Potential Future Innovative Strategy for Pancreatic Cancer: Intra-Arterial Chemotherapy

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Disclosures

- Sirtex
- Medtronic
- BD
- Cordis
- Trisalus Life Sciences

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Objectives

- Overview of Pancreatic Cancer
- Locally Advanced Pancreatic Cancer (LAPC)
- Treatment of LAPC with Intra-Arterial Gemcitabine – Mechanism of Action
- Clinical Data
- Future Directions – TIGeR PaC Phase III Clinical Trial

Pancreatic Cancer

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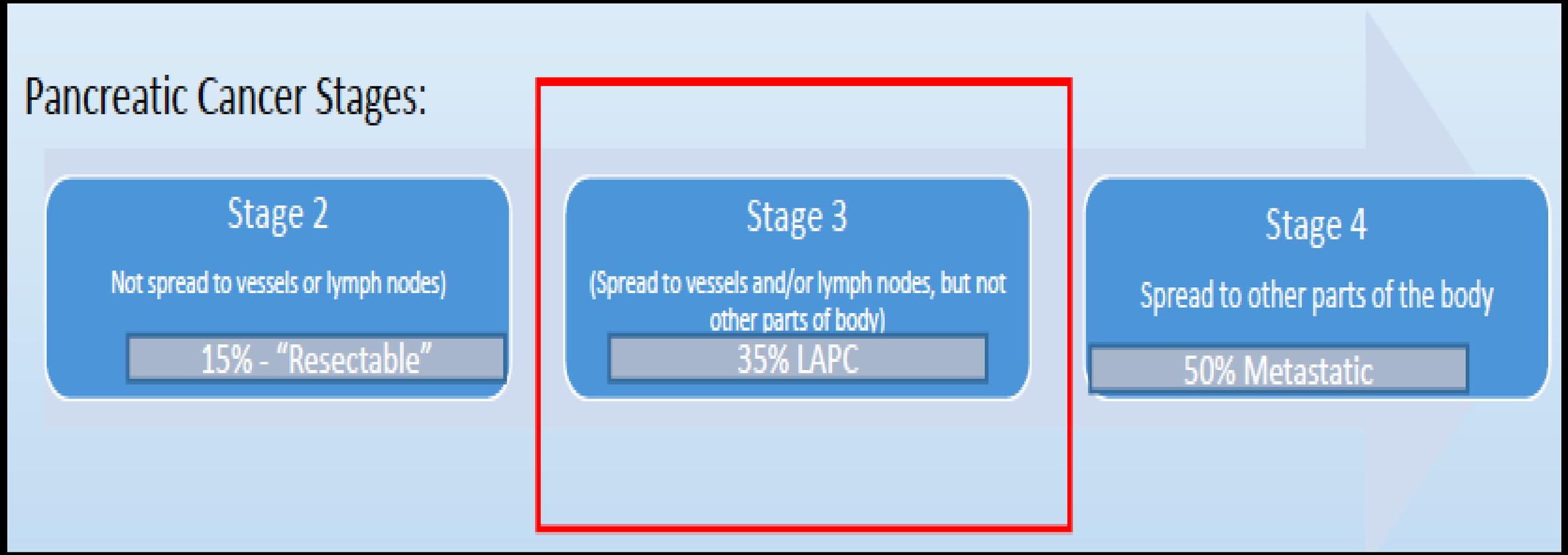
Pancreatic Cancer

- Pancreatic cancer is 3rd leading cause of cancer death in USA (projected 2nd leading cause by 2030)
  - 54,000 new cases per year in USA
  - Worldwide > 300,000 new cases/year

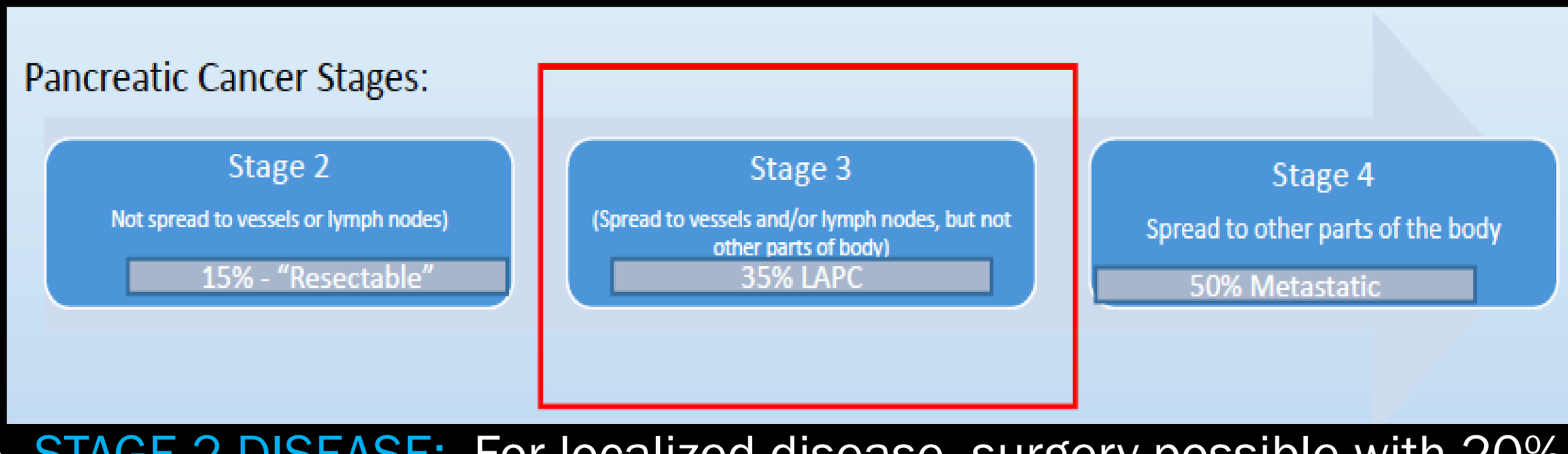
PANCREATIC CANCER STAGING



Pancreatic Cancer Staging

Stage	Tumor Description
0	• Confined to the top layers of pancreatic duct cells • Has not invaded deeper tissues • Has not spread outside of the pancreas
IA	• Confined to pancreas • Measures 2 centimeters (cm) or less in longest dimension • Has not spread to nearby lymph nodes or other parts of the body
IB	• Confined to pancreas • Measures greater than 2 cm • Has not spread to nearby lymph nodes or other parts of the body
IIA	• Extends beyond the pancreas • Does not involve major blood vessels or nerves • Has not spread to lymph nodes or other parts of the body
IIB	• May or may not extend beyond the pancreas • Does not involve the major blood vessels or nerves • Has spread to nearby lymph nodes or other parts of the body
III	• Growing outside the pancreas into nearby major blood vessels or nerves • May or may not have spread to nearby lymph nodes • Has not spread to other parts of the body
IV	• Cancer has spread to distant sites (sometimes called advanced or metastatic cancer)

Pancreatic Cancer



- STAGE 2 DISEASE: For localized disease, surgery possible with 20% 5 year survival
- STAGE 3 DISEASE: For locally advanced pancreatic cancer (LAPC):
  - Not resectable because of vascular involvement (> 180 degree involvement of the SMA, Celiac or SMV/PV obstruction not amenable to reconstruction), Only local pancreatic lymph node involvement
  - Systemic chemotherapy is standard of care and treated similar to metastatic disease
  - Current best standard of care: 15-16 months median survival

Pancreatic Cancer

- Gemcitabine and nab-paclitaxel (Abraxane®) was demonstrated to be superior over Gemcitabine alone[1]

- Challenges to Current Standard of Care
  - Limited Drug Penetration into Pancreatic Cancer
  - Systemic Side Effects / Toxicity

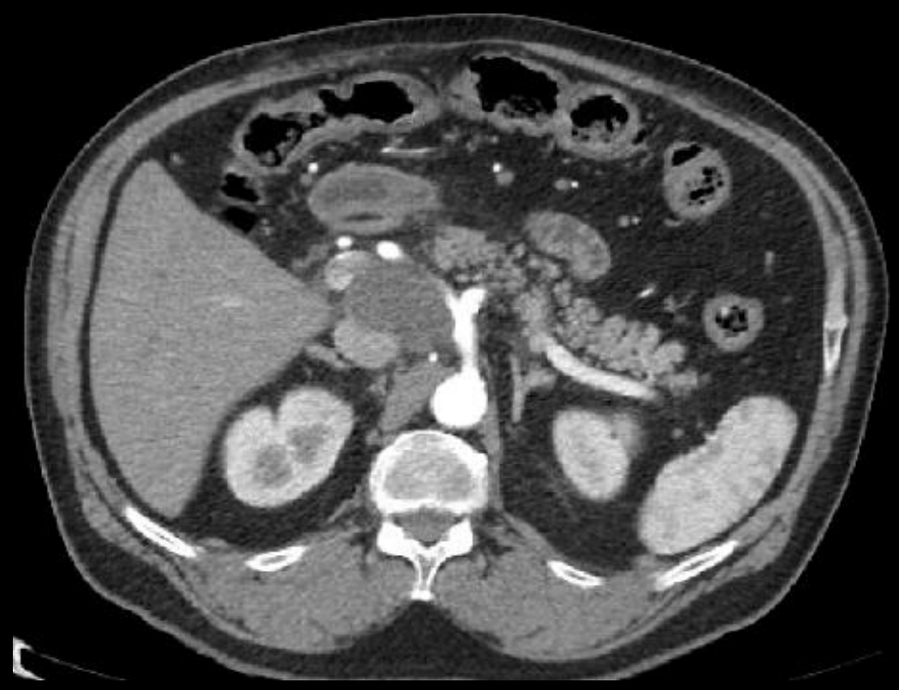
  - Survival for pancreatic cancer has only minimally improved over several decades. Advancements in therapy are urgently needed.

