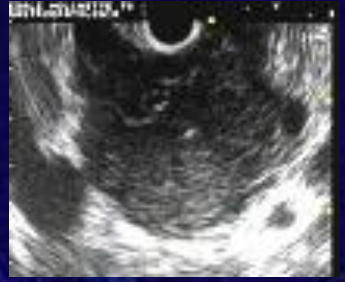
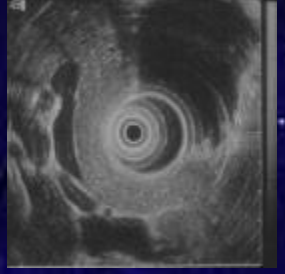




EchoTip Ultra Fiducial Needle: a new tool in echoendoscopy

Symposium “Pancreatic cancer”

Friday, June 22nd

Semana Digestiva 2018
20 a 23 de junho
Alfândega do Porto

Sociedade Portuguesa de Gastrenterologia

ORGANIZAÇÃO PROGRAMA RESUMOS CURSOS PRÁTICOS INSCRIÇÕES PATROCÍNIOS EDIÇÕES ANTERIORES

“HUMANIZAR COMPETÊNCIAS, DESAFIAR OS LIMITES”

Thanks to: Pierfrancesco Franco, MD
Department of Oncology, Radiation Oncology
University of Turin School of Medicine
Turin, Italy

Claudio G. De Angelis
Department of Gastroenterology
Endoscopy and Endosonography Center
NETs and Pancreatic diseases Center
Molinette Hospital – University of Turin

TURIN

Some introductory concepts: what are we talking about?

1° the 7th most frequent cancer in Europe

2° 4th leading cause of cancer mortality in the USA

3° Radical surgery with R0 resection is the only curative option

4° Only 10-20% of patients at presentation have resectable disease:

Morganti et al, Ann Surg 2010
Gilbert et al Ann Oncol 2017

Some introductory concepts: what are we talking about?

5° Up to 40-50% of pts have locally advanced disease

6° Metastatic disease at diagnosis in 30-40% of cases

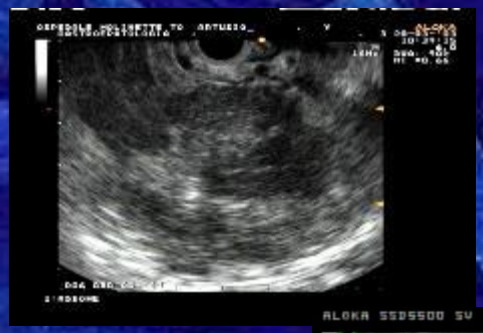
7° <25% of pts survive > 1 yr; >5% of pts survive > 5 yrs; 18-24% of pts with margine negative resection alive at 5 yrs.

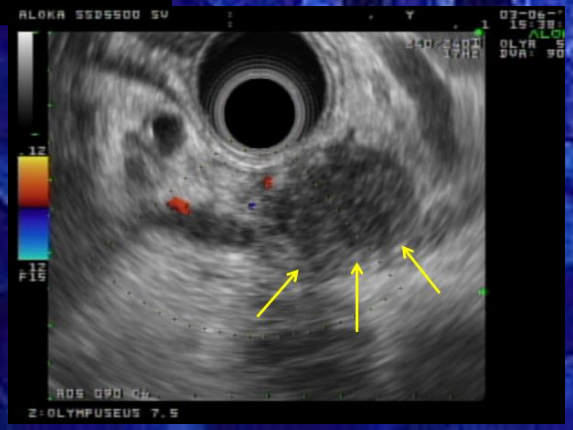
Morganti et al, Ann Surg 2010
Gilbert et al Ann Oncol 2017

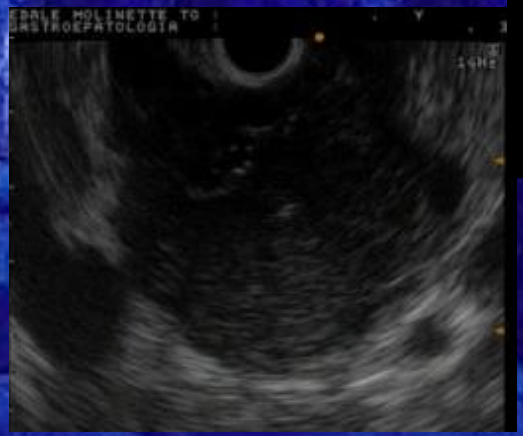
FIELD OF INTEREST:

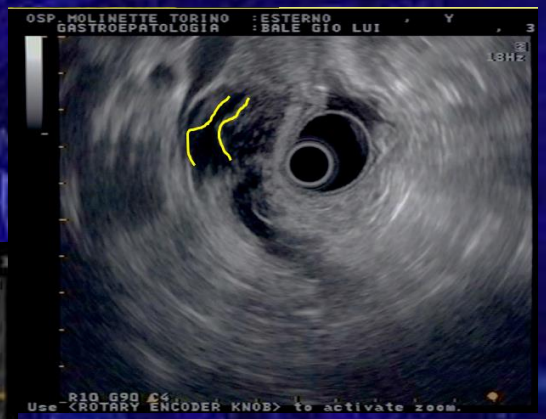
★ BORDERLINE RESECTABLE DISEASE

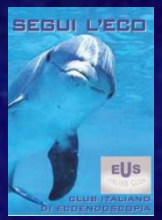
★ LOCALLY ADVANCED DISEASE (UNRESECTABLE)



