Pathology at Digital Age: Beyond Microscopy

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Centre de Recherche sur l'Inflammation PARIS MONTMARTRE

unity Addressing Unmet Needs through Innovation in hepatology and gastroenterology

Digital Pathology

- Conversion of stained tissue section into a digital image through a scanner

Glass slide

Virtual slide
(Whole slide imaging)

Digital Pathology

The future Gold Standard of Pathology

Many Advantages

- Technical aspects
  - No fading, no breakage
  - Avoid cumbersome logistics of glass slides
  - Improve tracability & workflow

- Practical issues
  - Virtual slides instantaneously accessed and retrieved
  - **A way to standardize histological diagnosis**
  - **Telepathology (off-site diagnosis & 2nd opinion)**
  - **Perform image analysis**
  - Provide Image banking, Incorporate into Patient databases & Facilitate MDT meetings

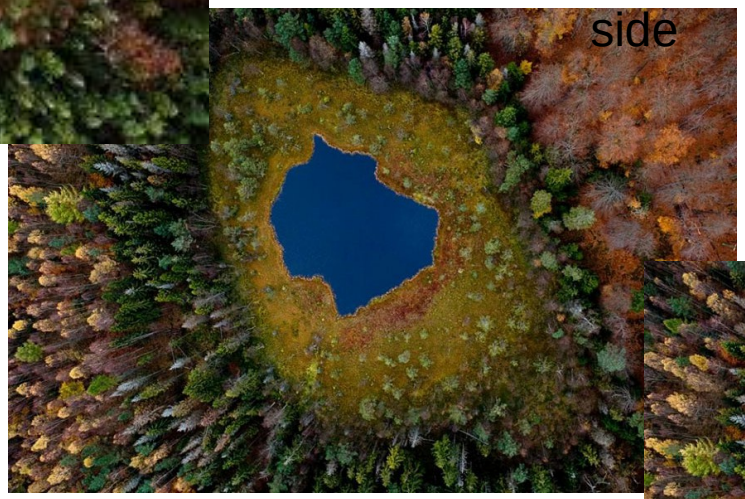
- Powerful teaching tool

Cheng CL et al J Clin Pathol 2013

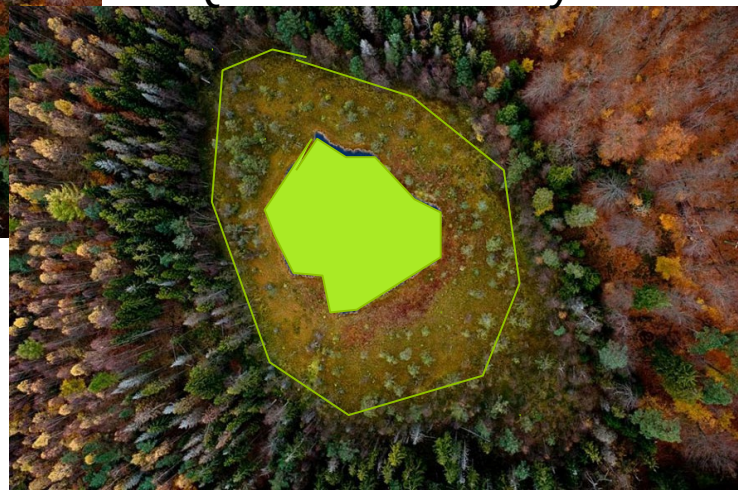
In Practice

1. A “bird’s-eye” view

2. Comparison of ≠ slides side by side



3. Quantitative analysis




POOR
FAIR
GOOD
GREAT

Concordance between digital pathology and light microscopy in general surgical pathology: a pilot study of 100 cases

- Pilot study including 100 biopsies / minor resections with various degrees of complexity
- Cases diagnosed 1 year before by light microscopy and reassessed by the same pathologist (blinded to the original diagnosis)

Table 1 Illustrates the range of cases selected for this study

Level	Skin	Gynaecology	Head and Neck	Gastrointestinal
1	Sebaceous cyst (2) Pilar cyst Fibroepithelial polyp (2)	Normal fallopian tube (5)	Normal oral cavity Oral fibroepithelial polyp (2) Allergic nasal polyp (2)	Normal appendix Acute appendicitis Chronic cholecystitis (3)
2	Intradermal naevus (2) Molluscum contagiosum Dermatofibroma Seborrheic keratosis	Endocervical polyp (2) Endometrial polyp (3)	Radicular cyst (2) Vocal cord polyp (2) Chronic sialadenitis	Normal rectum Normal colon (2) Normal duodenum (2)
3	Schwannoma Neurofibroma (2) Glomus tumour (2)	Proliferative endometrium (2) Secretory endometrium Menstrual endometrium Lichen sclerosus	Normal tonsil (2) Inverted nasal papilloma Warthin's tumour Pleomorphic adenoma	Reactive gastritis Reactive gastritis with intestinal metaplasia Colon—hyperplastic polyp Colon—adenoma (2)
4	Bowen's disease (3) Blue naevus (2)	CIN I (2) CIN II CIN III (2)	Granular cell tumour (2) Giant cell granuloma (3)	Barrett's oesophagus (3) Inflammatory bowel disease (2)
5	Basal cell carcinoma Squamous cell carcinoma Lentigo maligna Melanoma Spitz naevus	Endometrioid adenocarcinoma (2) Squamous cell carcinoma (3)	Ameloblastoma Vocal cord dysplasia (2) Tongue—dysplasia Tonsil—squamous cell carcinoma	Rectum—adenocarcinoma (2) Stomach—adenocarcinoma Candida oesophagitis Colon—regenerative atypia

Concordance in 95/100 cases
Slight discordance (5 cases) with no clinical consequence

