8^ edizione

Top Ten

IN GASTROENTEROLOGIA

17-18 MARZO 2017

ISEO (BS)

Iseo Lago Hotel - Via Colombera, 2

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IRCCS – Ospedale San Raffaele, Milano

Nuove strategie per la diagnosi precoce del tumore pancreatico

Tumore del pancreas

Componente strutturale	Istotipo	Incidenza vs tumori
Epitelio insulare	Tumore endocrino	1%-2%
Epitelio duttale	**Adenocarcinoma duttale**	**90%**
Epitelio acinare	Tumore acinare	1%

227.000 deaths annually worldwide

Siegel R, Cancer J Clin 2014

I NUMERI DEL CANCRO IN ITALIA 2016

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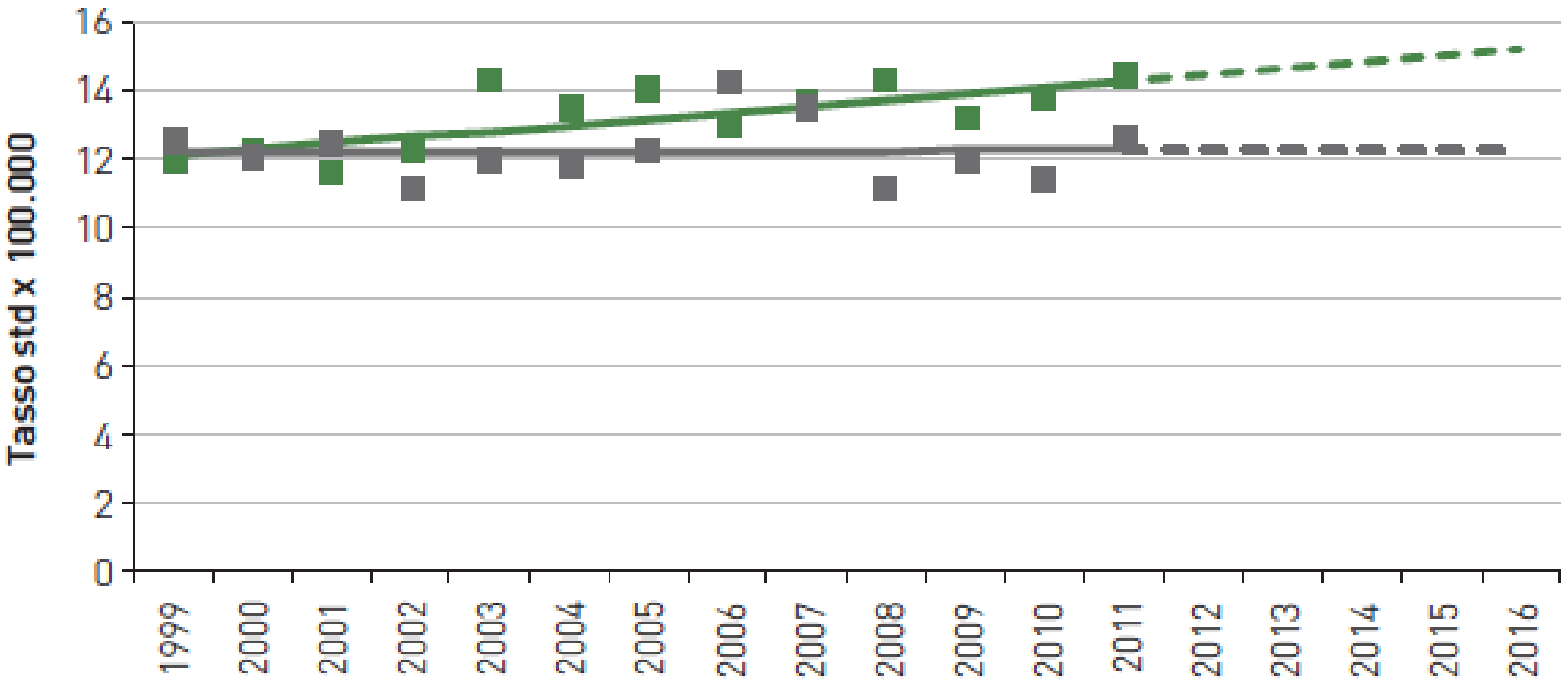
Rango	Tutta la popolazione
1°	Polmone (19%)
2°	Colon-retto (11%)
3°	Mammella (7%)
4°	Stomaco (6%)
5°	Pancreas (6%)

