



Central Manchester University Hospitals **NHS**  
NHS Foundation Trust

**Manchester Cancer**



**Pancreatic Cancer UK**

26 October 2022

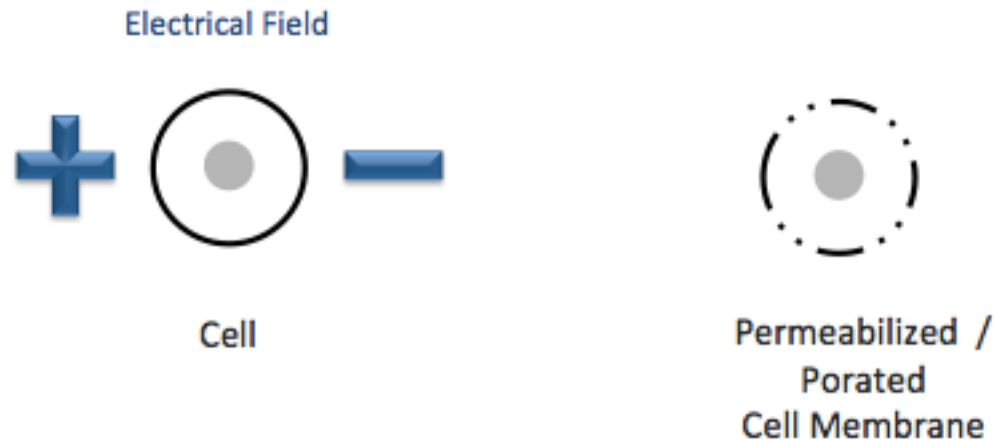
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Manchester Royal Infirmary, CMFT

# ELECTROPORATION

- It is a phenomenon that occurs in cell membranes as cells are exposed to an electrical field of sufficiently high intensity.
- The electric field acts as physical stimulus, bringing abrupt alterations in cell membrane that results in increased permeability

## Electroporation

Is the process of creating nanopores ( “holes” ) in the cell membrane using an electrical field

