OVERVIEW ON PANCREATIC CANCER MULTIMODAL MANAGEMENT

Florence, 23rd of January 2020

"Basic and translational oncology"
Italian-French Erasmus Intensive Course in Oncology organized in collaboration with
European Master of Genetics - University Paris7-Paris5

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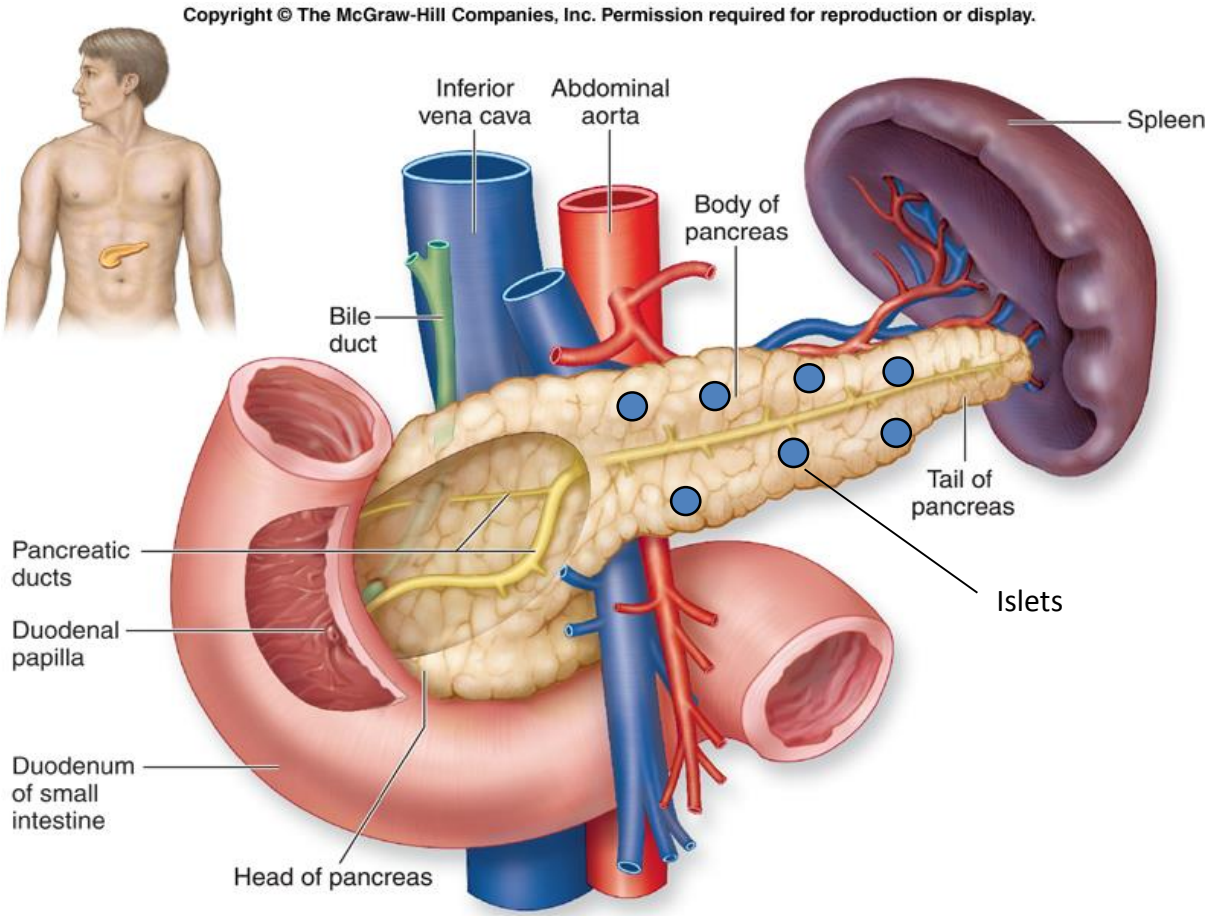
Where's the pancreas?



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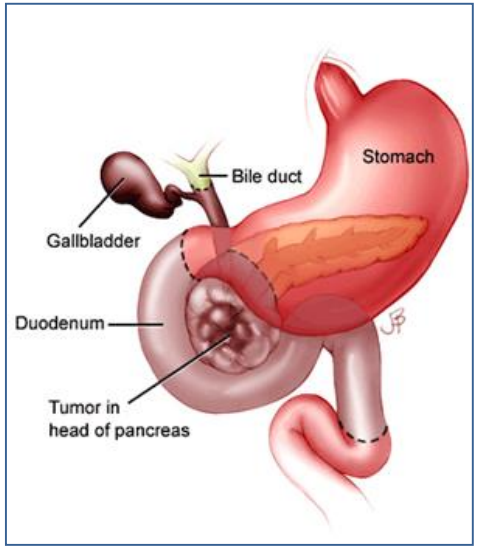
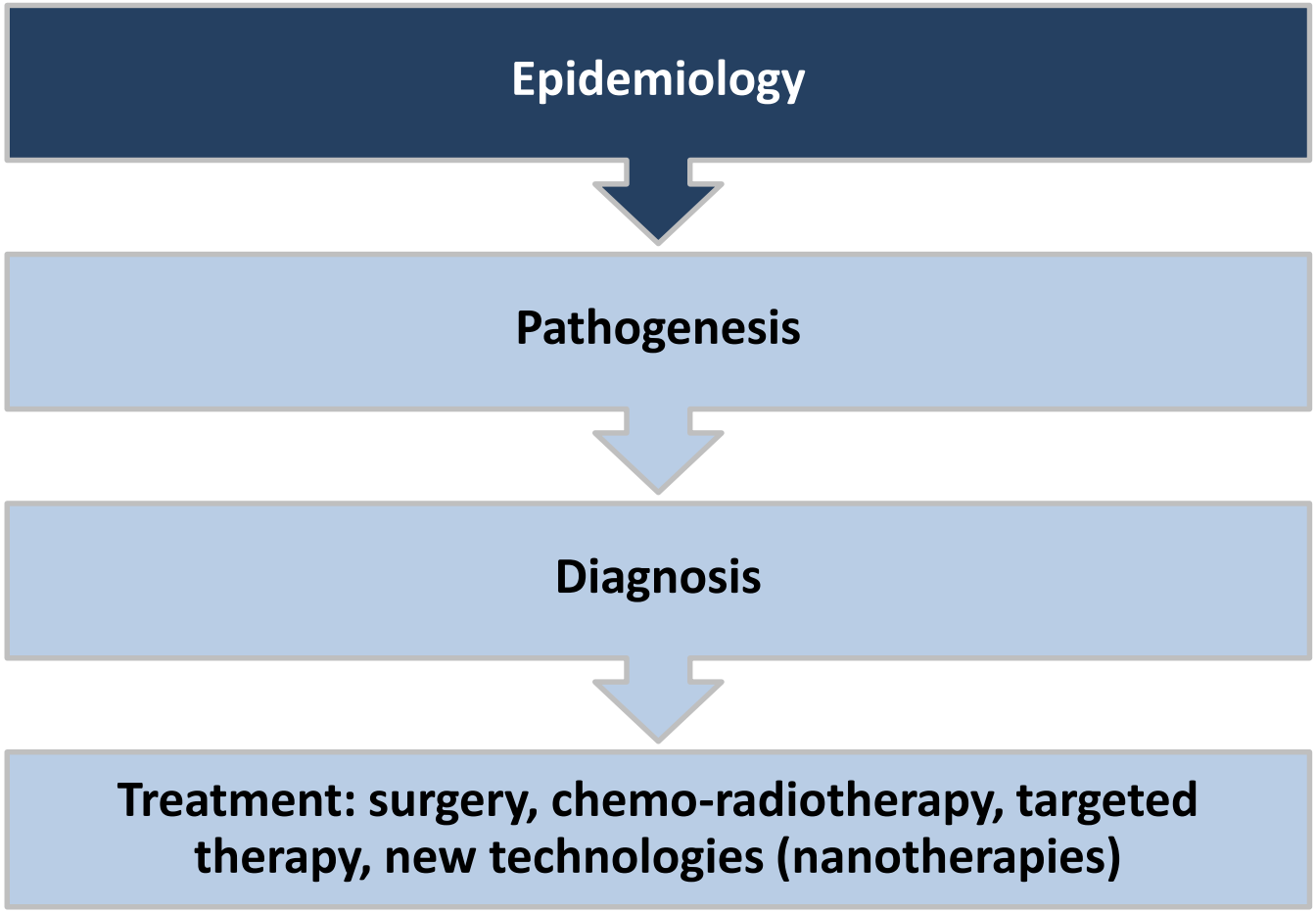
"The challange" of pancreatic cancer (PDAC)

- No screening program available
- Late presentation and diagnosis
- Fast growth and progression
- Complex surgery (=perioperative morbidity and mortality)



Highlights



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Pancreatic tumors

- 95% develop from the exocrine portion of the pancreas
- 75% of all pancreatic carcinomas occur within the head or neck of the pancreas
- Hystology: most (90%) are Ductal Adenocarcinomas (PDAC)
- Other subtypes: Lynphoma, Sarcomas, Cystic neoplasm, etc.

Epidemiology (PDAC)

- Incidence: 8-10 cases per 100,000 persons per year in U.S.
- Most countries have incidence rates of 8-12 cases per 100,000 persons per year.
- India is less than 2 cases per 100,000 persons per year.
- Race and country: slightly higher in black males, Hawaiian, Korean, Czech, Latvian, and New Zealand Maori
- Gender influence: slightly higher in females (recent years)
- Cigarette smoking, diabetes and obesity, chronic pancreatitis: suspected for increasing incidence

Inherited risk factors and genetics

- Familial clustering up to 10%
- Peutz-Jeghers, Fanconi's syndrome (BRCA, DNA repair, Lynch, FAP)

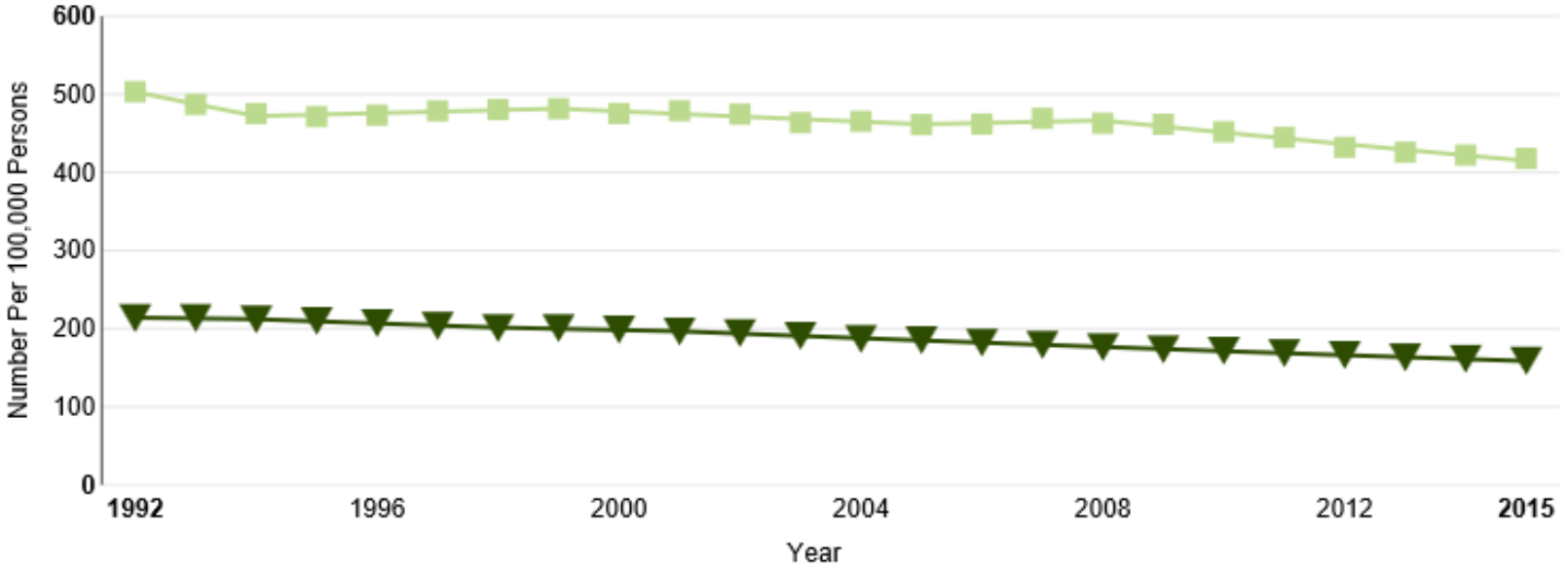
	Gene*	Chromosome	Risk ratio
Familial breast and ovarian cancer	*BRCA2*	13	3·5–10
Familial atypical multiple mole melanoma syndrome	*CDKN2A (P16)*	9	9–47
Peutz-Jeghers syndrome	*STK11 (LKB1)*	19	132
Hereditary pancreatitis	*PRSS1; SPINK1*	7; 5	50–80
Hereditary non-polyposis colorectal cancer (Lynch syndrome)	Multiple	Multiple	9
Familial pancreatic cancer	*PALB2*	16	6
Familial pancreatic cancer (monoallelic); ataxia-telangiectasia (biallelic)	*ATM*	11	Unknown

*Gene synonyms are shown in parentheses.