[1] Von Hoff DD, et al. N Engl J Med. 2013;369(18). PMID: 24131140

Locally Advanced Pancreatic Cancer

- Local Control appears to be important for symptoms and survival in locally advanced pancreatic cancer (LAPC)

- Several Potential Means for Local Control:
  - Radiation (SBRT, Proton Beam, MR Linac)
  - Irreversible Electroporation (IRE) – Nanoknife
  - Adenovirus/Gene Therapy
  - High intensity focused ultrasound (HIFU)
  - Transarterial chemoembolization
  - Tumor treating electrical field

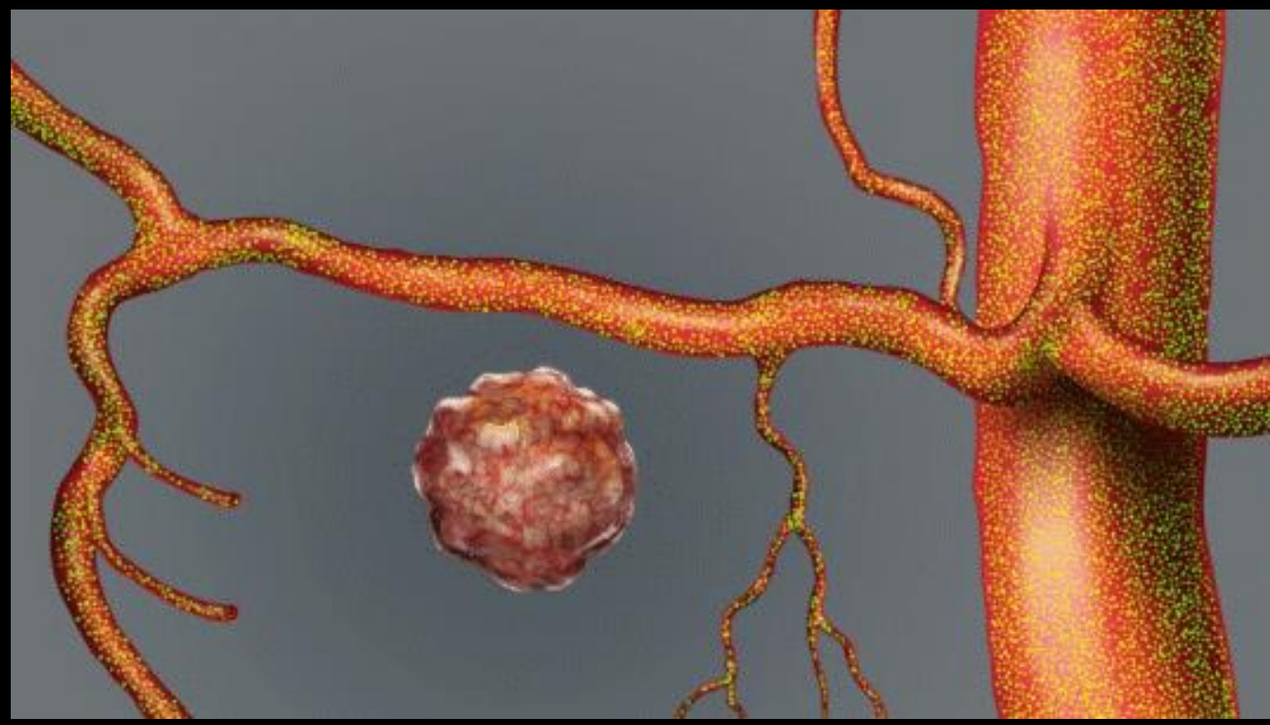


Technical Problem: Present Chemotherapy Regimens Have Limited Efficacy in Hypovascular Tumors

Hypervascular Tumor Treatment with Current Therapies

Liver tumors are highly vascularized

- Large tumor feeders – excellent targets for systemic therapy
- Can be accessed and treated with current local therapy techniques



Hypovascular Tumors Post Major Barrier to Chemotherapy Treatment Success

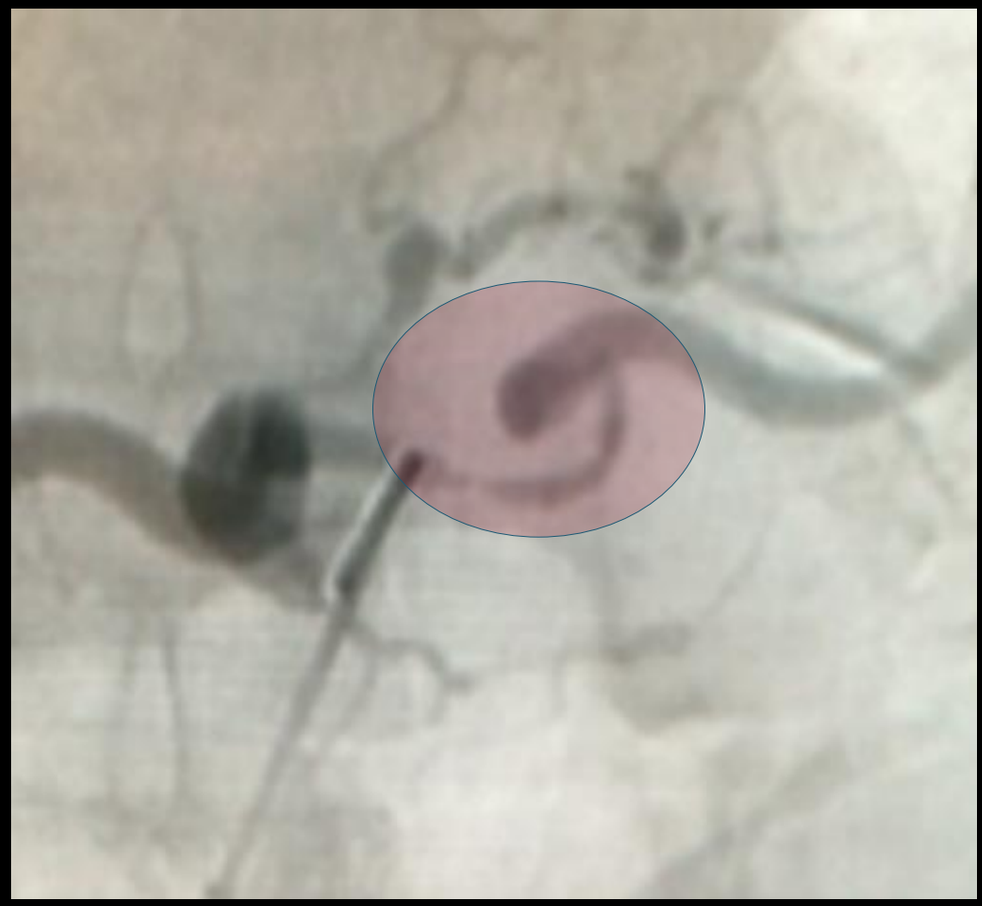
Pancreatic tumors have poor blood supply

- No visible tumor feeder vessels
- Systemic chemotherapy doesn't reach tumor tissue
- Inability to identify or engage tumor feeder vessels → local therapy is ineffective

Technical Problem

Liver tumors highly vascularized:

- Large tumor feeders – excellent targets for therapy
- Large branches within tumor - easily visualize tumor



Pancreas tumors are hypovascular:

- Challenge: Inability to identify or engage tumor feeder vessels
- Opportunity: Familiar anatomy for interventionalist

One Possible Solution:

Trans-Arterial Micro-Perfusion (RenovoTAMP)

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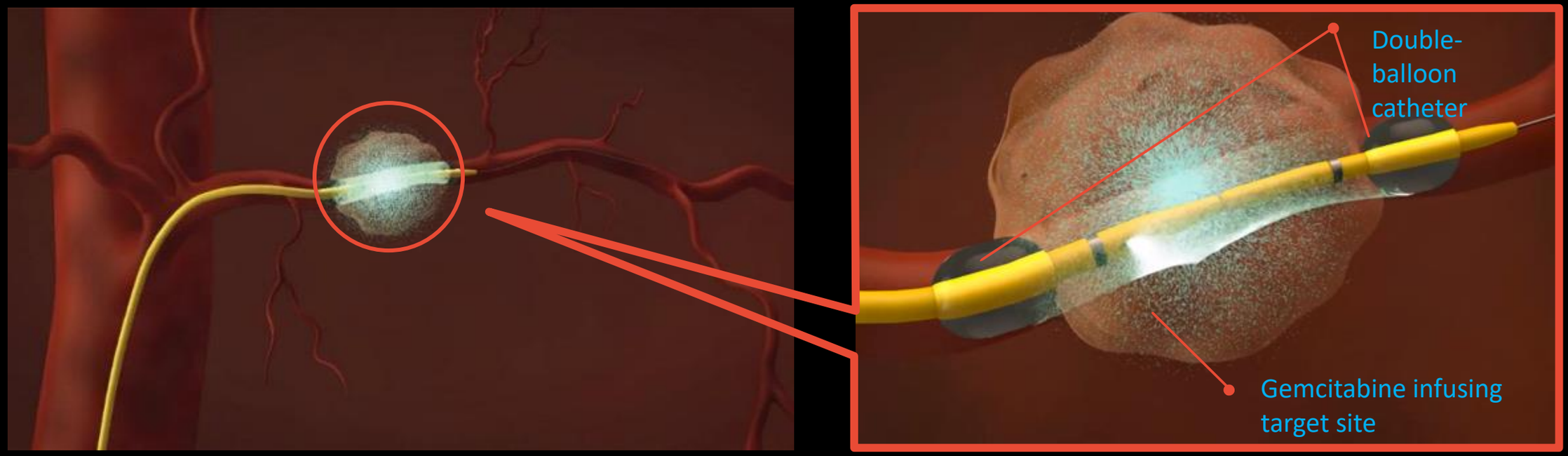
RenovoCath Allows for Targeted Therapy



The **RenovoCath™ System** isolates the anatomy and micro-perfuses targeted tissue with gemcitabine