AIOM
Associazione Italiana di Oncologia Medica

AIRTUM

Incidenza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Sopravvivenza a 5 anni dalla diagnosi

Pancreas	6,9 (6,8-7,0)	7,2 (6,7-7,7)
Colon	57,0 (56,8-57,3)	60,8 (60,4-61,3)
Prostata	83,4 (83,1-83,6)	88,6 (88,1-89,0)
Mammella femminile	81,8 (81,6-82,0)	85,5 (85,1-85,8)

Diagnosi precoce

Ad oggi non esistono metodi per la diagnosi precoce del carcinoma del pancreas. La malattia è di solito per lungo tempo asintomatica; solamente il 7% dei casi è diagnosticato in stadio iniziale.


¡HOLA
Y
ADIOS

PANCREATIC CANCER

The facts:

Sporadic PC	**90%**
Familial PC	7%
Inherited Cancer Syndromes	3%

GENERAL POPULATION SCREENING WOULD BE GREAT!

However...

Overall lifetime risk of developing PC is relatively low, close to 1% and does not meet some of the criteria established by WHO

Hruban RH et al. Adv Surg 2010
www.who.int/cancer/detection/variouscancer/en

By contrast, only patients with a significant increased risk of develop PC could opt to screening test

- Sporadic PC 90%
- **Familial PC 7%**
- **Inherited Cancer Syndromes 3%**

CAPS, FaPaCa, Ducth Study
MRI and EUS have been proposed

- **Sporadic PC** **90%**
- Familial PC 7%
- Inherited Cancer Syndromes 3%

SURGERY IS CURRENTLY THE ONLY CHANCE FOR CURE

80% of cases present at an advanced stage

53% already have distant metastase at time of diagnosis

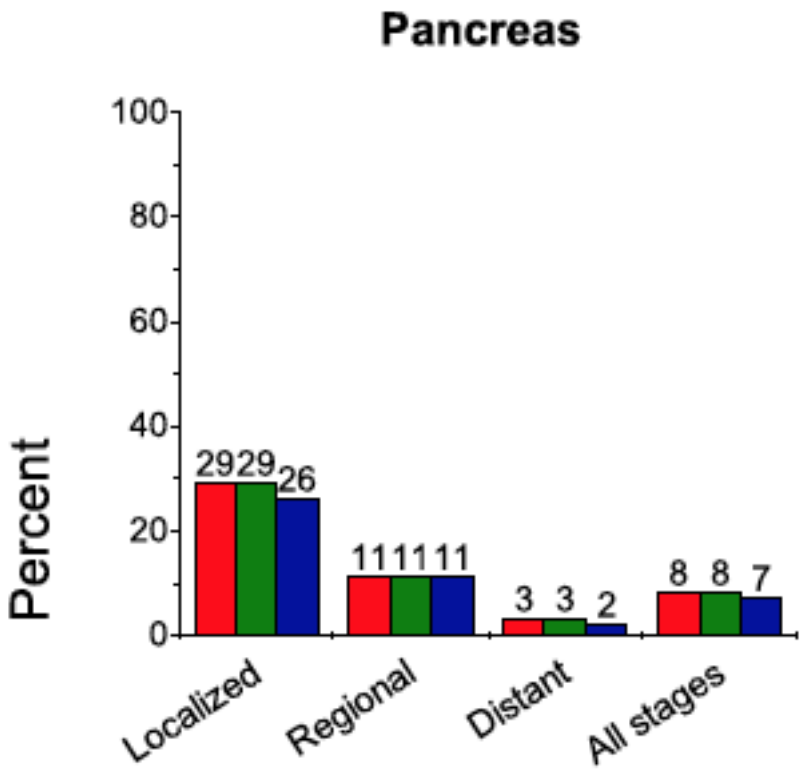
10% of cases are treated surgically with a curative intent

