Optimal use of new drugs and new tools in pancreatic cancer and PNET
- Perioperative strategies in borderline/resectable patients
- Advanced stage
- PNET

JL Van Laethem, MD, PhD
## The clinical Pancreatic Cancer landscape

### Entity

<table>
<thead>
<tr>
<th>Entity</th>
<th>Incidence</th>
<th>Survival with optimal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>15-20%</td>
<td>22-24 mo</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>7%</td>
<td>dependent on resectability</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>15-20%</td>
<td>9-15 mo</td>
</tr>
<tr>
<td>Metastatic</td>
<td>60-70%</td>
<td>6-12 mo</td>
</tr>
</tbody>
</table>

**LOCOREGIONAL TO SYSTEMIC DISEASE**
High rate of R1 resection (incomplete resection)

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>New R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbeke et al.</td>
<td>57%</td>
<td>85%</td>
</tr>
<tr>
<td><em>BJS 2006</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esposito et al.</td>
<td>14%</td>
<td>76%</td>
</tr>
<tr>
<td><em>Ann Surg Oncol 2008</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

> 1-1.5 mm

- Cumulative Survival (proportion)
- **R1 = 1.5 mm**
- Med | Surv | P
| > 1.5 | 18.4 | .0005 clear v involved
| 0-1.5 | 22.4 | .6445 clear v clear by 1.5 mm
| 0     | 13.2 | .0413 clear by 1.5 mm v involved

- No. at risk
  - Clear > 1.5 mm: 169 72 30 15 9 3 1 1 1
  - Clear 0-1.5 mm: 64 30 6 1 1 1 1 1 1
  - Involved: 132 34 14 2 1 1 1 1 0
→ Surgery + adjuvant Chemo

- ¼ of pts died within first year
- ½ of pts recurred

Better patients selection is needed

*Oettle, H. et al. JAMA 2007, JAMA 2013*
Neoadjuvant/induction therapy

Neoadjuvant Therapy of Pancreatic Cancer: The Emerging Paradigm?

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aMedical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; bDepartment of Radiation Oncology, University of Michigan Health System, Ann Arbor, Michigan, USA; cDepartment of Surgery, Bay Area Medical Center, Aurora Health Care, Marinette, Wisconsin, USA; dDepartment of Pathology and Immunology, eDepartment of Surgery, and fDivision of Medical Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

LOSS OF CHANCE TO CURE...

or

BETTER SELECTION OF PATIENTS ??
AIMS OF PERI-OPERATIVE THERAPY

Increase resectability
- ↑ R0 resection rates, convert borderline to resectable, tumour shrinkage

Target occult disease
- Micrometastases may already exist in the majority of patients

Early intervention
- Avoid treatment delays (diagnosis → surgery → adjuvant therapy)

Unique window
- Identify patients with rapid progression who can be spared ineffective surgery
- Study the effects of interventional therapy on tumour biology and response

Puleo et al. WJG 2015;21:2281-93
Induction/neoadjuvant therapy: the keys for selection
Define properly resectable vs borderline resectable vs LAPC!

- Clinical selection/patients’ technical preparation!
- Radiological selection (vascular staging)
- Molecular selection (prognostic factors)
- Therapeutic selection (predictive factors for molecular driven therapy)

Collison, Nat Med 2011
Definition of resectability by expert multidisciplinary board

**Resectable**
- Normal tissue plane between tumour and vessels

**Borderline**
- VMS or portal vein*
- AMS < 180° (abutment)

**Non Resectable**
- AMS > 180°
- Abutment or encasement Coeliac trunk
- Thrombosis VMS or Portal vein

Non resectable R0

Tumor non resectable before treatment

Resectable ≠ R0 Resectable

*Chun et al. Ann Surg Oncol 2010
Rapport AFC 2010
TABLE 2. M. D. Anderson criteria for resectability of pancreatic cancer

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Resectable</th>
<th>Borderline resectable</th>
<th>Locally advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>No extension; normal fat plane between the tumor and the artery</td>
<td>Tumor abutment ≤ 180° (one half or less) of the circumference of the artery; periarterial stranding and tumor points of contact forming a convexity against the vessel improve chances of resection</td>
<td>Encased (&gt; 180°)</td>
</tr>
<tr>
<td>Celiac axis/hepatic artery</td>
<td>No extension</td>
<td>Short-segment encasement/abutment of the common hepatic artery (typically at the gastroduodenal origin); the surgeon should be prepared for vascular resection/interposition grafting</td>
<td>Encased and no technical option for reconstruction usually because of extension to the celiac axis/splenic/left gastric junction or the celiac origin</td>
</tr>
<tr>
<td>SMV/PV</td>
<td>Patent</td>
<td>Short-segment occlusion with suitable vessel above and below; segmental venous occlusion alone without SMA involvement is rare and should be apparent on CT images</td>
<td>Occluded and no technical option for reconstruction</td>
</tr>
</tbody>
</table>

SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein; CT, computed tomography.