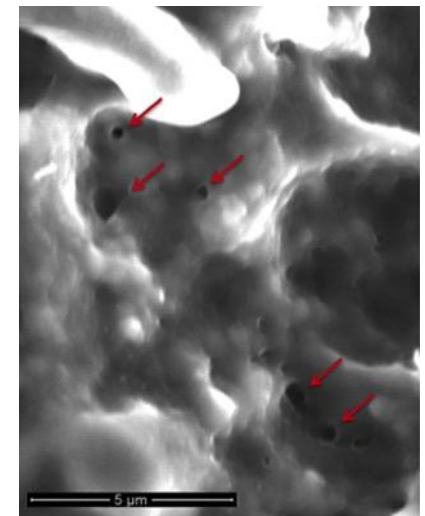


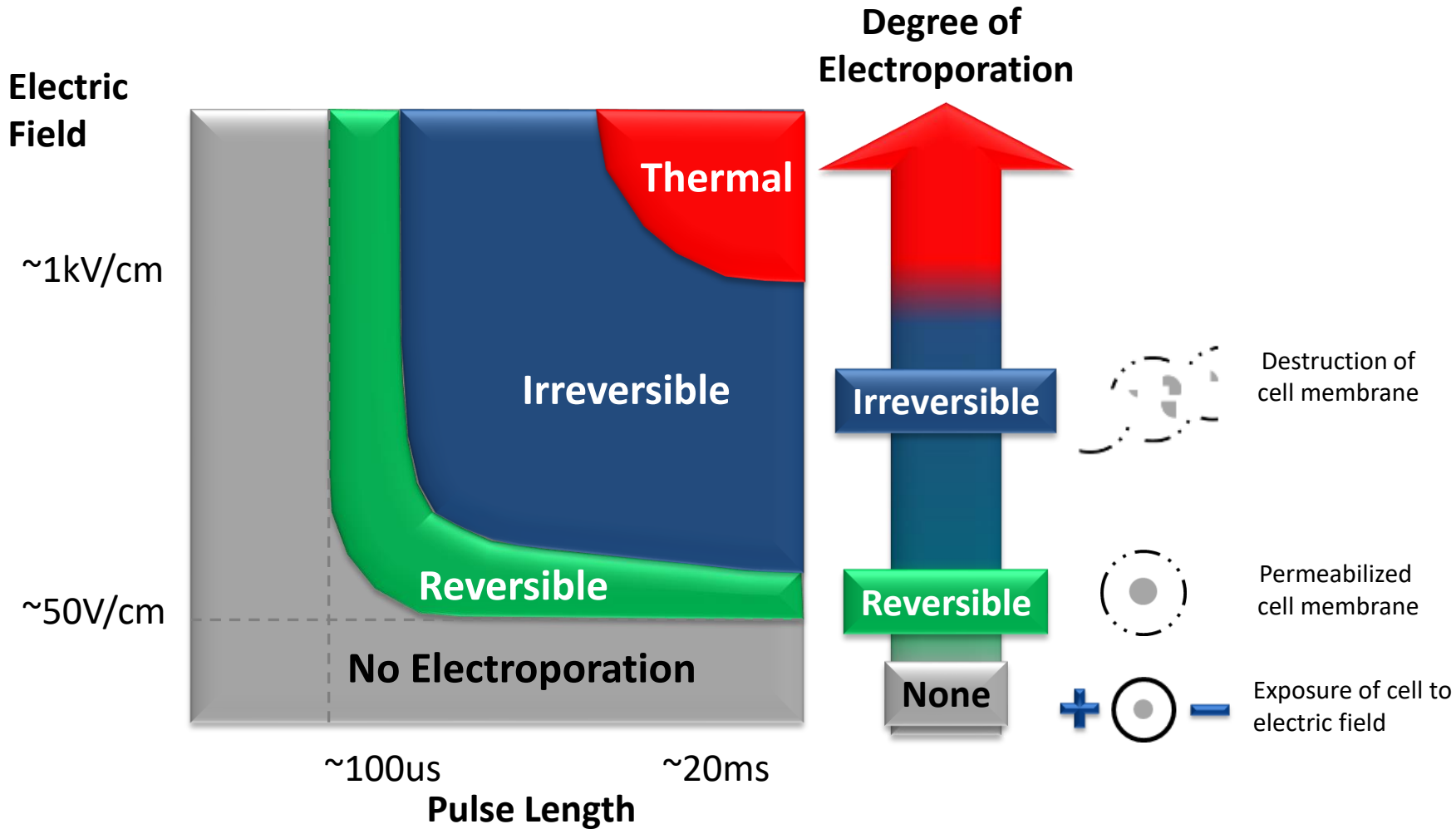
# Irreversible Electroporation Definition

- A tumor ablation technique using a **non-thermal technology** to create innumerable permanent **nanopores in the cell membrane** to **disrupt cellular homeostasis**.
- This disruption of cellular homeostasis initiates **apoptosis** which leads to **permanent cell death**.