Table 1: **Inherited disorders with increased risk of pancreatic ductal adenocarcinoma**[4,15,16]

Kamisawa T. Lancet 2016

Epidemiologic features of all cancers in USA



Year	1975	1980	1985	1990	1995	2000	2005	2010
5-Year Relative Survival	48.7%	49.1%	52.5%	57.7%	61.6%	66%	67.7%	69.5%

Data from SEER (National Cancer Institute: Surveillance Epidemiology End Result program)

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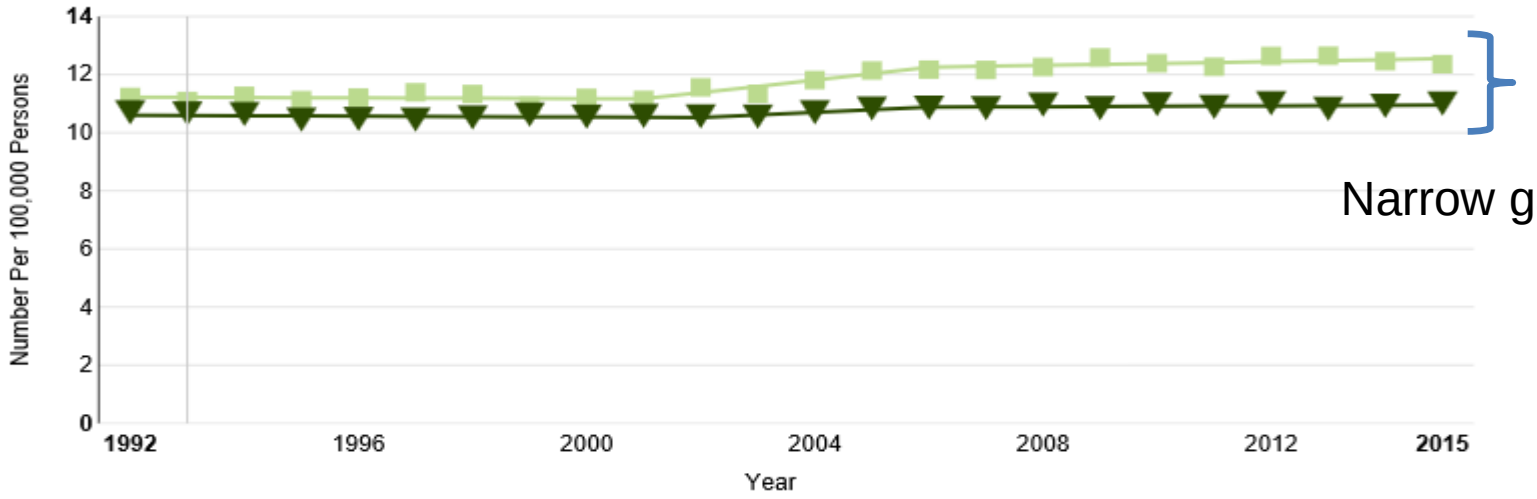
Epidemiologic features of pancreatic cancer



Year	1975	1980	1985	1990	1995	2000	2005	2010
5-Year Relative Survival	3%	3.3%	3.2%	3.7%	3.6%	5.1%	6.2%	8.3%

Incidence and mortality of pancreatic cancer have been slightly increasing during recent years in the USA. It means that survival and medical improvement are very poor. 4th leading cause of cancer related death.

Data from SEER (Surveillance Epidemiology End Result programNational Cancer Institute: Surveillance)

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Highlights

Epidemiology

Pathogenesis

Diagnosis

Treatment: surgery, chemoradiotherapy, targeted therapy, new technologies (nanotherapies)

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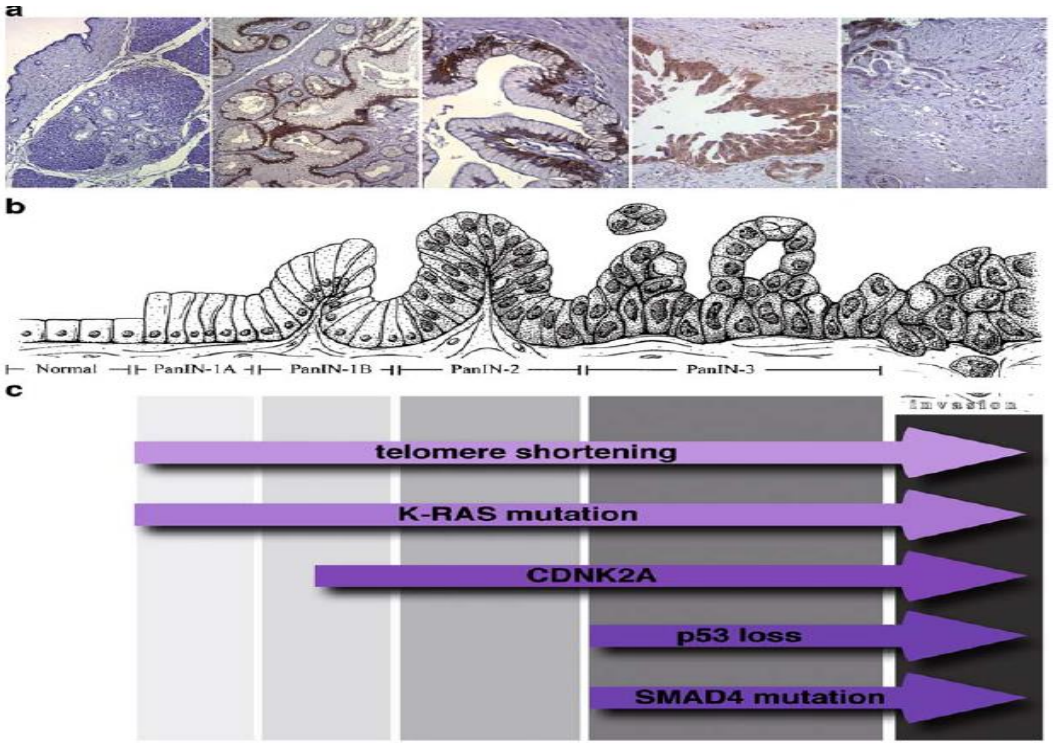
Pathogenesis: several molecular steps (hits)

Normal epithelium → *Pancreatic in situ neoplasia* → *Invasive Carcinoma*

- Mitogenic pathways
  - single gene mutations,
  - epigenetic modifications
- Cell Cycle pathways
- Evasion of apoptosis
- DNA repair changes
- Epithelial-mesenchymal transition



Mijialevich. Langenbecks Arch Surg 2010, Abbas S. Surg Oncol 2013

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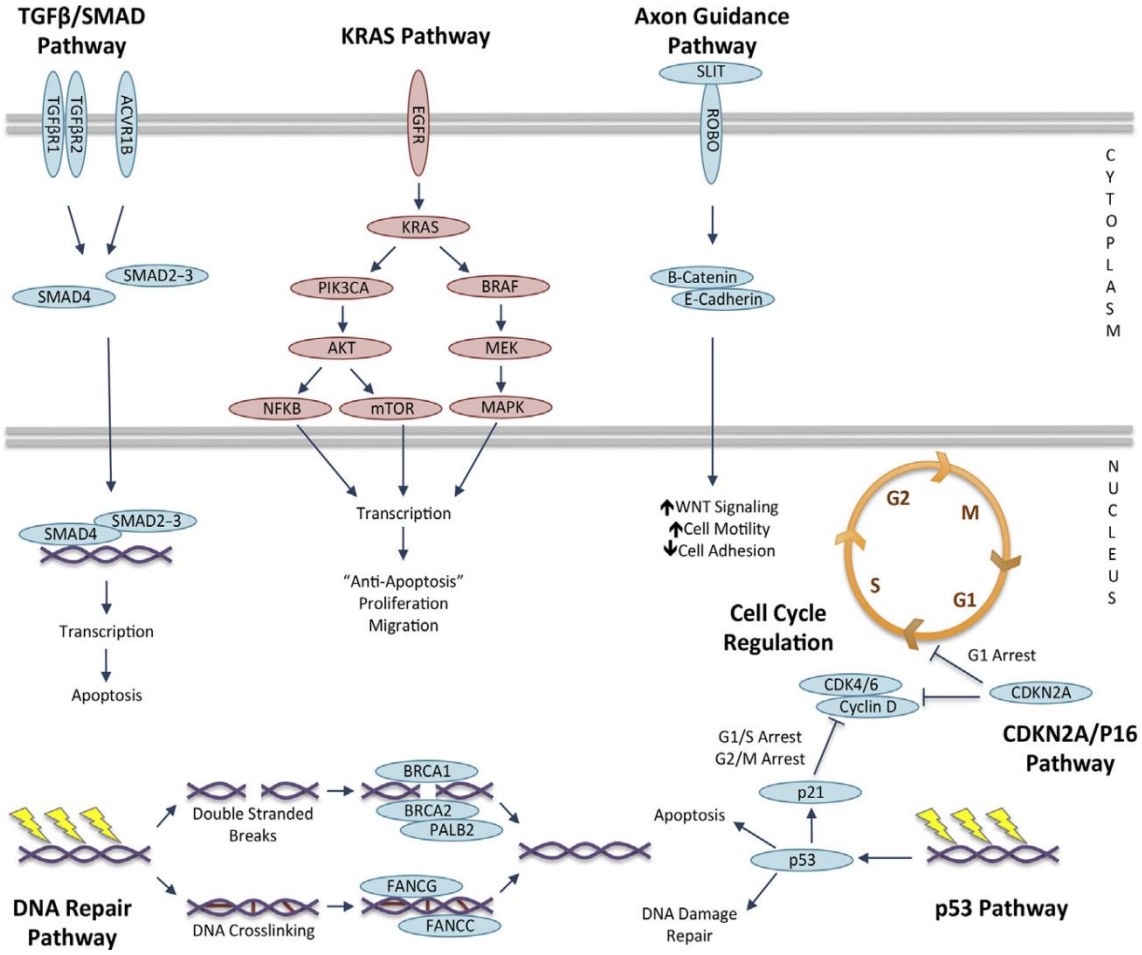
Major molecular pathways and processes involved in pancreatic cancer