Ideal surgical candidate- 5 year survival rate of 20-30%

Hidalgo M. N Engl J Med 2010

Cancer Statistics, 2017

Rebecca L. Siegel, MPH[1]; Kimberly D. Miller, MPH[2]; Ahmedin Jemal, DVM, PhD[3]



Five-Year Relative Survival Rates by Stage at Diagnosis and Race

CA CANCER J CLIN 2017;67:7–30

PANCREATIC CANCER

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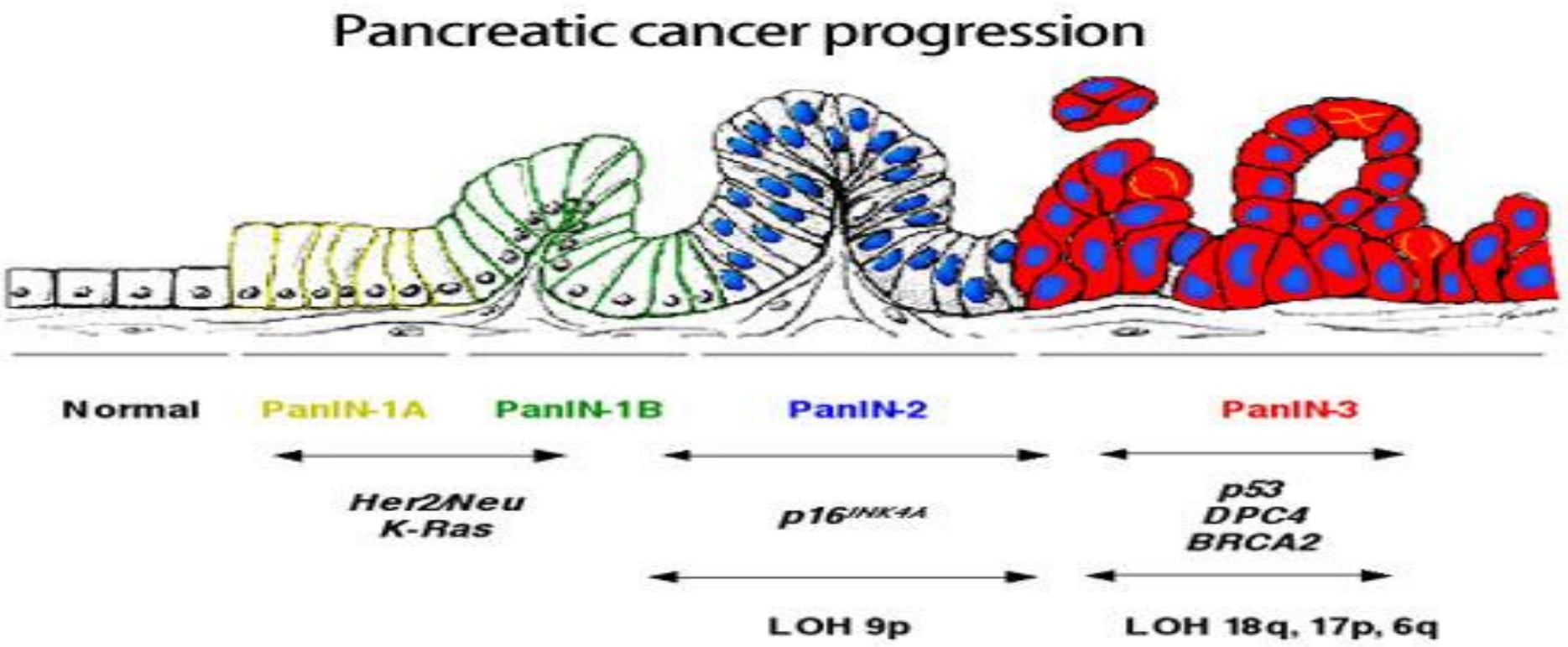
imperative need!!

detection at an earlier stage and development of effective therapies “cornerstones” for cancer death reduction

SCREENING STRATEGIES

Which is the “earliest stage” of pancreatic ductal adenocarcinoma ?