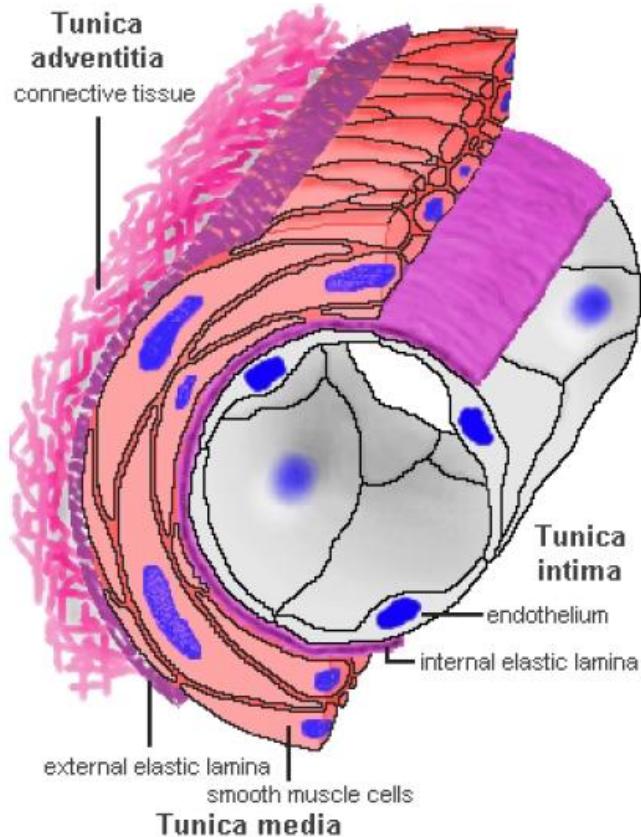
Electron Microscope







# Cellular vs. Non-cellular Tissue Effects

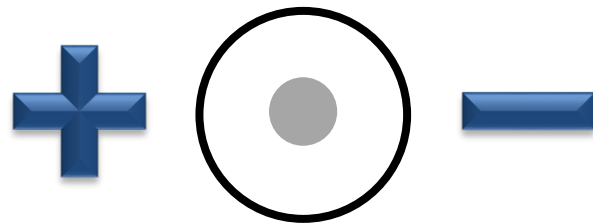


Fibrous and Collagen structures are not affected

- Intact adventitia & laminae visible at 2 days with no smooth muscle cells present
- Endothelium largely repopulates at 2 days
- Smooth muscle repopulated at 2 weeks

# IRE Effects

Electrical Field



Cell

IRE  
Irreversible Electroporation



Apoptosis

Potential Immune  
System Response



*Macrophages aid in  
clearing cell debris - Phagocytosis*

Images from AngioDynamics – Porcine Liver Animal Model

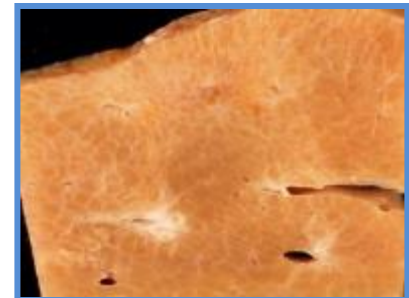
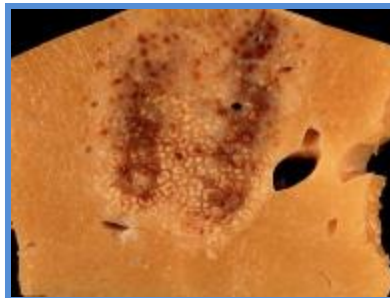
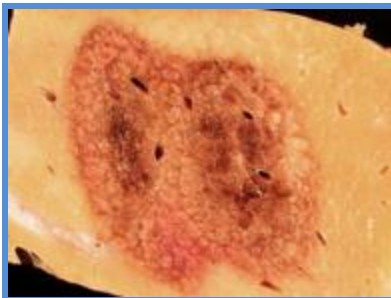
1 day