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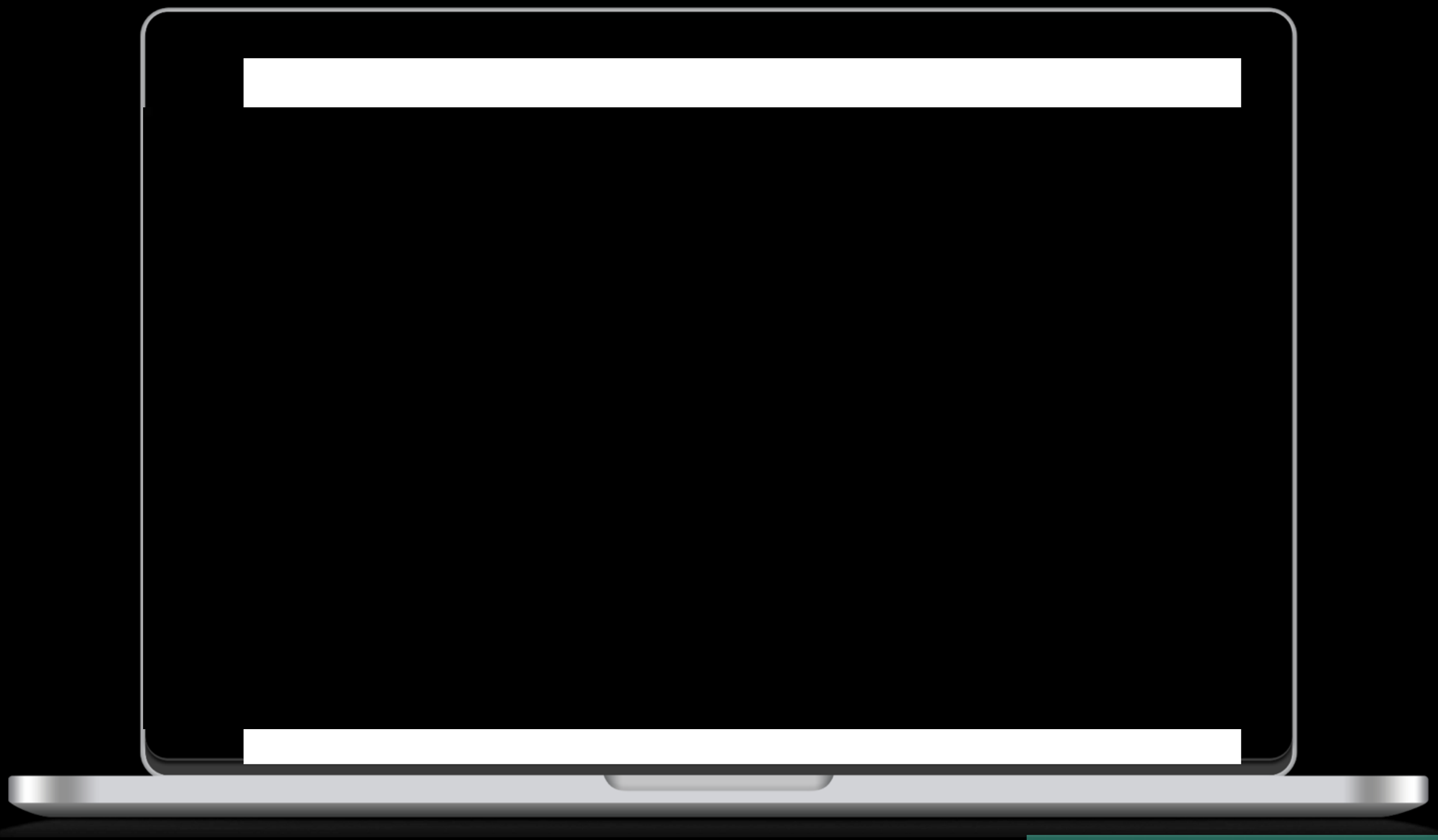
Targeted Delivery to Pancreatic Cancer: Trans-Arterial Micro-Perfusion (RenovoTAMP)



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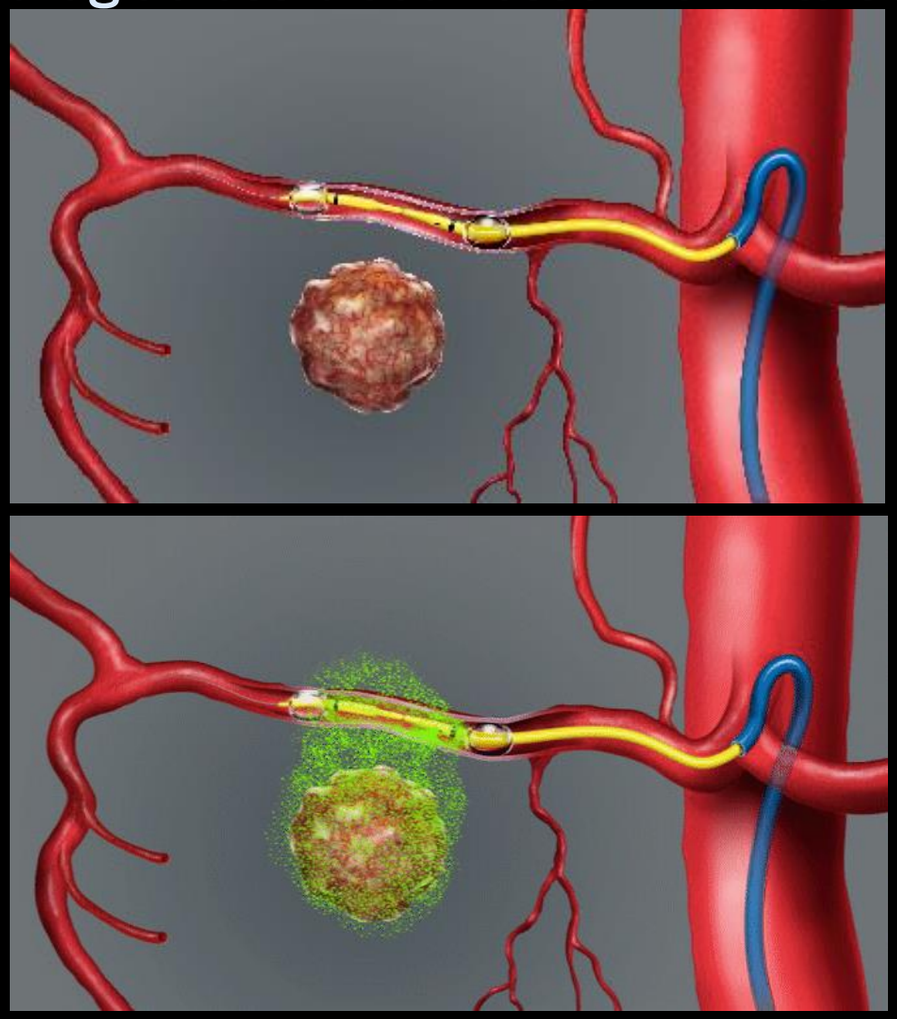
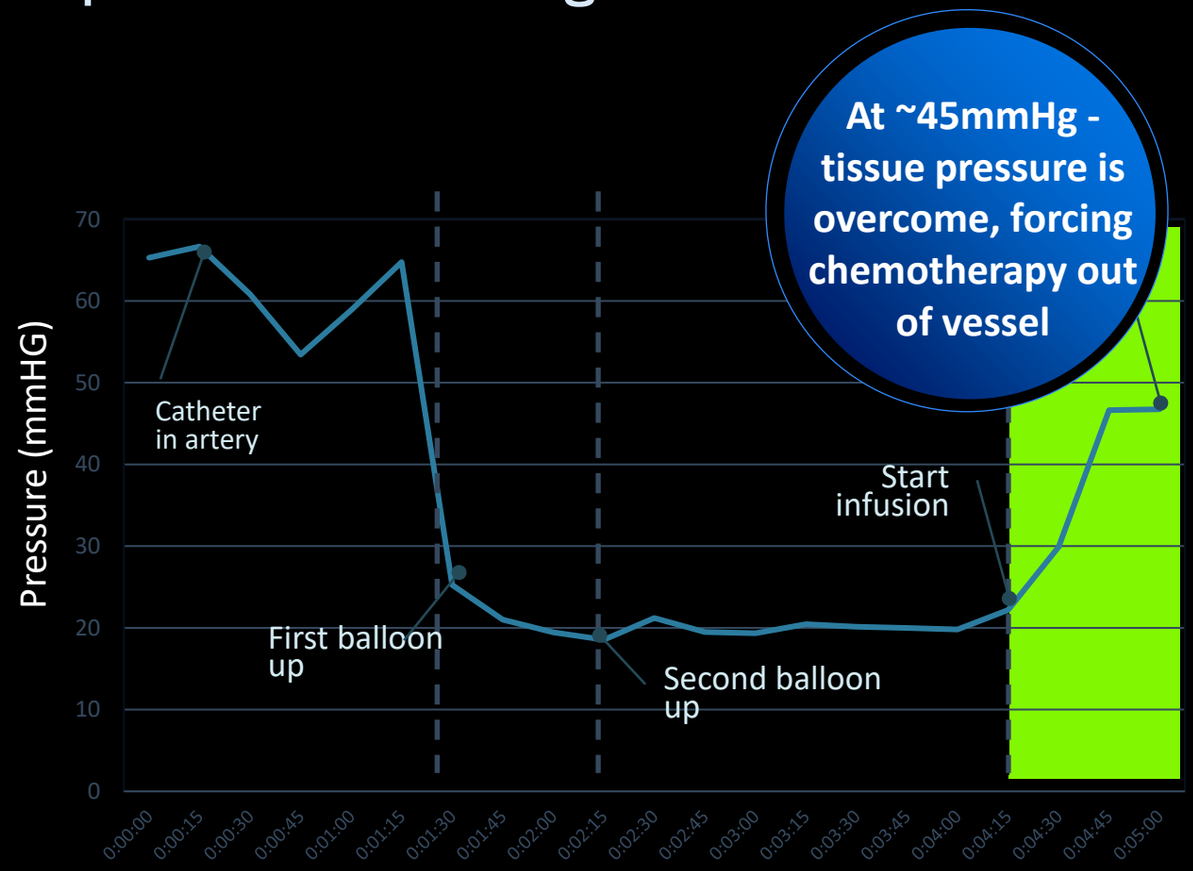
Trans-Arterial Micro-Perfusion (RenovoTAMP)

