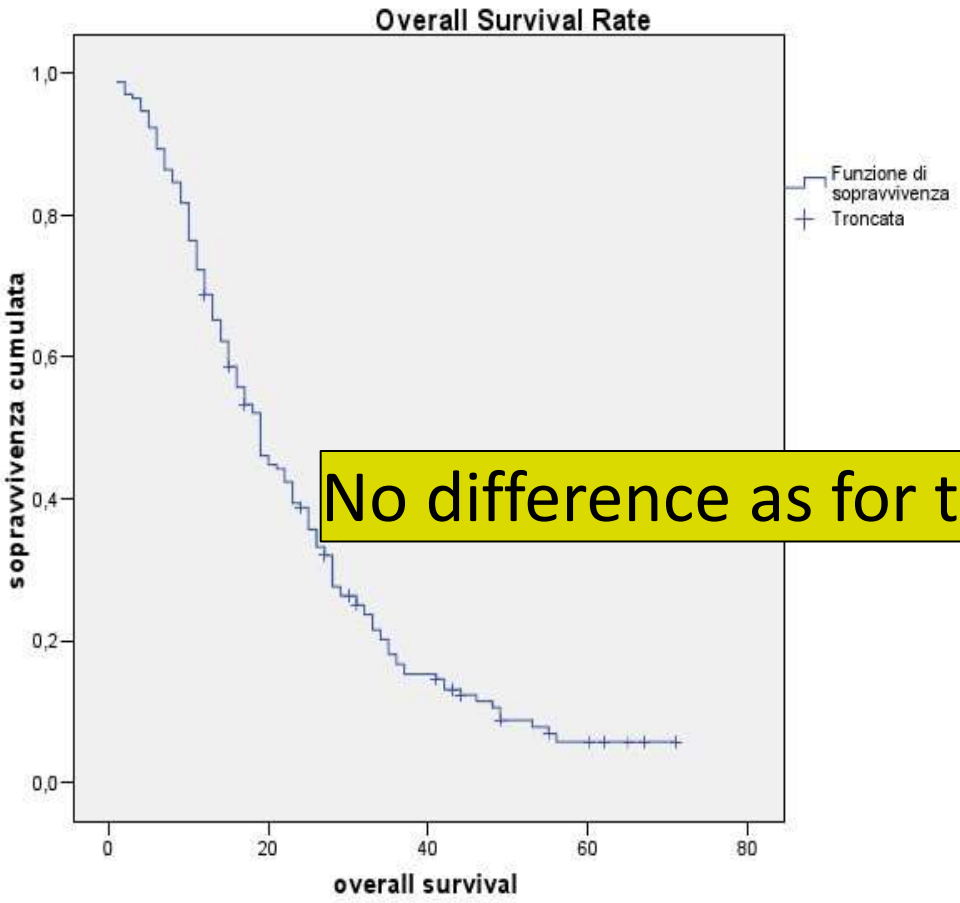


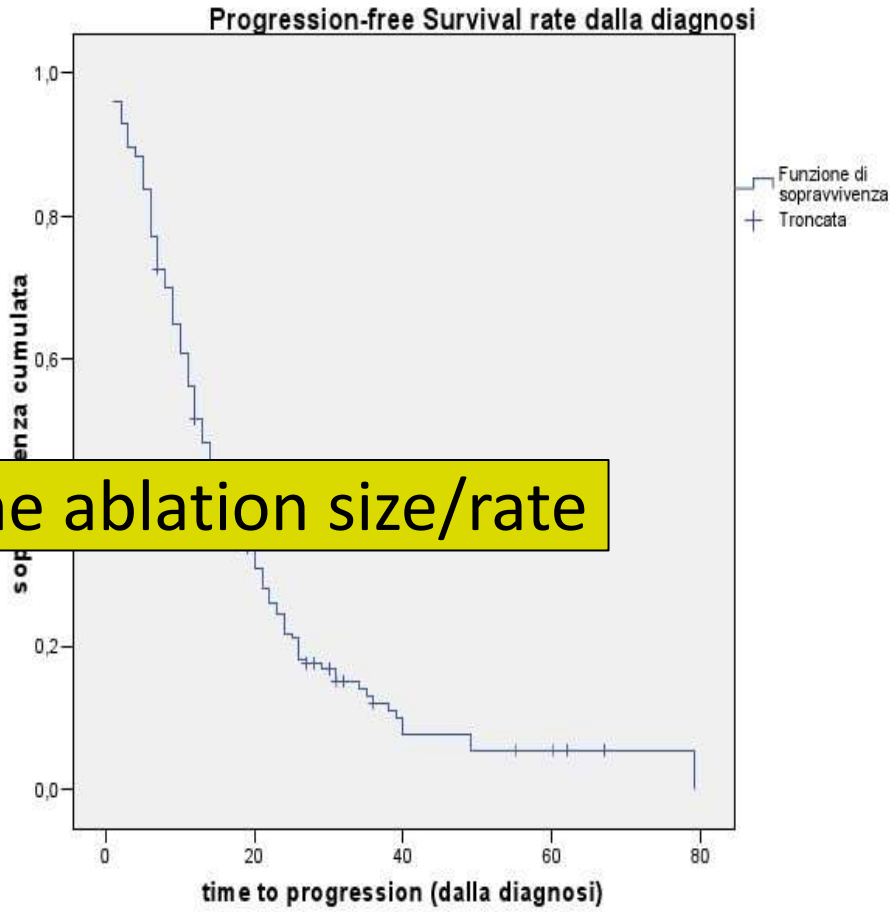
	CHT/RT*	RFA CT/RT
Median Survival	11 months	**21 months**
1-year survival	50%	**76%**
2-years survival	19.3%	**46%**

P=0.01

200 pts overall survival

200 pts P.F. survival





No difference as for the ablation size/rate

20 months

13 months

[CANCER RESEARCH 64, 4024–4029, June 1, 2004]

In Situ Tumor Ablation Creates an Antigen Source for the Generation of Antitumor Immunity

Martijn H. M. G. M. den Brok,[1,2] Roger P. M. Sutmuller,[1] Robbert van der Voort,[1] Erik J. Bennink,[1] Carl G. Figdor,[1] Theo J. M. Ruers,[2] and Gosse J. Adema[1]

[1]Department of Tumor Immunology, Nijmegen Center for Molecular Life Sciences, Nijmegen, the Netherlands, and [2]Department of Surgery, University Medical Center Nijmegen, Nijmegen, the Netherlands

OPINION

Thermal ablation of tumours: biological mechanisms and advances in therapy

Katrina F. Chu and Damian E. Dupuy

NATURE REVIEWS | CANCER

Science to Practice: Can Local Radiofrequency Ablation of Tumors Generate Systemic Immunity against Metastatic Disease?