3 days

7 days

14 days

Gross



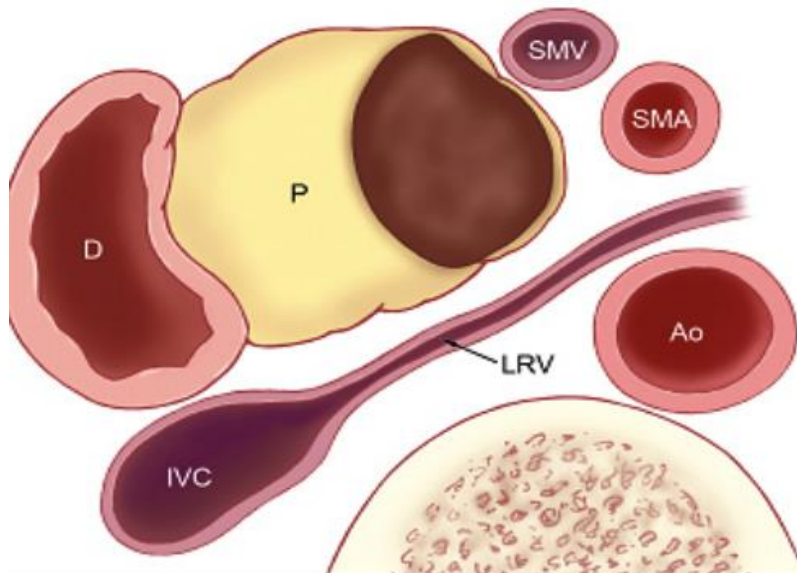


# PANCREATIC CANCER

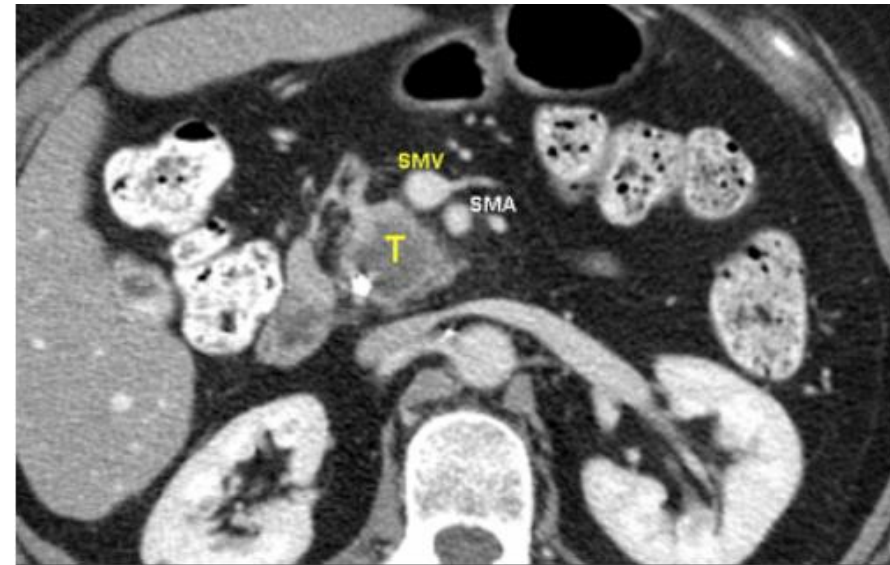
- At presentation, 80% of patients are not surgical candidates
  - 50% presence of metastatic deposits
  - 30% locally advanced disease



## STAGE I – II: RESECTABLE



This is an illustration of a resectable (stage I, II) pancreatic cancer. Note how the tumor (dark brown) is contained within the pancreas.



This is a CT scan of a resectable adenocarcinoma of the pancreatic head.

# STAGE III PANCREATIC CANCER

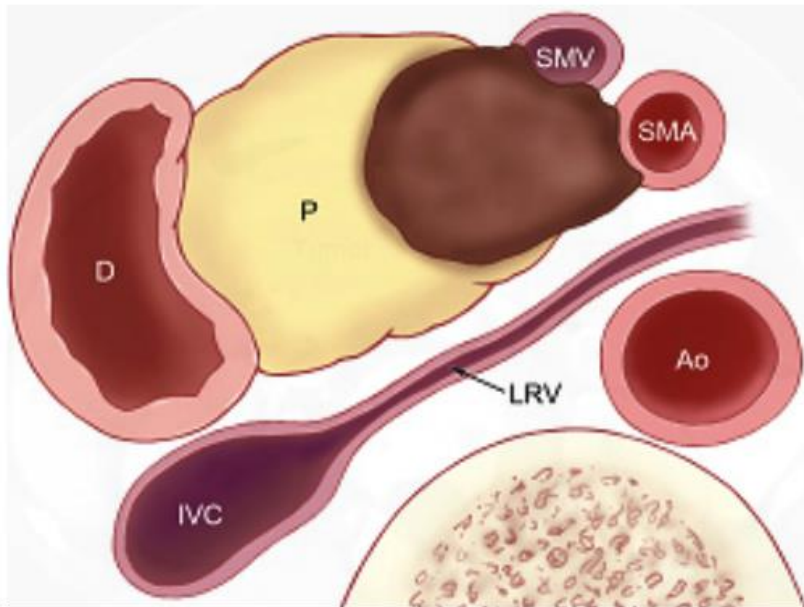
- A pancreatic tumor that affects any major blood vessel but has no evidence of distant metastases is classified as stage III
- According to the degree of vascular involvement, stage III pancreatic cancer is further stratified in 2 categories:
  - 1 Borderline resectable (BRPC)
  - 2 Locally advanced (LAPC) and unresectable