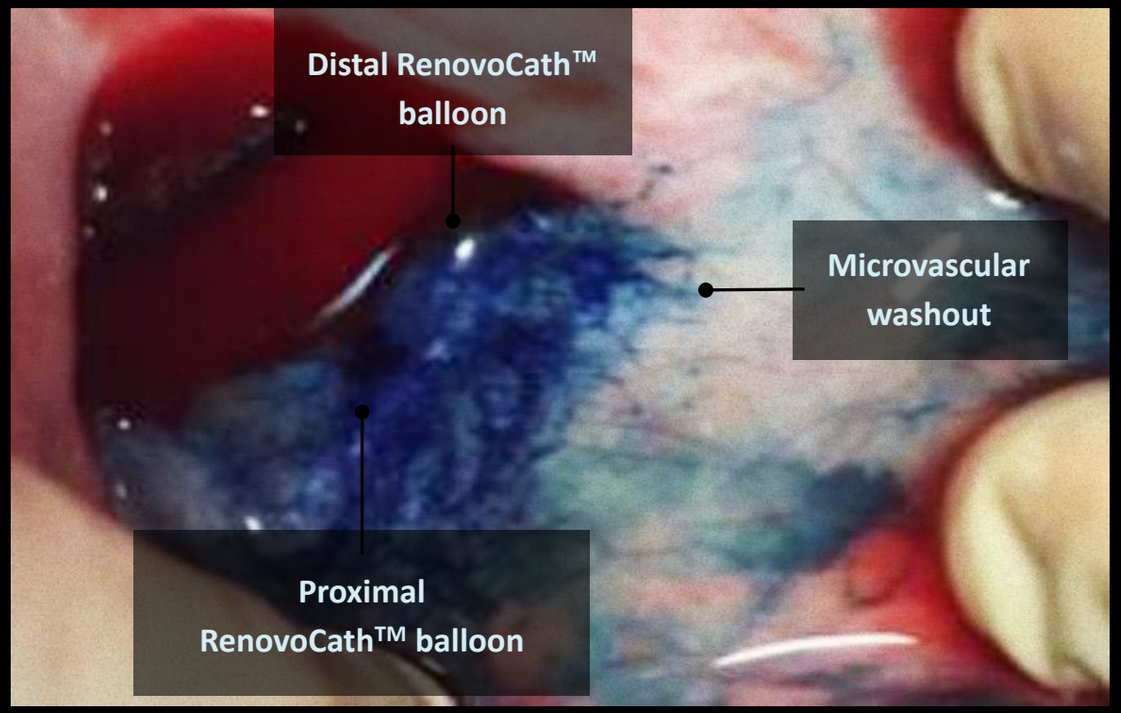
Blood vessel segment is isolated to deliver drug across blood vessel wall into tissue



Mechanism: after vessel isolation, increase in pressure forces drug into tissue



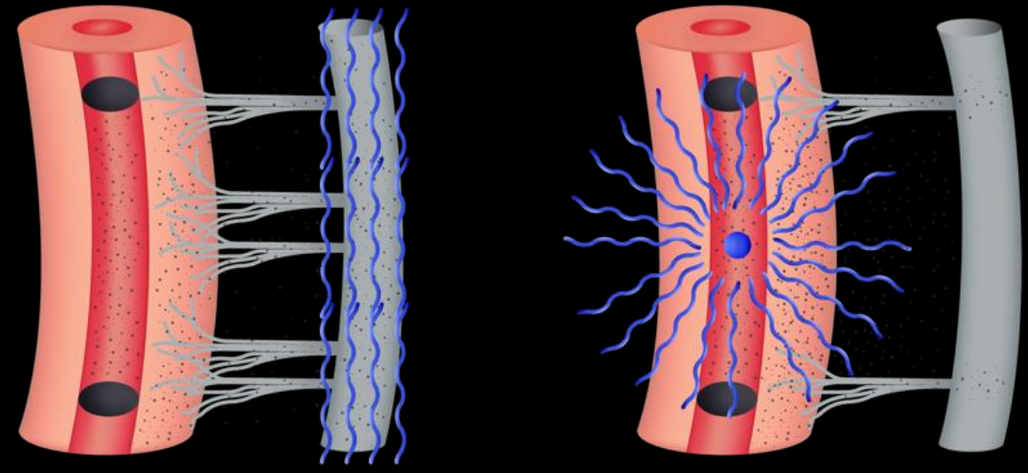
Mechanism : Trans-Arterial Micro-Perfusion (TAMP) combined with radiation



Radiation reduces venous outflow by decreasing the microvasculature

Native vasculature and IA chemo lead to **Micro-vascular washout**

Irradiated vasculature and IA chemo lead to **Diffusion**



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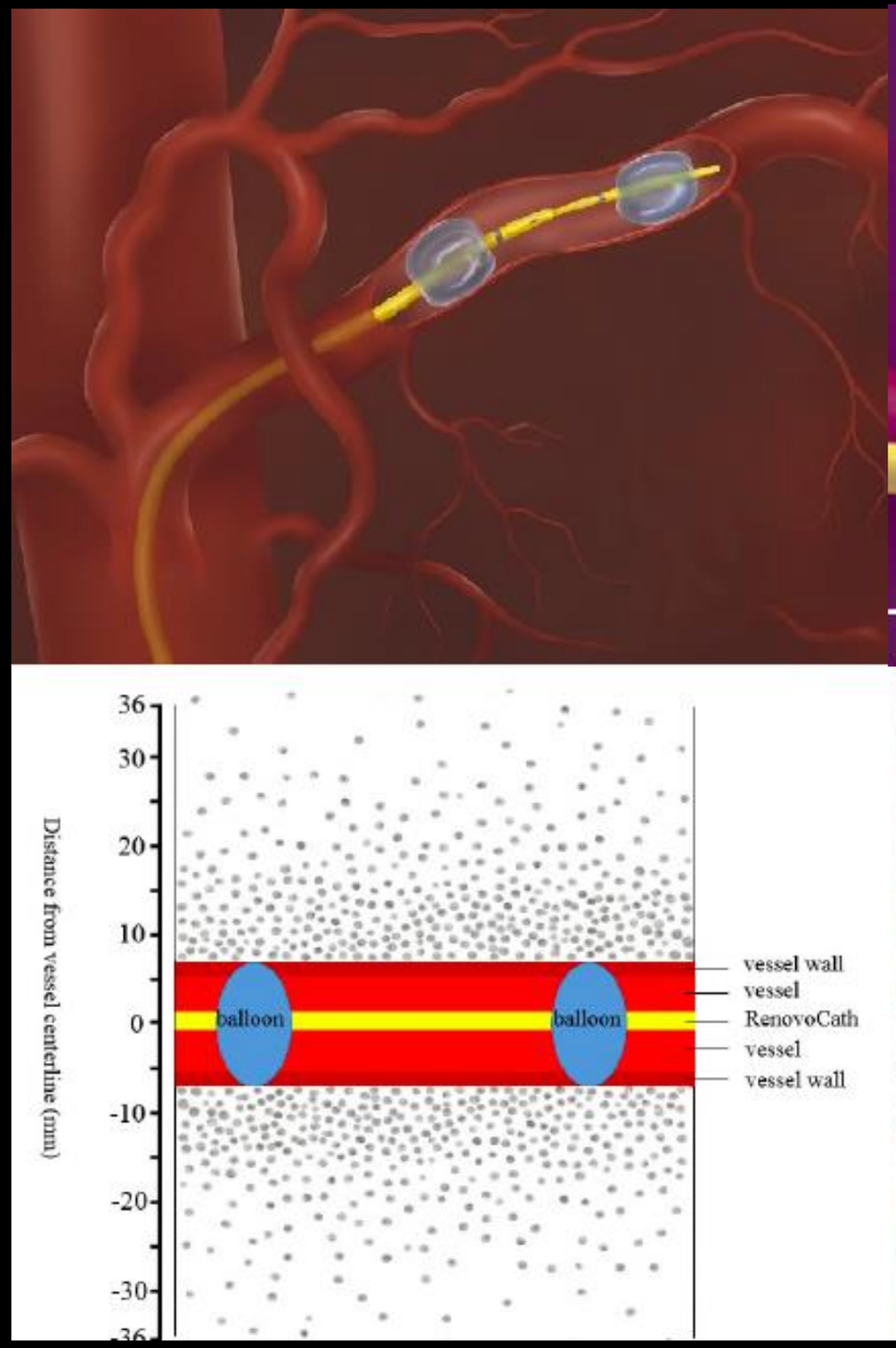
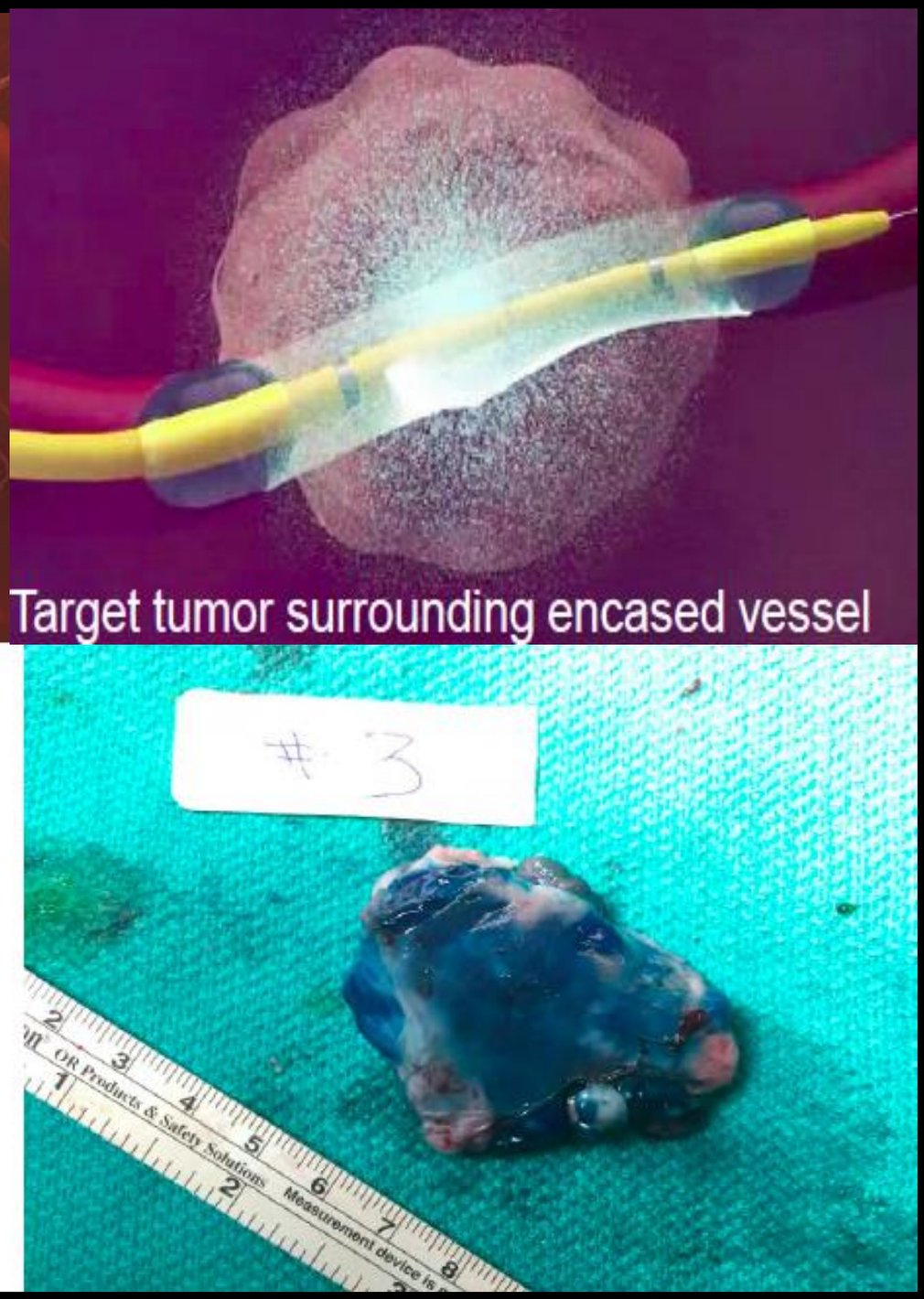
RenovoCath for Transvascular Drug Delivery