Houghton JP J Clin Pathol 2014

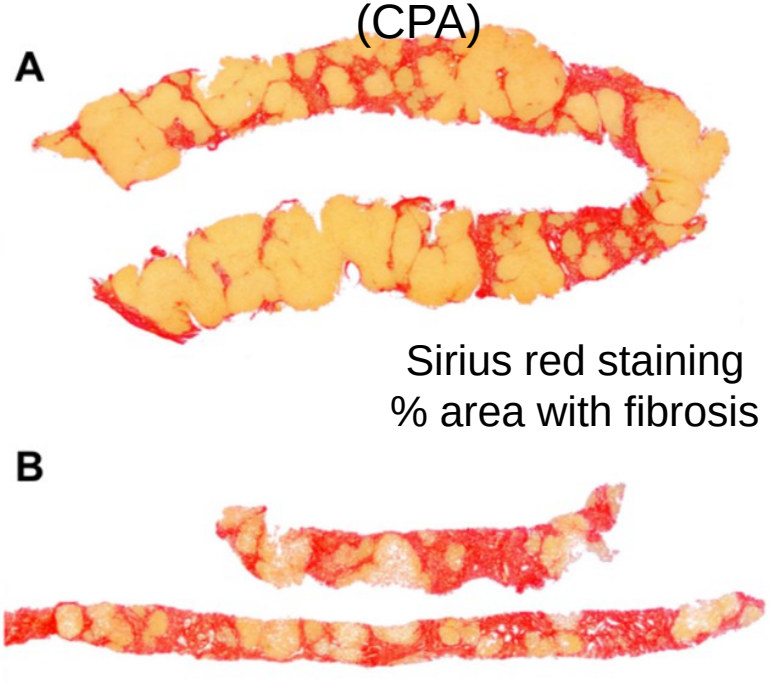
Image Analysis

A quantitative objective evaluation with a Wide Range of Applications

Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis

- 64 patients with cirrhosis

Fibrosis assessed by ½ quantitative scoring systems and quantitative analysis (CPA)



Sirius red staining
% area with fibrosis

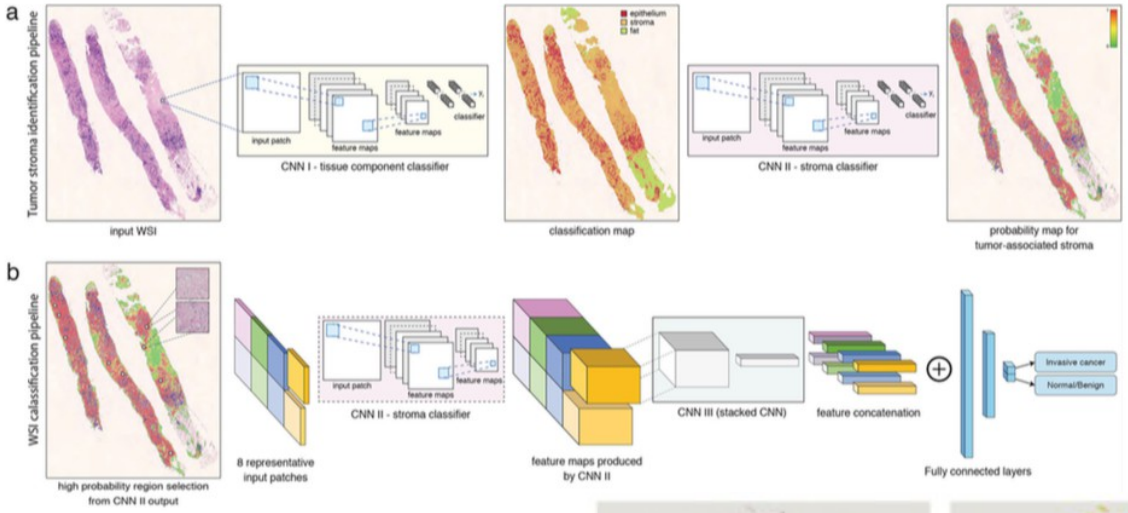
Conclusions: Cirrhosis can be accurately sub-classified using quantification of fibrosis with CPA, and furthermore CPA is the only independent predictor of clinical decompensation amongst all other histological sub-classification systems described to date.

Tsochatzis E J Hepatol 2014

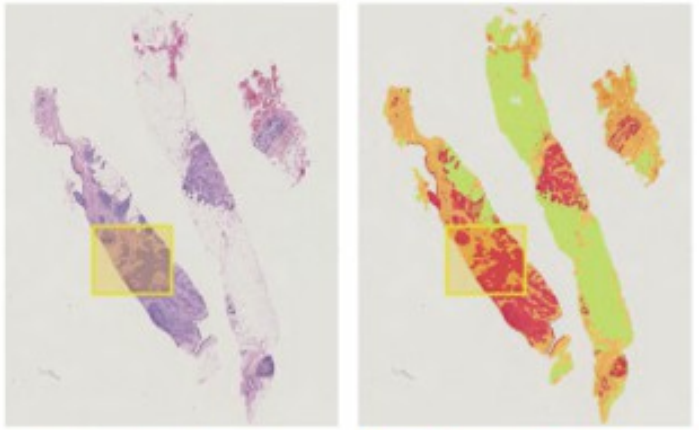
Using deep convolutional neural networks to identify and classify tumor-associated stroma in diagnostic breast biopsies

Image Analysis and Artificial Intelligence

- Develop computerized algorithms and generate deep-learning algorithms (conventional neural networks)



- Classification and tumor stroma characterization in breast biopsies [Epithelium (red), stroma (orange) & fat (green)]