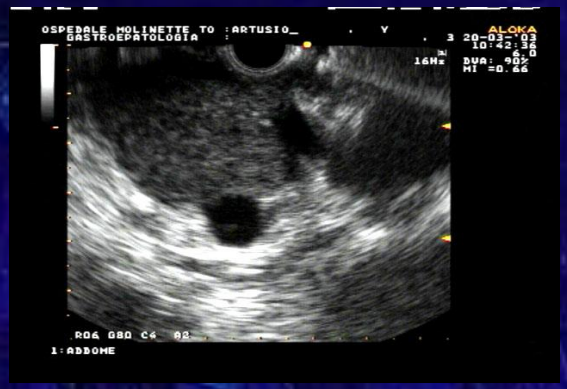


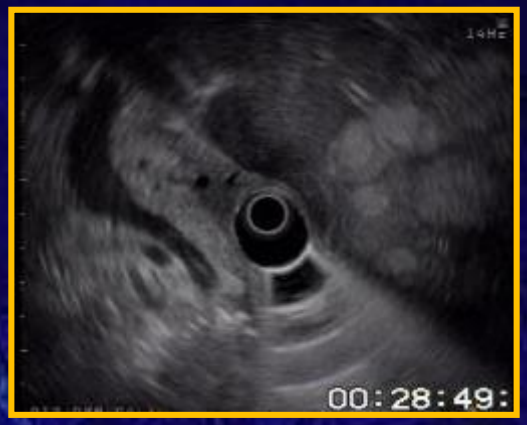


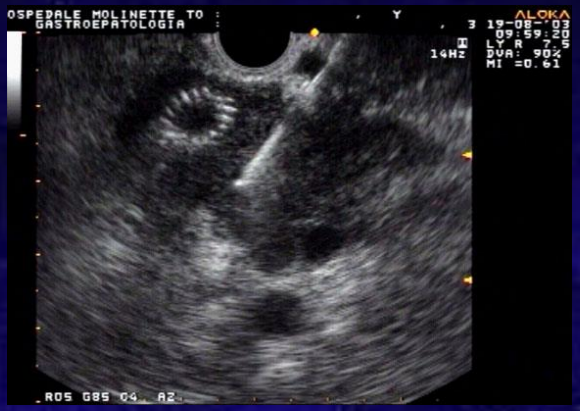




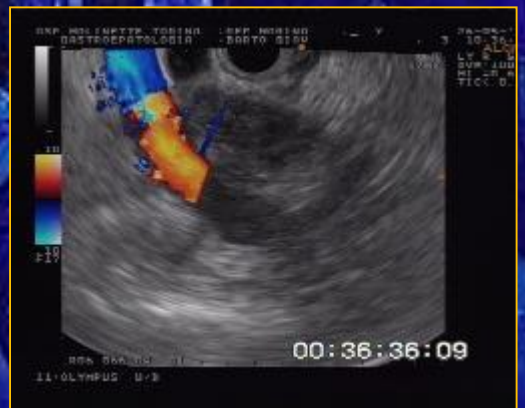
EGEUS
EUROPEAN GROUP FOR ENDOSCOPIC ULTRASONOGRAPHY







«Recent data clearly demonstrated that we need better CT to decrease metastatic rate and better RT to increase locoregional control»



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Research

Original Investigation

Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib

The LAP07 Randomized Clinical Trial

Pascal Hammel, MD; Florence Huguet, MD; Jean-Luc van Laethem, MD; David Goldstein, MD; Bengt Glimelius, MD; Pascal Artru, MD; Ivan Borbath, MD; Olivier Bouché, MD; Jenny Shannon, MD; Thierry André, MD; Laurent Mineur, MD; Benoist Chibaudel, MD; Franck Bonnetain, PhD; Christophe Louvet, MD

The LAP07 randomized clinical trial

What benefit can erlotinib add to gemcitabine in the LAPC setting?

Does chemoradiotherapy improve OS in the case of disease control after 4 months of induction with gemcitabine

First randomization: 4 months induction chemotherapy with gemcitabine alone vs induction with gemcitabine and erlotinib.

Second randomization: all patients who were free of progression and who had a WHO performance status of 2 or less at 4 months, were randomized to receive chemoradiotherapy (RT 54 Gy + capecitabine) or chemotherapy alone.

Hammel et al; JAMA 2016

The LAP07 randomized clinical trial

Research

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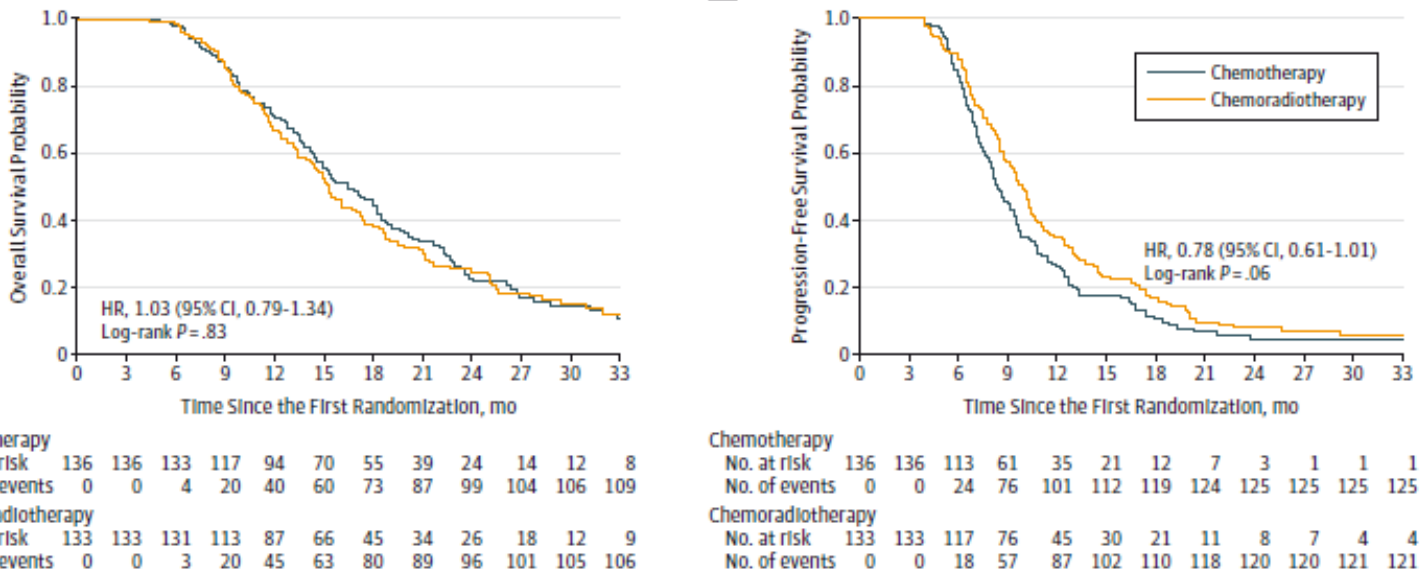
Figure 3. Kaplan-Meier Curves of Overall Survival and Progression-Free Survival, According to the Second Randomization