Courtesy of Gauri Varadhachary, MDACC
Non-metastatic Pancreatic Cancer: Resectable, Borderline Resectable, and Locally Advanced-Definitions of Increasing Importance for the Optimal Delivery of Multimodality Therapy

Douglas B. Evans, MD, Ben George, MD, and Susan Tsai, MD, MHS

Pancreatic Cancer Program, Department of Surgery, The Medical College of Wisconsin, Milwaukee, WI. Pancreatic Cancer Program, Department of Medicine, The Medical College of Wisconsin, Milwaukee, WI

<table>
<thead>
<tr>
<th>Vascular structures which determine the stage of disease for localized pancreatic cancer</th>
<th>Borderline resectable</th>
<th>Locally advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>May be considered for resection after neoadjuvant therapy</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Tumor-artery anatomy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA (usually pertains to a tumor of the pancreatic head/uncinate)</td>
<td>≤180° (abutment)</td>
<td>&gt;180° encasement but ≤270°</td>
</tr>
<tr>
<td>Celiac artery (usually pertains to a tumor of the pancreatic body)</td>
<td>≤180° (abutment)</td>
<td>&gt;180° but does not extend to the aorta and amenable to celiac resection (with or without reconstruction)</td>
</tr>
<tr>
<td>Hepatic artery (usually pertains to a tumor of the pancreatic neck/head)</td>
<td>Short segment abutment/encasement without extension to celiac artery or HA bifurcation</td>
<td>&gt;180° encasement with extension to celiac artery and amenable to vascular reconstruction</td>
</tr>
<tr>
<td><strong>Tumor-vein anatomy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMV-PV</td>
<td>&gt;50% narrowing of SMV, PV, SMV/PV, or short segment occlusion, with a distal and proximal target for reconstruction</td>
<td>Occlusion without option for reconstruction; it would be very unusual to have a situation where cavernous transformation of the portal vein (which cannot be reconstructed—without a suitable distal [SMV] or proximal [PV] target for reconstruction) became operable</td>
</tr>
</tbody>
</table>

SMA superior mesenteric artery; SMV superior mesenteric vein; PV portal vein; SMV-PV superior mesenteric-portal vein; HA hepatic artery; NA not applicable
EBM in this setting is poor and based on outdated definition of resectability…

- **Resectable/borderline**
  - No phase III
  - One ongoing (GEMOX)
  - Phase II with a mixed of regimens (CT, chemoRT)
  - Borderline definition is evolving
  - ESPAC-5 ongoing: feasibility R phase II

- **LAPC**
  - 2 small phase III, conflicting for upfront chemoRT
  - Retrospective data positive for induction CT → chemoRT
  - Negative phase III (LAP07)
  - Most of the tumors were unresectable?
  - Need for specific studies

- **Neoadjuvant approach** → S or upfront S

- **Induction chemotherapy** → chemoRT?S?
POSSIBLE CONFOUNDING FACTORS LEADING TO HETEROGENEITY

- Type of (radio)chemotherapy regimen used
- Trials included in meta-analyses (prospective vs retrospective; phase II)
- Number/type of institutes included in individual trials
- Low number of patients in individual trials
- Lack of a control arm in most trials
- Resectability criteria used in participating centres
- Definition of borderline resectable pancreatic cancer used
- Definition of R0 resection
Is resection prognostic for survival?

**Initially resectable:**
- Drastic improvement in median OS for resected vs non-resected patients after neoadjuvant therapy
- BUT unclear if this represents selection of patients not progressing between diagnosis and restaging

**Initially unresectable:**
- Median survival more than doubled for resected vs non-resected patients after neoadjuvant therapy
- BUT as only one third of patients are converted to resectable, this needs to be balanced against toxicity of neoadjuvant therapy
- Do these converted patients represent a ‘borderline resectable’ subgroup?
TOXICITY CONSIDERATIONS

Grade 3/4 toxicity associated with neoadjuvant therapy

<table>
<thead>
<tr>
<th>Grade 3/4 toxicity, %</th>
<th>Andrulli et al 2012</th>
<th>Muru Assifi et al 2011</th>
<th>Gillen et al 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>31</td>
<td>39.9</td>
<td>29.4</td>
</tr>
<tr>
<td>Initially resectable</td>
<td>29</td>
<td>37.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Initially unresectable</td>
<td>33</td>
<td>46.2</td>
<td>31.1</td>
</tr>
</tbody>
</table>

Morbidity and mortality rates in patients undergoing resection after neoadjuvant therapy