«Early» Targetable lesions



PanIN-1: hyperplastic and benign
PanIN-2: low grade dysplasia
PanIN-3: high-grade dysplasia or carcinoma in situ
Invasive PC: cancerous ductal cells move through the basement membrane

Invasive PC

- **Minute PC** (<10mm) → stage IA (rarely detcted)
- **Small PC** (< 20mm)→ stage IB (10% of diagnosed PC, 45% metastatic)
- **Large PC** (> 20mm) → stage II **90% diagnosed PC**

Chari ST et al. Pancreas 2015

Only 20% of PC's are elegible for resection with curative intent with average size of 30 mm.

Lesions with

- PanIN-3,
- invasive cancer confined to the pancreas (Stage 1A – 1B)
- resectable PC (Stage II)

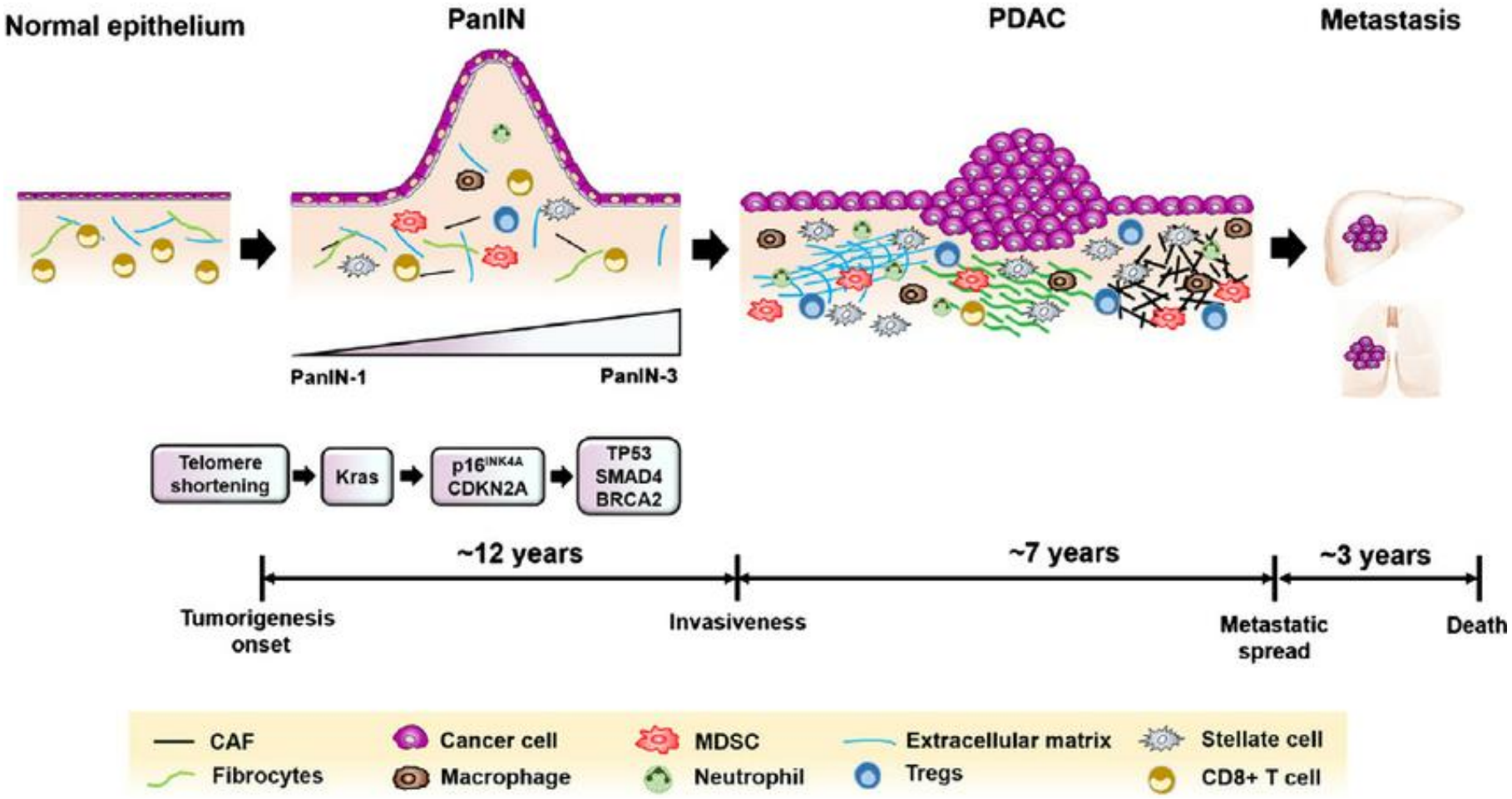
can be considered «early» as they are all resectable