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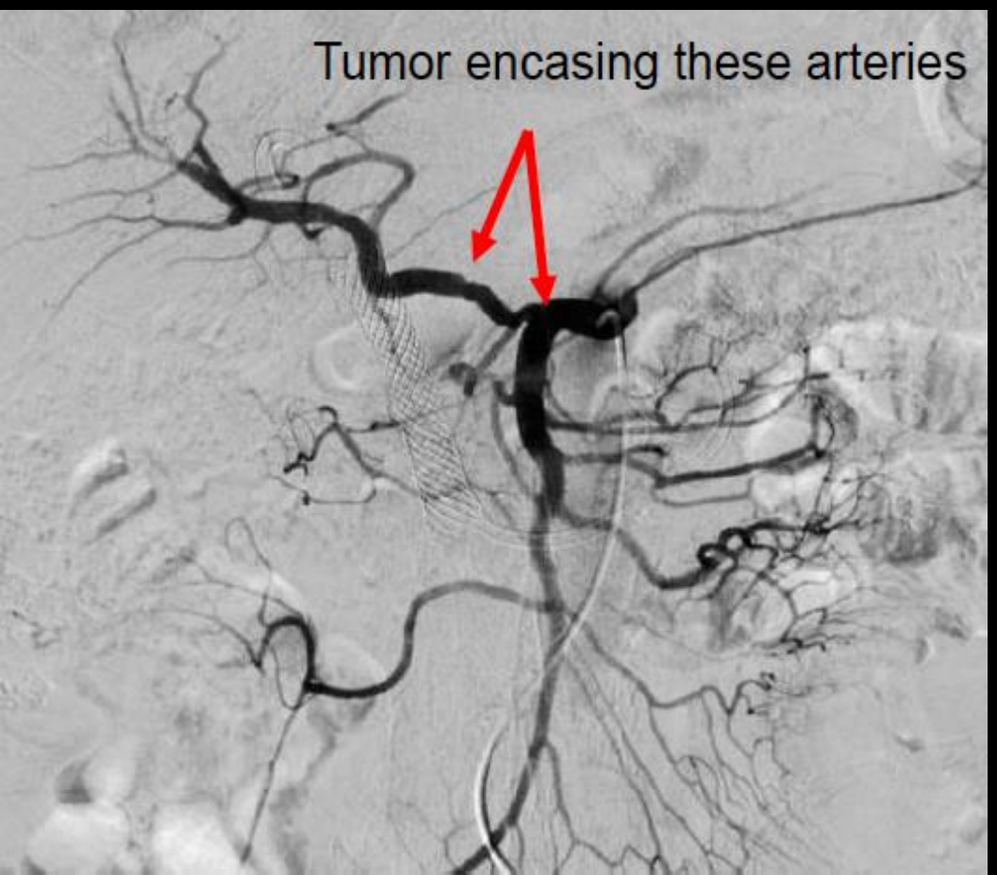
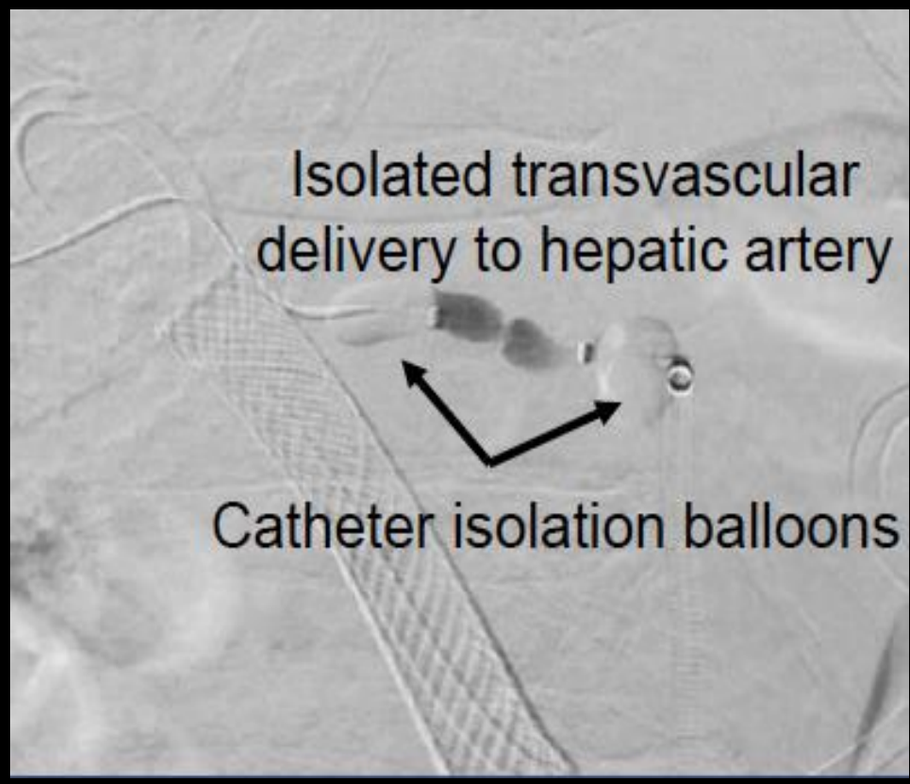
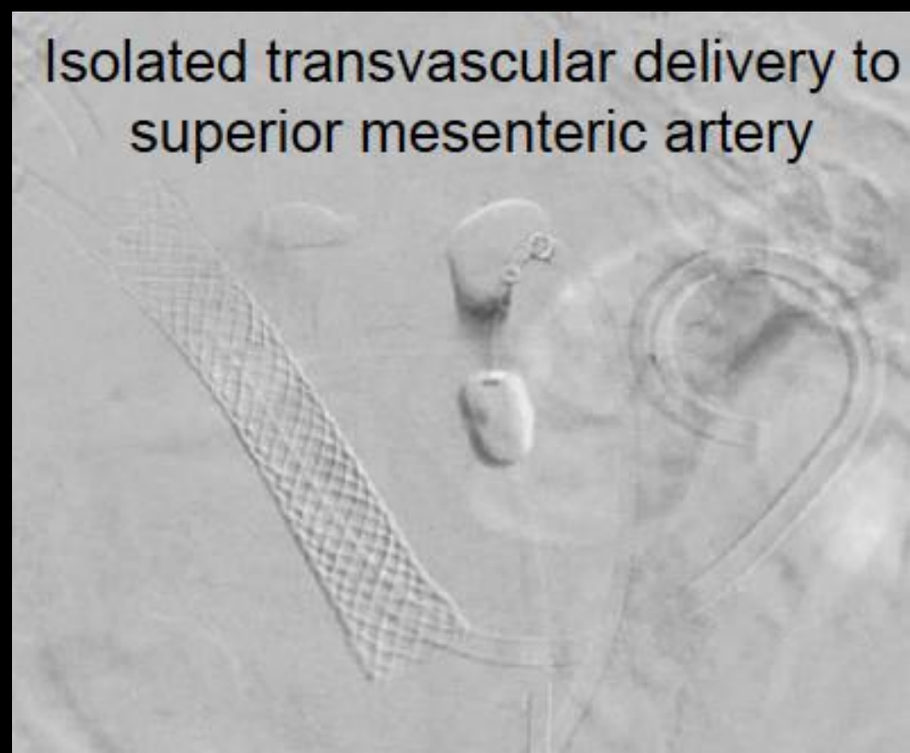
Case Example







Clinical Trials and Results

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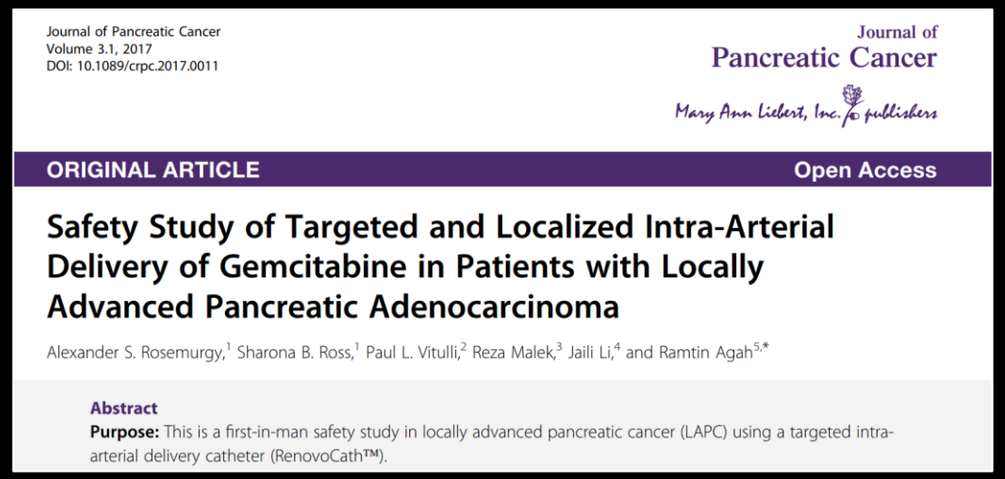
RenovoCath in Pancreatic Cancer: Phase I/II Studies to Explore Clinical Endpoints



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Journal of Pancreatic Cancer

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ORIGINAL ARTICLE Open Access

Safety Study of Targeted and Localized Intra-Arterial Delivery of Gemcitabine in Patients with Locally Advanced Pancreatic Adenocarcinoma

Alexander S. Rosemurgy,[1] Sharona B. Ross,[1] Paul L. Vitulli,[2] Reza Malek,[3] Jaili Li,[4] and Ramtin Agah[5,*]

Abstract

Purpose: This is a first-in-man safety study in locally advanced pancreatic cancer (LAPC) using a targeted intra-arterial delivery catheter (RenovoCath™).