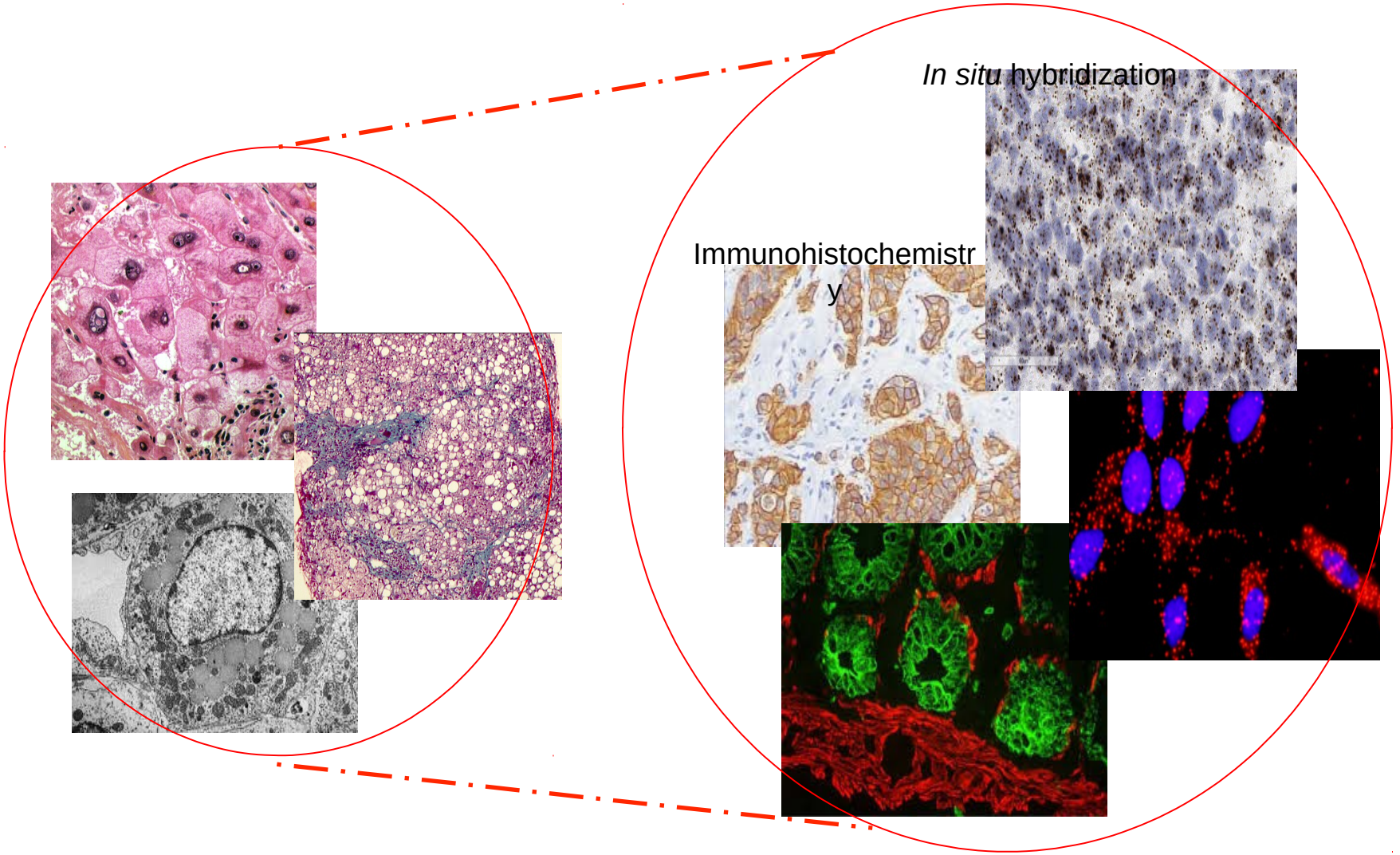


Benjordi BE Modern Pathol 2018

Beyond Microscopy

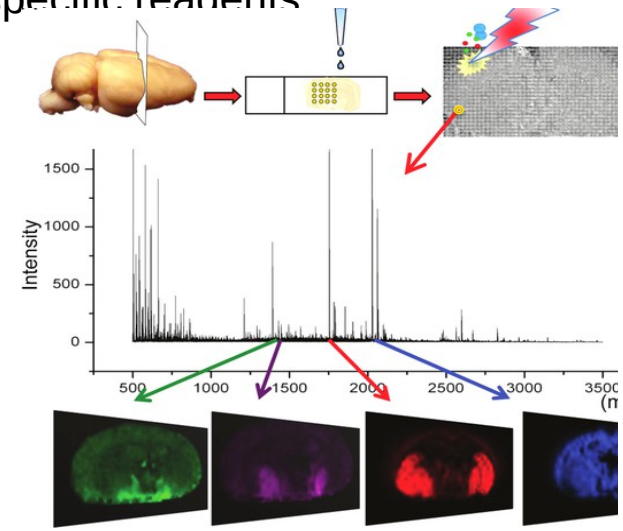
New Molecular imaging approaches

From Conventional Histology to Molecular Imaging



MALDI Imaging

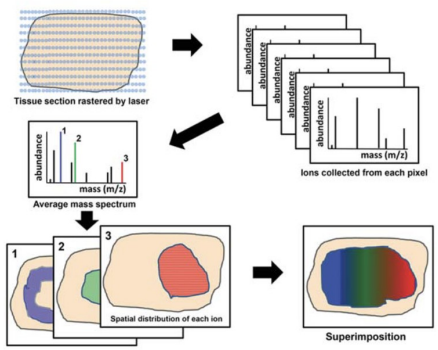
- Combines a proteomic approach with morphological analysis
  - Spatial distribution of biomolecules in intact tissue samples
  - **Hundreds** of proteolytic ions detected **simultaneously** on a **single** tissue section **without** the need for target-specific reagents



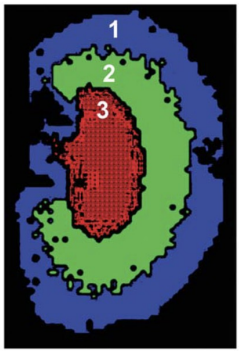
Caprioli RM Anal Chem 1997

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Painting the Liver With Lasers: The Future of Liver Histology?