Defining «Early» PC

- Definition of the earliest actionable lesion in the progression of PC is challenging
- PC with any degree of invasion is biologically advanced → propensity for systemic micrometastasis
- Even with the potential of micrometastatic disease the survival of surgical patients is better vs not surgical
- Size is related to survival

As far back as possible in the diagnostic timeline

Timeline of Progression
PanIN-1 → Large PC



Yachida S, Nature 2010

Timeline of Progression
PanIN-1 → Large PC

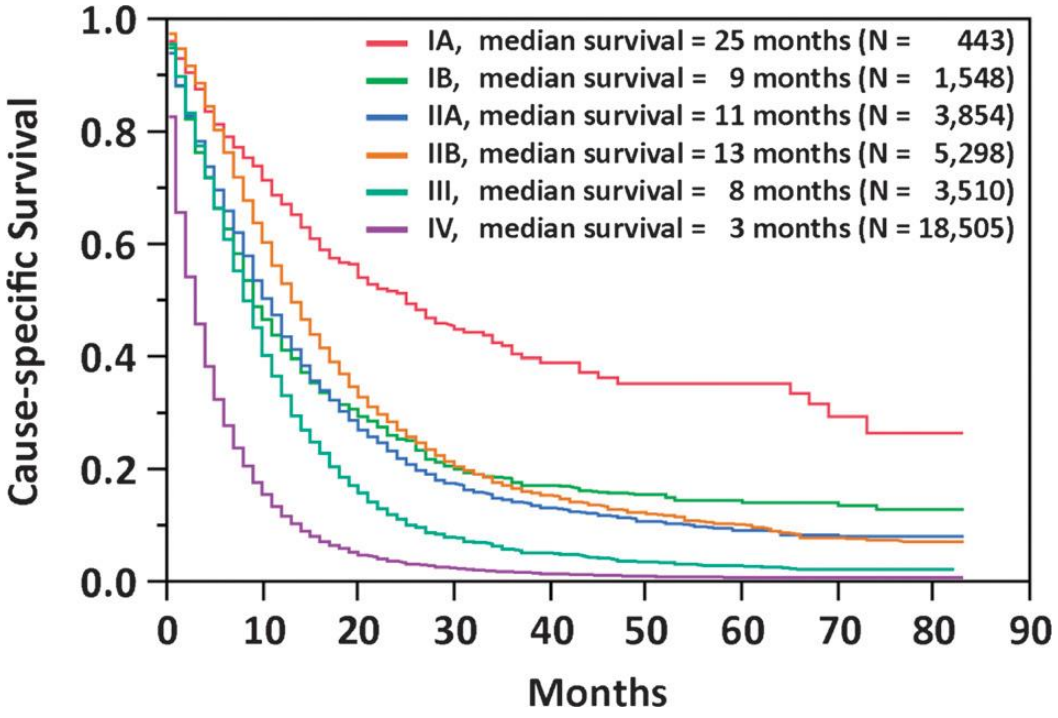
- Genetic timeline for progression from initiation of the malignant clone to metastatic disease → 2 decades