RR1- Dose Escalation Safety Study

- Primary Endpoint: Safety, Max Tolerated Dose, Dose Limiting Toxicity
- Secondary Endpoint: Survival
- Completed July 2016

20 Patients

- 101 Treatments

RR2 – Observational Registry

- Primary endpoints: Survival, tumor response
- 6 centers Initiated Jan. 2016
- Limited to patient with Prior Radiation: March 2017
- Limited to one active site w/ Initiation of Phase 3 TIGeR-PaC: May 2018

25 Patients

- 96 Treatments

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Results: Phase I and II Clinical Trials

- To date, 43 patients treated with Intra-Arterial Gemcitabine using RenovoCath between the 2 studies from May 2015 to Dec 2018

  (2 patients rolled over from safety to registry study)

- Average age of patient enrolled was 69.9 years

- 24 of 43 patients had prior treatment before IA therapy :
  - Chemotherapy (n=11)
  - Chemoradiation (n=12)
  - Prior surgery (n=1).

- Median gemcitabine dose was 1000mg/m^2
  - Full 1000mg/m^2 dose administered to 33 of the 43 patient cohort

Results: Phase I and II Clinical Trials

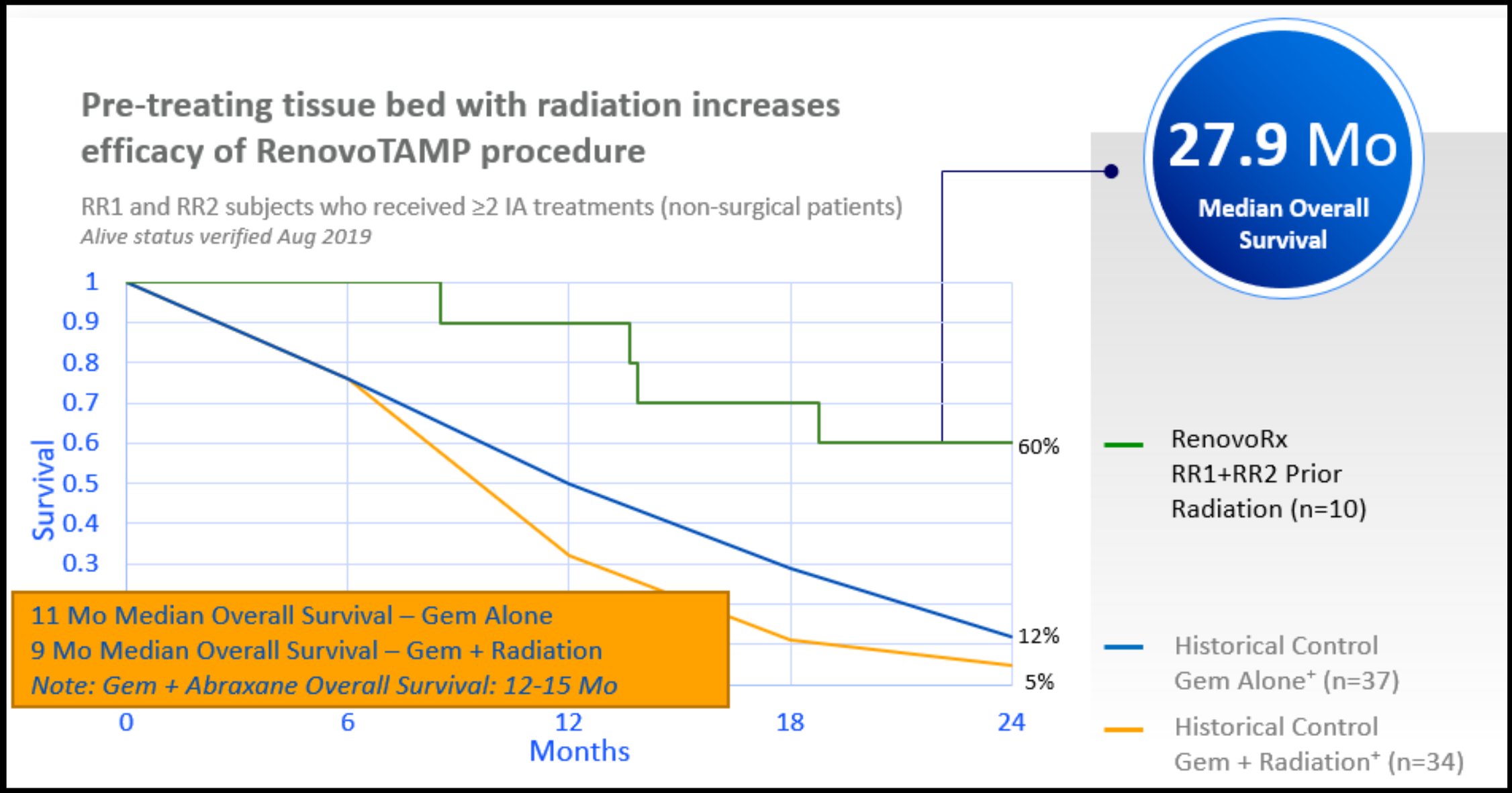
On average each pt. received four intra-arterial treatments, ranging from 1-14 treatments

13 of 43 patients completed the planned 8 treatments of IA therapy

Reasons for early discontinuation of IA therapy:

- Tumor progression (n=12)
- Patient/physician preference (n=8)
- Serious adverse events (n=6)
- Others (n=4)

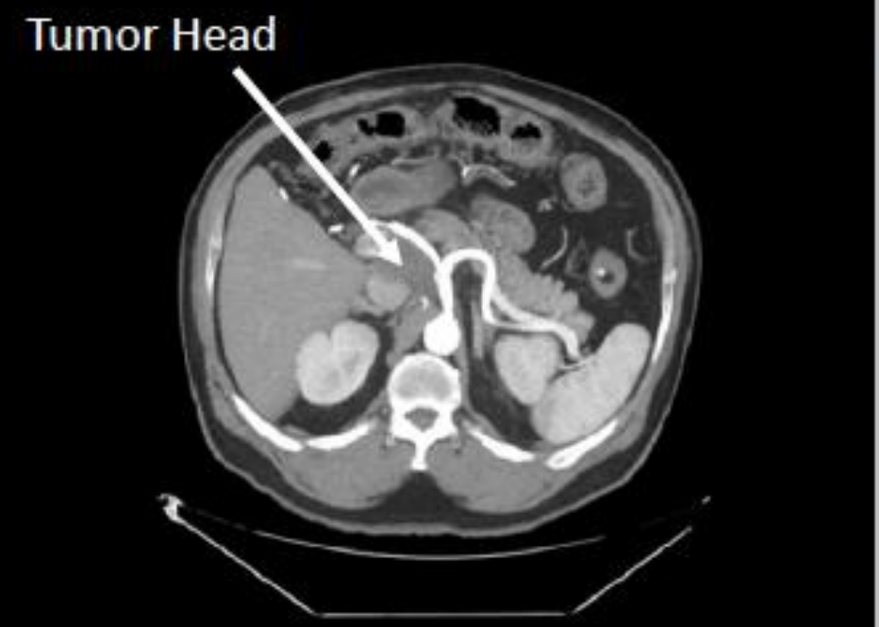
Promising Data from Phase 1/2 and Observational Registry Studies Advanced Clinical Development Program to Phase 3