<table>
<thead>
<tr>
<th>Gillen et al 2010</th>
<th>Morbidity, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>34.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Initially resectable</td>
<td>26.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Initially unresectable</td>
<td>39.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

- No difference in Grade 3/4 toxicity between patient groups
- Grade 3/4 toxicity higher with neoadjuvant vs adjuvant therapy (8.4%-22%)\(^1,2\)
- Higher morbidity and mortality rates among resected patients initially considered unresectable
  - Possibly reflects a more extensive/aggressive surgical approach rather than any effect of neoadjuvant therapy\(^3\)

The options do exist but controlled data are lacking

- Chemoradiation (with chemo induction?)
- Gemcitabine-based chemo? Platinum? Cape?
- FOLFIRINOX
- Gemcitabine + Abraxane
- … How to choose?
Role of chemoradiation in pancreatic cancer

- Adjuvant: not a standard – may be optionnal

- Neoadjuvant: not a standard but more and more used in borderline tumors (after induction CT); with capecitabine as radiosensitizer (Mukherjee-Lancet Oncol 2014)

- Unresectable LAPC: no benefit proven – optional in a subpopulation of selected pts after induction CT? (LAP 07 study, JAMA, in press, Hammel et al)
FOLFIRINOX > GEM in mPDAC
…and in LAPC?

Stratified Log-rank test, \( p<0.0001 \)

HR=0.57 : 95%CI [0.45-0.73]

RR= 31% vs 9%!

Number at risk
Gemcitabine  171 134  89  48  28  14  7  6  3  3  2  2  2
Folfirinox  171 146 116  81  62  34  20 13  9  5  3  2  2

Conroy, NEJM 2011
NEOADJUVANT FOLFIRINOX (± CRT) CAN LEAD TO CURATIVE INTENT SURGERY

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Résection</th>
<th>R0 (ITT)</th>
<th>ypNO</th>
<th>ypRC</th>
<th>ypRC cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paniccia A et al. 2014 (+ RCT 44%)</td>
<td>20 Brl</td>
<td>85 %</td>
<td>100 % (85%)</td>
<td>41 %</td>
<td>1 cas</td>
<td></td>
</tr>
<tr>
<td>Ferrone CR et al. 2015 (+ RCT 25%)</td>
<td>25 LA, 15 Brl</td>
<td>75 % (Brl : pas de détails)</td>
<td>92 % (69%)</td>
<td>65 % (si résécables d'emblée, 21 %) p &lt; 0,001</td>
<td>2 cas</td>
<td></td>
</tr>
<tr>
<td>Blazer M et al. 2014 (+ RCT 44-60%)</td>
<td>25 LA, 18 Brl</td>
<td>64 % 44 %</td>
<td>91 % (58%) 82 % (36%)</td>
<td>ns</td>
<td>2 cas</td>
<td></td>
</tr>
<tr>
<td>Christians KC et al. 2014 (+ 100% RCT)</td>
<td>18 Brl</td>
<td>66%</td>
<td>100 % (66%)</td>
<td>83 %</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pietrasz D et al. 2014 (patients tous opérés; 66% RCT)</td>
<td>42 Brl + 4 résect 33 LA</td>
<td>92 % 64 %</td>
<td>83 % (76%) 85 % (54%)</td>
<td>75 % 67 %</td>
<td>12 cas (15 %)</td>
<td></td>
</tr>
<tr>
<td>Marthey L et al. 2014 (+ RCT)</td>
<td>77 LA</td>
<td>36 %</td>
<td>89 % (32%)</td>
<td>75 %</td>
<td>4 cas (14 %)</td>
<td></td>
</tr>
</tbody>
</table>

LA : locally advanced  
Brl : borderline resectable
– Therapeutic sequence feasible
– Large and comparative prospective trial needed

M.H Katz et al., ASCO 2015, A 4008
DOWNSTAGING/DOWNSIZING OF BORDERLINE/UNRESECTABLE TUMOURS
Locally Advanced Pancreatic Adenocarcinoma: Reassessment of Response with CT after Neoadjuvant Chemotherapy and Radiation Therapy

47 pts evaluated:
33 with R0 resection
14 with R1 or no resection

Partial regression with SMV/PV: PPV 100% for R0
Partial regression with any vascular axis: PPV 91%

Cassinoto, Radiology 2014
Downstaging/downsizing is achievable
→ surgical exploration after chemoradiation !!

After RCT

Persistant arterial encasement

Coeliac trunk

Tumor

ypT0N0R0
NAB-PACLITAXEL (Abraxane)

- **Mechanism of action**

Albumin binds to caveolin-1 receptors and causes the formation of caveolae, to transport albumin across the endothelial membrane.