PREPARATION SCHEME



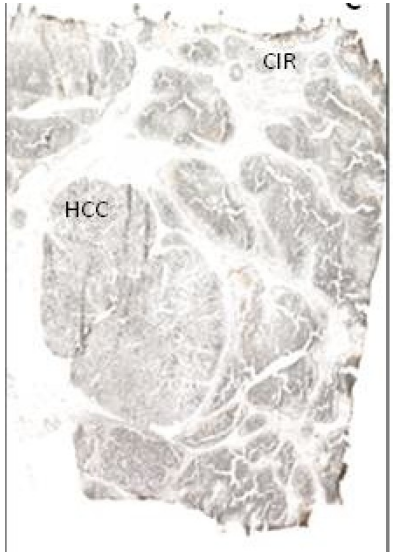
MALDI TISSUE IMAGE

Editorial Beyoglu D & Idle JR, 2014

MALDI : *The Principle*

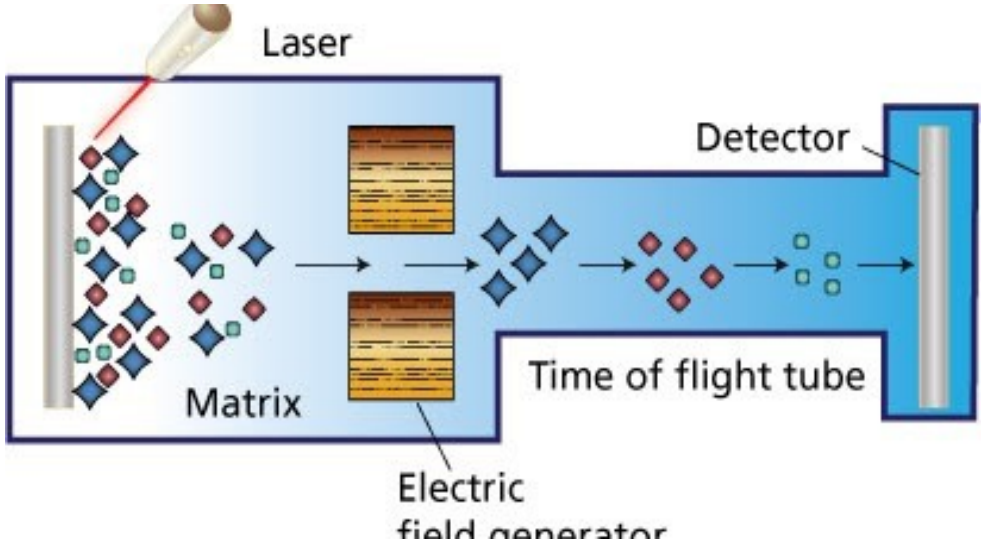
- **Matrix Associated Laser Desorption/Ionization - Time of Flight (MALDI-TOF)**

Molecules from the tissue section are ionized and subsequently measured by a detector according to their respective TOF (related to their m/z value)



Tissue section

Mass spectrometer

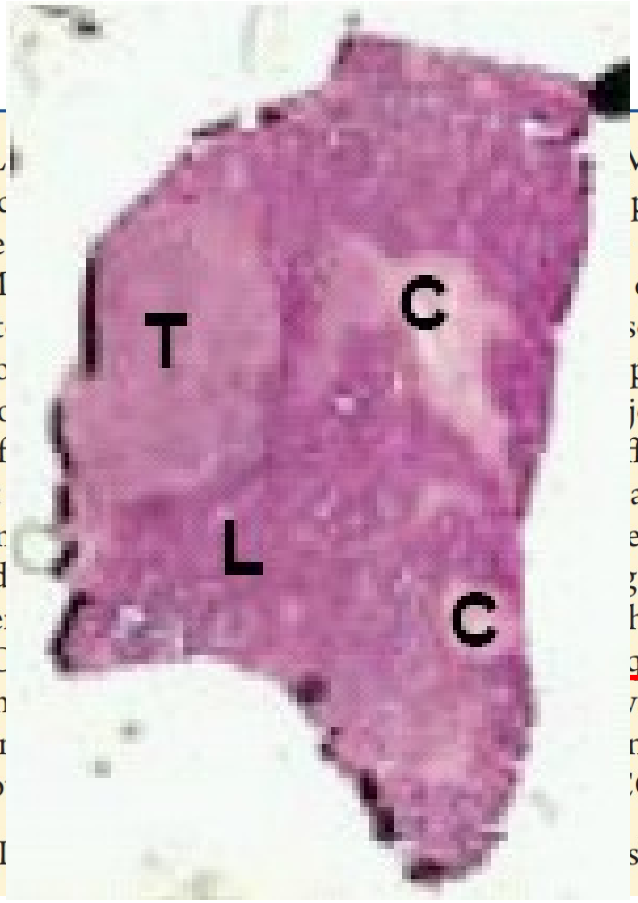


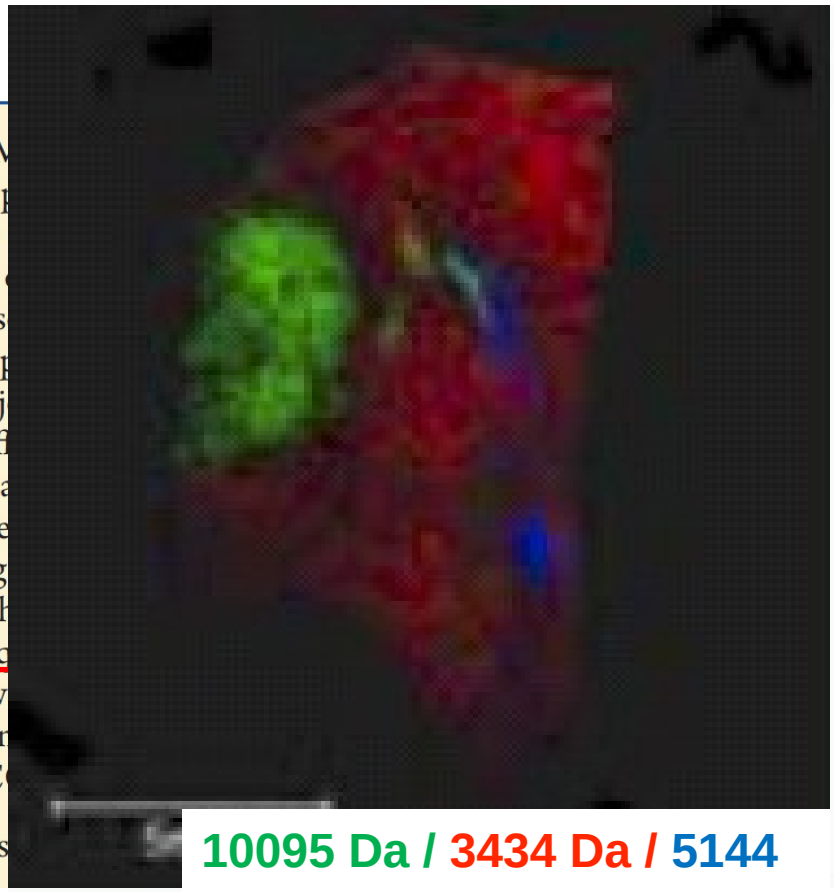
Journal of proteome research

ARTICLE

pubs.acs.org/jpr

Imaging Mass Spectrometry Provides Fingerprints for Distinguishing Hepatocellular Carcinoma from Cirrhosis