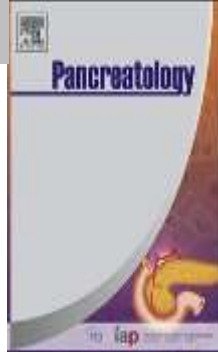
Rebecca Waitz, MD[1]
Stephen B. Solomon, MD[2]
Departments of Immunology[1] and Radiology[2]
Memorial Sloan-Kettering Cancer Center
1275 York Ave
New York, NY 10021
solomons@mskcc.org

HHS Public Access
Author manuscript
J Vaccines Vaccin. Author manuscript; available in PMC 2017 September 20.

Published in final edited form as:
J Vaccines Vaccin. 2016 April ; 7(2): . doi:10.4172/2157-7560.1000310.

Pre-resectional Radiofrequency Ablation as a Neoadjuvant *in situ* Tumor Vaccine

Fumito Ito[1,2] and **Sharon S Evans[3,*]**



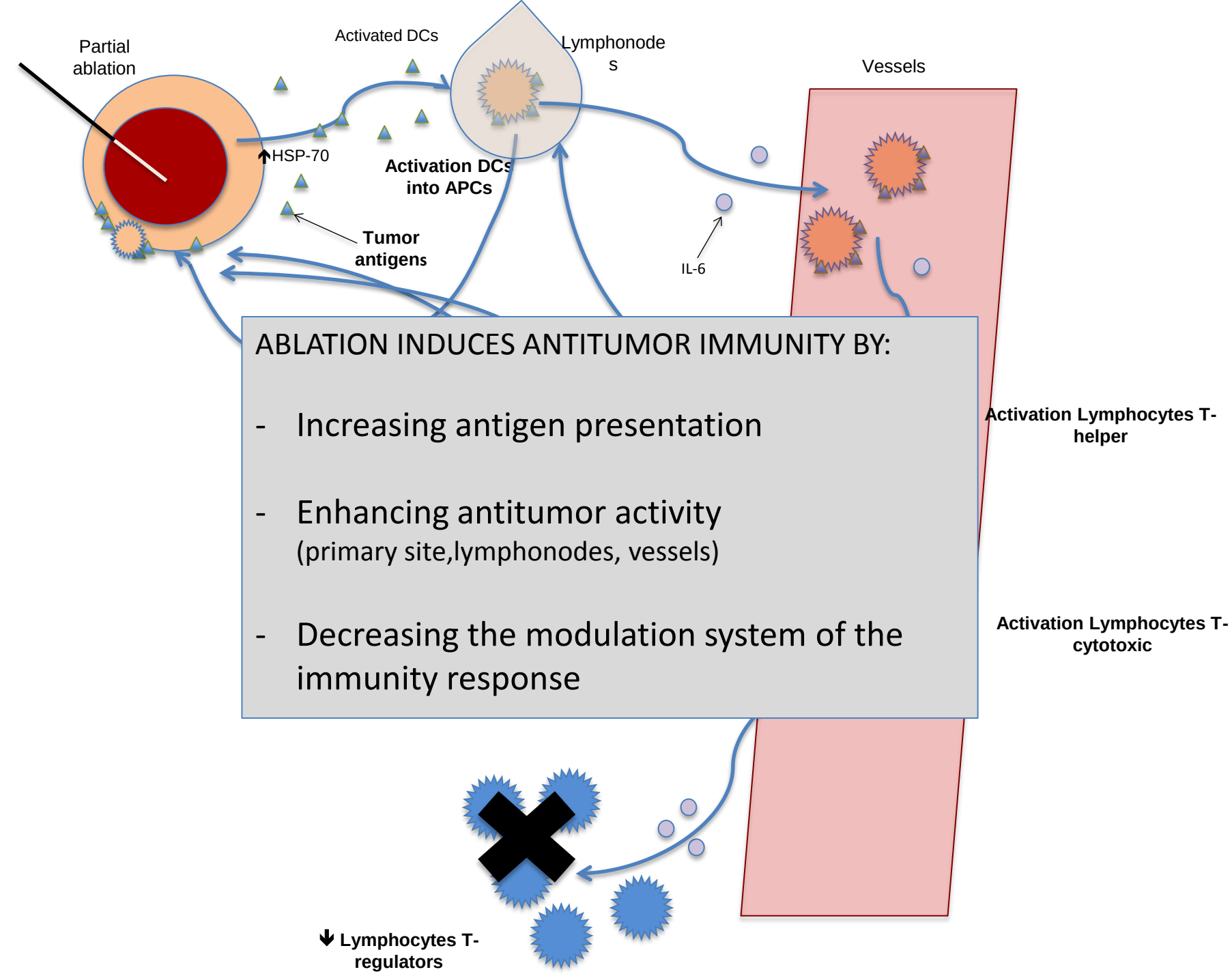
Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients☆

Alessandro Giardino [a,*], Giulio Innamorati [b], Stefano Ugel [c], Omar Perbellini [d], Roberto Girelli [a], Isabella Frigerio [a], Paolo Regi [a], Filippo Scopelliti [a], Giovanni Butturini [a], Salvatore Paiella [f], Matilde Bacchion [e], Claudio Bassi [f]