Pancreatic cancer

Signal-transduction pathways	Embryonic signaling pathways	Other processes
• RAS • EGFR • COX • TGF-β SMAD4 • HGF • Src	• Hedgehog • Notch • Wnt	• Methylation • miRNA • Cancer stem cell

Matthaios D. Oncology 2011, Tatarian T. Surg Clin N Am 2016

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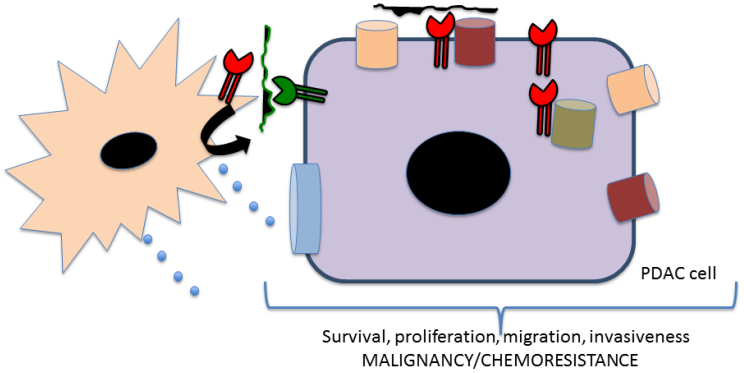
Stromal-tumour interaction

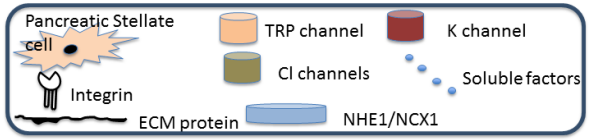
The stroma can reach 50% of tumour tissue

Actors: Pancreatic Cancer Cells (PCC), Pancreatic Stellate Cells (PSC), Extracellulare Matrix (ECM), Inflammatory Cells

Tumour Microenvironment (TME)

- Growth factors
- Neo-angiogenesis
- Resistance to Chemotherapy





Lunardi S. Cancer Letter 2013; Arcangeli A. Philos Trans R Soc Lon B Biol Sci 2014

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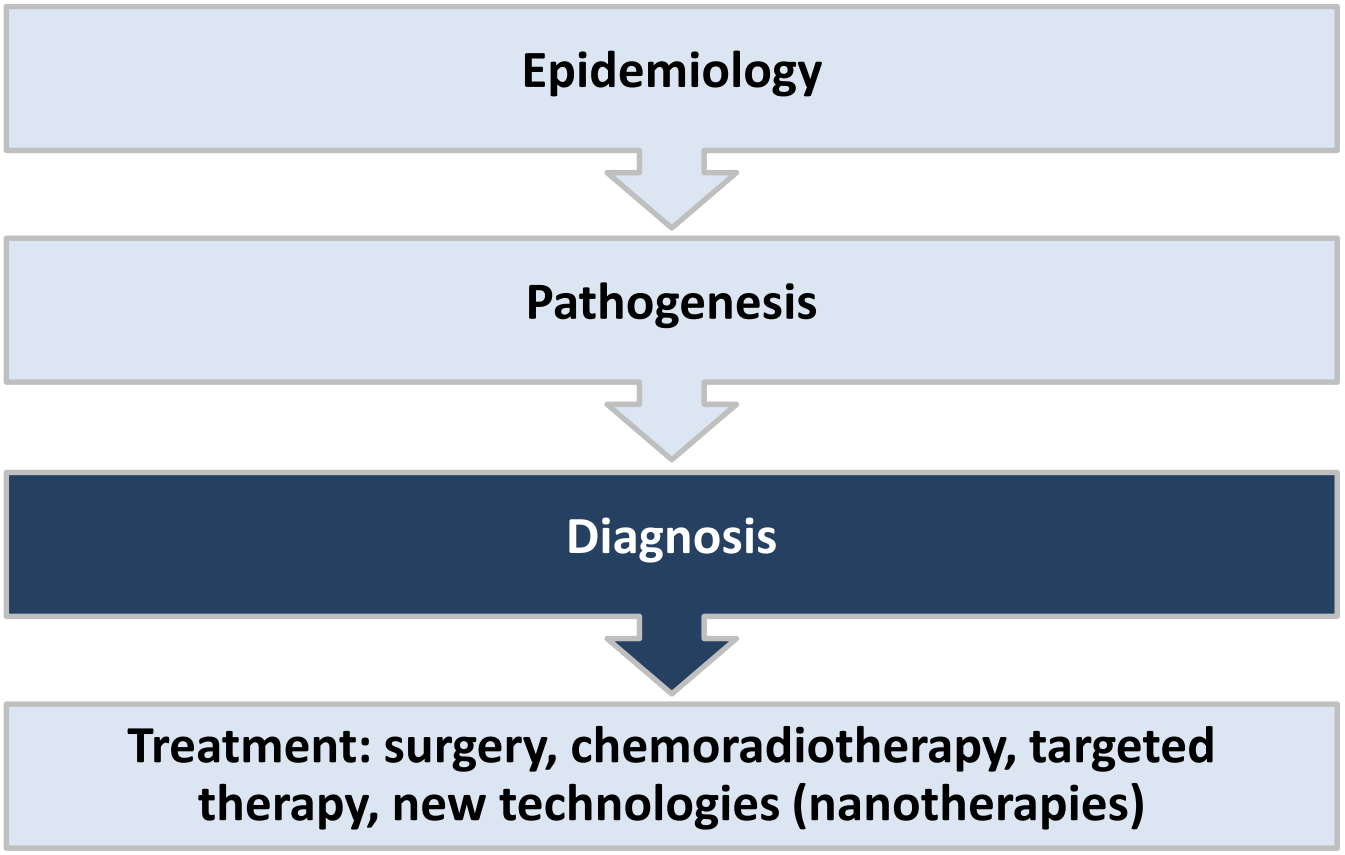
Highlights



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Diagnosis of pancreatic cancer

- Symptoms: jaundice, pain, pruritus, diabetes, nausea and vomiting, palpable mass

- Imaging: CT (diagnosis and resectability), NMR, EUS (Computed Tomography, Nuclear Magnetic Resonance, Endoscopic Ultrasonography)

- Blood check: CA 19.9 (Biomolecular marker) raised in 75-85% of patients (if >300 U/mL mostly unresectable)

- Biopsy: CT/EUS-guided fine-needle aspiration

TNM Staging (AJCC 2016)

Pancreas

T1	Tumour 2 cm or less	
	T1a	Tumour 0.5 cm or less
	T1b	Tumour greater than 0.5 cm and less than 1 cm
	T1c	Tumor greater than 1 cm but no more than 2 cm
T2	Tumour more than 2 cm but no more than 4 cm	
T3	Tumour more than 4 cm in greatest dimension	
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery	
N1	Metastases in 1 to 3 nodes	
N2	Metastases in 4 or more nodes	

M category unchanged

Stage

Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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Pancreatic cancer survival: Stage-related (Overall 5-ys survival: <8%)

The stage (TNM) of disease in highly correlated with survival (Data from NCI 2008)

7 % of patients are diagnosed in the early stages
(localized stage)

26 % of patients are diagnosed in the stage of nodes' invasion or invasion to adjacent structures
(regional stage)

52 % of patients are diagnosed when metastases are present
(distant stage)

14 % of patients receive no formal or incorrect staging
(unstaged)

5-yrs survival is highly stage-correlated :
16.4 % for the "localized"
7.0 % for the "regional"
1.8 % for the "distant"
4.3 % for the "unstaged"

**Data from NCI (National Cancer Institute, USA)*

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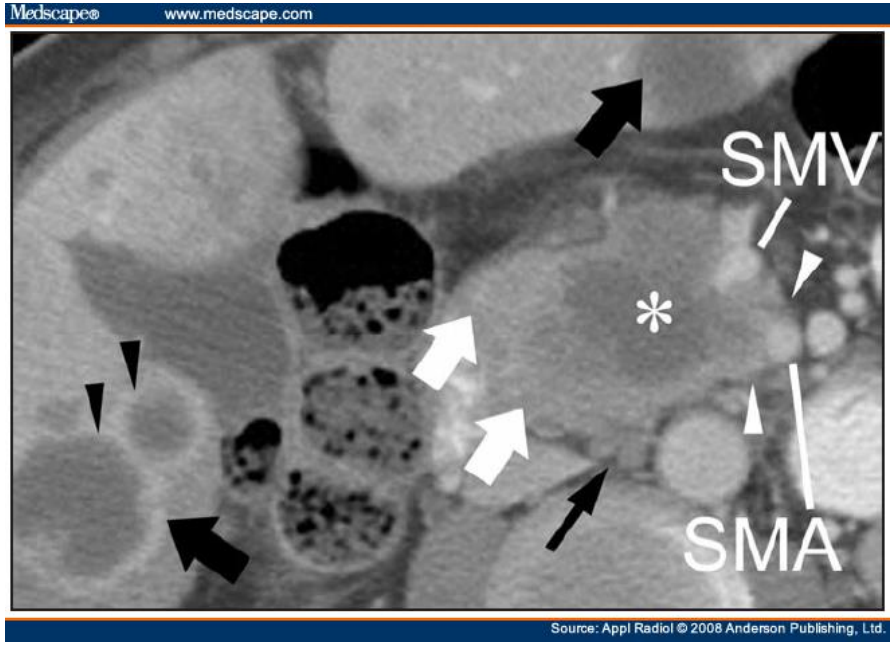
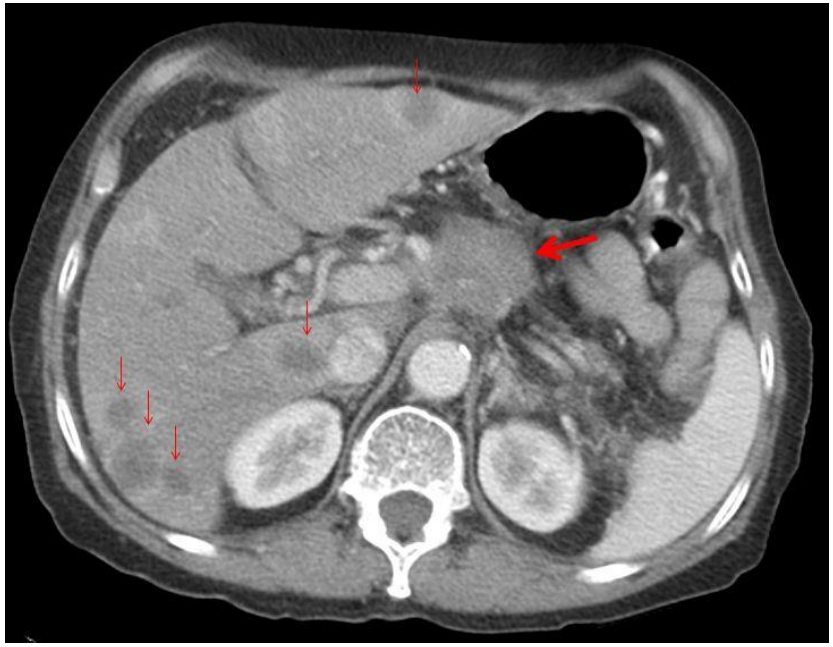
Pancreatic cancer: vascular invasion or metastasis at presentation





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Highlights

Epidemiology

↓

Pathogenesis

↓

Diagnosis

↓

Treatment : surgery, chemoradiotherapy, targeted therapy, new technologies (nanotherapies)