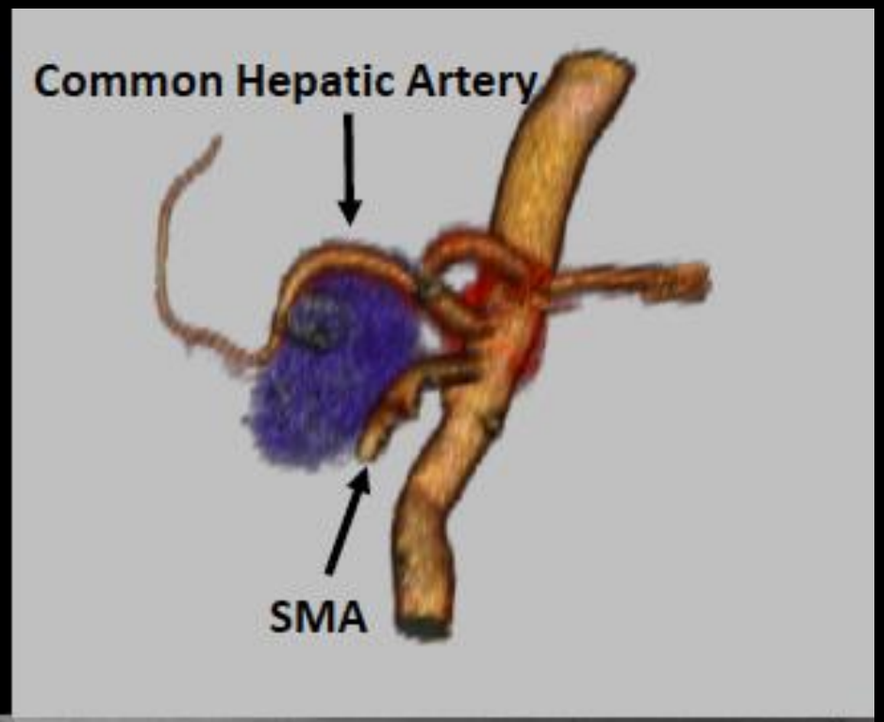


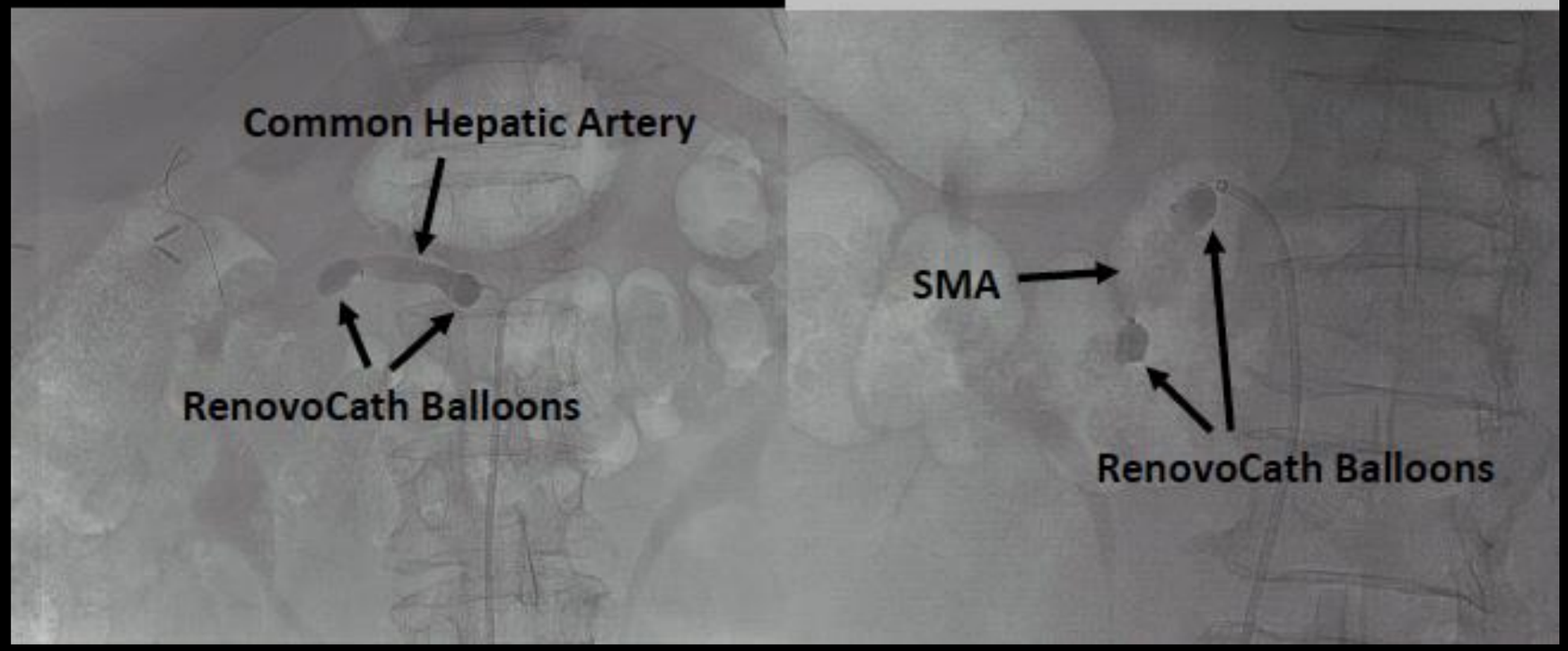
*Chauffert, B. et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. Annals of Oncology 19, 1592–1599 (2008).

^ Loehrer, P. J. et al. Alone Versus Gemcitabine Plus Radiotherapy in Patients With Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial. Journal of Clinical Oncology 29, 4105–4112 (2011).

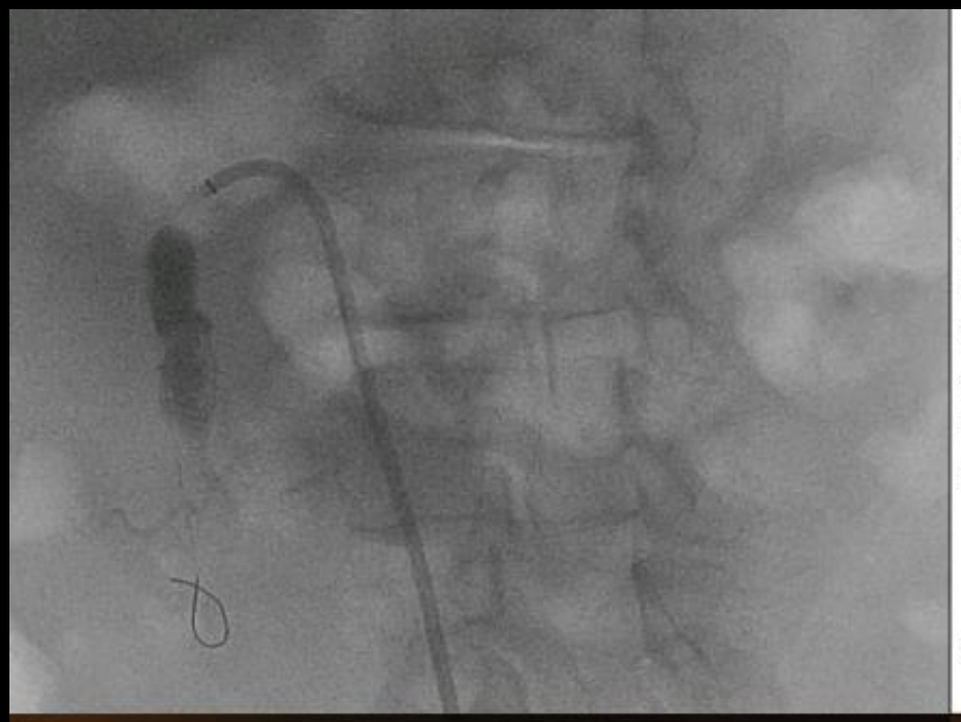
CT Imaging Provides a Simple Approach to the Vasculature

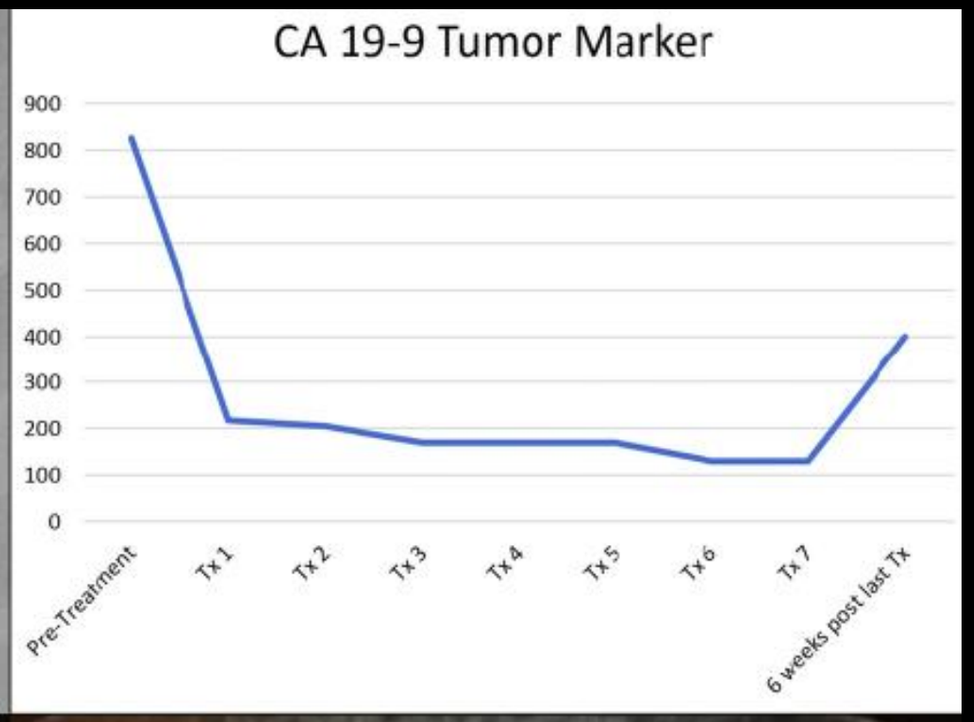






Case Example





Limitations of the Previous Studies

- Relatively Small Number of Patients
- Non-Randomized
- Selection Bias

Future Directions:

TIGeR-PaC Randomized Phase 3 Clinical Trial

This study is to test the efficacy of approach as part of a phase 3 randomized clinical trial

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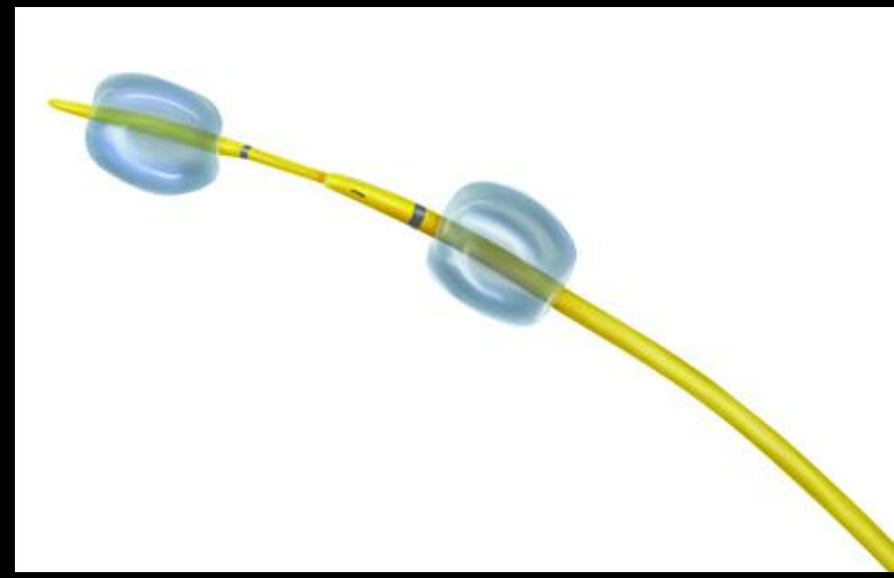
TIGeR-PaC Randomized Clinical Trial – Phase 3 Multicenter Trial

Trans (Intra)-arterial Gemcitabine vs. Continuation of IV Gemcitabine and Nab-Paclitaxel following Radiotherapy for Locally Advanced Pancreatic Cancer (TIGeR-PaC Randomized Clinical Trial)