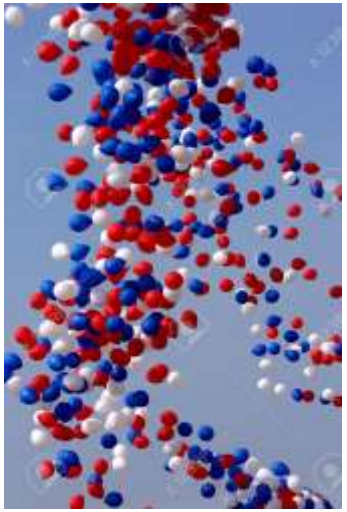
- This study provides the first experimental evidence that RFA can produce multiple early and late effects on systemic immune reactions in pancreatic cancer patients

- Rfa trigger and enhances adaptive immune response

- General trend towards a decrease of immunosuppressive chemokines


Partial ablation
Activated DCs
Lymphonodes
Vessels
HSP-70
Activation DCs into APCs
Tumor antigens
IL-6
ABLATION INDUCES ANTITUMOR IMMUNITY BY:
- Increasing antigen presentation
- Enhancing antitumor activity (primary site,lymphonodes, vessels)
- Decreasing the modulation system of the immunity response
Activation Lymphocytes T-helper
Activation Lymphocytes T-cytotoxic
Lymphocytes T-regulators

FROM A LOCAL TREATMENT….



RELEASE OF ANTIGENS

….TO A SYSTEMIC RESPONSE ?

MORBIDITY and MORTALITY

UNEVENTFUL COURSE: **75%**

- SYSTEMIC COMPLICATIONS : 2%

- ABDOMINAL COMPLICATIONS: **23%**
  - **11.5%** Associated surgery related
  - **12.5%** RFA related

MORTALITY RATE: 1 %
- 1 liver failure
- 3 duodenal bleeding/injuries

LAST CHANGES

BEFORE

2007-2012

205 pts.

Duodenal injuries : 3.9%

PM trombosis: 2.9%

Mortality : 2%

AFTER

2012-2016

183 pts.

Duodenal injuries: 0%

PM trombosis: 0%

Mortality: 0%

DIAGNOSIS AND STAGING

↓

RANDOMIZATION 100 CASI

GROUP A: **RFA-CHT-RT**

GROUP B: **CHT-RT**

LAPAROTOMY

+

RFA

(PALLIATIVE SURGERY)

CHT

+

External RT

+

CHT

CHT

+

External RT

CHT

RESTAGING

MINIMALLY INVASIVE APPROACH

- **LAPAROSCOPY**
- **PERCUTANEOUS US GUIDED**
- **ENDOSCOPIC US GUIDED**

PERCUTANEOUS US - RFA

(Mirko D'Onofrio)

30 Cases : body-tail

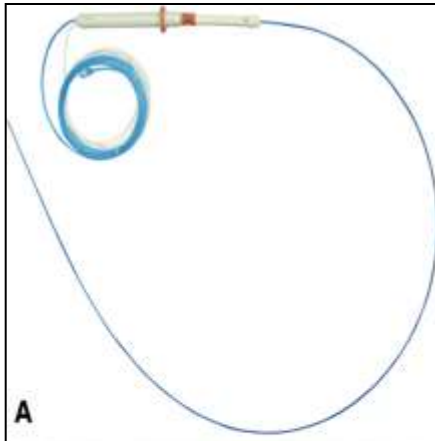
Median size : 3.5 cm.

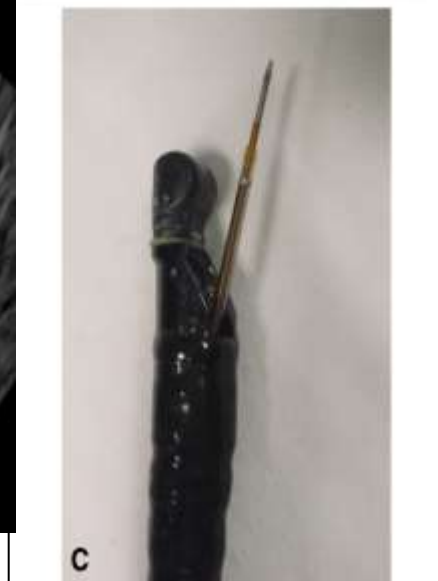
Median hospital stay: 2 days

No complications , no mortality

EUS-RFA

Monopolar 19 gauge





PILOT STUDY: EUS-RFA

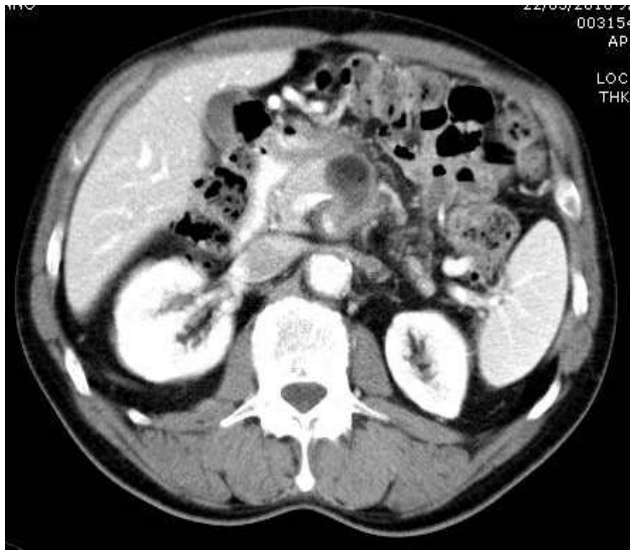
12 Cases : head/body-tail

Median size : 5.1 cm. (3.5-7.5)