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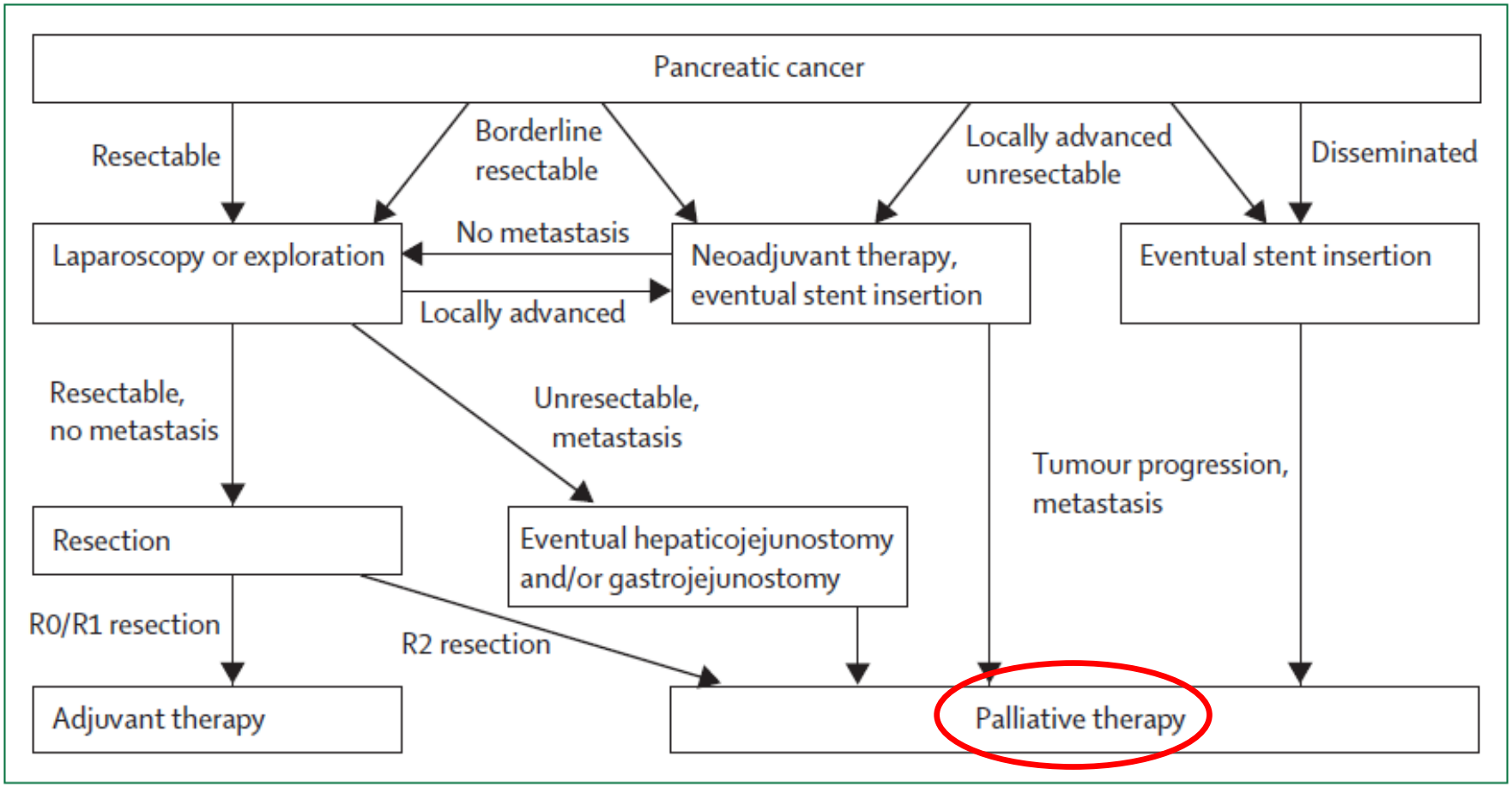
Clinical algorithm for PDAC



Hartwig. Lancet Oncol 2013

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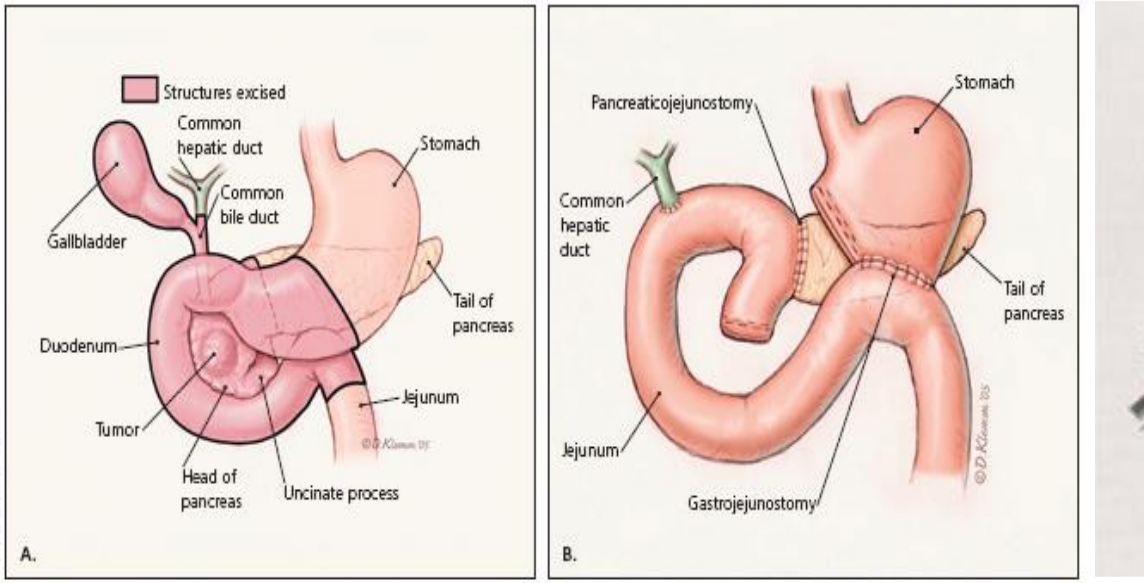
Surgery for pancreatic cancer (Survival increases from <5% to up 20%)

Head and Neck

Body and Tail



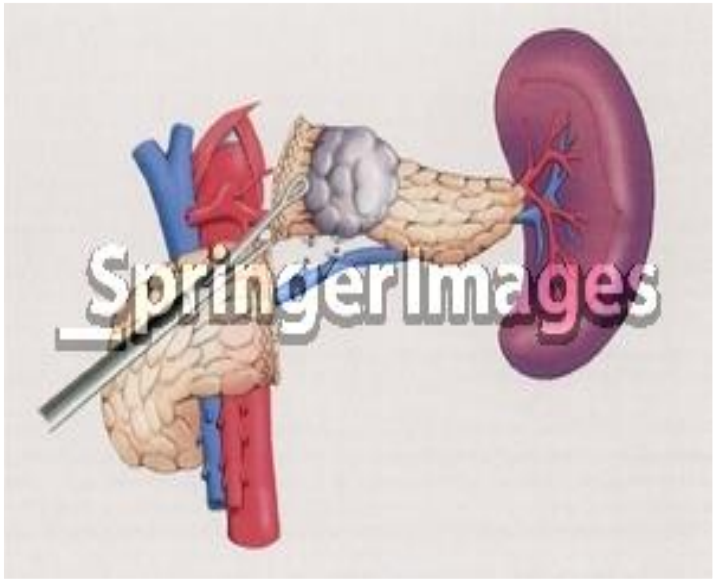


Figure 3. The Whipple procedure. Before the procedure *(A)*. After the procedure; note the anastomosis of the hepatic duct and the remaining pancreas and stomach to the jejunum *(B)*.

McDowell. Ann Surg 2015

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Contraindications to surgery

- Metastases (liver or other)
- Carcinosis (positive cythology in peritoneal lavage)
- Vascular invasion (major arteries)
- Older age or general medical controindications

Good surgeons vs. surgeons too good

- A correct lymphadenectomy (>12 nodes retrieved) is imperative for staging

but

- Extended lymphadenectomy vs. standard: few advantages

Xu X. World J Surg Oncol 2013; Jang JY. Ann Surg 2014

Prognostic factors (in those few operated with radical intent)

Positive

- Radical surgery
- High-volume centres
- Biomolecular markers
- Adjuvant therapy
- Socio-economic and cultural level

Negative

- Vascular invasion
- Node positive
- Dimension of the tumour (>3-4 cm)
- CA 19.9 > 50 U/ml

Lim JE. Ann Surg 2003, Fong Y. Ann Surg 2005

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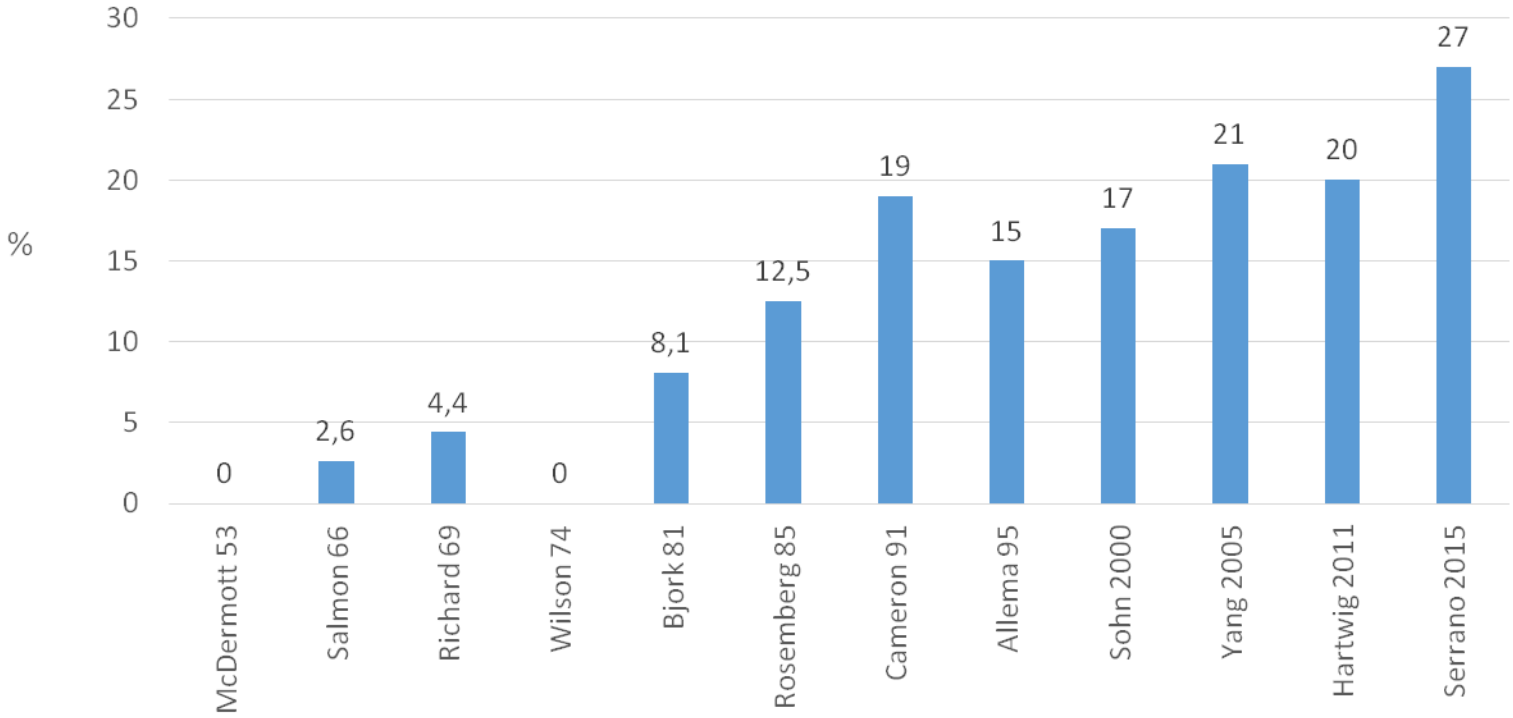
5-Year Survival Rate of resected pancreatic cancers (<30% over years)