Transcytosis is the transport of albumin across the endothelial barrier from within the blood vessel to the tumor's interstitium.

SPARC is then secreted by the tumor to attract and retain albumin-bound nutrients within the tumor cell.
Etude MPACT : nab-P + Gemcitabine vs Gemcitabine

Overall Survival

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI)</th>
<th>75% Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>333/431 (77)</td>
<td>8,5 (7,89 – 9,53)</td>
<td>14,8</td>
</tr>
<tr>
<td>359/430 (83)</td>
<td>6,7 (6,01 – 7,23)</td>
<td>11,4</td>
</tr>
</tbody>
</table>

HR : 0,72 (IC 95 : 0,617-0,835)  
P = 0,000015

Secondary Endpoint | Nab-P + Gem | Gem | HR      | p          |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>5,5 months</td>
<td>3,7 months</td>
<td>0,69</td>
<td>0,000024</td>
</tr>
<tr>
<td>Response rate</td>
<td>23%</td>
<td>7%</td>
<td>p = 1,1 x 10^{-10}</td>
<td></td>
</tr>
<tr>
<td>Tumoral control rate</td>
<td>48%</td>
<td>33%</td>
<td>p = 7,2 x 10^{-6}</td>
<td></td>
</tr>
</tbody>
</table>

Von Hoff. et al., NEJM 2013
GEM/Nab-P in neoadjuvant setting

Nab-paclitaxel Effects in Human PDA Stroma

A

B

Untreated
CT-XRT
Nab-paclitaxel + Gemcitabine

C

D

CAF In Human Sample

Alvarez et al, BJC 2013
Study of 16 patients with resectable pancreatic cancer

Treatment with 2 cycles of nab-paclitaxel + gemcitabine before surgery

12 patients underwent surgery
  - 11 had an R0 resection
  - 1 had an R1 resection

10/12 were PDA according to final pathological analysis. Of these:
  - 1 had a complete pathological response (GR T0)
  - 6 had a major pathological response (GR T1)
  - 1 had a partial response (GR T2)
  - 2 had no response (GR T3)

Long-term outcomes:
  - PFS: 22.2 mo; OS: 30.6 mo (good pathological response)
  - PFS: 10.1 mo; OS: 16.9 mo (poor pathological response)
S1505: NAB-PACLITAXEL + GEMCITABINE VS FOLFIRINOX IN PATIENTS WITH RESECTABLE PANCREATIC CANCER

**Key eligibility criteria**
- ECOG PS 0-1
- Histologically proven disease
- Resectable primary tumour on CE CT/MRI (central radiology review)
- No involvement of the celiac artery, common hepatic artery, or superior mesenteric artery
- No involvement (or <180° interface between tumour and vessel wall) of the portal vein or superior mesenteric vein, and patent portal vein/splenic vein confluence
- No evidence of metastatic disease
- Adequate bone marrow, hepatic and renal function
- No prior therapy for pancreatic cancer

**N=112**

- **Primary Objective:** Two-year overall survival
- **Secondary Objectives:**
  - Toxicities of each regimen
  - Proportion of patients going to surgery
  - Proportion of patients achieving R0 resection
  - Pathologic response rates
  - Patterns of recurrence (locoregional, distant)
  - Disease-free survival from resection
  - To evaluate liquid biomarkers (correlative science)

**Randomized phase II “pick the winner” design**
- Minimum two-year OS: 40%; assuming a 58% alternative hypothesis, 88% power and a 1-sided significance of 0.05
- If minimum activity is established, 90% probability of selecting the better regimen with an OS hazard ratio of at least 1.4

*Patients not resectable at restaging are withdrawn from study
†Adjuvant radiation per MD discretion at the end of all chemotherapy
Randomized Phase II trial of FOLFIRINOX alone, FOLFIRINOX followed by conventional chemo-radiotherapy or FOLFIRINOX followed by SBRT in patients with borderline resectable pancreatic cancer
- Cancer du pancréas borderline (relecture centralisée des scanners avant inclusion)
- Inclusion avant chimio néoadjuvante
- Restaging après 4 cures
- Randomisation si non progression et patient opérable
- Stratification : atteinte veineuse vs atteinte artérielle, centre
Tumor response evaluation is crucial → early evaluation → downstaging (+vascular!)

- Pathology
  - Evans grades
  - CAP « college of american pathologists » grades

- MDCT, MRI → DCE/DW-MRI
- PET-CT (tracers?)