Median hospital stay: 2 days

No complications , no mortality

Coagulative necrosis in all cases



EUS-RFA: a promising method

- MORE PRECISE PLACEMENT OF THE NEEDLE DUE TO THE HIGH-RESOLUTION IMAGES
- IMPEDANCE FEED - BACK
- CONTROL OF GASTRIC/DUODENAL WALL DURING THE PROCEDURE
- M.I. PROCEDURE ADVANTAGES:

- *No surgical trauma (and specific complications)*
- *Short hospital stay*
- *Brief chemotherapy discontinuation*
- *It is repeatable*
- *It can be performed in pts unfit for surgery (PS or comorbilities)*

Review Article

Endoscopic Ultrasound-Guided Radiofrequency Ablation of the Pancreatic Tumors: A Promising Tool in Management of Pancreatic Tumors

Kinesh Changela,[1] Rashmee Patil,[2] Sushil Duddempudi,[1] and Vinaya Gaduputi[3]

Echoendoscopic ablative therapy for solid pancreatic tumors.
Paik WH[1], Seo DW[2]. 2017

REVIEW

Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety

María-Victoria Alvarez-Sánchez, Bertrand Napoléon

Endoscopic Radiofrequency Ablation of the Pancreas.
Rustagi T[1], Chhoda A[2]. 2017

Endoscopy-guided ablation of pancreatic lesions: Technical possibilities and clinical outlook

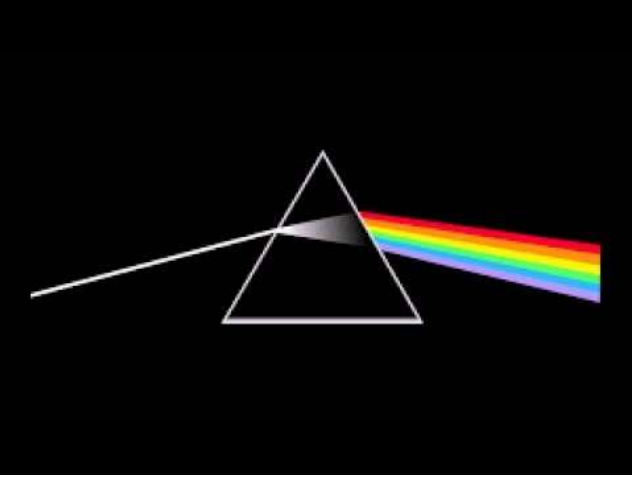
Marianna Signoretti, Roberto Valente, Alessandro Repici, Gianfranco Delle Fave, Gabriele Capurso, Silvia Carrara

Initial experience of EUS-guided radiofrequency ablation of unresectable pancreatic cancer.
Song TJ[1], Seo DW[1], Lakhtakia S[2],

New Indications for Endoscopic Radiofrequency Ablation.
McCarty TR[1], Rustagi T[2]. 2017

Endoscopic ultrasound guided radiofrequency ablation in pancreas.
Seicean A, Tefas C, Ungureanu B, Săftoiu A.

RFA: dalla chirurgia alla mini-invasiva

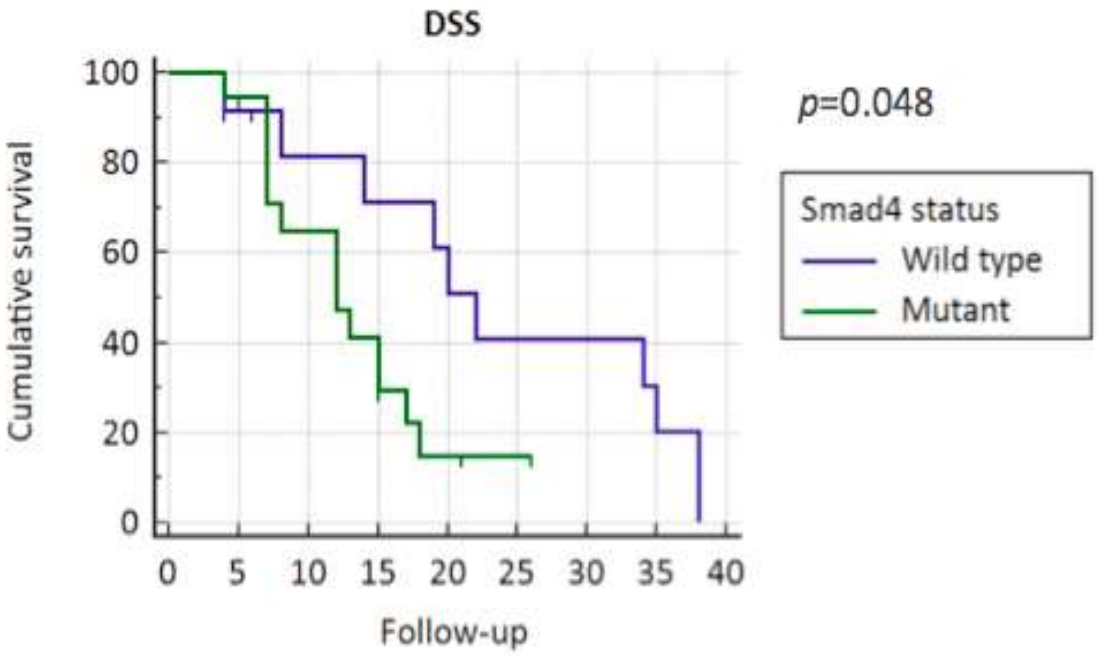


The dark side of the moon

What radiologist and surgeon see

Tumor biology

SMAD4 status and survival after RFA



SMAD4 wild-type: 22 months

SMAD4 mutated: 12 months

2-ys wild-type: **40.7%**

2-ys mutated: 14.8%

MVA: SMAD4 status was the only independent predictor of survival (p=0.05; HR=2.9 [1.001-8.8])