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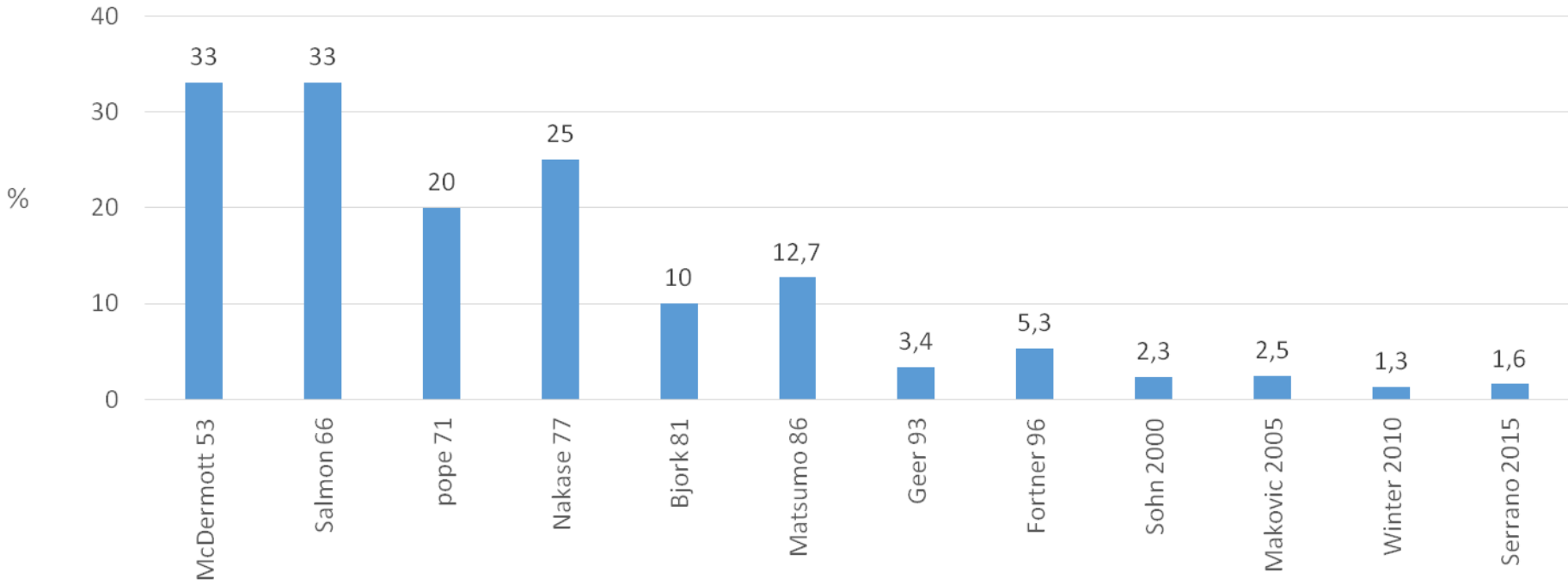
Perioperative Mortality



Due to rarity of disease and complexity of surgery, it should be performed in highly experienced Centres with high volumes of patients (more than 1/month)!

Palliative surgical treatment of pancreatic cancer

- Jaundice
- Duodenal outflow obstruction
- Pain

- Survival's expectacy of more than 6 months
- Acceptable clinical condition

PALLIATIVE SURGERY, ENDOSCOPIC/PERCUTANEOUS TREATMENTS, NEUROLYSIS

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The role of laparoscopy/robotic in pancreatic cancer

- Diagnosis and Staging (biopsy, citology)
- Palliative surgery
- Curative surgery

- No survival advantages
- Trends to better perioperative recovery (early adjuvant chemotherapy?)

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Adjuvant therapy

- Neoadjuvant: radiochemotherapy (gemcitabine+RT, 5-FU+cisplatinum+RT) or chemotherapy only (gemcitabine, cisplatinum or FOLFIRINOX) Promising results but still experimental
- Adjuvant: Surgery + gemcitabine superior to surgery alone (5-yrs survival 21 vs. 9%)– Better: gemcitabine + capecitabine

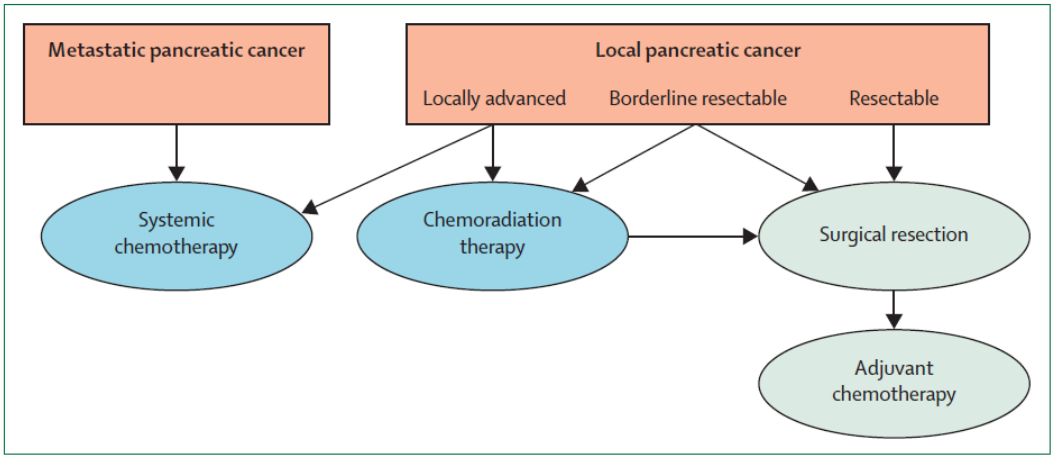
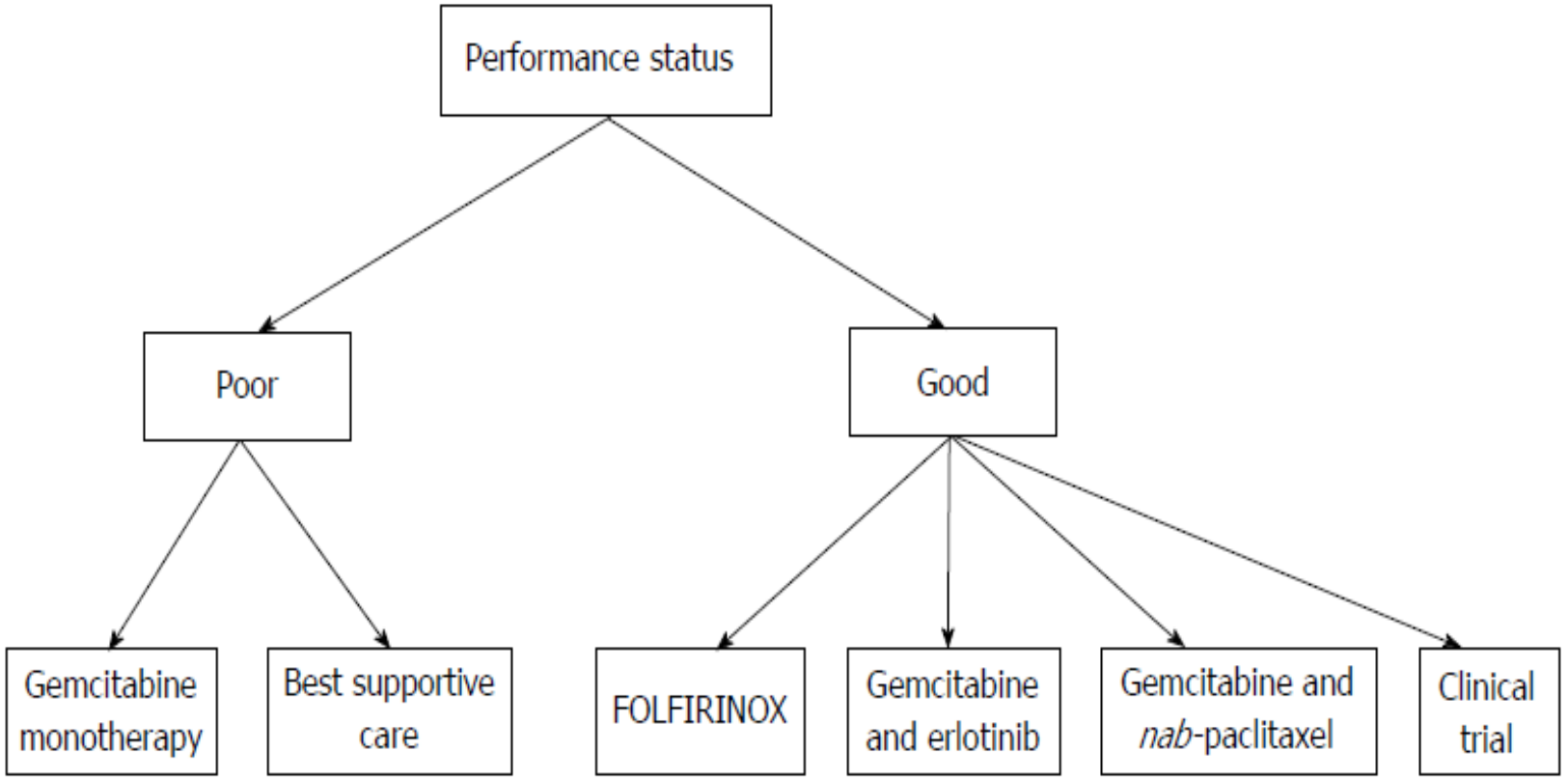


Figure 5: Schematic algorithm of treatment for pancreatic cancer

Oettle H. JAMA 2007; Neuhaus P "CONKO-001". Clin Oncol 2008; Ghosn M. World J Gastronterol 2014, Kamisawa T. Lancet 2016; Neoptolemos JP. Lancet 2017

Metastatic PDAC



Ghosn M. World J Gastronterol 2014

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Standard therapies have reached their maximum. Can we improve pancreatic cancer survival otherwise?

Yes we can!

No, we cannot yet

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State of the art in the field of pancreatic cancer research

- Urgency to pass “from bench to bedside”
- New drugs based on the molecular single patient profile
- Older drugs with enhanced delivery and kinetics
- Choice of “the right drug for the right patient”

“Targeted or Tailored therapy”

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Neoplastic progression. Every step as a possible target for molecular therapy

- Self-sufficiency (in growth signals)
- Insensitivity to growth-inhibitory signals
- Evasion of apoptosis
- Sustained angiogenesis
- Limitless replicative potential
- Tissue invasion
- Metastasis
- Escape from immune surveillance
- Epigenetic modifications (metilation, acetylation, miRNA)
- Resistance to chemotherapy

Hanahan e Weinberg. Cell 2000

The ideal characteristics of a cancer target (molecular marker)

- Highly expressed in the tumoral cells
- High density found in tumoral tissues
- Homegeneous distribution in tumoral tissues
- Poorly (or absent) expressed in adjacent tissues
- Easily to detect
- Easily to quantify

- Differences in markers' tissues distribution could play a role in the failure of conventional therapy

- THE THERAPEUTIC TARGET SHOULD BE IDENTICAL TO THE TRACING TARGET (Therapy & Diagnosis)

Molecular biomarkers in pancreatic cancer: predictive role

Management of pancreatic adenocarcinoma

Table Prognostic and Predictive Biomarkers in Pancreatic Cancer

Prognostic Biomarker	Prognostic Value
CA 19-9	Poor prognosis if elevated, particularly postoperatively[13,21,31-33]
SMAD4 or DPC4	Poor prognosis if inactivated[45,54-57]
CSC markers ($CD44^+CD24^+ESA^+$, $CD133^+$, ALDH, Nestin, and c-Met)	Poor prognosis if elevated[73,74,76,77]
Histologic parameters	Poor prognosis if necrosis, vascular invasion, lymphatic invasion, and perineural invasion are present[121-123]
Predictive Biomarker	**Companion Therapy**
Fanconi anemia signaling proteins (BRCA2 and PALB2)	Mitomycin-C, platinum-based chemotherapy (cisplatin), and PARP inhibitors (mitoxantrone, iniparib, and olaparib)[100-104,107,108]
SPARC or osteonectin	Albumin-bound paclitaxel (nab-paclitaxel)[117-119]