- Circulating markers
  - CA 19-9
  - Circulating tumoral cells
  - Circulating tumoral DNA/liquid biopies

- Correlation between imaging, blood and pathology!
Histologic Grading of the Extent of Residual Carcinoma Following Neoadjuvant Chemoradiation in Pancreatic Ductal Adenocarcinoma

A Predictor for Patient Outcome

Dayali Chatterjee, MD; Matthew H. Katz, MD; Asif Rashid, MD, PhD; Gauri R. Varadhachary, MD; Robert A. Wolff, MD; Hua Wang, MD, PhD; Jeffrey E. Lee, MD; Peter W. T. Pisters, MD; Jean-Nicolas Vauthey, MD; Christopher Crane, MD; Henry F. Gomez, MD; James L. Abbruzzese, MD; Jason B. Fleming, MD; and Huamin Wang, MD, PhD

Cancer 2012
Non-metastatic Pancreatic Cancer: Resectable, Borderline Resectable, and Locally Advanced-Definitions of Increasing Importance for the Optimal Delivery of Multimodality Therapy

Douglas B. Evans, MD¹, Ben George, MD², and Susan Tsai, MD, MHS¹

**TABLE 4** Proposed classification for response to neoadjuvant therapy

<table>
<thead>
<tr>
<th>Method of assessment</th>
<th>Responder</th>
<th>Stable disease</th>
<th>Nonresponder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient performance status (to include pain assessment)</td>
<td>Improved</td>
<td>Not worse</td>
<td>Worse</td>
</tr>
<tr>
<td>Imaging of the primary tumor (CT/MRI/PET, etc.)</td>
<td>Improved or no progression</td>
<td>No progression</td>
<td>Local or distant progression on cross-sectional imaging</td>
</tr>
<tr>
<td>Biomarker Profile (including CA19-9* and other emerging biomarkers)</td>
<td>Suggests treatment response (for example, a normalization of CA19-9, other biomarkers being developed)</td>
<td>Not worse</td>
<td>Suggests progressive disease</td>
</tr>
<tr>
<td>How to use the above information</td>
<td>All three required to be a “Responder”</td>
<td>All three required to be considered as having “Stable Disease”</td>
<td>Any of the three would define a “Nonresponder”**</td>
</tr>
</tbody>
</table>

* CA19-9 must be measured when the serum bilirubin has normalized and such biomarkers should be assessed before treatment is initiated and at each re-staging evaluation

** Assuming clinical symptoms leading to a decline in performance status are not medically correctable
MODULATING PDAC COMPONENTS FOR IMPROVING NEOADJUVANT STRATEGIES
Pancreatic cancer is hypoperfused

Von Hoff, Korn and Mousses  *Cancer Cell*, 2009
Targeting tumor stroma: PEGPH20 :# HA

- High tumor interstitial pressure
- Compression of tumor blood vessels
- Hypoxia
- Protumorigenic growth factors and cytokines accumulate in the HA-rich tumor ECM
- Limited access of systemic therapies

Tumor
- ↓ Tumor interstitial pressure (16)
- ↑ Vascular/tumor perfusion (16, 40)
- ↓ Hypoxia (17)
- ↑ Access of systemic therapies to the tumor accompanied by increased efficacy (16, 40, 41)

Tumor Extracellular Matrix
- Depletion of HA, remodeling of the TEM (16, 17, 40, 41)
- HMW HA → LMW HA; HA fragments released into the circulation as a result of systemic/tumor HA depletion (42), leading to decreased tumor IP
- Possible release of protumorigenic cytokines and growth factors

Malignant and Tumor Stromal Cells
- ↓ Activation of CD44/RHAMM signaling and ↓ tumor growth (43)
- ↓ EMT/metastasis (17)
- ↓ Possible that HA depletion may decrease available precursors for glycolysis thereby contributing to growth inhibition by PEGPH20 (44)
SHH depletion changes the histological structure of PDAC
Neoadjuvant GVAX Results in Immune Cell Infiltration and Upregulation of PD-1 & PD-L1 in Clinical Whipple Specimens Two Weeks after Treatment

A. Intratumoral lymphoid aggregates
B. Peritumoral lymphoid aggregates
C. Immune cell markers
D. PD-L1 upregulation on tumor/monocytes (left); PD-1 upregulation on T cells (right)

DCE-MRI:
Increased Tumor Perfusion Post-PEGPH20 Treatment

<table>
<thead>
<tr>
<th></th>
<th>Mean $K_{trans}$</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>End of Cycle 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>0.057</td>
<td>0.147</td>
<td>0.242</td>
<td>0.212</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.011</td>
<td>0.091</td>
<td>0.018</td>
<td>0.034</td>
<td></td>
</tr>
</tbody>
</table>

$K_{trans}$ (min$^{-1}$)
New challenges in perioperative management of pancreatic cancer

Francesco Puleo, Raphaël Maréchal, Pieter Demetter, Maria-Antonietta Bali, Annabelle Calomme, Jean Closset, Jean-Baptiste Bachet, Jacques Deviere, Jean-Luc Van Laethem
Early and standardized evaluation of tumor response in neoadjuvant strategy based on Gem-Nab-P therapy