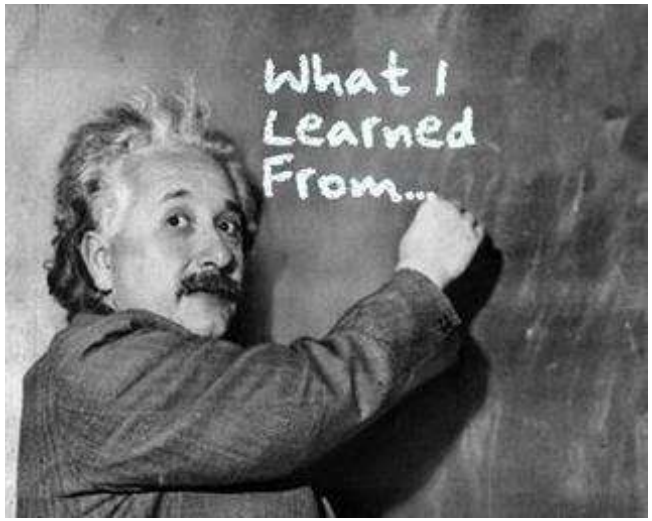
CONCLUSIONI 1

- La RFA è indicata solo in protocolli di *"terapia multimodale integrata"*
- La RFA è proponibile nel pz non candidabile a resezione dopo CT neoadiuvante
- Il ruolo della immunomodulazione necessita di studi dedicati, meglio interpretabili in assenza di trauma chirurgico
- La selezione "biologica" del paziente diventerà essenziale (SMAD4)
- L'approccio mini-invasivo è (oggi) largamente preferibile

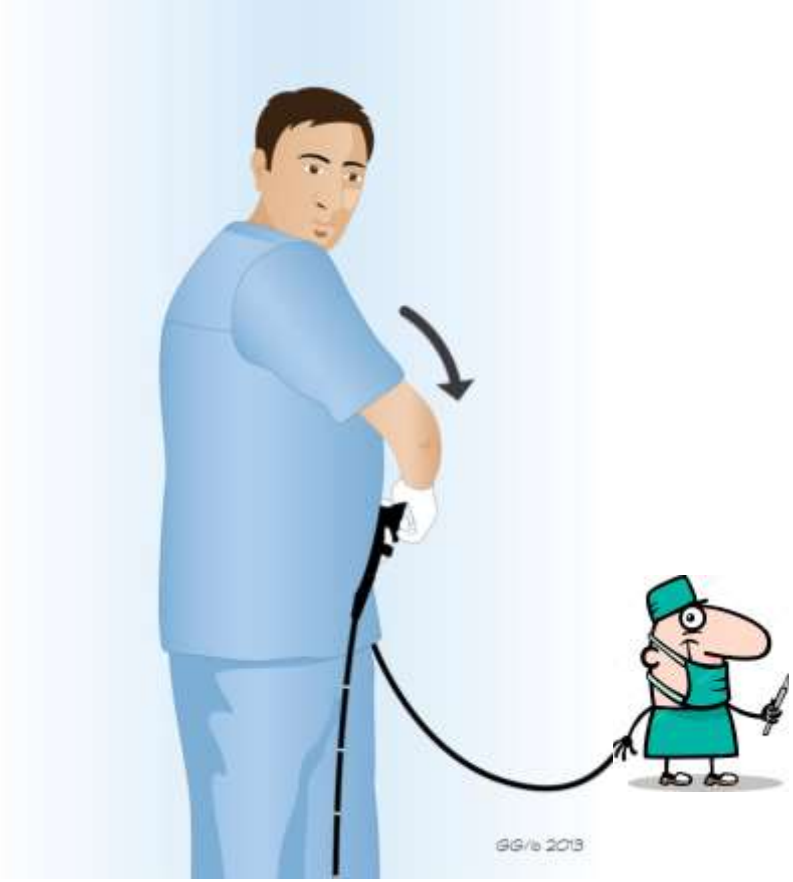
CHIRURGIA PANCREATICA PESCHIERA
"Ospedale F. Pederzoli"

CONCLUSIONI 2

- RFA chirurgica è fattibile ma presenta rischi maggiori
- RFA i.o. ha permesso di definire parametri e principi della RFA pancreatica
- Oggi non è più giustificabile una RFA chirurgica “di principio”
- L’approccio mini-invasivo può cambiare la storia della RFA pancreas


What I
Learned
From...