Ansari D. Br J Surg. 2011, Jazieh KA. Semin Radiat Oncol 2014

Molecular biomarkers in pancreatic cancer: predictive role

CA19.9; SMAD4; Stem Cells Markers; BRCA2; FA, FH, PALB2

«Systematic review of immunohistochemical biomarkers to identify prognostic subgroups of patients with pancreatic cancer»

Conclusions: «None of the molecular markers described can be recommended for routine clinical use»

Ansari D. Br J Surg. 2011, Jazieh KA. Semin Radiat Oncol 2014

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Molecular therapeutic targets in pancreatic cancer

Molecular Targets and Novel Agents in Pancreatic Cancer*

Target†	Frequency (%)‡	Novel agents
HER family		
EGFR	90	mAbs: cetuximab, panitumumab (ABX-EGF), EMD 72000; TKIs: gefitinib (ZD1839, Iressa), erlotinib (OSI-774, Tarceva), EKB-569
HER-2/*neu*	10	Trastuzumab (Herceptin), CI-1033
VEGF pathway		mAbs: bevacizumab; TKIs: sorafenib, sutinib, PTK787
VEGF		
VEGF receptors		
Ras-Raf-MEK-ERK signaling pathways		
Ras	90	FTIs: R115777 (tipifarnib), SCH66336, BMS-214662
Raf		Bay 43-9006 (sorafenib)
MEK		CI-1040
PI3K/Akt pathways		17-AAG (nonspecific)
Akt		CCI-779, RAD001
mTOR	67	Curcumin (nonspecific), bortezomib (PS-341, VELCADE) (nonspecific)
NF-κB		
Other molecular targets		
COX-2	75	Celecoxib, rofecoxib
LOX		LY293111
IL-8	70	ABX-IL8

Hochster HS. Cancer 2006

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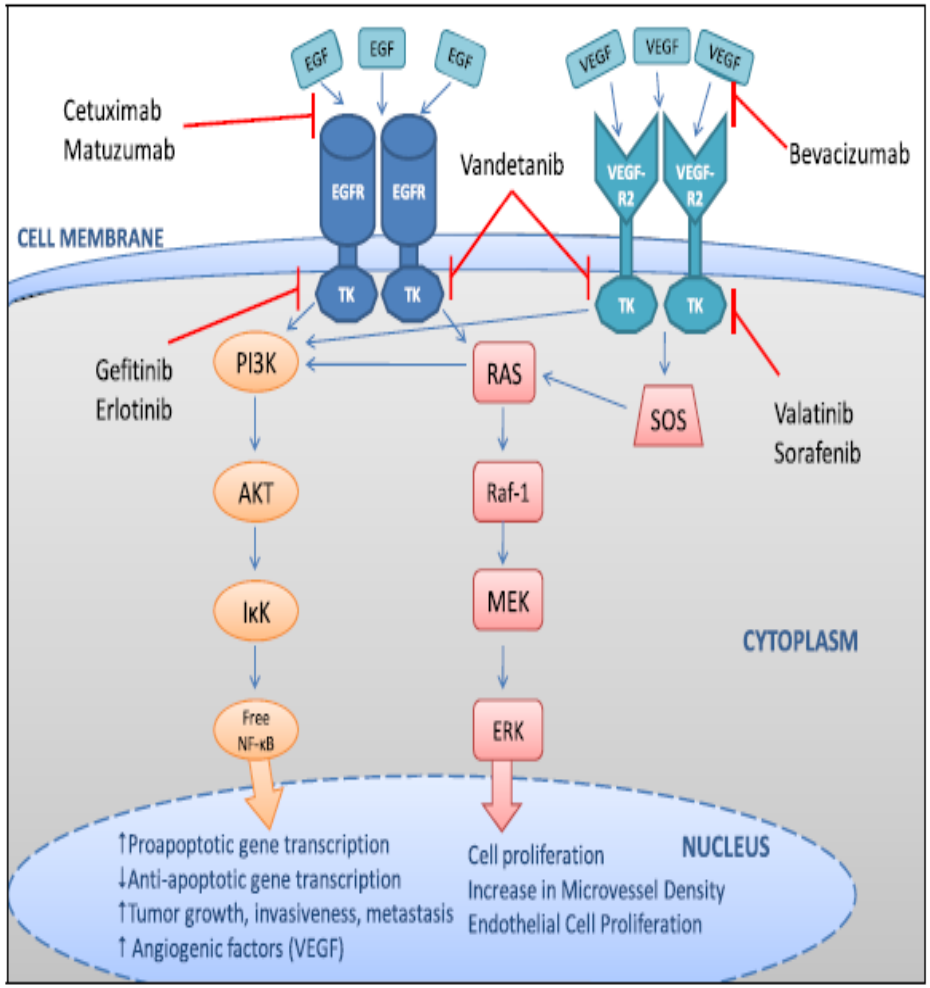
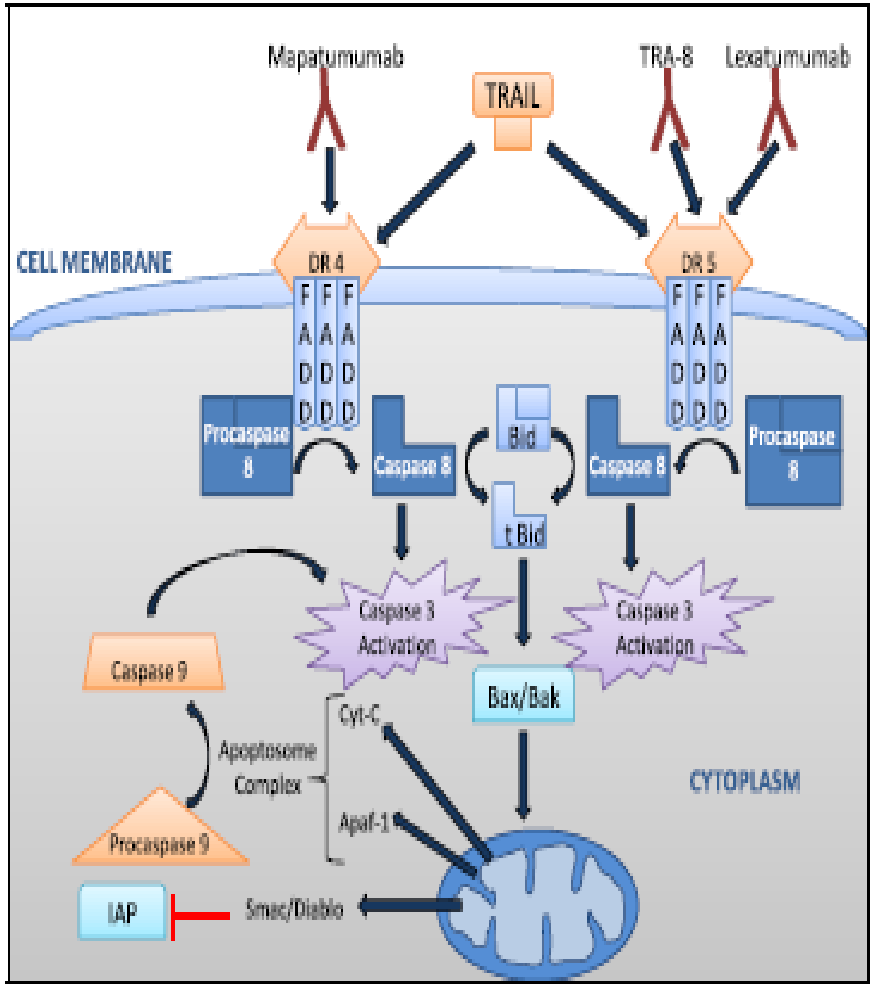
Targeted therapy in pancreatic cancer





Borja-Cacho D. Am J Surg 2008

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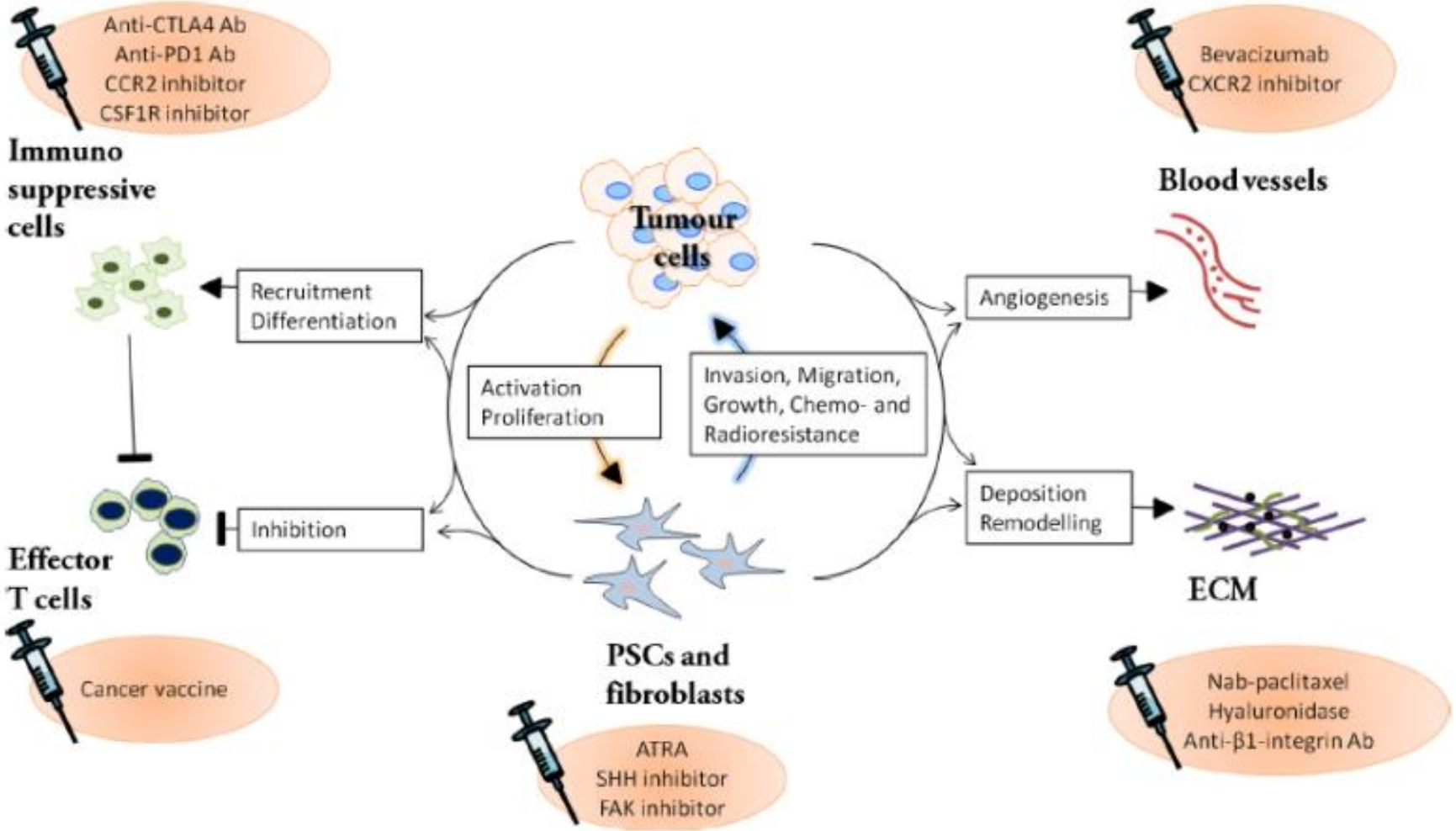
Stromal-tumour interaction as a possible target for new therapies