Screening period:
EUS-FNA for histology
Evaluation: Clinic
Biologic
Radiologic

Neoadjuvant CT for 4-12 weeks
Surgery
Adjuvant CT for 20 weeks
Post-operative time: 6 - 8 weeks

Post-operative time: 6 - 8 weeks

J0
Fonctionnal Imaging (diffusion/perfusion MRI)

hENT1
dCK
SPARC
CXCR4
CTC / circulating DNA

hENT1
dCK
SPARC
CXCR4
CTC / circulating DNA

hENT1
dCK
SPARC
CXCR4
CTC / circulating DNA

NEOPAX study, Van Laethem et al

Iwanicki-Caron et al. Am J Gastroenterol 2012
ADC HISTOGRAM ANALYSIS : RESPONDERS

T2: early response

Shift towards right = Responder

Diameter Δ 28% : R
Volume Δ 54% : R
Non Responders

Shift towards left = Non Responder
Gemcitabin + nabpaclitaxel

Downstaging can be predicted!
Perioperative (short) window of opportunity

Tissue

NEOADJUVANT THERAPY

PAC

Tissue

ADJUVANT THERAPY (adapted)

Prognostic factors

Predictive tools

- early molecular imaging
- biomarkers
- dynamic response
- path. Response
- molecular response
- avatar mouse model
- microimaging

Adaptative intensified / personnalised/innovative therapy
Preoperative Assessment of Pancreatic Cancer with FDG PET/MR Imaging versus FDG PET/CT Plus Contrast-enhanced Multidetector CT: A Prospective Preliminary Study

### Table 2

<table>
<thead>
<tr>
<th>Reviewer and Modality</th>
<th>$A_\tau^*$</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/MR imaging</td>
<td>0.891 (0.671, 0.984)</td>
<td>62 (5/8)</td>
<td>100 (12/12)</td>
<td>85 (17/20)</td>
</tr>
<tr>
<td>PET/CT + MDCT</td>
<td>0.776 (0.537, 0.929)</td>
<td>62 (5/8)</td>
<td>83 (10/12)</td>
<td>75 (15/20)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.109</td>
<td>NA</td>
<td>.500</td>
<td>.500</td>
</tr>
<tr>
<td>Reviewer 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/MR imaging</td>
<td>0.859 (0.632, 0.972)</td>
<td>87 (7/8)</td>
<td>75 (9/12)</td>
<td>80 (16/20)</td>
</tr>
<tr>
<td>PET/CT + MDCT</td>
<td>0.797 (0.560, 0.941)</td>
<td>75 (6/8)</td>
<td>58 (7/12)</td>
<td>65 (13/20)</td>
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<tr>
<td>$P$ value</td>
<td>.561</td>
<td>&gt;.999</td>
<td>.625</td>
<td>.375</td>
</tr>
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</table>

### Table 3

<table>
<thead>
<tr>
<th>Reviewer and Modality</th>
<th>N Staging (%)</th>
<th>M Staging (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reviewer 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/MR imaging</td>
<td>40.0 (4/10)</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>PET/CT + MDCT</td>
<td>10.0 (1/10)</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.250</td>
<td>NA</td>
</tr>
<tr>
<td>Reviewer 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/MR imaging</td>
<td>40.0 (4/10)</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>PET/CT + MDCT</td>
<td>10.0 (1/10)</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.250</td>
<td>NA</td>
</tr>
</tbody>
</table>
Preoperative Assessment of Pancreatic Cancer with FDG PET/MR Imaging versus FDG PET/CT Plus Contrast-enhanced Multidetector CT: A Prospective Preliminary Study

Intratumoral heterogeneity of $^{18}$F-FDG uptake predicts survival in patients with pancreatic ductal adenocarcinoma

Seung Hyup Hyun¹, Ho Seong Kim³, Seong Ho Choi², Dong Wook Choi², Jong Kyun Lee³, Kwang Hyuck Lee³, Joon Oh Park³, Kyung-Han Lee¹, Byung-Tae Kim¹, Joon Young Choi¹

Positron emission tomography response evaluation from a randomized phase III trial of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas

Intratumoral heterogeneity of $^{18}$F-FDG uptake predicts survival in patients with pancreatic ductal adenocarcinoma