10095 Da / 3434 Da / 5144 Da

ABSTRACT: MAL
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MALDI IMS. We f
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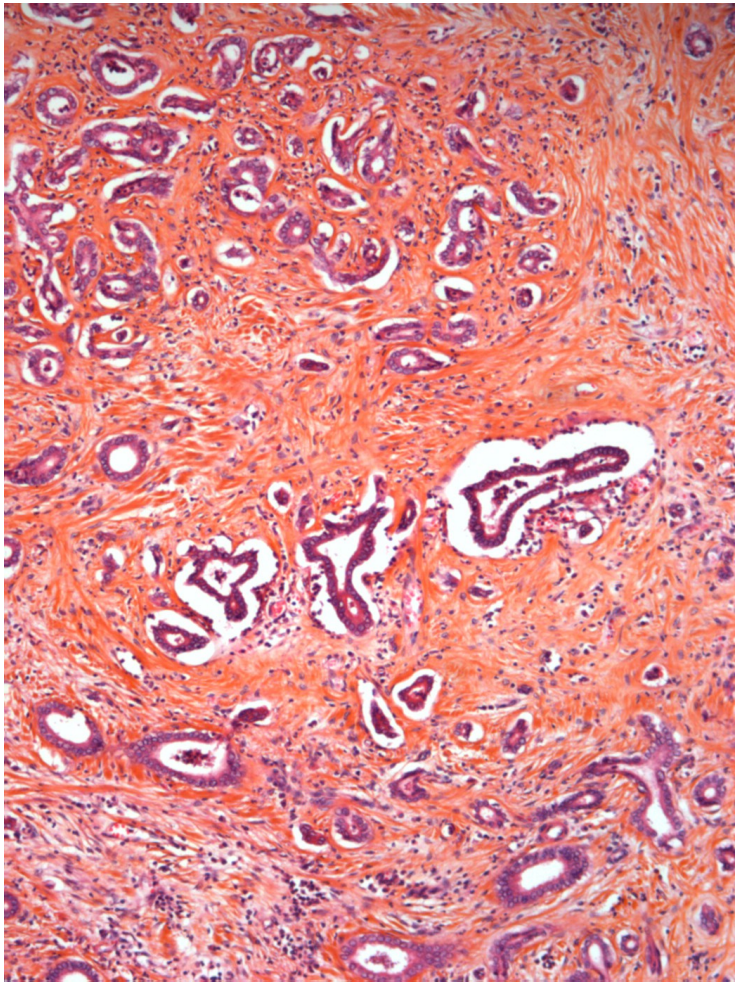
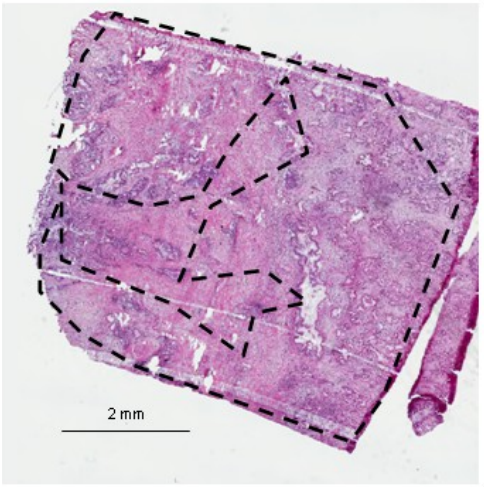
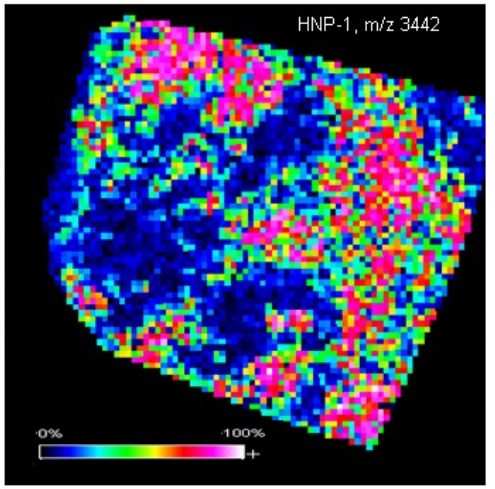
KEYWORDS: MAI