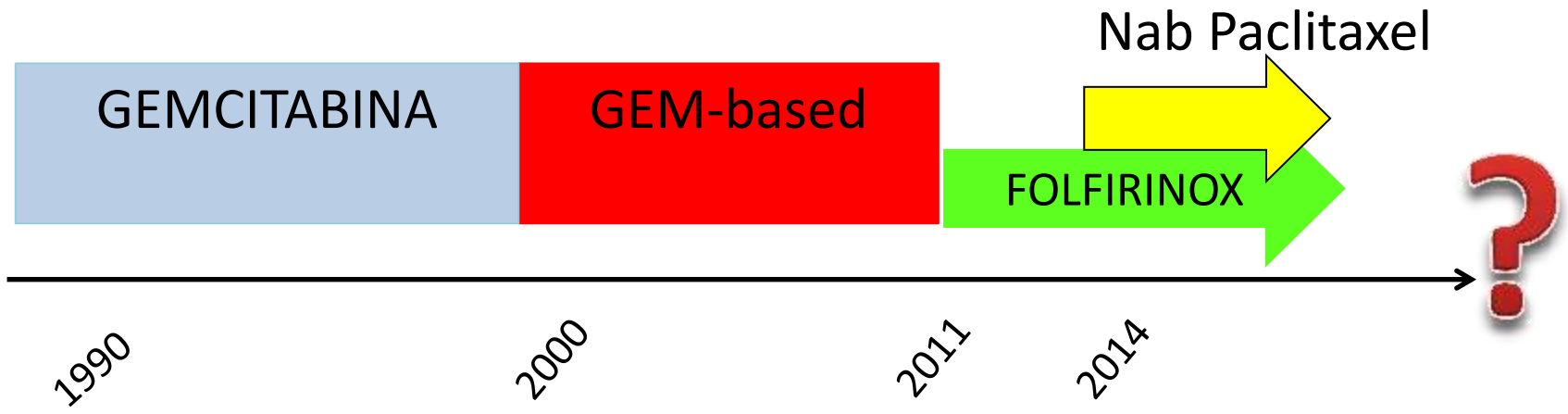
KEEP
CALM
IT'S A
WORK IN
PROGRESS



THANK YOU FOR THE ATTENTION

rgirelli@ospedalepederzoli.it

Chemotherapy in LAPC

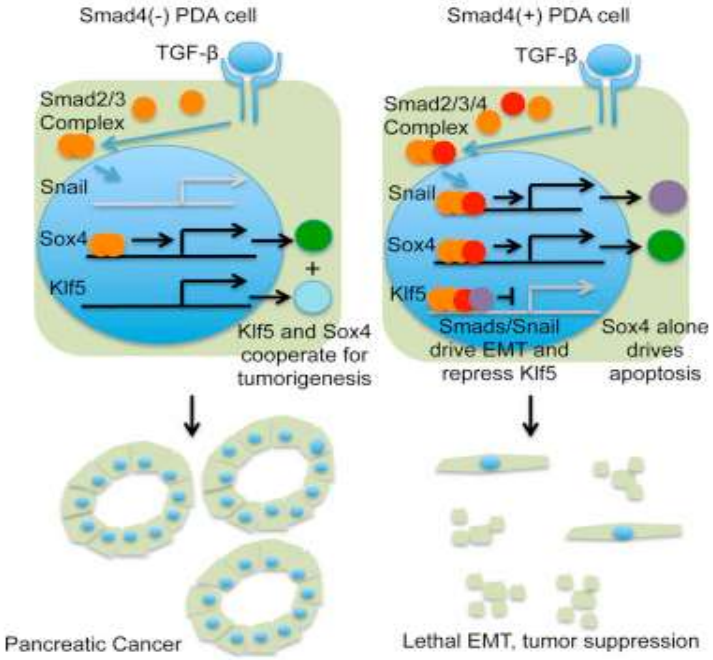


Median OS **11.4** ms
GERCOR. Huguet F, JCO, 2007

Median OS **16.4** ms → ?
LAP 07 Huguet F, JCO 2014
Roumbouts J, Ann Surg Oncol 2016

SMAD4 and PDAC

- Oncosuppressor
- Frequently mutated in PDAC (up to 55%)
- When **wild-type** → local tumor growth in **78%** of cases
- When **mutated** → metastatic growth in **75%** of cases
- Gene analysis through [IHC] (cheap, reliable and less *time-consuming*)



Iacobuzio-Donahue, JCO,2009
David, Cell, 2016

LEARNING CURVE : further changes

1- t°C never above 80°C

2- RFA limited to the “core” of the tumor

3- single cool-tip probe: UNIBLATE

STAY AWAY FROM DUODENUM !

ABLATIVE THERAPY IN LAPC

- ONE STEP IN A MULTIMODAL SETTING
- THE IMMUNE SYSTEM CAN PLAY A ROLE
- **MINIMAL INVASIVE APPROACH SHOULD BE PREFERRED**
- **PTS WITH PERSISTENT LAPC NOT SUITABLE FOR SURGERY**
- **SELECTION OF PATIENTS WILL BE THE FUTURE (SMAD4)**

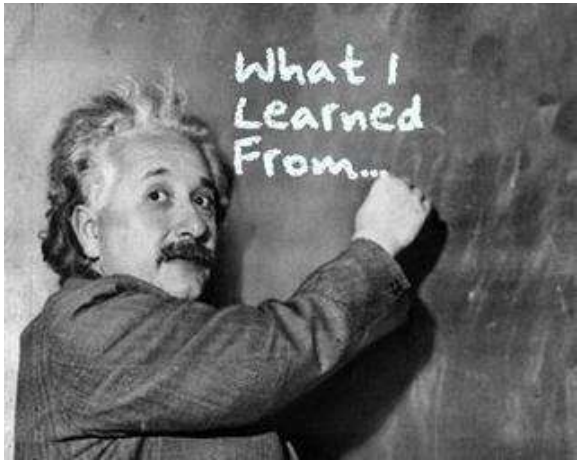
TAKE HOME MESSAGE

L’INTERESSE SCIENTIFICO IN RFA&PDAC E’ IN AUMENTO

MAGGIOR OMOGENEITA’ DI TECNICA E METODICA (STUDI CONFRONTABILI)

RFA TROVA POSTO NEL TRATTAMENTO MULTIDISCIPLINARE DI PDAC

APPROCCIO MININVASIVO (PERCUTANEO/ EUS)