Seung Hyup Hyun$^1$, Ho Seong Kim$^1$, Seong Ho Choi$^2$, Dong Wook Choi$^3$, Jong Kyun Lee$^3$, Kwang Hyuck Lee$^3$, Joon Oh Park$^3$, Kyung-Han Lee$^1$, Byung-Tae Kim$^1$, Joon Young Choi$^1$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (1-year increase)</td>
<td>1.01</td>
<td>0.987–1.023</td>
</tr>
<tr>
<td>Sex, men vs. women</td>
<td>1.28</td>
<td>0.878–1.889</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II B vs. IIA</td>
<td>1.88</td>
<td>1.04–3.40</td>
</tr>
<tr>
<td>III-IV vs. IIA</td>
<td>5.17</td>
<td>2.84–9.41</td>
</tr>
<tr>
<td>Tumour size (cm)$^a$</td>
<td>1.28</td>
<td>1.13–1.44</td>
</tr>
<tr>
<td>Serum CA19-9 (U/ml, log$_2$ scale)$^a$</td>
<td>1.13</td>
<td>1.07–1.19</td>
</tr>
<tr>
<td>Entropy$^a$</td>
<td>12.74</td>
<td>3.42–47.42</td>
</tr>
<tr>
<td>TLG (log$_2$ scale)$^a$</td>
<td>1.28</td>
<td>1.14–1.44</td>
</tr>
</tbody>
</table>

![Images of PET scans](a.png)  
![Images of PET scans](b.png)  
![Images of PET scans](c.png)  
![Images of PET scans](d.png)
Positron emission tomography response evaluation from a randomized phase III trial of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas


![Graph showing survival rates](image)

- **nab-P + Gem, MR**
- **Gem, MR**
- **nab-P + Gem, NMR**
- **Gem, NMR**

Log-rank *P* < 0.001

 Patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-P + Gem, MR</td>
<td>39</td>
<td>93</td>
</tr>
<tr>
<td>Gem, MR</td>
<td>39</td>
<td>67</td>
</tr>
<tr>
<td>nab-P + Gem, NMR</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Gem, NMR</td>
<td>39</td>
<td>60</td>
</tr>
</tbody>
</table>

![Survival curves](image)
INTEGRATED RESEARCH IN ONCOLOGY

- Baseline state
- Prognosis
- Drug development
- Prediction of response (early)
- Resistance
- Therapy
PUTATIVE BIOMARKERS OF PLATINUM AND PARP INHIBITORS RESPONSIVENESS

Druggable oncogenes:

ERBB2, MET, FGFR1, CDK6, PIK3R3, PIK3CA3: low prevalence

BRCA1, BRCA2, PALB2: genomic markers of defective DNA maintenance

Waddel, Nature 2015
Conclusions of periop strategy

- Define accurately the (non)resectability
- Plan the strategy
- Induction with active chemotherapy (RR=30-40%) then/or Chemoradiation (RR=40%); R0 resection=>? 40-80%
- Evaluate early the response by Dyn Imaging
- Evaluate response by « score » (clinical, CA 19.9, imaging?)
- Evaluate path response as endpoint
- Go to molecular-driven therapy asap
- Role of antistromal therapy?
PROPOSED PERI-OPERATIVE STRATEGIES FOR CLINICAL TRIALS IN DIFFERENT PATIENT SUBGROUPS

1. **Resectable**
   - **Neoadjuvant CT/CRT**
     - Disease progression
     - Surgery for RO resection

2. **Borderline resectable**
   - **Neoadjuvant CT/CRT**
     - Surgical exploration
     - Resectability?
     - Continue CT or 2nd line CT

3. **Locally advanced**
   - **Induction CT/CRT**
     - Disease progression
     - Post-treatment tissue and blood samples acquisition for translational studies

---

1. Patients’ selection based on predictive and prognostic biomarker
2. Functional imaging assessment

---

Puleo et al. WJG 2015;21:2281-93
Neoadjuvant therapy vs induction therapy

Unresectable mCRC
Induction therapy with FOLFOXIRI+ beva
or cetuximab → resectability?

Unresectable LAPC
Induction therapy with FOLFIRINOX
Or Gem/Nab-P then chemoradiation
→ pCR? Resectability?
Table 4: Authors’ Recommended Indications for the Use of GaTate PET/CT in Gastrointestinal and Pancreatic NETs

- Exclude more advanced disease prior to surgical intervention
- Localize primary tumor in patients with biochemical suspicion of NET
- Identify primary tumor in patients with known metastatic NET
- Confirm diagnosis of NET in patients with anatomic lesions that are suspicious for NET
- Identify patients who are likely to benefit from octreotide hormonal therapy or PRRT with $^{177}$Lu- or $^{90}$Y-DOTATATE

Note.—PRRT = peptide receptor radionuclide therapy.
SSTR PET/CT +/- FDG PET/CT

Table 5: FDG PET/CT and SSTR PET/CT in the Spectrum of NET Grading

<table>
<thead>
<tr>
<th>ENETS Grade</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ki-67 (%)</td>
<td>≤2</td>
<td>3–20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>SSTR PET/CT</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>FDG PET/CT</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

Note. — Plus (+) and minus (−) signs indicate intensity of uptake.