## NCCN Guidelines Version 2.2019 Pancreatic Adenocarcinoma

### CRITERIA DEFINING RESECTABILITY STATUS<sup>a</sup>

| 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 $\leq 180^\circ$ contact without vein contour irregularity.  |
| Borderline Resectable <sup>b</sup> | <p><b>Pancreatic head/uncinate process:</b></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.</li> <li>• Solid tumor contact with the SMA of <math>\leq 180^\circ</math></li> <li>• 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 noted if present, as it may affect surgical planning.</li> </ul> <p><b>Pancreatic body/tail:</b></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with the CA of <math>\leq 180^\circ</math></li> <li>• Solid tumor contact with the CA of <math>&gt;180^\circ</math> without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category].</li> </ul> | <ul style="list-style-type: none"> <li>• Solid tumor contact with the SMV or PV of <math>&gt;180^\circ</math>, contact of <math>\leq 180^\circ</math> 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.</li> <li>• Solid tumor contact with the inferior vena cava (IVC).</li> </ul>                   |
| Unresectable <sup>b</sup>          | <ul style="list-style-type: none"> <li>• Distant metastasis (including non-regional lymph node metastasis)</li> </ul> <p><b>Head/uncinate process:</b></p> <ul style="list-style-type: none"> <li>• Solid tumor contact with SMA <math>&gt;180^\circ</math></li> <li>• Solid tumor contact with the CA <math>&gt;180^\circ</math></li> </ul> <p><b>Body and tail:</b></p> <ul style="list-style-type: none"> <li>• Solid tumor contact of <math>&gt;180^\circ</math> with the SMA or CA</li> <li>• Solid tumor contact with the CA and aortic involvement</li> </ul>  | <p><b>Head/uncinate process:</b></p> <ul style="list-style-type: none"> <li>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)</li> <li>• Contact with most proximal draining jejunal branch into SMV</li> </ul> <p><b>Body and tail:</b></p> <ul style="list-style-type: none"> <li>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)</li> </ul> |

# BORDERLINE RESECTABLE PC



This is an illustration of a borderline resectable pancreatic cancer due to tumor extension to the superior mesenteric artery (SMA).