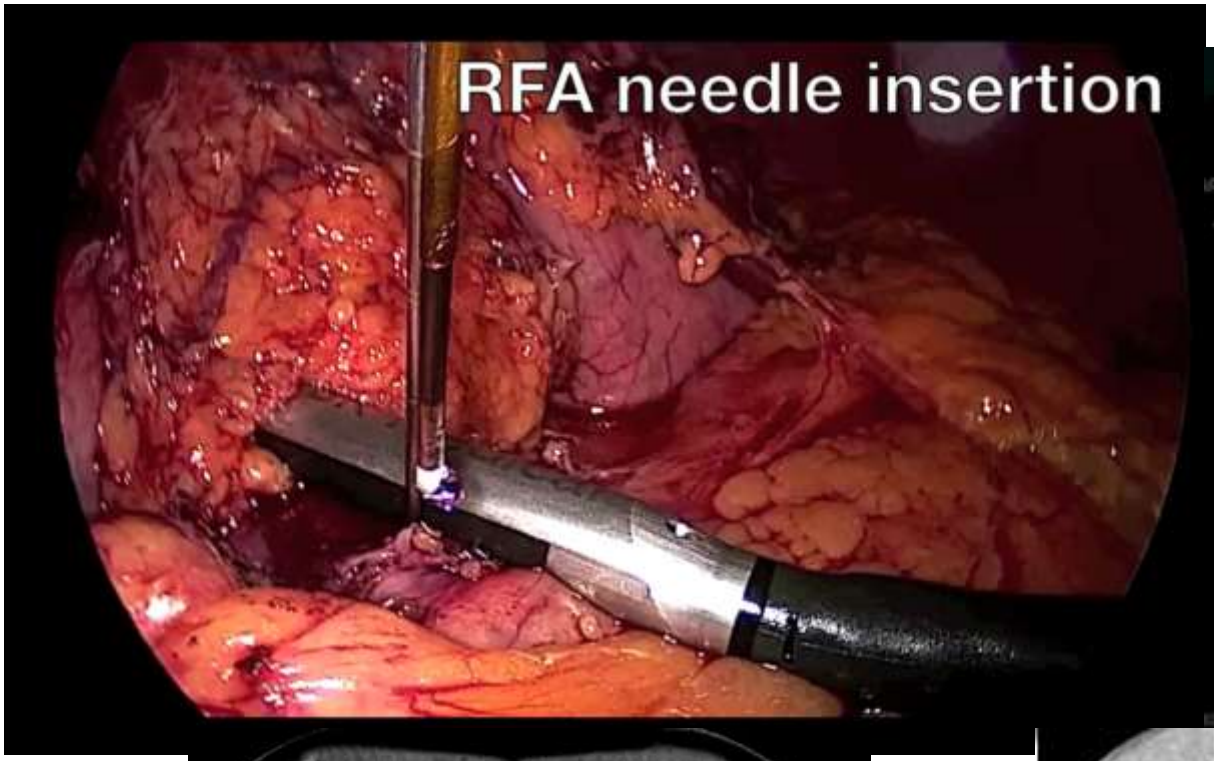


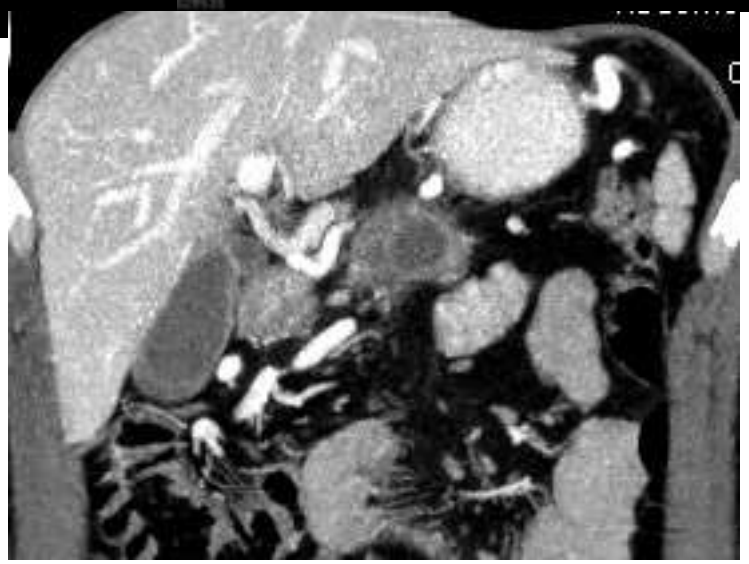
Indicazioni alle ablazioni: conclusioni

- Tumore localmente avanzato (Stadio III)
- Tipizzazione citologica
- Sempre in associazione a CT/RT (terapia multimodale)
- Preferibilmente dopo terapia neoadiuvante
- Approccio mini-invasivo (US o EUS guidato)
- Selezione pz su diversi parametri (non solo radiologici)
- Selezione pz su criteri “biologici”

CHIRURGIA PANCREATICA PESCHIERA
"Ospedale F. Fedarzoli"

LAPAROSCOPIC APPROACH





PELICAN trial

Pancreatic Locally advanced Irresectable Cancer Ablation in the Netherlands:

A randomized controlled superiority phase III multicenter trial

A study of the Dutch Pancreatic Cancer Group:

DPCG
Dutch Pancreatic Cancer Group

June , 2016

SMAD4 and PDAC

The presence of the wild type SMAD4 could help to select patients who would benefit from local ablative approach like RFA