Median OS: 16.5 months (CT) vs 15.2 months (RT-CT) (HR:1.03;p=0.83)

Median PFS: 8.4 months (CT) vs 9.9 months (RT-CT) (HR: 0.78;p=0.06)

Hammel et al; JAMA 2016


Research

Original Investigation

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LAP07 trial – pattern of failure

After second randomization

- ❑ **Overall, 88% of pts had tumor progression**
- ❑ **Locoregional: 39%**
- ❑ **Systemic: 52%**
- ❑ **Unknown type: 9%**

- ❑ **Locoregional progression: 32% (RT-CT) vs 46% (CT)**
- ❑ **Systemic progression: 60% (RT-CT) vs 44% (CT)**

RT-CT: longer period without treatment (6.1 vs 3.7 months; p=0.02)

Hammel et al; JAMA 2016

Research

Original Investigation

Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib

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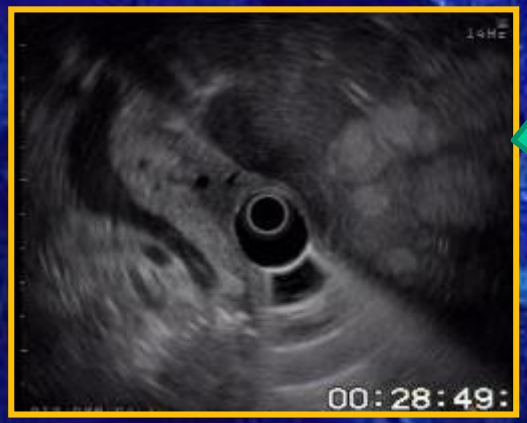
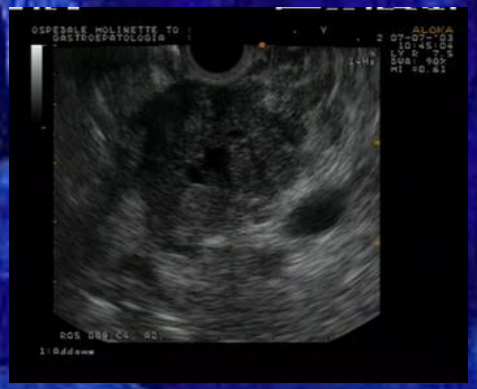
LAP07 trial – pattern of failure

LAP07 trial – take home messages

- ✓ **Need for better CT to decrease metastatic rate**
- ✓ **Need for better RT to increase loco-regional control**





Hammel et al; JAMA 2016

Research

Original Investigation

Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer

Alliance for Clinical Trials in Oncology Trial A021101

Matthew H. G. Katz, MD; Qian Shi, PhD; Syed A. Ahmad, MD; Joseph M. Herman, MD; Robert de W. Marsh, MD; Eric Collisson, MD; Lawrence Schwartz, MD; Wendy Frankel, MD; Robert Martin, MD; William Conway, MD; Mark Truty, MD; Hedy Kindler, MD; Andrew M. Lowy, MD; Tanios Bekaii-Saab, MD; Philip Philip, MD, PhD; Mark Talamonti, MD; Dana Cardin, MD; Noelle LoConte, MD; Perry Shen, MD; John P. Hoffman, MD; Alan P. Venook, MD

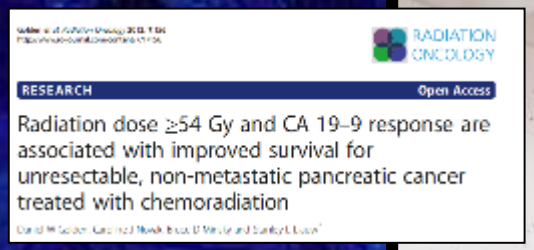
Pre-op combination therapy - Alliance trial A021101

- ❑ **68% of pts underwent surgery**
- ❑ **Median OS: 22 months**

Katz et al , JAMA Surg 2016

- ✓ **Need for better CT to decrease metastatic rate**
- ✓ **Need for better RT to increase loco-regional control**

How to increase loco-regional control?


RADIATION ONCOLOGY

RESEARCH Open Access

Radiation dose ≥54 Gy and CA 19–9 response are associated with improved survival for unresectable, non-metastatic pancreatic cancer treated with chemoradiation

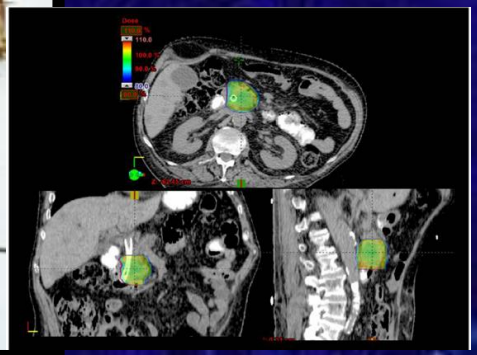

RADIATION ONCOLOGY

RESEARCH Open Access

SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience

Stereotactic Body Radiation Therapy

- ❑46 pts with ULAPC
- ❑Concurrent CT (5-FU)
- ❑3DCRT/S&S IMRT
- ❑RT dose > 54 Gy – HR: 0.47 (p=0.028)



Anish Kapoor – Shooting into the Corner - 2009

How to increase loco-regional control?

Stereotactic Body Radiation Therapy

Critical Review

Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials

Fausto Petrelli, MD,* Tiziana Comito, MD,† Antonio Ghidini, MD,† Valter Torri, MD,‡ Marta Scorsetti, MD,§ and Sandro Barni, MD*

Dose escalation with SBRT

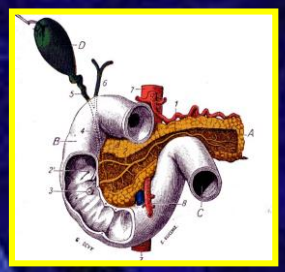
- Ablative RT dose
- Hypofractionated schedule
- Accelerated treatment (few fractions)
- Easier integration with

The advantages of SBRT in terms of treatment time, satisfactory OS and PFS, and LRC indicate that it is an effective option for inoperable PC. Rate of resection improve from 0-20% to 50-56% of pts. Severe adverse events: =<10%.