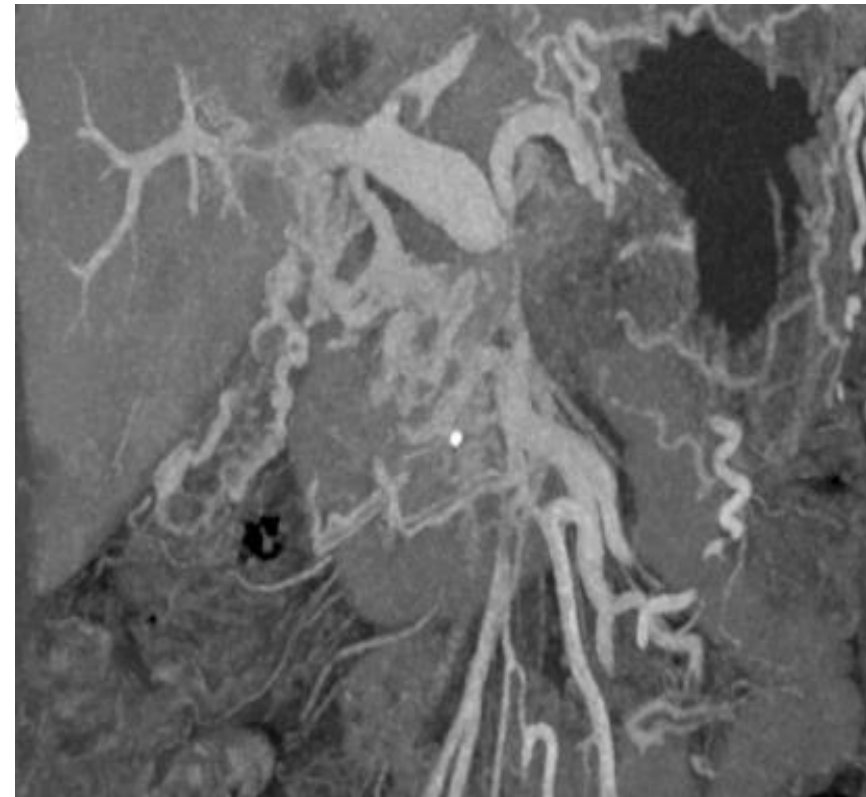
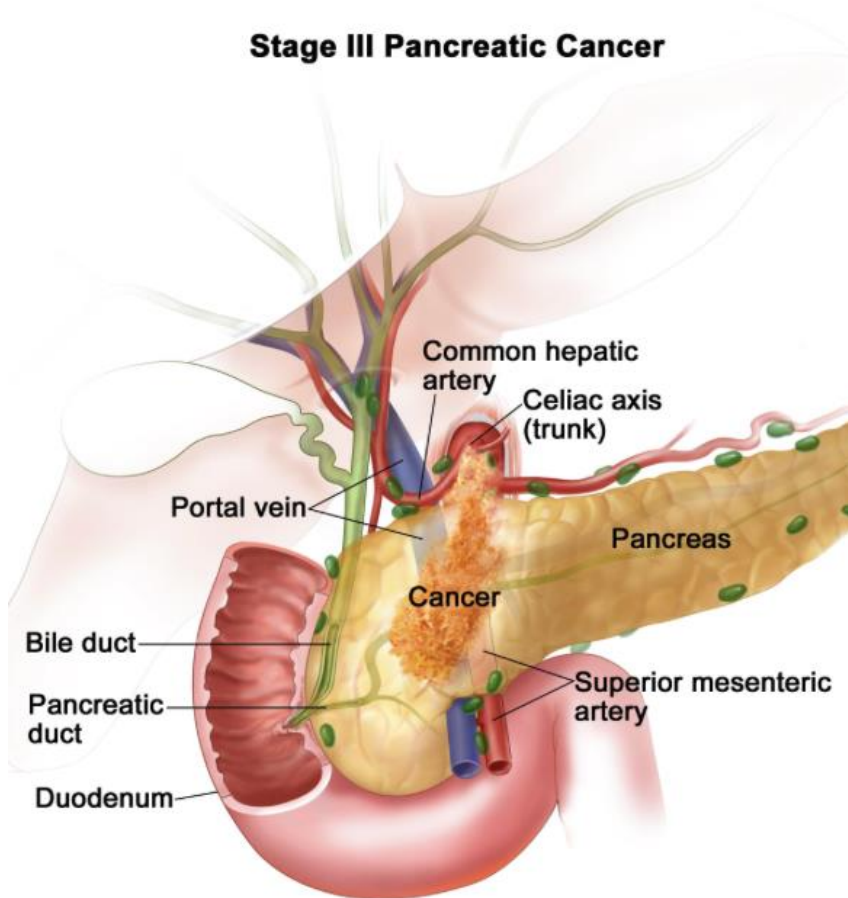
# STANDARD OF CARE FOR STAGE III BRPC