- Clinical timeline from resectable to unresectable
  - Onset of symptoms → related to unresectable disease
  - PC undetectable by CT > 6 months before symptom

Pelaez Luna M, Am J Gastsroenterol 2007

- Lesions < 2 cm are mostly resectable but quite always undetected by **CT** (lack of sensitivity in identifying small cancers → **not good method for early detection.**

Early Detection and Treatment



Stage 1A 5 yrs OSR = 40%
Due to metastatic disease

Chari ST et al. Pancreas 2015

Only **PanIN-3** (carcinoma in situ) which is a preinvasive lesion can be considered the only target lesion **CURABLE**

TABLE 1. Effect on 5-Year Survival by Changing the Relative Proportion Between Stages*

	Current Proportions	Doubling of Survival	Tripling of Survival	Quadrupling of Survival
Stage				
IA	1.3	5.9	12.7	22.6
IB	4.7	13.4	21.8	28.8
IIA	11.6	22.0	26.6	26.2
IIB	16.0	19.9	17.9	13.1
III	10.6	8.7	5.8	3.2
IV	55.8	30.1	15.1	6.1
Relative proportion parameter	1.0	1.5	2.0	2.7
Average 5-y survival	4.1%	8.2%	12.3%	16.4%

*A Cox proportional hazards model was used, with stratification for stage and sex, and a penalized spline with 4 degrees of freedom for age at diagnosis, and changing the relative proportion between paired, sequential stages.

Challenges in early detection

- Symptoms
  - Cancer specific → advanced PC
  - Early symptoms → uncommon, unspecific
- PC relatively rare → Who to Screen
- Biomarkers
- Imaging

Challenges in early detection

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Screening

Restricted to subject at high risk of having or developing sporadic PC

- **Late onset (>50 yrs) DM**
  - Recent onset → 25% of PC subjects develop DM **6-36** months prior diagnosis (**window for early diagnosis**)
  - 50 – 67% PC subjects have DM
  - Paramount importance DD Pc induced Type 3c DM vs Type 2 DM (less 1% of subjects with late onset of DM will have PC)

Chari ST et al. Gastroenterology 2005

Challenges in early detection

- Symptoms
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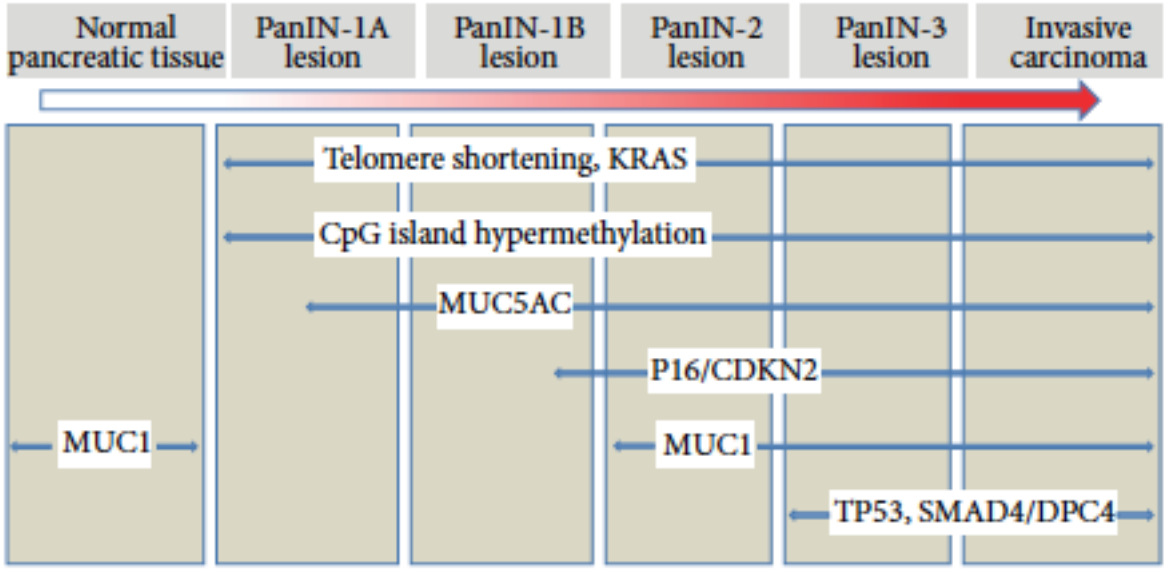
- PC relatively rare → Who to Screen
- Biomarkers
- Imaging