OUR EXPERIENCE

2007 2017

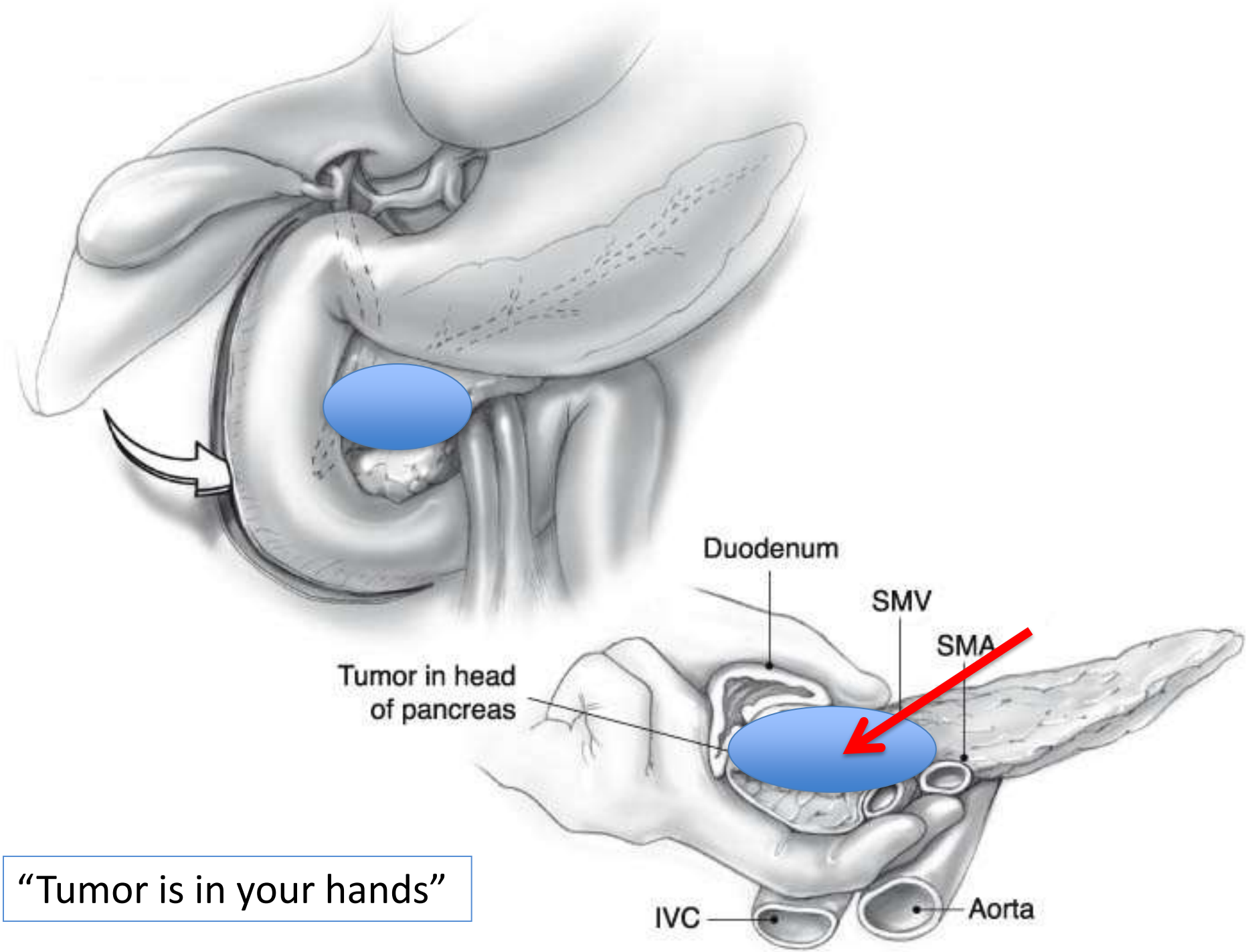
1. PILOT STUDY: feasibility and safety (1-50 pts)

2. LONG TERM RESULTS (1-100 pts)

3. REDUCE MORBIDITY & MORTALITY (100 - 388 pts)

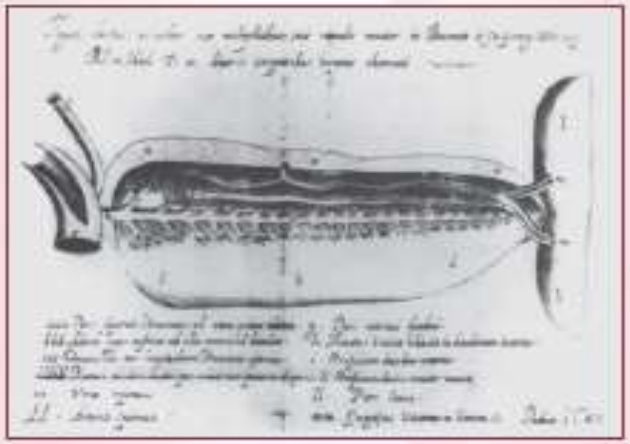
4. MINIMALLY INVASIVE TECHNIQUES

5. PROSPECTIVE RANDOMIZED TRIALS



"Tumor is in your hands"

ABLAZIONI PANCREATICHE



Verona
10/11 Novembre 2017
Aula Magna Policlinico GB Rossi

PRESIDENTE ONORARIO

Prof. Paolo Pederzoli
Ospedale Pederzoli - Peschiera del Garda, Verona

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Radiofrequency ablation for locally advanced pancreatic cancer: *SMAD4* analysis segregates a responsive subgroup of patients

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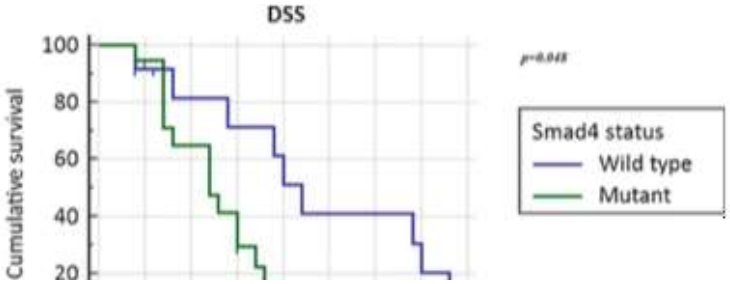
RETROSPETTIVO
30/101 PAZIENTI
DIAGNOSI-RFA 5 MESI
60% Smad4 –



th wild-type

Table 2 Univariate and multivariate analysis of factors associated with survival

Variable	*p* value	Median DSS, months (95% CI)	2-year survival, %
Tumor site	0.012		
Head		17 (11–23.01)	32.3
Body-tail		8 (7.97–18.02)	0
CA 19–9 (> 100 mU/L)	0.003		
No		19 (9.60–28.39)	36.3
Yes		8 (5.07–10.92)	0
SMAD4 loss	0.048		
No		22 (17.49–26.5)	64.9
Yes		12 (6.97–17.02)	14.8

PELICAN trial

Pancreatic Locally advanced Irresectable Cancer Ablation in the Netherlands:

A randomized controlled superiority phase III multicenter trial

A study of the Dutch Pancreatic Cancer Group:

DPCG
Dutch Pancreatic Cancer Group

NEOADIUVANTE + RFA vs. CT alone

June , 2016

284 patients

DECEDUTI PER MALATTIA	**60%**
VIVENTI malattia in progressione malattia stabile liberi da malattia	**27,4%** 15% 10% 2,4%
LONG SURVIVORS (3-5 anni)	**12,1%**

Coming soon: risultati del PRT