How to increase accuracy during RT treatments:

How to increase loco-regional control?

The answer is to deliver higher doses of radiation but much more precisely.



1° the Stereotactic Body Radiation Therapy (SBRT):

- an external beam RT method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of large fractions, taking into account respiratory and other involuntary motion of the target lesion during RT.

How to increase accuracy during RT treatments:

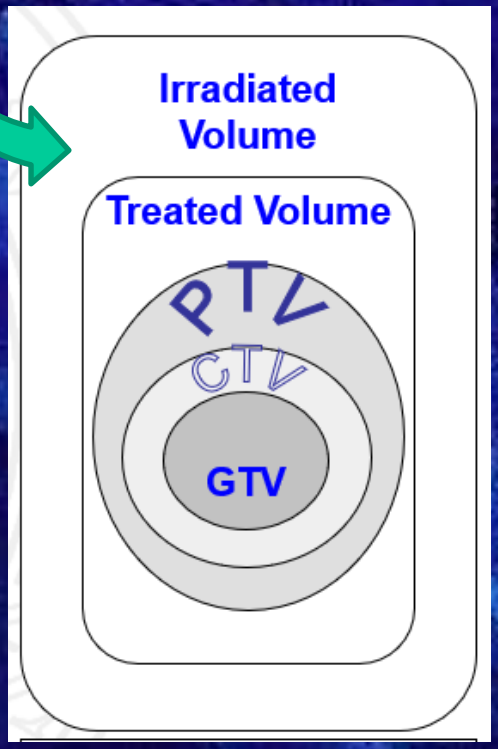
How to increase loco-regional control?

1. Delivering of adequate radiation dose to the pancreas is limited by the radiosensitivity of tissues around it. This has resulted in increasing interest in techniques with **greater conformality** such as :
2. image-guided RT (IGRT),
3. intensity-modulated RT (IMRT),
4. 4D-CT and more recently tracking techniques such as the CyberKnife.
5. The pancreas is a soft-tissue organ and is not visualized on radiographic imaging during RT treatment planning; bony landmarks are usually used as surrogate markers to localize the organ, but it moves a lot with respect to bony anatomy due to respiration and variability of GI filling.

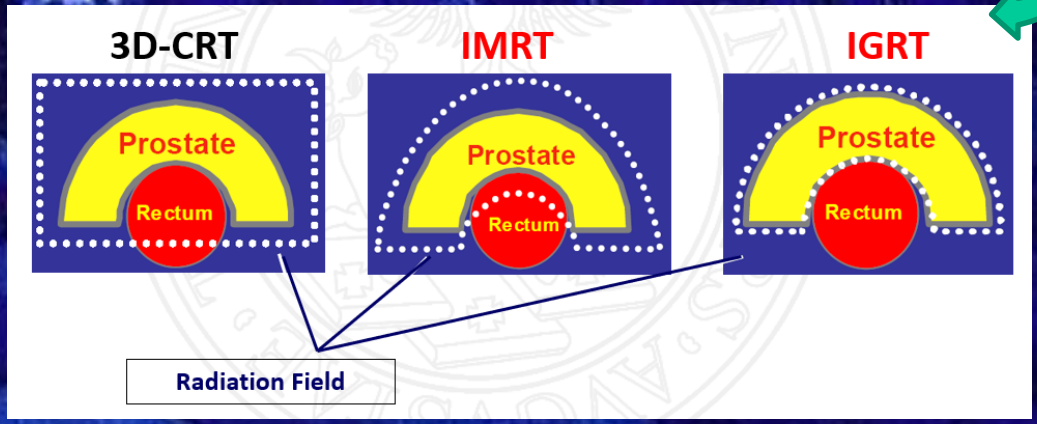
How to increase accuracy during RT treatments:

How to increase loco-regional control?

Target volumes in Radiation Therapy:
(Gross TV, Clinical TV, Planning Target V)



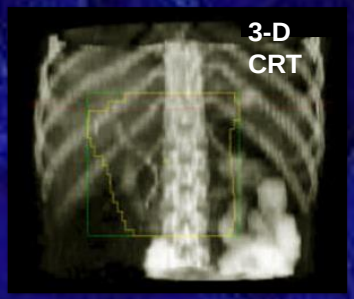
The Magic Bullet: "Conformality"

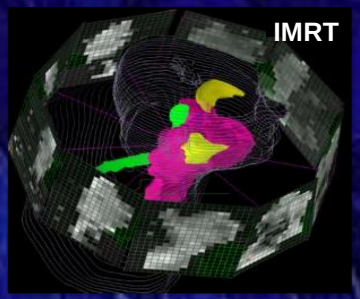


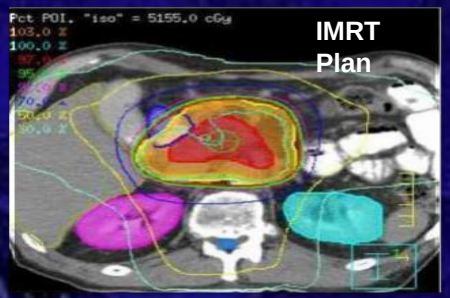
How to increase accuracy during RT treatments:

How to increase loco-regional control?