- Multimodality treatment including chemotherapy, radiotherapy and surgery should be considered
- Neoadjuvant chemotherapy is often used in BRPC because it increases the likelihood of achieving R0 margins, it can treat micrometastatic disease and it decreases the need for vascular reconstruction. It might identify those patients who will progress to metastatic disease and spare them from unnecessary surgery
- Surgical resection remains the cornerstone for curative treatment of BRPC



# LOCALLY ADVANCED PC

Stage III Pancreatic Cancer

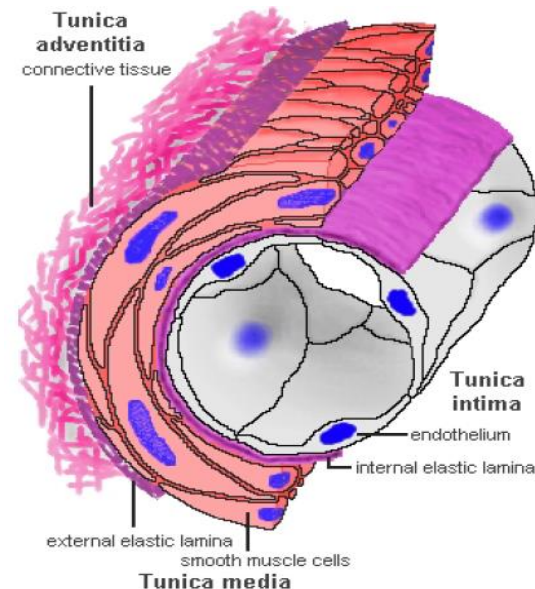


# STANDARD OF CARE FOF STAGE III LAPC

- In LAPC surgical resection is not possible
- The use of chemotherapy aims to downstage the tumour making it resectable. However, this is infrequent
- Radiotherapy and chemoradiotherapy play a role in the local control of patients with LAPC demonstrating stability following chemotherapy alone
- Although most deaths from PC are caused by metastatic disease, local failure is a cause of death in 30% of patients<sup>1</sup>

## IRE: RATIONAL IN LAPC

- 20-30% of patients with PC present with LAPC. With current available treatments, only a modest increase in survival is achieved due to local progression and metastatic disease.
- RFA, MWA and Cryoablation have been used in this disease but surrounding structures are often damaged as a result of heat or cold effects. Blood flow in large vessels creates a heat sink effect that largely decreases the ability to ablate cancer cells in their proximity. Ablation-related thermal injuries can induce pancreatitis
- On the basis of current evidence, IRE seems to be safe and technically feasible. Because of the advantage of preserving the surrounding structures it can be used in tumours close to vital structures, such as blood vessels and bile ducts.





# POTENTIAL EFFICACY

- In a prospective series of LAPC, 54 pts underwent IRE. Evaluated for OS and propensity matched to 85 stage III pts treated with standard chemotherapy and radiotherapy
  - ✓ Increase in local progression-free survival ( $p=0.01$ )
  - ✓ Distant progression-free survival ( $p=0.02$ )
  - ✓ Overall survival ( $p=0.03$ )
  - ✓ Significant improvement in median pain score ( $p=0.04$ )
  - ✓ Overall decreased use of narcotics ( $p=0.03$ )
  - ✓ After 20 months of follow-up, no survival difference between the groups remained because of rapid progression of distant disease



# POTENTIAL EFFICACY

- The largest series: 200 prospectively-collected cases of LAPC treated with open IRE. All pts underwent induction chemotherapy and 52% received chemoradiotherapy. 150 received IRE alone and 50 had surgical resection plus IRE for margin enhancement
  - ✓ With a median follow-up of 29 months, 6 patients (3%) had experienced local recurrence
  - ✓ Median OS was 24.9 months