Normal pancreatic tissue
PanIN-1A lesion
PanIN-1B lesion
PanIN-2 lesion
PanIN-3 lesion
Invasive carcinoma
Telomere shortening, KRAS
CpG island hypermethylation
MUC5AC
P16/CDKN2
MUC1
MUC1
TP53, SMAD4/DPC4

Screening Biomarkers

The Ideal Biomarker

- Universally present in preinvasive cancer (PanIN-3) and curable-stage PC and absent in patients without neoplasia
- Practical, noninvasive, inexpensive, widely accessible highly sensitive and specific

- Ca19/9 the only clinical available biomarker is
  - insensitive for early invasive PC
  - Doesn't identify high-grade PanIN

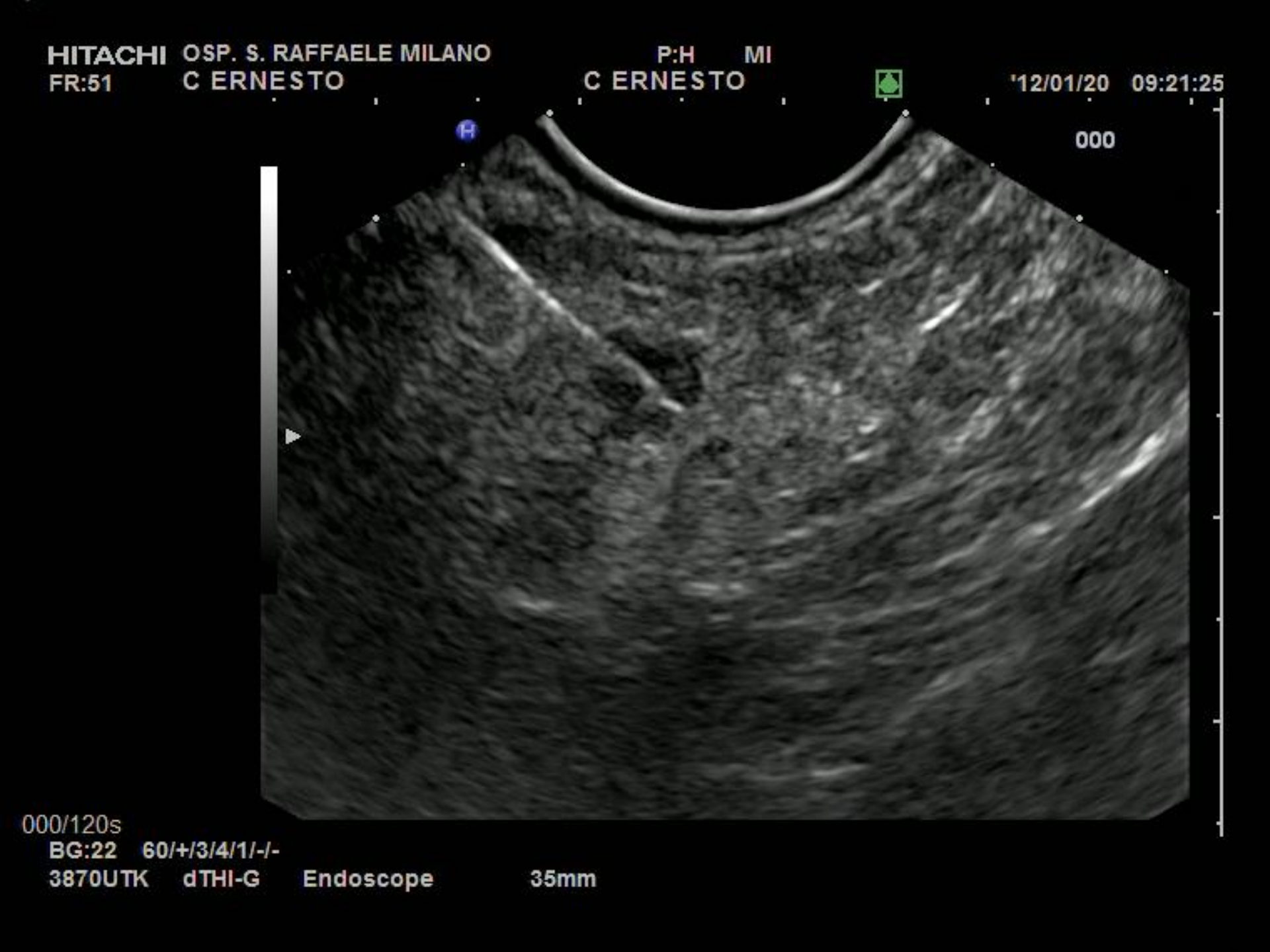
Screening Biomarkers

- Stool DNA
  - Potential possibility of «one test fits all» GI tumors
- Saliva
  - Salivary extracellular RNA biomarkers to discriminate PC from non-PC patients
- Circulating Tumor Cells
  - The dissemination of tumor cells in the circulation in PC is thought to occur very early in the disease progression

- Mucins
  - Blood based biomarkers
  - EUS-FNA specimens
  - Autoantibodies against specific tumor associated mucin antigens
- Pancreatic juice
  - EUS-FNA based

Imaging

- Currently Early PC is not detected by routine cross-sectional imaging
  - **MDHCT** is insensitive to detect
    - ✓PanIN-3
    - ✓Minute/small invasive PC
  - **MRI + MRCP and EUS**
    - ✓EUS and MRI are better than CT for the detection of small, predominantly cystic, pancreatic lesions, with good to excellent concordance of lesion number, size and location between EUS and MRI/MRCP. EUS, MRI/MRCP and CT identified pancreatic lesions in 42.6%, 33.3% and 11% of screened HRIs, respectively.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Imaging

- **EUS+FNA**