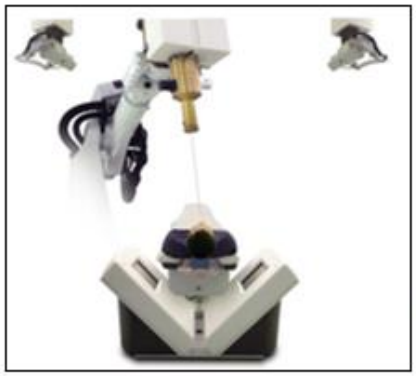
Evolution of Radiation Therapy







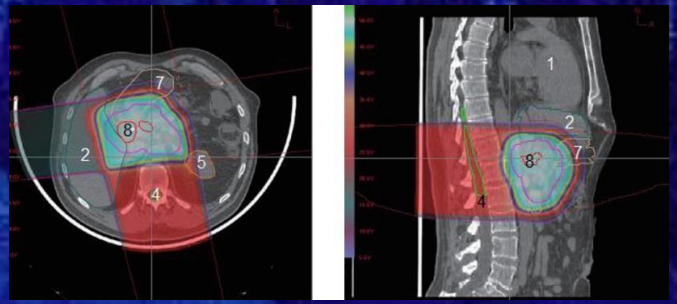

TOMOTHERAPY


CYBER-KNIFE


TRILOGY


SYNERGY

Proton Beam



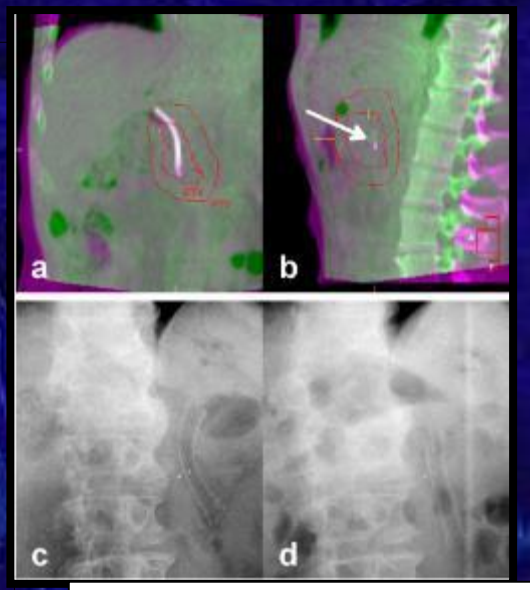
How to increase accuracy during RT treatments:

How to increase loco-regional control?

Evolution of Radiation Therapy

Are fiducial markers useful ?

- Low soft tissue contrast of CBCT (cone beam CT)
- Fiducial markers potentially useful; stent might be surrogate fiducial
- 11 pts with both fiducial and stent
- Bony anatomy vs stent vs fiducials
- Stent better than bony anatomy for tumor position in 67% of scans
- Difference fiducials vs stent: > 5 mm in 46% scans and > 10 mm in 20%
- Larger PTV margin needed if bony anatomy or stent compared to fiducials



van der Horst et al , IJROBP 2014


Physics Contribution

Limited Role for Biliary Stent as Surrogate Fiducial Marker in Pancreatic Cancer: Stent and Intratumoral Fiducials Compared

Astrid van der Horst, PhD,* Erica Lens, MSc,* Silvia Wognum, PhD,* Rianne de Jong, RTT,* Joanne E. van Hooft, MD, PhD,† Geertjan van Tienhoven, MD, PhD,* and Arjan Bel, PhD*

Are fiducial markers useful ?


BMC Cancer

STUDY PROTOCOL Open Access

Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas

Pre-op combination therapy – Alliance trial A021501

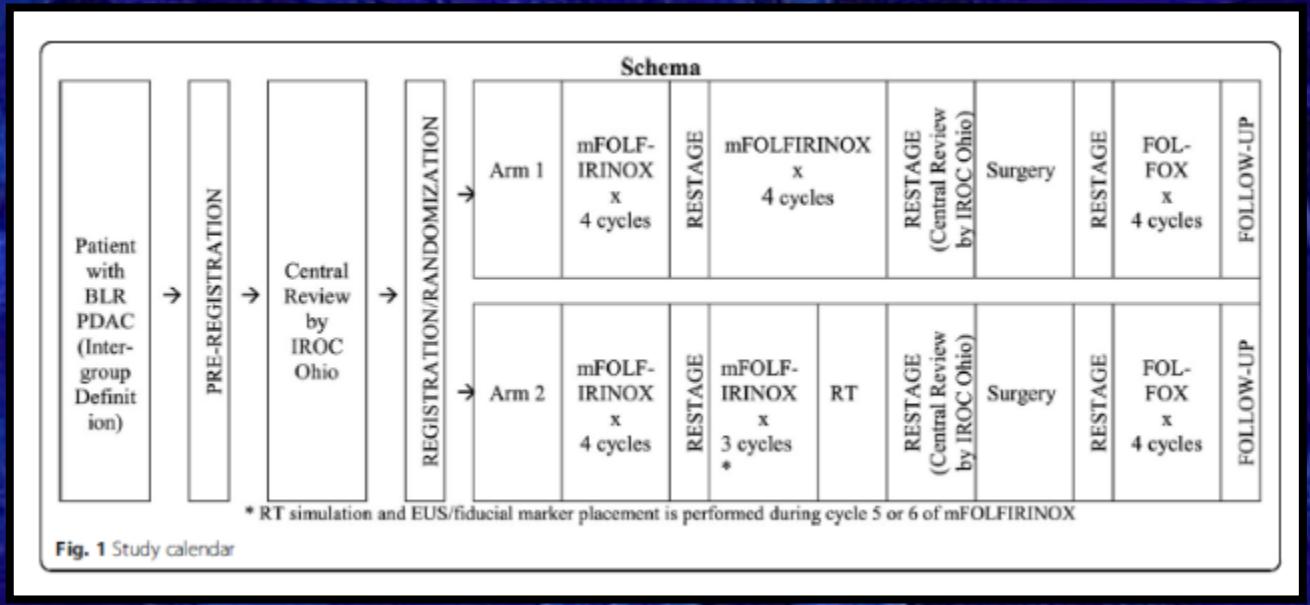


Fig. 1 Study calendar

- SBRT: 6.6 Gy x 5 fr (33 Gy)
- Hypofractionated IGRT: 5 Gy x 5 fr (25 Gy)

Fiducial markers required !

Katz et al , BMC Cancer 2017

Evolution of Radiation Therapy

Are fiducial markers useful ?

Question:

Is there a role for fiducial markers during RT or SBRT for pancreatic cancer?