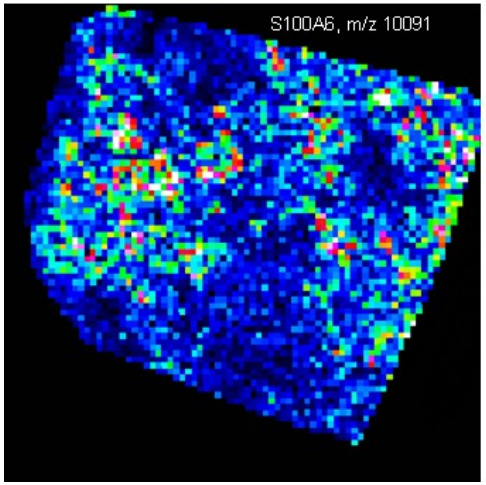
Le Faouder J et al. J Proteome Res 2011

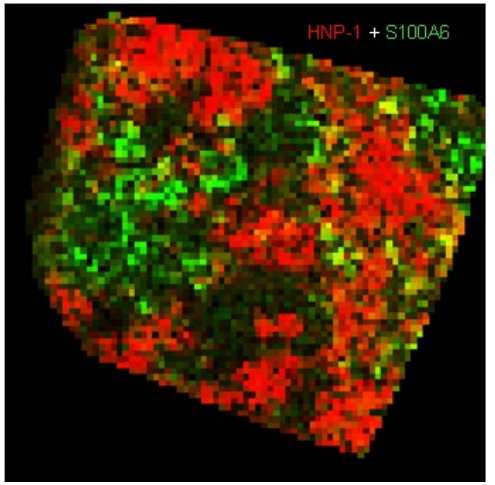
Intra-Tumor Heterogeneity







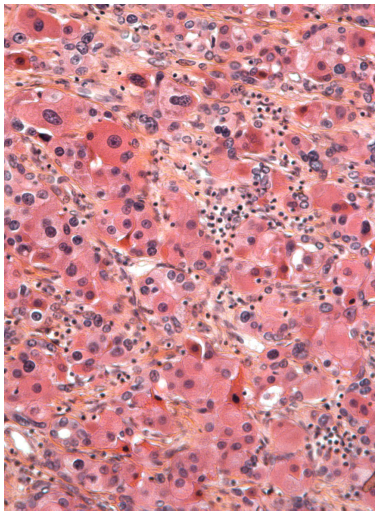


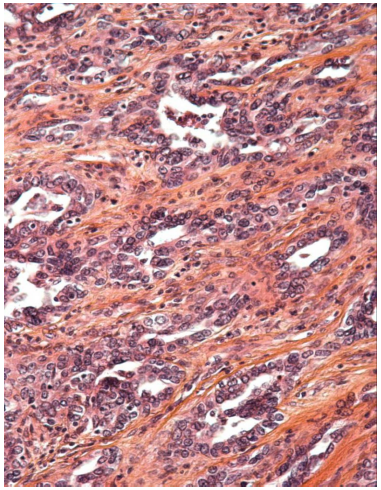


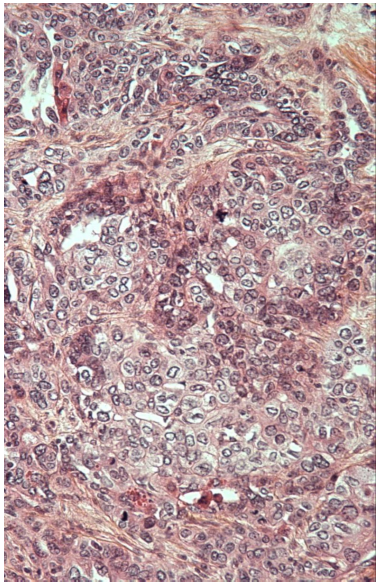
Hilar Cholangiocarcinoma

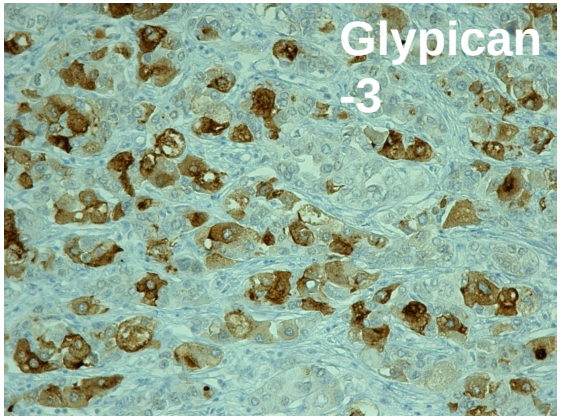
Le Faouder J et al Proteomics 2014

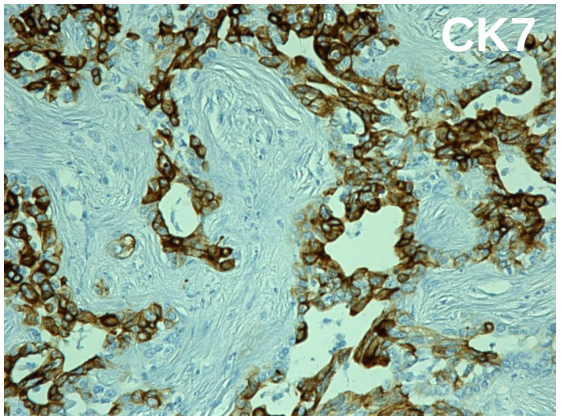
71 year-old ♀, Primary Biliary Cholangitis
Combined Hepato-Cholangiocarcinoma





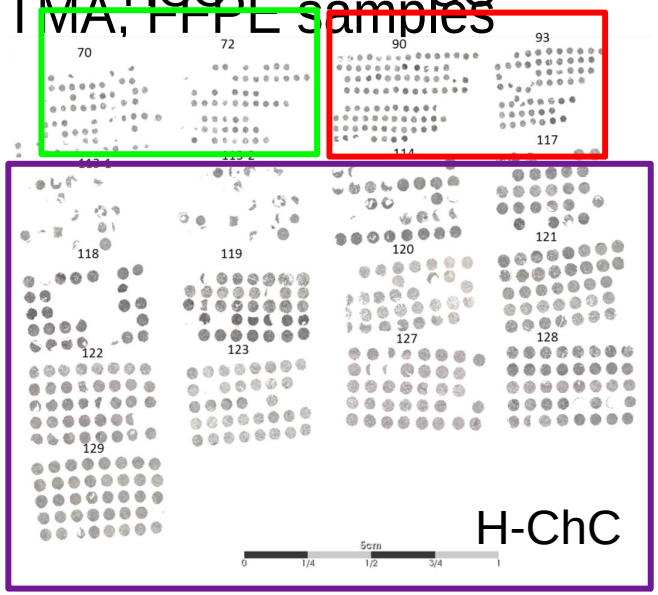




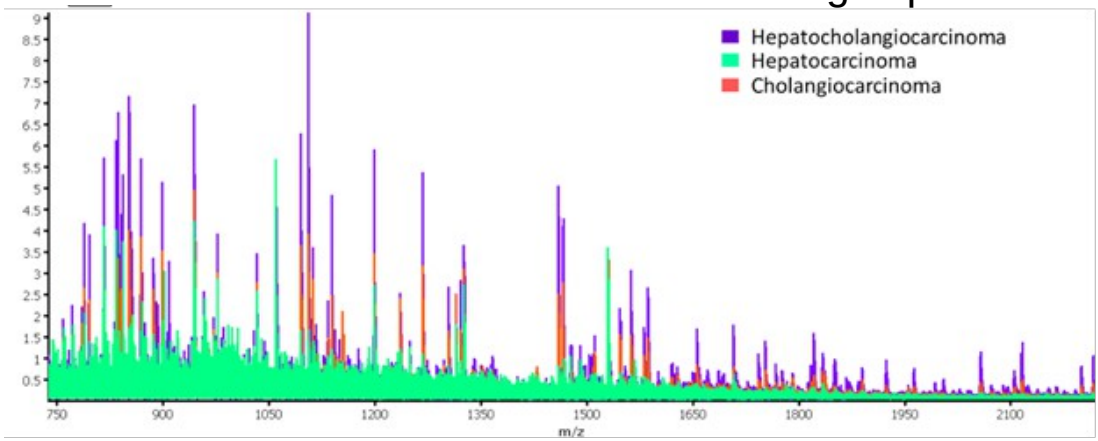


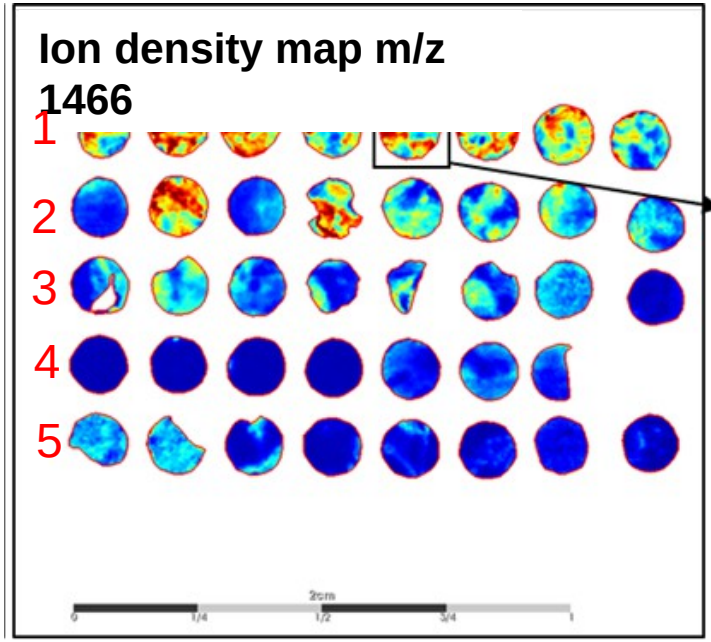
MALDI imaging of H-ChC

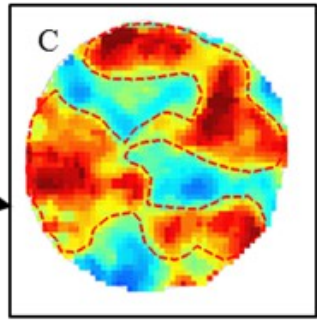
- Protein profiles of H-ChC (n=60), CC (n=29) & HCC (n=23)
- TMA, FFPE samples