Lunardi S. Cancer Letter 2013; Arcangeli A. Philos Trans R Soc Lon B Biol Sci 2014

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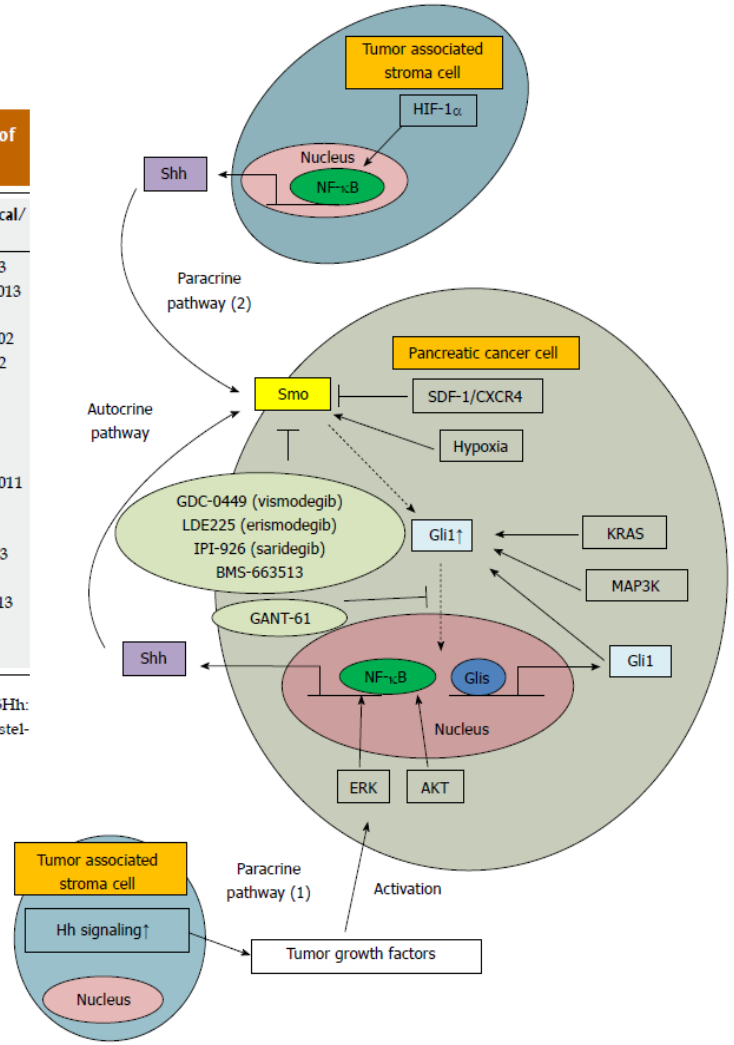
Targeted therapy pancreatic cancer microenvironment

Table 1 Recent and ongoing preclinical and clinical studies of experimental therapies targeting tumor microenvironment of pancreatic ductal adenocarcinoma

Stromal component	Therapeutic target	Treatments in preclinical and clinical trials	Up to date preclinical/ clinical trial results
PSCs/fibroblasts	FAP	Sibrotuzumab (colorectal cancer)	Hofheinz *et al*[99], 2003
ECM	Hyaluronan	PEGPH20	Strimpakos *et al*[91], 2013
	MMPs	BAY 12-9566	Moore *et al*[100], 2003
		Marimastat	Bramhall *et al*[101], 2002
Immune cells	PD-L1	BMS-936559	Brahmer *et al*[102], 2012
	CTLA-4	Ipilimumab	Le *et al*[95], 2013
	$CD8^+$ T cells	GVAX	Lutz *et al*[93], 2011
			Laheru *et al*[94], 2008
	CD40	CP-870,893	Beatty *et al*[103], 2013
Signaling pathways mediating tumor-stroma interactions	Smo/SHh	Vismodegib (GDC-0449)	Stephenson *et al*[90], 2011
		IPI-926	
	Type II TGFβ receptor	Trabedersen	Oettle *et al*[92], 2009
	γ-secretase (Notch pathway)	PF-03084014 (preclinical)	Yabuuchi *et al*[78], 2013 (preclinical)
	HGF/c-met	Many different compounds (solid cancers)	Venepalli *et al*[104], 2013 (solid cancers)
	Different molecules in NF-κB cascade	Many different compounds (*i.e.*, curcumin, proteasome inhibitor)	Arlt *et al*[105], 2012

ECM: Extracellular matrix; MMP: Matrix metalloproteinase; PD-L1: Programmed death receptor ligand 1; CTLA-4: Cytotoxic T-lymphocyte antigen 4; SHh: Sonic hedgehog; Smo: Smoothened; TGFβ: Transforming growth factor β; HGF: Hepatocyte growth factor; NF-κB: Nuclear factor κ-B; PSC: Pancreatic stellate cell; FAP: Fibroblast activation protein.



Example: Targeting the Hedgehog pathway

Rucki AA. World J Gastroenterol 2014

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Molecular targets in pancreatic cancer: Clinical Phase II Studies

Table 3. Selected Strategic Targets in Pancreatic Cancer.*

Target	Agent	Drug Class	Mechanism of Action	Trial Phase	Reference
SPARC	Nanoparticle albumin-bound paclitaxel	Cytotoxic agent	SPARC, expressed in cancer cells and stroma in the pancreas, binds nanoparticle albumin-bound paclitaxel, increasing local drug delivery	3	Li and Saif[75]
IGF-IR	MK 0646, AMG 479, R1507	Monoclonal antibody	Inhibits ligand binding activation of the IGF-IR and cell proliferation	3	Hewish et al.[78]
Death receptor	AMG 655, CS1008	Monoclonal antibody	Agonist antibodies to membrane death receptors induce apoptosis	2	Li and Saif,[75] Derosier et al.[79]
Mucin-1	90Y-hPAM4	Radioimmunoconjugate	Targets mucin-1 expressed in pancreatic-cancer cells and delivers radiation load	1–2	Gold et al.[80]
Hedgehog pathway	GDC-0449, IPI-926	Small-molecule inhibitor	Inhibits smoothened receptor, resulting in inhibition of cell proliferation; targets cancer stroma and cancer stem cells in the pancreas	1	Olive et al.,[29] Jimeno et al.[32]
c-kit, PDGFR, FGFR	Masitinib	Small-molecule inhibitor	Multikinase inhibitor targets c-kit, PDGFR, and FGFR3 and affects the FAK pathway; masitinib was shown to enhance the antiproliferative effects of gemcitabine in preclinical studies	3	Li and Saif[75]
MEK	AZD6244	Small-molecule inhibitor	Targets and inhibits MEK, decreasing cell proliferation	2	Chung et al.[81]
Src	AZD0530, dasatinib	Small-molecule inhibitor	Targets and inhibits Src kinase, resulting in inhibition of cell proliferation and invasion	2	Rajeshkumar et al.[77]
RAS	Sarilasib	Small-molecule inhibitor	Dislodges all forms of RAS from the plasma membrane, inhibiting RAS signaling	2	Haklai et al.[82]
PSCA	AGS-1C4D4	Monoclonal antibody	Binds membrane PSCA; specific mechanisms of cell killing undetermined	2	Wente et al.[83]
Mesothelin	MORAb-009	Monoclonal antibody	Binds membrane mesothelin; specific mechanisms of cell killing undetermined	2	Hassan et al.[84]
TNF-α	TNFerade	Gene therapy	Adenoviral gene therapy increases intratumoral concentration of TNF-α	3	Murugesan et al.[85]

* The abbreviation c-kit denotes stem-cell factor receptor; FAK focal adhesion kinase; FGFR fibroblast growth factor receptor; IGF-IR type I insulin-like growth factor receptor; MEK mitogen-activated protein kinase–extracellular-signal–regulated kinase, PDGFR platelet-derived growth factor; PSCA prostate stem-cell antigen; SPARC secreted protein, acidic, cysteine-rich; and TNF-α tumor necrosis factor α.

Hidalgo M. NEJM 2010

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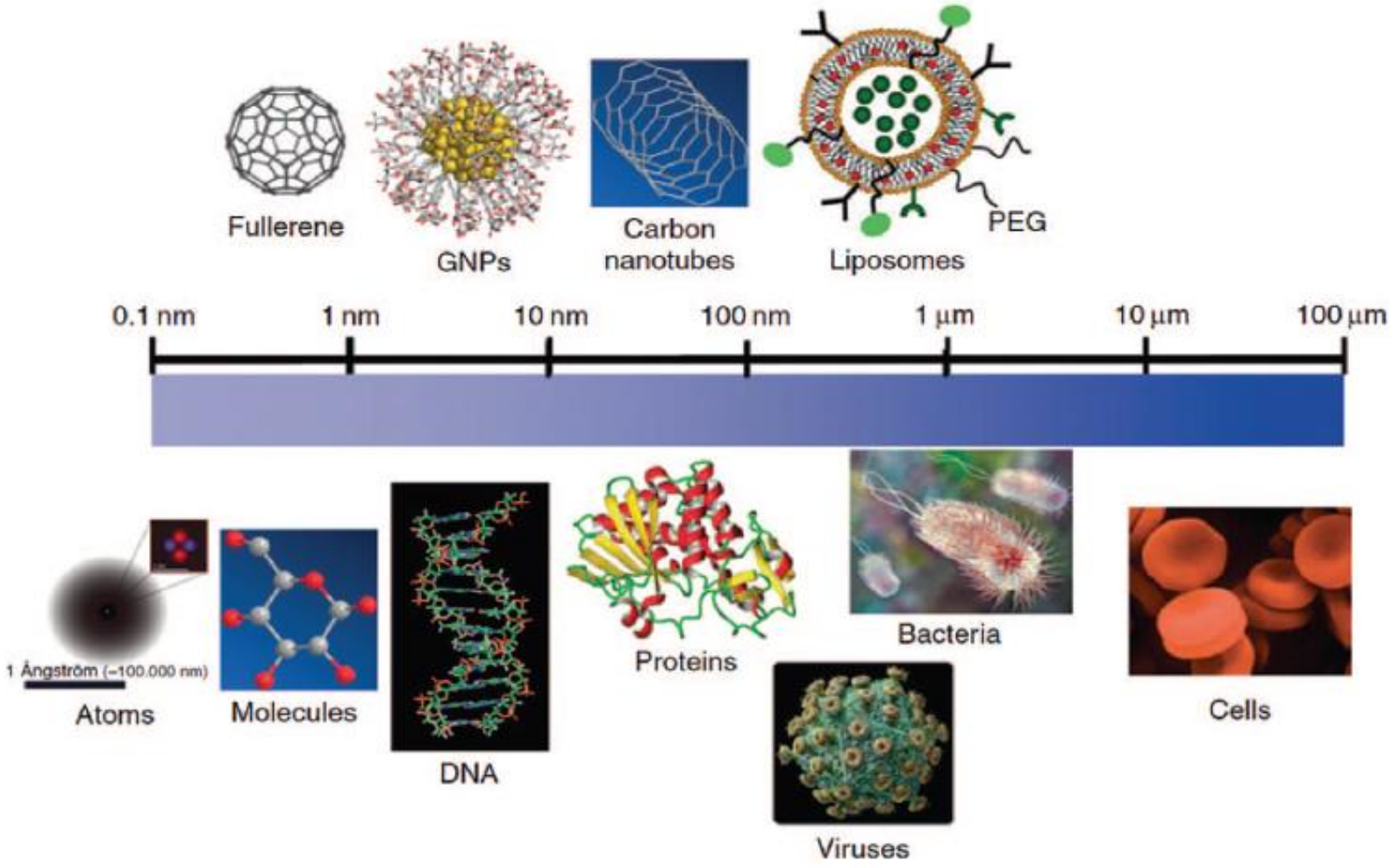
Targeted therapy

- Increased median survival (1 year) described with erlotinib only and bevacizumab (in addition to gemcitabine). Few months, high costs

- The standard is actually gemcitabine only (no radiotherapy) - Capecitabine (oral FU) as a second line – FOLFIRINOX (adj or met).