Answer: Yes

van der Horst et al , IJROBP 2013

van der Horst et al , IJROBP 2014

Karava et al , Radiat Oncol 2017

Lens et al , Acta Oncol 2014

Katz et al , BMC Cancer 2017

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- Fiducial markers are inert radiopaque spheres, coils, or seeds (made of gold or platinum or other metallic alloys)
- Can be implanted inside or adjacent to the tumor in order to aid image-guided radiation therapy (IGRT)
- IGRT allows precise delivery of radiation to the tumors while minimizing radiation to normal tissues
- but requires presence of multiple reference points through which the tumor can be identified and tracked = **FIDUCIAL MARKERS**.
- Before development of EUS-FNA, fiducial markers have been placed either by surgery or percutaneous route under ultrasound or CT guidance.

Han J et al. Interventional EUS for Pancreatic Tumors

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- EUS-guided fiducial markers placement for pancreatic cancer was **first reported** in a case series of 13 patients with mediastinal and abdominal malignancies
- A 19-gauge FNA needle (MEDI-Globe, Achenmühle, Germany, or Sonotip II, Wilson-Cook, Winston-Salem, NC, USA) was used.
- Fiducials: gold cylinders long 3 or 5 mm with a diameter of 0.8mm > insertion of the FNA needle into the tumor > stylet removed > a fiducial manually placed into the needle > stylet used to push the fiducial through the needle lumen into the tumor.
- Repeat to place three to six fiducials.
- Fluoroscopy was also used to verify location of fiducial placement
- EUS-guided fiducial marker placement was successful in 11 of 13 patients (84.6%).

Pishvaian AC et al. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc 2006;64:412-417.

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- Further studies of EUS-guided fiducial marker placement followed:

Table 2. Summary of Published Studies and Current Study on Endoscopic Ultrasonography-Guided Fiducial Placement in Gastrointestinal Malignancy

Study	Type of study	No. of cases	Needle used, gauge	Type of fiducials (length×diameter, mm)	Technical success, no. (%)	Adverse events (no. of cases)
Pishvaian *et al.*[7] (2006)	P	13	19	Gold (3 or 5×0.8)	11 (85)	Cholangitis (1)
Varadarajulu *et al.*[9] (2010)	R	9	19	Gold (5×0.8)	9 (100)	None
Park *et al.*[6] (2010)	P	57	19	Visicoil (2.5×0.8)	56 (98)	Minor bleeding (1)
DiMaio *et al.*[4] (2010)	R	30	22	Visicoil (10×0.35)	29 (97)	Fever (1)
Sanders *et al.*[5] (2010)	P	51	19	Gold (5×0.8)	46 (90)	Mild pancreatitis (1)
Ammar *et al.*[8] (2010)	C	13	22	Visicoil (10×0.35)	13 (100)	None
Khashab *et al.*[12] (2012)	R	29	19	Gold (5×0.8)	39 (100)	None
		10	22	Visicoil (10×0.35)		
Choi JH, et al: 2014	R	32	19	Gold (3×0.8)	32 (100)	Mild pancreatitis (1)
Total		244			235 (96)	5 (2)

P, prospective; R, retrospective; C, case series.

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- Further studies of EUS-guided fiducial marker placement followed:

Table 1 Efficacy and safety of endoscopic ultrasound-guided fiducial placement.

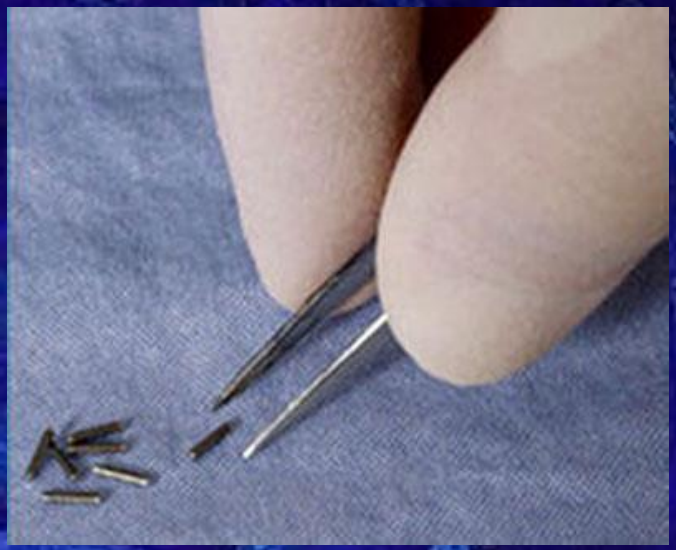
Study	Patients (#)	Cancer (type)	Efficacy (%)	Adverse events (# of patients)
Pishvaian AC et al. [3]	13	Mediastinal and abdominal malignancies	84.6	Infectious complication (1)
Varadarajulu S et al. [31]	9	Pancreatic cancer	100	None
Ammar T et al. [27]	13	Abdominal malignancies	100	None
Park WG et al. [30]	57	Pancreatic cancer	94	Needle malfunction (1), and minor bleeding (1)
Sanders MK et al. [29]	51	Pancreatic cancer	90	Mild pancreatitis (1)
DiMaio CJ et al. [5]	30	Gastrointestinal malignancies	97	Infectious complication (1)
Choi JH et al. [2]	32	Pancreatic and hepatic malignancy	100	Mild pancreatitis (1)
Majumder S et al. [21]	77	Pancreatic cancer	90	Abdominal pain (3), vomiting (1), mild pancreatitis (1)
Davila Fajardo R et al. [32]	23	Pancreatic cancer	100	Minor bleeding (1)

Chavalitdhamrong Disaya et al. EUS-guided placement of fiducials … Endosc Int Open 2015; 03: E373–E377

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- Both prospective and retrospective studies demonstrated safety and technical feasibility of EUS-guided fiducial placement in solid pancreatic tumors.
- Moreover, EUS-guided fiducial placement can be done without the use of fluoroscopy, is safer than the surgical approach and has several advantages over then percutaneous one.
- However, further refinements in fiducial deployment are needed, there is a lack of dedicated accessories
-

ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT



The fiducials were **back-loaded** into the tip of the needle.

Or they could be FRONT-LOADED into the needle after placing it into the tumor removing the stylet and then reintroducing it for pushing the fiducials in the lesion.