Table 6: Authors’ Recommended Indications for the Selective Use of FDG PET/CT with SSTR PET/CT

- Ki-67 > 5%
- Worrisome lesions with little or no activity on the CT component of SSTR PET/CT
- Clinical or radiologic evidence of disease progression within <6 months despite Ki-67 <5%
**18F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors**

Tina Binderup¹,², Ulrich Knigge²,³, Annika Loft¹, Birgitte Federspiel⁴, and Andreas Kjaer¹,²

---

**Table 2. Univariate analysis of OS and progression free survival, SUVmax**

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUVmax &gt; 7</td>
<td>4.3</td>
<td>1.3-14.3</td>
</tr>
<tr>
<td>SUVmax &gt; 8</td>
<td>6.1</td>
<td>1.8-20.2</td>
</tr>
<tr>
<td>SUVmax &gt; 10</td>
<td>6.5</td>
<td>1.7-17.4</td>
</tr>
</tbody>
</table>

**PFS**

| SUVmax > 4       | 5.4  | <0.001  |
| SUVmax > 5       | 3.7  | 1.7-6.4  |
| SUVmax > 6       | 2.6  | 1.2-5.0  |

---

Multivariate analysis for PFS:

SUV max > 3 = best PFS than CgA (460 pmole/l), WHO and Ki 67 index
Pancreatic neuroendocrine tumors: correlation between histogram analysis of apparent diffusion coefficient maps and tumor grade

Jose Antonio Sousa Pereira, Elsa Rosado, Maria Bali, Thierry Metens, Shih-Li Chao

Table 3. Significant differences in ANOVA and post hoc comparisons (p values)

<table>
<thead>
<tr>
<th></th>
<th>mADC</th>
<th>ADC5</th>
<th>ADC10</th>
<th>ADC25</th>
<th>ADC50</th>
<th>ADC75</th>
<th>ADC90</th>
<th>ADC95</th>
<th>Skew</th>
<th>Kurtosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlvSG2</td>
<td>0.049</td>
<td>0.208</td>
<td>0.185</td>
<td>0.104</td>
<td>0.069</td>
<td>0.034</td>
<td>0.038</td>
<td>0.029</td>
<td>0.941</td>
<td>0.488</td>
</tr>
<tr>
<td>GlvSG3</td>
<td>0.004</td>
<td>0.019</td>
<td>0.017</td>
<td>0.007</td>
<td>0.008</td>
<td>0.008</td>
<td>0.018</td>
<td>0.041</td>
<td>0.036</td>
<td>0.010</td>
</tr>
<tr>
<td>G3vSG2</td>
<td>0.469</td>
<td>0.460</td>
<td>0.467</td>
<td>0.419</td>
<td>0.519</td>
<td>0.686</td>
<td>0.838</td>
<td>0.990</td>
<td>0.056</td>
<td>0.168</td>
</tr>
</tbody>
</table>

The bold numbers represent the statistically significant p-values < 0.05
KI 67 GRADING BY EUS-FNA (SUGIMOTO, WJG, 2015)

Table 1 Comparison of specimens obtained by endoscopic ultrasonography-guided fine needle aspiration and surgery

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Size (mm)</th>
<th>Location of tumor</th>
<th>No. of needle passes</th>
<th>Needle (G)</th>
<th>EUS-FNA specimen</th>
<th>Surgery specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ki-67 index</td>
<td>Ki-67 index (*/10HPF)</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>71</td>
<td>Tail</td>
<td>5</td>
<td>19</td>
<td>&lt;2.0%</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>79</td>
<td>Head</td>
<td>4</td>
<td>22</td>
<td>0.8%</td>
<td>&lt;2.0%</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>44</td>
<td>Head</td>
<td>2</td>
<td>22</td>
<td>1.8%</td>
<td>0.1%</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>51</td>
<td>Body</td>
<td>3</td>
<td>22</td>
<td>0.4%</td>
<td>1.97%</td>
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<td>5</td>
<td>M</td>
<td>75</td>
<td>Tail</td>
<td>3</td>
<td>22</td>
<td>7.0%</td>
<td>7.13%</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>Body</td>
<td>3</td>
<td>22, 25</td>
<td>4.54%</td>
<td>&lt;20%</td>
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<tr>
<td>7</td>
<td>F</td>
<td>46</td>
<td>Head</td>
<td>3</td>
<td>22</td>
<td>&lt;2.0%</td>
<td>7.5%</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>55</td>
<td>Head</td>
<td>2</td>
<td>25</td>
<td>1.8%</td>
<td>&lt;1.0%</td>
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</table>