  - ✓is the most sensitive tool and the adjunct of FNA increase specificity
  - ✓Enhancements to EUS (elastography or CEUS) or ancillary methods (pancreatic juice biomarkers) needed to improve DD true early lesions from false positive lesions (age or environmental related)
  - ✓Technology for molecular imaging during EUS could improve in the future the EUS-FNA performance
- **Molecular Imaging**
  - ✓Allows visualization of biological processes at molecular level
  - ✓Early detection and localization
  - ✓Identification of metastatic disease in “surgical” candidates

Imaging - Future

- Imaging modalities that can define aspect of «normal» pancreas in older subjects with lifetime exposure to smoking, alcool, obesity, diabetes
- Identification of high-risk lesions to guide EUS-FNA
  - Noninvasive molecular imaging methods
  - New EUS technologies (CEUS, elastography, digital image analysis, enhanced resolution for B-Mode imaging)
  - New pancreatic juice biomarkers

Conclusions

The development of effective methods for early detection requires committed collaboration of numerous scientific and clinical disciplines.

Detection of PC prior to invasion is a primary goal

The long, presymptomatic dwell time at both precancerous and early T1 cancer stages may actually provide a relatively wide window of opportunity for screening detection.

The ideal markers would reflect the molecular alterations that accompany the evolution frompancreatic precancer to preinvasive cancer and that result from exfoliated cells or secreted markers

Imaging techniques (MRI + EUS) are also essential to confirm presence of early PC in subjects in whom biomarker studies predict their presence.