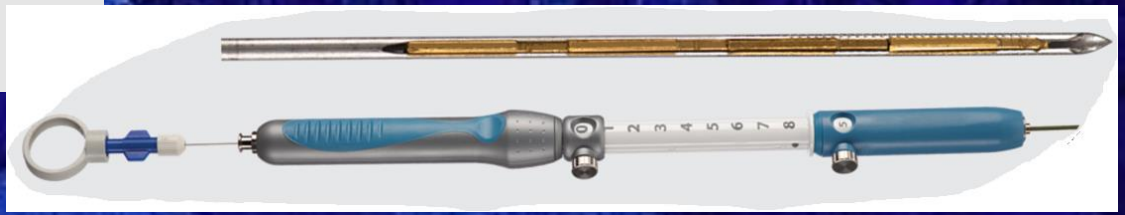
ENDOSCOPIC ULTRASOUND-GUIDED FIDUCIAL MARKER PLACEMENT

- We would need ……specifically designed needles able to carry multiple fiducials, stacked each other and separated by spacers that can be delivered in one pass……

Fuccio L et al. Expert Rev Gastroenterol Hepatol 2014

- Recently Cook Medical developed a new multifiducial delivery system, now commercially available (and other two-fiducials delivery system are near to be approved):

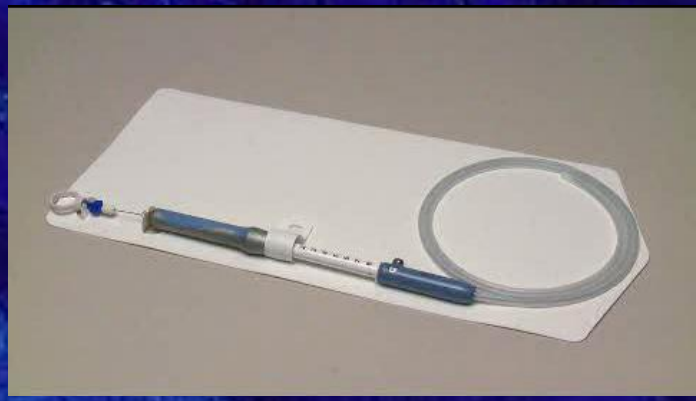
EchoTip® Ultra
FIDUCIAL NEEDLE



COOK MEDICAL
www.cookmedical.com

THE NEW GENERATION FIDUCIALS NEEDLE

- Four pure gold fiducials **preloaded** in the distal tip.
- Handle design facilitates marker placement.
- No need to reload for up to four marker placements, saving valuable procedure time.
- 22G needle provides a flexible delivery platform.
- Tactile feel when marker is deployed.
- Coiled sheath facilitates exceptional needle flexibility.



THE NEW GENERATION FIDUCIALS NEEDLE

EchoTip® Ultra
FIDUCIAL NEEDLE

Stylet and Thumb Ring

4 Preloaded Gold Fiducials

0.43 mm diameter

3.4 mm

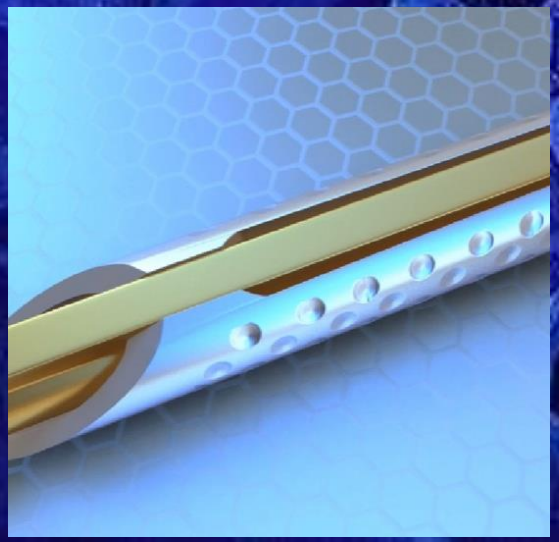
5 mm

0.64 mm diameter

EchoTip® Ultra
FIDUCIAL NEEDLE

.....allows implicit placement of up to four preloaded fiducials in challenging anatomical locations under EUS guidance.

This can potentially enhance your procedural efficiency, which can benefit you, radiation oncologists and your patients

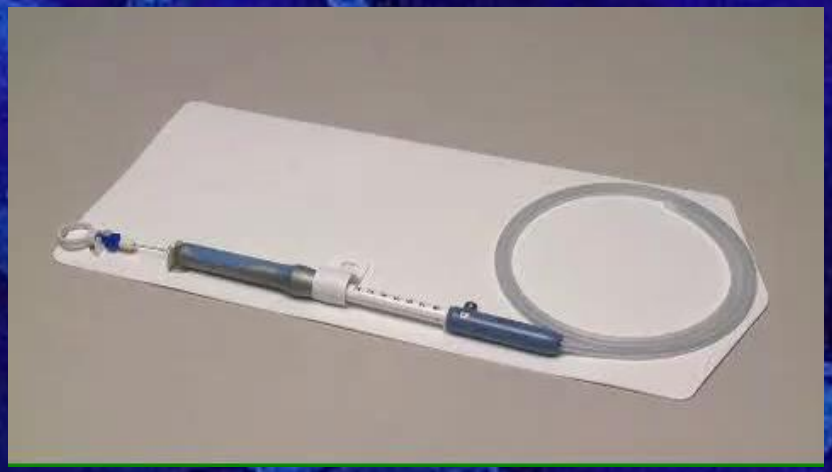


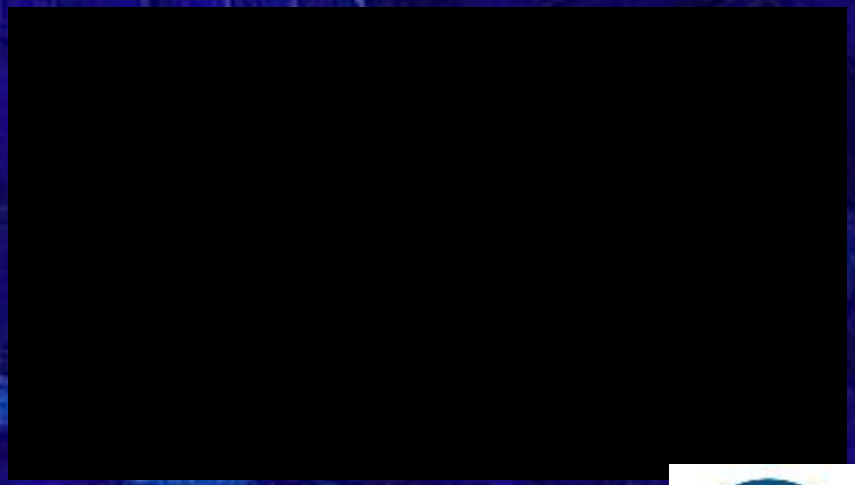
Narrowed area of laser cut at distal end provides two benefits:

1. Tactile feedback as fiducial is advanced through the slot
2. Reduces inadvertent deployment as needle is maneuvered to next position

EchoTip® Ultra
FIDUCIAL NEEDLE

Could potentially allow for a **shorter, more efficient, procedure** when compared to traditional methods of manually loading fiducials





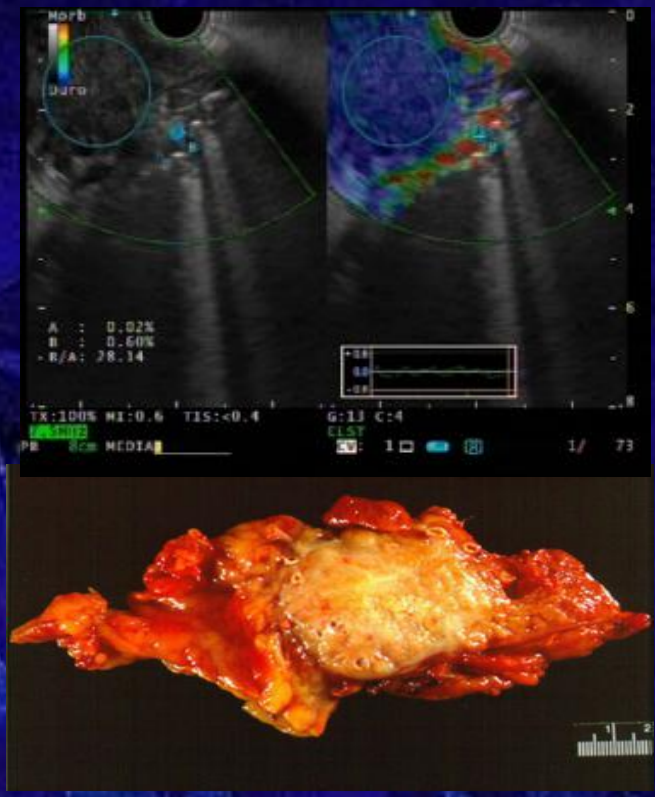
WHAT'S GOOD

- Preloaded fiducials (user friendly, less time-consuming)
- Very flexible coiled sheath (easy to use even in difficult position)
- Good visibility.
- Focal dose escalation of a higher dose (54Gy in 6 fractions).
- Precise delivery of the high-dose region to the vascolar abutment => R0 resections.
- Reduce dose to adjacent organ such as stomach and duodenum => less toxicity

DIFFICULTIES

- Tumor hardness
  (may deviate the needle)
- Tactil feel

(the fiducial release may be difficult to feel when the needle is into the tumor).

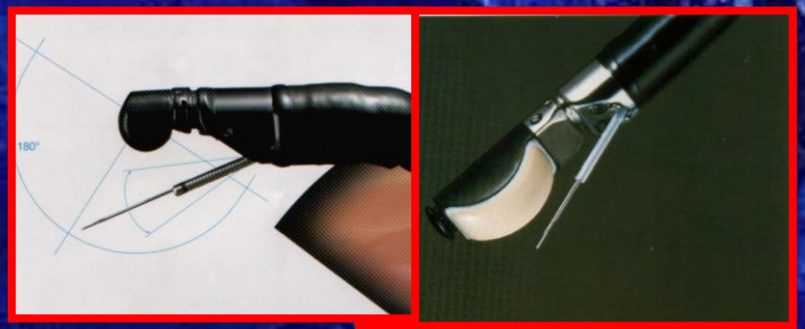


CAVEAT

- Possible perturbation in dose distribution in case of PROTON RT use (strongly influenced by fiducial composition and size): dose reductions up to 30% were observed

"CONCLUSIONS"

All these assumptions and some caveats must be evaluated in the next future with a more widespread use of these new fiducial needles in clinical studies



Application of IGRT to Locally Advanced Unresectable PC do require the USE of FIDUCIALS to track the precise location of the tumor

EUS-guided fiducial placement is safe, feasible and effective.

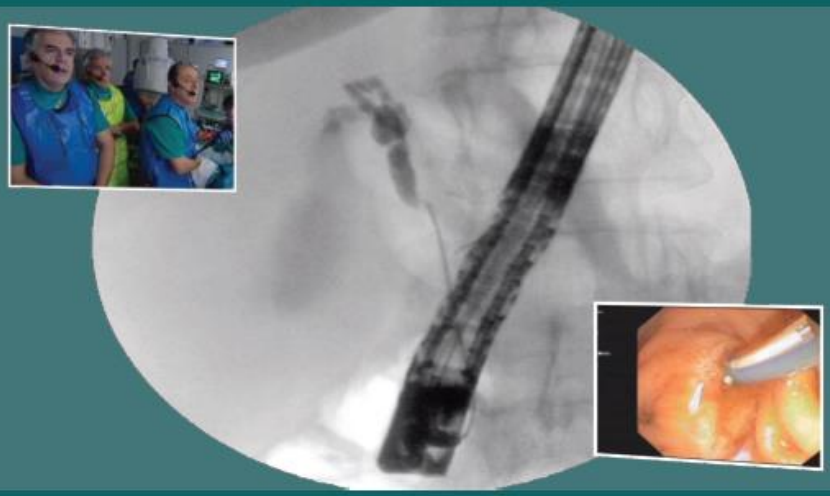
Recent technical advances in EUS devices for fiducial placement are very promising and will allow a more widespread use of these new application of therapeutic EUS in the treatment of pancreatic cancer

www.egeus.org

International Live Course

4th EUS-ERCP connection the "EURCP" concept

Course Directors ***Claudio G. De Angelis - Thierry Ponchon***



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NOVEMBER 15-17, 2018

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