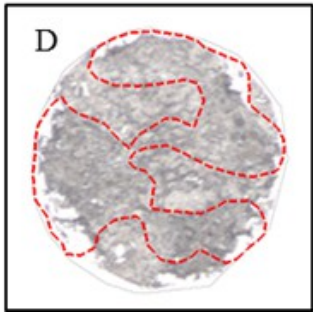


Average spectra



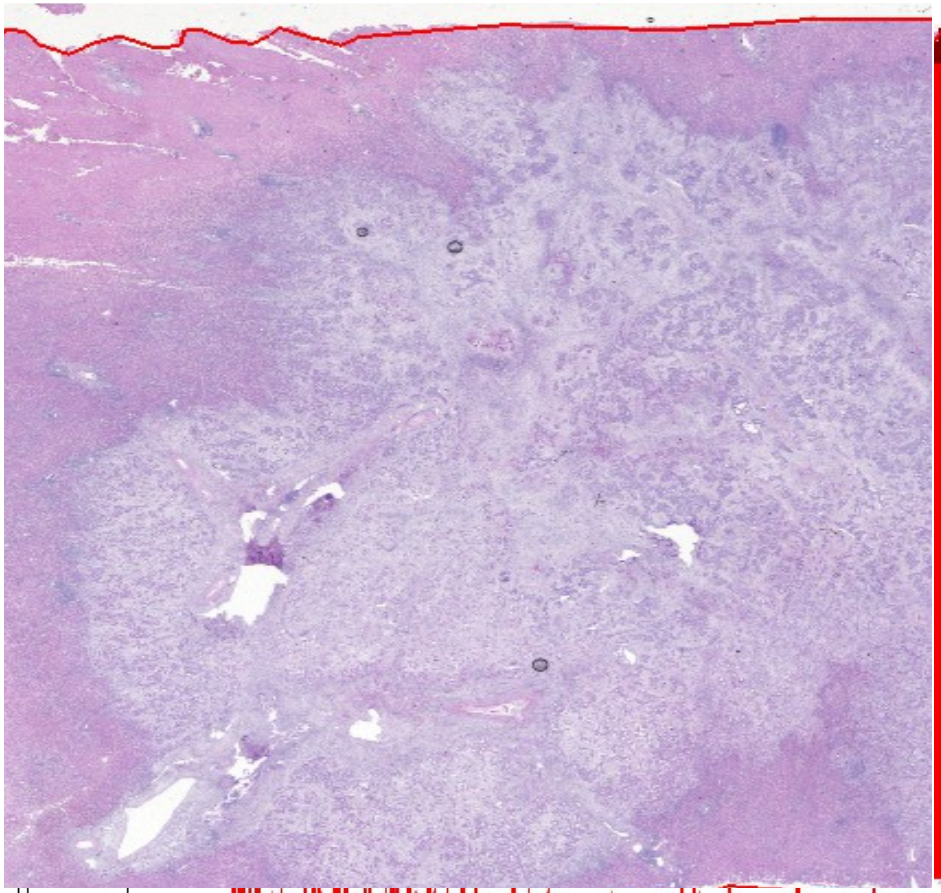


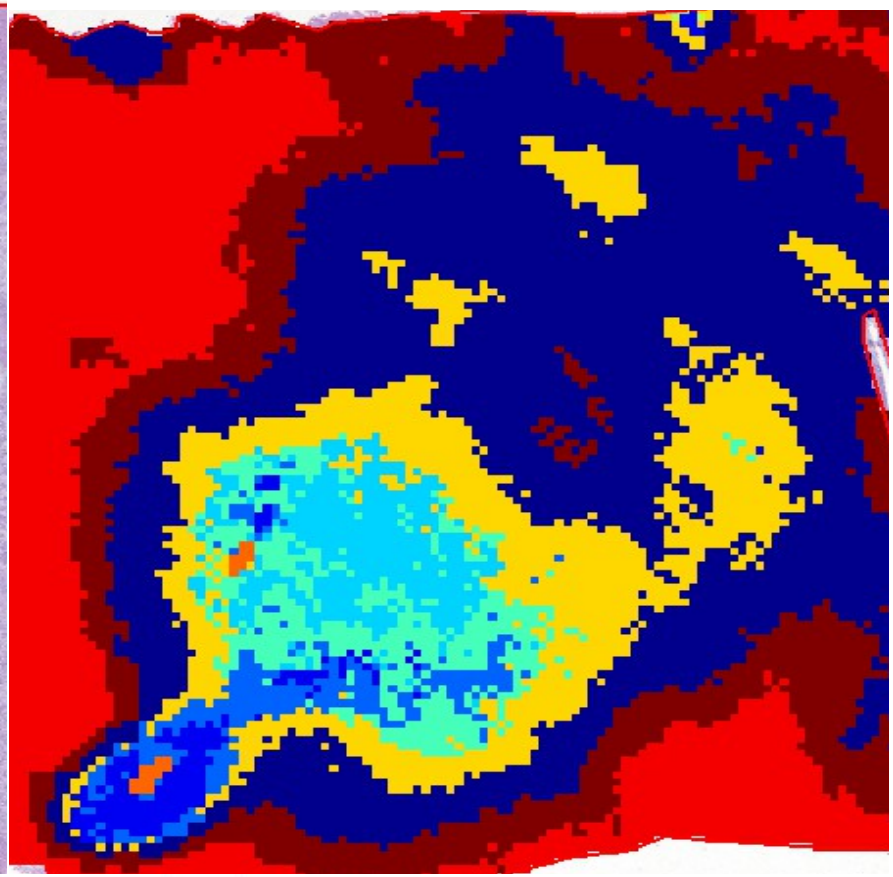


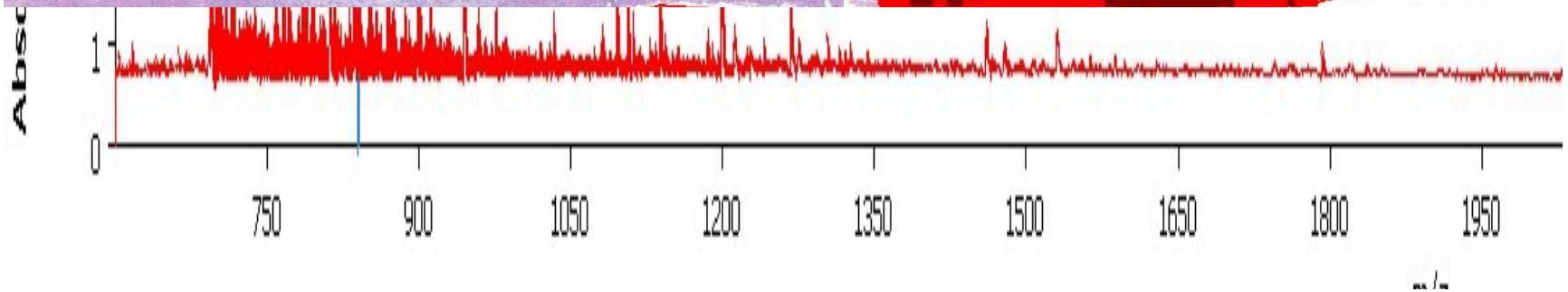


Gigante E (manuscript in preparation)

Spatial Specific Molecular Signatures

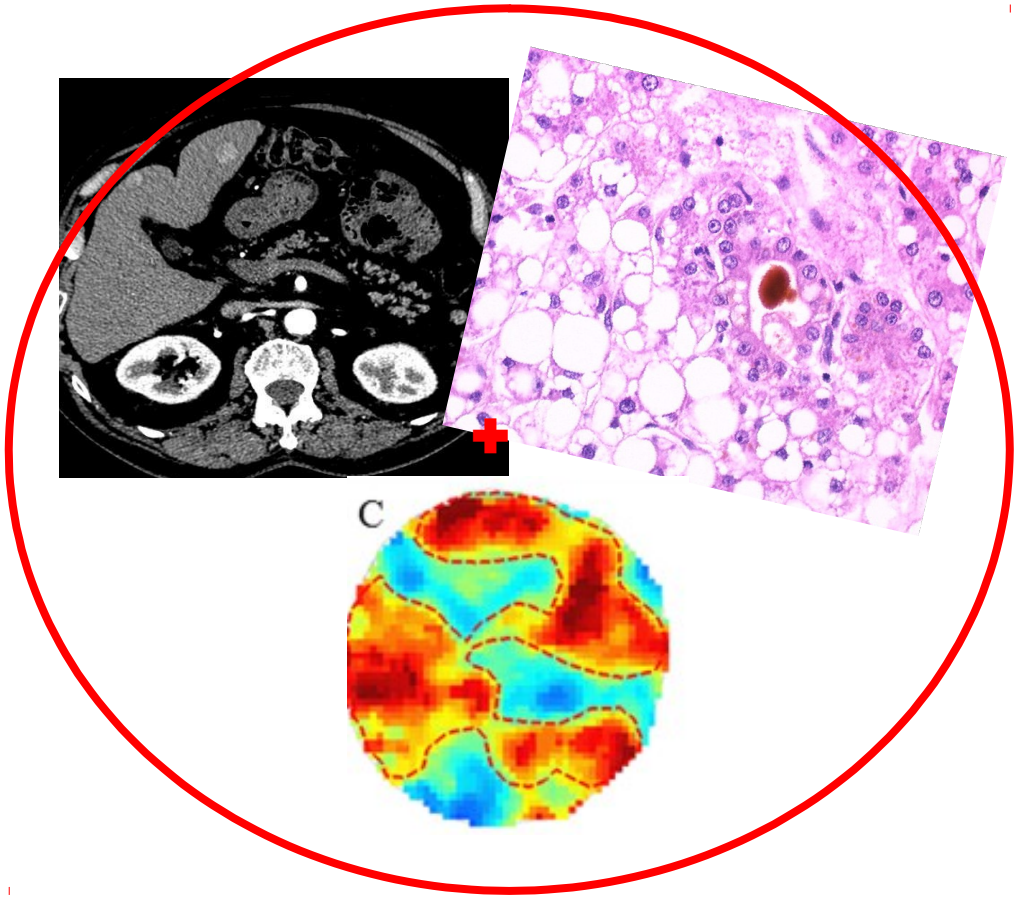






Towards « Integrated Diagnostics »

A Radiopathomic approach



Integrated Diagnostics: The Computational Revolution Catalyzing Cross-disciplinary Practices in Radiology, Pathology, and Genomics[1]

The concept of imaging-pathologic correlation is already close at heart for radiologists globally, who by training know the value of detailed correlation with pathologic findings. However, for many radiologists, this insight has no corollary in practical work, in the form of a rich and frequent exchange in clinical routine.

Lundström CF Radiology 2017

Conclusions

- Digital Pathology
  - The potential to transform the practice of diagnostic pathology
    - Allows image analysis, a way to remove subjectivity & variability
  - Increase the accuracy of diagnosis
    - Combining morphological (macro- and microscopic) & molecular features
  - Some limits to overcome
    - Weight of the pathological images, ...

- Beyond microscopy: emerging *in situ* molecular approaches
  - MALDI imaging: *In situ* label-free quantitative method able to provide molecular signatures directly from tissue sections

Inserm U 1149, CRI

- **« From inflammation to cancer in digestive diseases »** V Paradis
  - A Couvelard, N Guedj, J Cros, V Rebours, N Poté, A Beaufrère
  - F Cauchy, L de Mestier (Doc)
  - S Paisley, S Frendi (M2)
  - S Laouirem, J Le Faouder, M Albuquerque (IE)

Beaujon hospital

- Pathology (V Paradis)
- Radiology (V Vilgrain)
- Hepatology (F Durand)
- Liver surgery (O Soubrane)
- UNITY (D Valla)

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Centre de Recherche sur l'Inflammation PARIS MONTMARTRE

unity Addressing Unmet Needs through Innovation In hepaTology and gastroenterologY