Moore MJ. J Clin Oncol. 2007, Ghosn W J Gastroeneterol 2014, Conroy T. NEJM 2018

Nanoparticles



Morgan. Ann Surg 2016

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Nanotherapies in surgical disease

TABLE 1. Examples of Nanoscale Delivery Platforms

Category	Example	Size, nm	Particle Structure	Therapeutic Use
Organic	Liposomes	20–250	Spherical vesicle with lipid bilayer membrane structure and aqueous core	– Delivery of vaccines, toxoids, genes, anticancer, and anti-HIV therapeutics
	Dendrimers	1–30	Highly branched, monodispersed macromolecule with tendrils extending from a central core	– Delivery of therapeutics – Conjugation of chemotherapeutics
	Polymeric micelles/ nanofibers	30	Core-shell structures of spontaneously self-assembled amphiphilic copolymers	– Delivery of therapeutics, including pH sensitivity drug release – Imaging contrast agent – Solid tumor therapeutics
Carbon based	Fullerenes	1	Carbon nanomaterial, in the form of a hollow sphere, tube, ellipsoid, cylinder, etc	– Delivery of therapeutics – Conjugation to antibiotics as an antimicrobial agent – Imaging contrast agent – Tumor imaging and therapeutics – Gene delivery
Inorganic	Metal nanoparticles	1–100	Gold, copper, silver	– Optical, photoelectric, fluorescent, and photothermal properties – Imaging contrast agent – In vivo tumor imaging – Gene delivery – Breast cancer diagnostics
	Quantum dots	2 – 10	Colloid semiconductor nanocrystals composed of atoms from groups II–VI or III–V of the periodic table of elements	– Optical and fluorescent properties – Therapeutics delivery – Imaging contrast agent – Biomedical implants – Quantum optical semiconductor device

- Drug delivery, conjugation to chemotherapeutic agents, imaging contrast agent, gene delivery, biomedical implants

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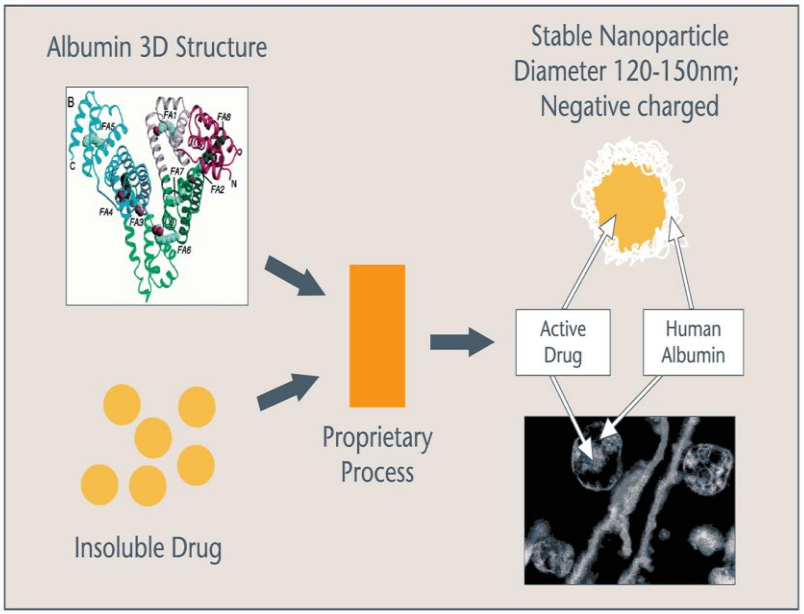
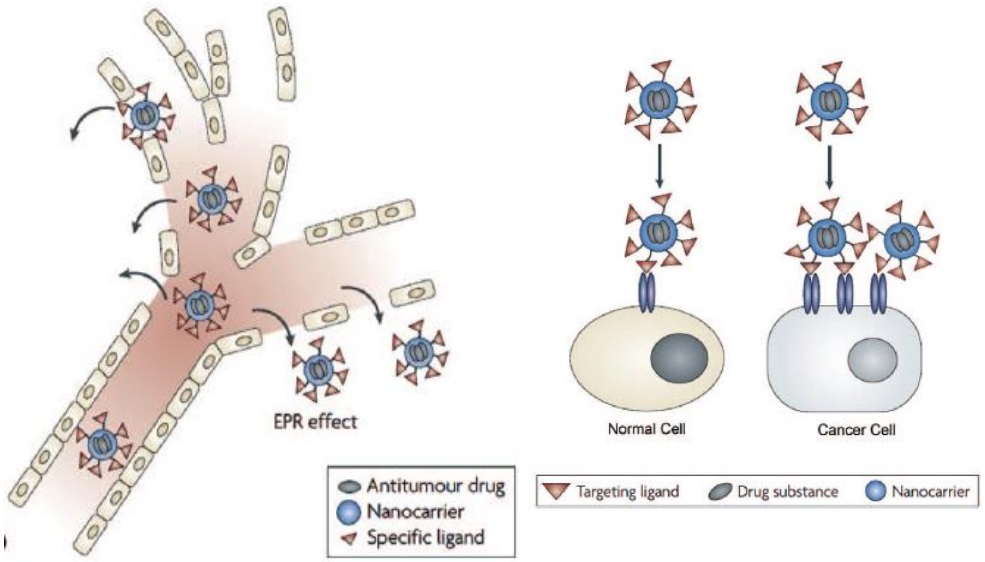
Nab-Paclitaxel

- Nanoparticles albumin bound – paclitaxel (SPARC)





- Increased concentration in the tumour microenvironment
- More efficacy – less dose delivered – reduction of adverse effects

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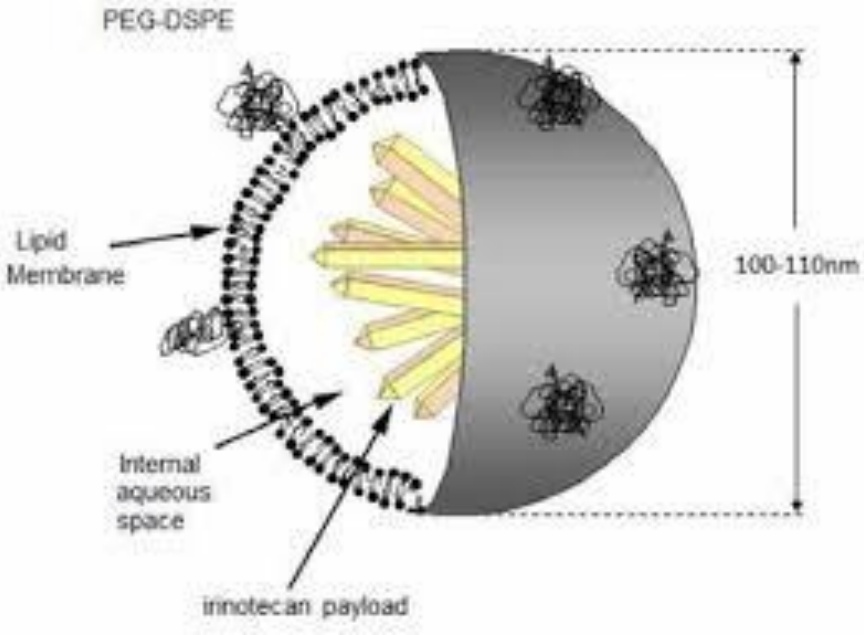
Naliri

- Nanoliposomal irinotecan (Topoisomerase)



- Increased concentration in the tumour microenvironment
- More efficacy – less dose delivered – reduction of adverse effects

Wang-Gillam . Lancet 2016

Multimodal treatment of pancreatic cancer

The patients of low socioeconomic status receive suboptimal management for pancreatic adenocarcinoma in USA (Florida). Low Socio Economic Status patients were less likely to:

- Receive surgical resection (16.5% vs 19.8%; P < .001)
- Chemotherapy (30.7% vs 36.4%; P < .001)
- Radiotherapy (14.3% vs 16.9%; P = .003)
- Among surgical patients, 30-day mortality was higher (5.1% vs 3.7%; P < .001)
- Overall median survival was significantly worse (5.0 months vs 6.2 months; P < .001)

But Better trends in Teaching or University Hospitals…….

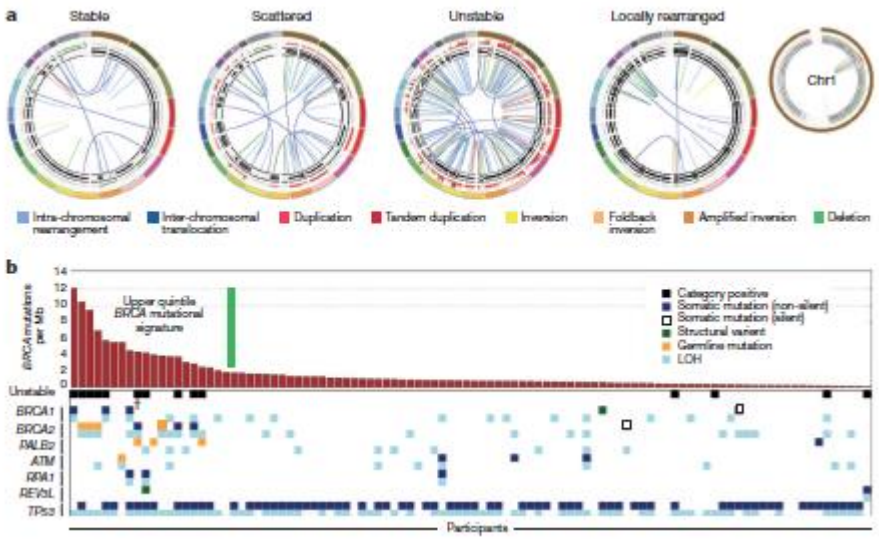
Cheung MC. Cancer 2010

Conclusions

ARTICLE

doi:10.1038/nature14169

Whole genomes redefine the mutational landscape of pancreatic cancer



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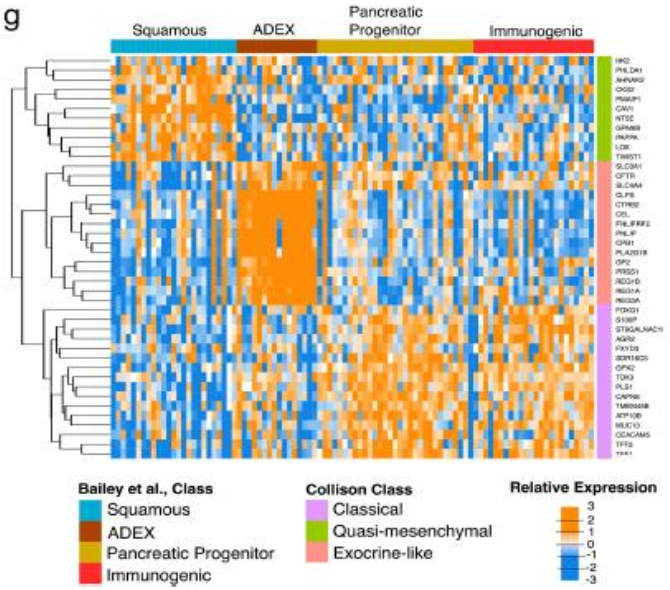
doi:10.1038/nature16965

Genomic analyses identify molecular subtypes of pancreatic cancer



- **Key message:** **The more subtypes the more targeted drugs**

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Thank you for your attention

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