# POTENTIAL EFFICACY

- ✓ Prospective observational study of 25 pts receiving percutaneous imaging-guided IRE for LAPC. To assess safety, QOL, pain perception, local progression, event free survival and OS. At 12mts median follow-up:
  - ✓ 8 months median event-free survival
  - ✓ 12 months median local progression
  - ✓ 17 months median OS from diagnosis
  - ✓ 11 months median OS from IRE
  - ✓ No 90-days mortality
  - ✓ 12 minor and 11 major complications in 10 patients



# POTENTIAL EFFICACY

- Retrospective series of 50 pts LAPC, treated with percutaneous CT-guided IRE. To assess safety profile and OS
  - ✓ No procedure related mortality
  - ✓ No 30-days mortality
  - ✓ Median OS from diagnosis 27.0 months
  - ✓ Median OS from IRE 14.2 months



# IRE @ MFT

- The sMDT will consider and select patients who will potentially benefit from IRE
- Pts with established radiological and a tissue diagnosis of LAPC will be referred for palliative chemotherapy to HPB Oncology team at The Christie NHS FT
- After completion of at least 3 months of standard chemotherapy, pts must undergo restaging with high quality CT. A PET scan can be considered to exclude occult metastatic disease



# IRE @ MFT

- Pts free from metastatic disease with no evidence of local disease progression, will be discussed again in the sMDT to ascertain the indication and feasibility for IRE
- An HPB surgeon trained in IRE will consult and assess the pt in clinic
- Pt must be well enough to tolerate a laparotomy and have no cardiac conduction abnormalities, given the risk of arrhythmia with high voltage electric current
- If the patient has a metal biliary stent, this will be replaced with a plastic one by endoscopy



# IRE @ MFT

- Multidisciplinary team trained in IRE will be in charge of the procedure. At least:
  - ✓ 1 HPB Consultant Surgeon
  - ✓ 1 HPB Consultant Anaesthetist
  - ✓ 1 HPB Interventional Radiologist
  - ✓ 1 AngioDynamic Technician
  - ✓ 1 IRE trained Theatre Nurse

This team will work alongside the rest of the medical and nursing staff involved in HPB surgical procedure in the HPB Theatres at MRI.

- Perioperative care will be analogous to that given for other pancreatic resections





# IRE @ MFT: SURGICAL PROCEDURE

- 1 Laparoscopy to exclude non detectable intra-abdominal disease
- 2 Mobilization of the tumor for a full and definitive assessment of its resectability
- 3 If it appears to be resectable, with or without the option of IRE margin accentuation, this will be the preferred choice
- 4 Once the resectability of the tumor has been excluded, the in-situ IRE will commence
- 5 Under ultrasound guidance, conducted by the radiologist, needles will be placed according to the technique described
- 6 At the end a biliary and/or gastro-jejunal bypass will be considered according to tumor location and patient characteristics

# WHY OPEN TECHNIQUE

- Is most commonly used because it is probably safer than laparoscopy or the percutaneous approach and allows for more accurate needle placement<sup>1</sup>
- Because radiological response often doesn't represent pathological response, at laparotomy it is possible to find that a tumor that was staged as LAPC is in fact resectable<sup>2-5</sup>
- Margin Accentuation: If an R1 resection is suspected, IRE can be used to sterilize surgical margins followed by surgical resection<sup>2</sup>
- IRE itself doesn't seem to increase the complexity of resection when used for margin accentuation<sup>2</sup>

1 Al Efishat M et al. *BMJ* 2015; 350: h521

2 Martin RC 2<sup>nd</sup> et al. *Ann of Surg* 2015; 262: 486-92

3 Katz MH et al. *Cancer*. 2012 Dec 1;118(23):5749-56

4 Dholakia AS et al. *J Radiat Oncol*. 2013 Dec 2(4): 413-425

5 Suker M et al. *Lancet Oncol* 2016; 17: 801-10

Review

Irreversible Electroporation in pancreatic ductal adenocarcinoma:  
Is there a role in conjunction with conventional treatment?

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