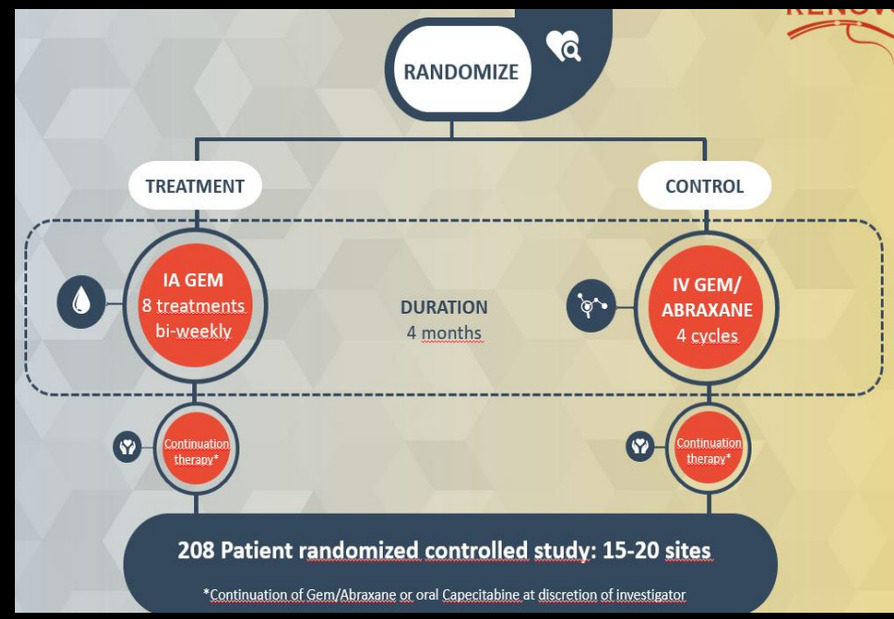
- Prospective multicenter randomized clinical Trial evaluating systemic therapy versus intraarterial gemcitabine for pancreatic cancer

- Primary Objective: Overall Survival from time of randomization

- Secondary Objectives: PFS, objective response rate, duration of response, HR-QOL, degree of peripheral neuropathy, incidence of neutropenia, tolerability, and safety

- Inclusion Criteria:

1. Histologically confirmed pancreatic adenocarcinoma with initial diagnosis within 6 weeks of consent
2. Locally advanced, unresectable disease, as defined by **NCCN Guidelines**
3. ECOG 0-1



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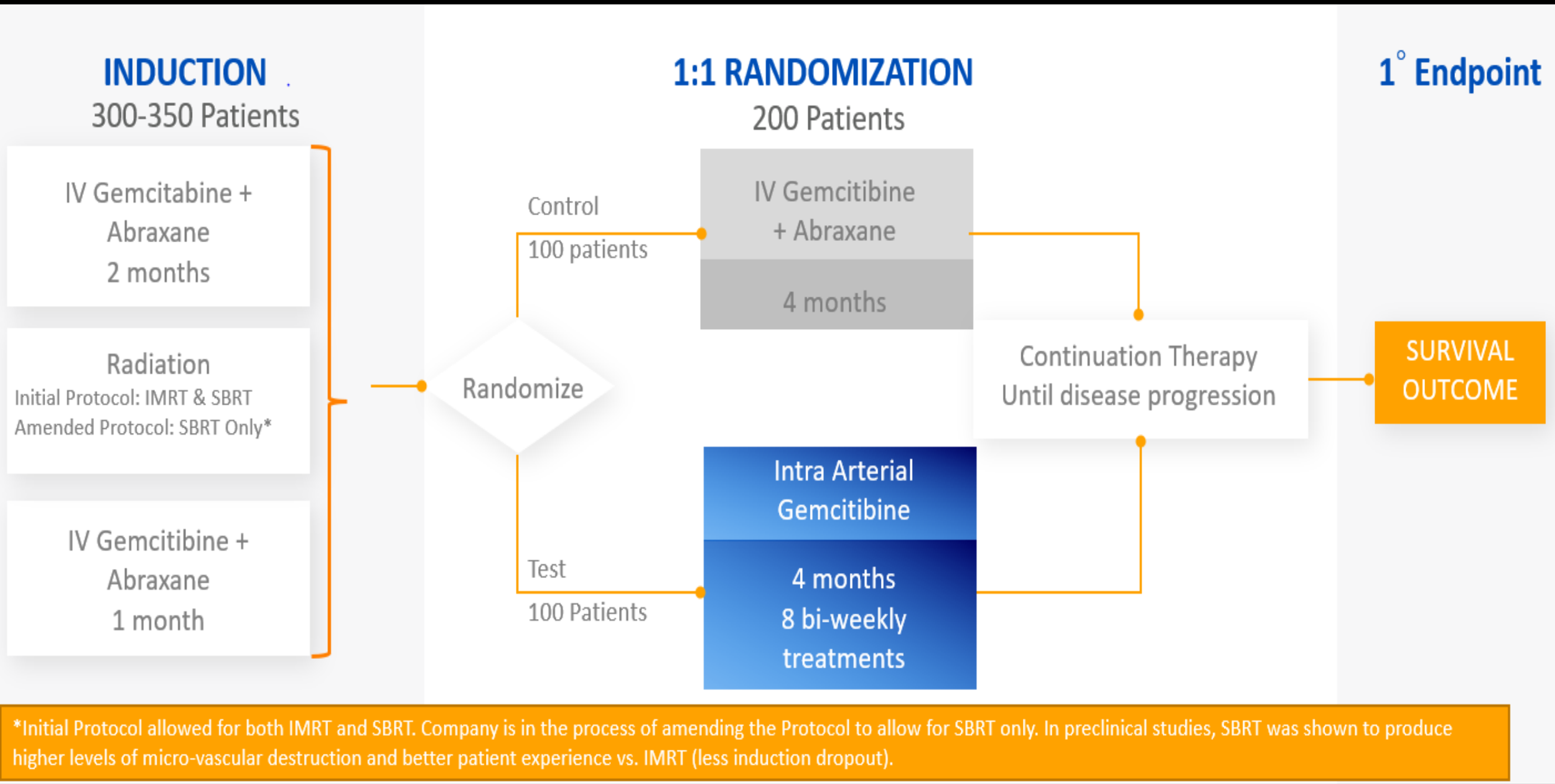
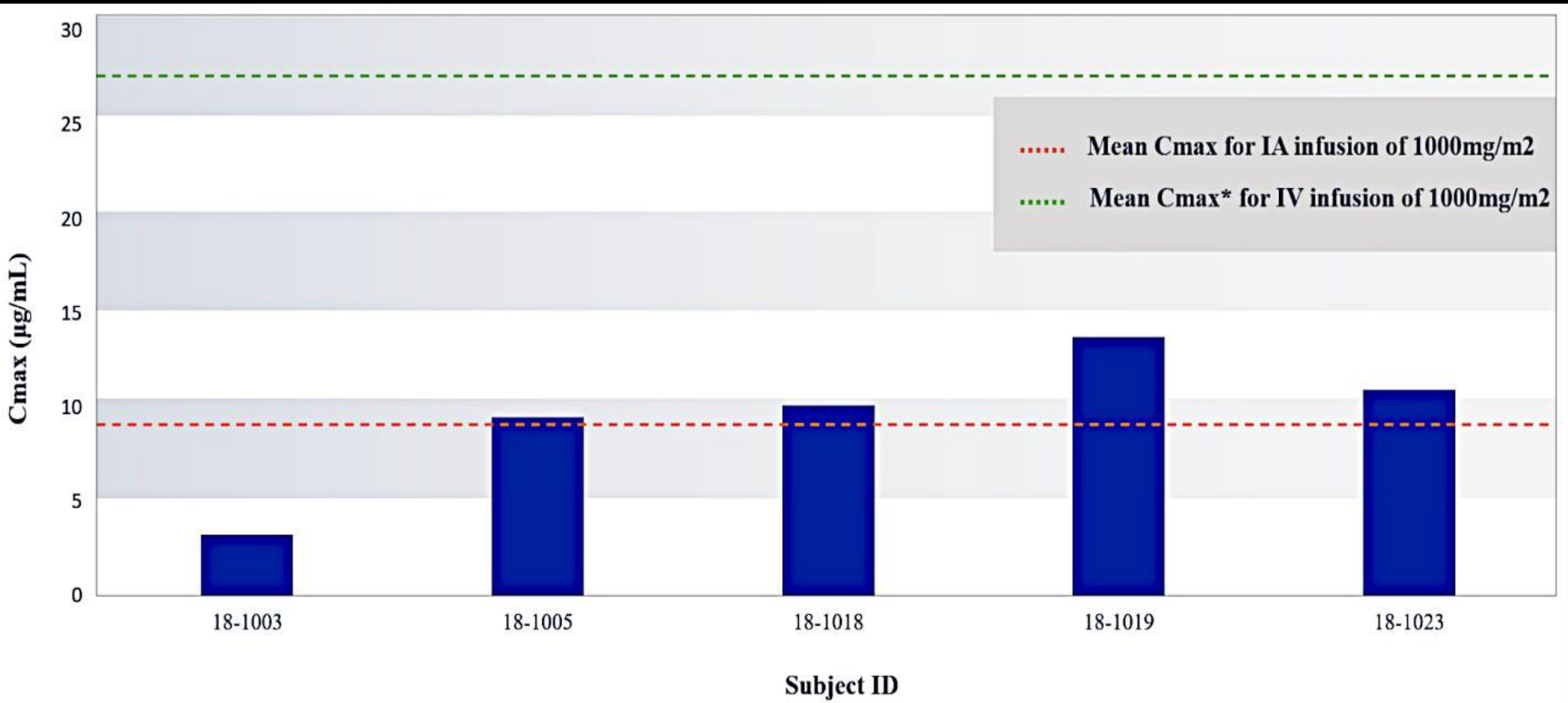
Phase 3 TIGeR-PaC RCT Study Schema



*Initial Protocol allowed for both IMRT and SBRT. Company is in the process of amending the Protocol to allow for SBRT only. In preclinical studies, SBRT was shown to produce higher levels of micro-vascular destruction and better patient experience vs. IMRT (less induction dropout).

Systemic Levels of Gemcitabine Reduced by 2/3 with RenovoTAMP vs IV Gemcitabine



**As reported in Caffo et al., Cancer Chemother. Pharmacol., 2010; Faivre et al., Ann. Oncol., 2002; Fogli et al., Ann. Oncol., 2001*

Conclusions

Localized intra-arterial delivery of gemcitabine using RenovoCath demonstrates encouraging results in stabilizing local disease

This benefit is especially pronounced in patients with prior induction therapy with radiation (median OS is 27.9 months)

The phase 3 multicenter, randomized TIGeR-PaC (clinical trial.gov #NCT03257033) will provide definitive evidence whether this therapy provides survival benefit

Thank You!