The 3rd APASL HCC Single Topic Conference
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東京大学
THE UNIVERSITY OF TOKYO

Role of Biopsy in the Era of Targeted Therapy

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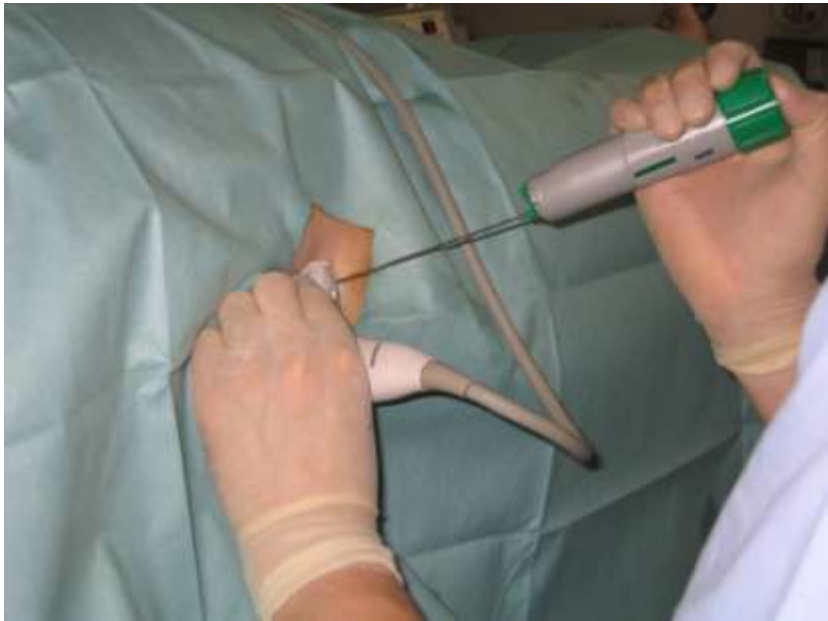
Outline

- ✓Introduction
- ✓Substitutions for LB
- ✓LB is still needed!
- ✓What will we get from LB?
- ✓Problems to be solved
- ✓Conclusion

Introduction

- First liver aspiration in 1883
- First percutaneous biopsy in1923
- Since then LB has been the gold standard in the diagnosis of diffuse and focal liver diseases



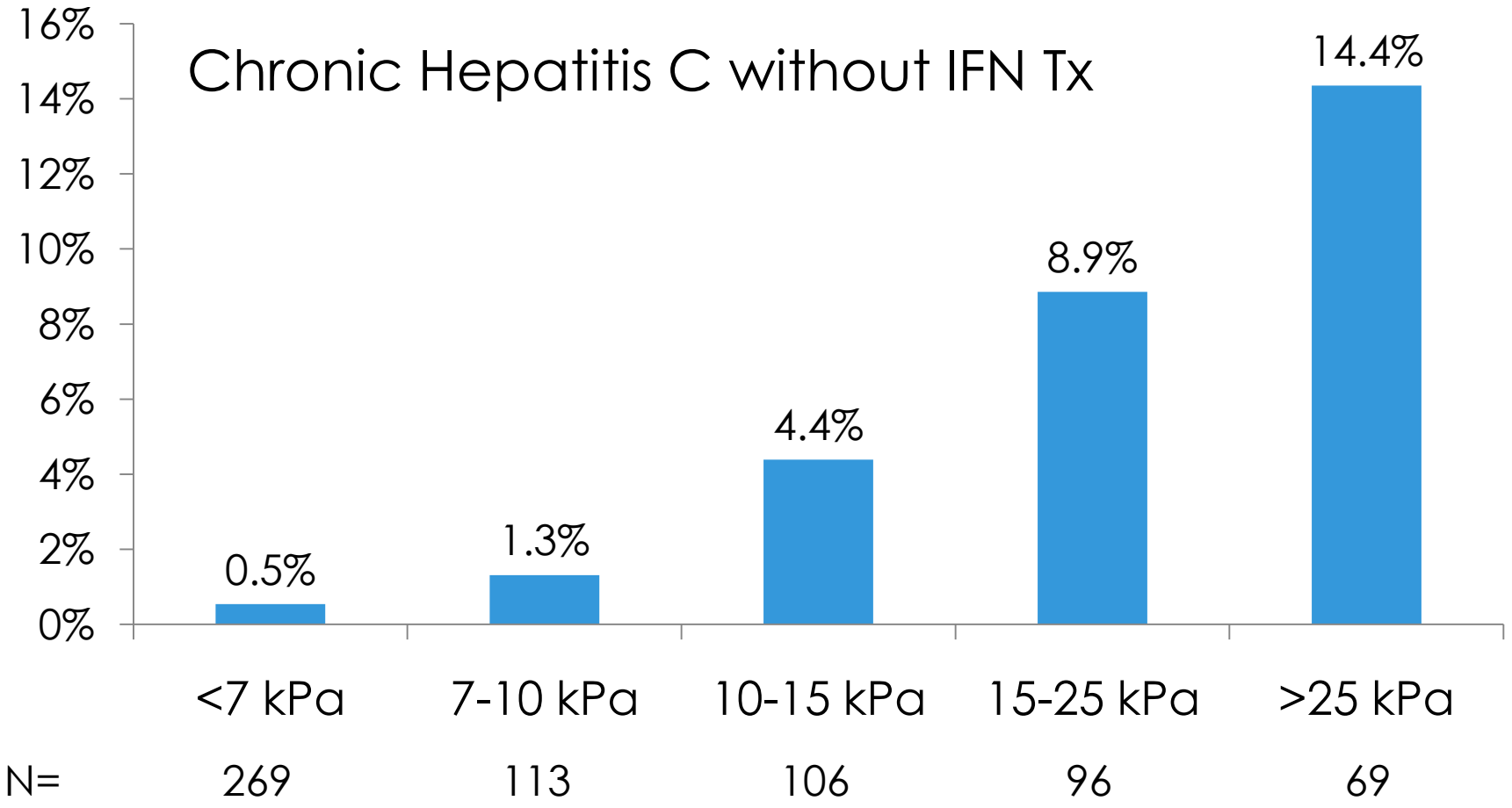
Drawbacks of LB

- Invasive procedure (morbidity ~3%)
- Sampling Error
- Interobserver variability
- Not suitable for repeated examination

Substitution for LB

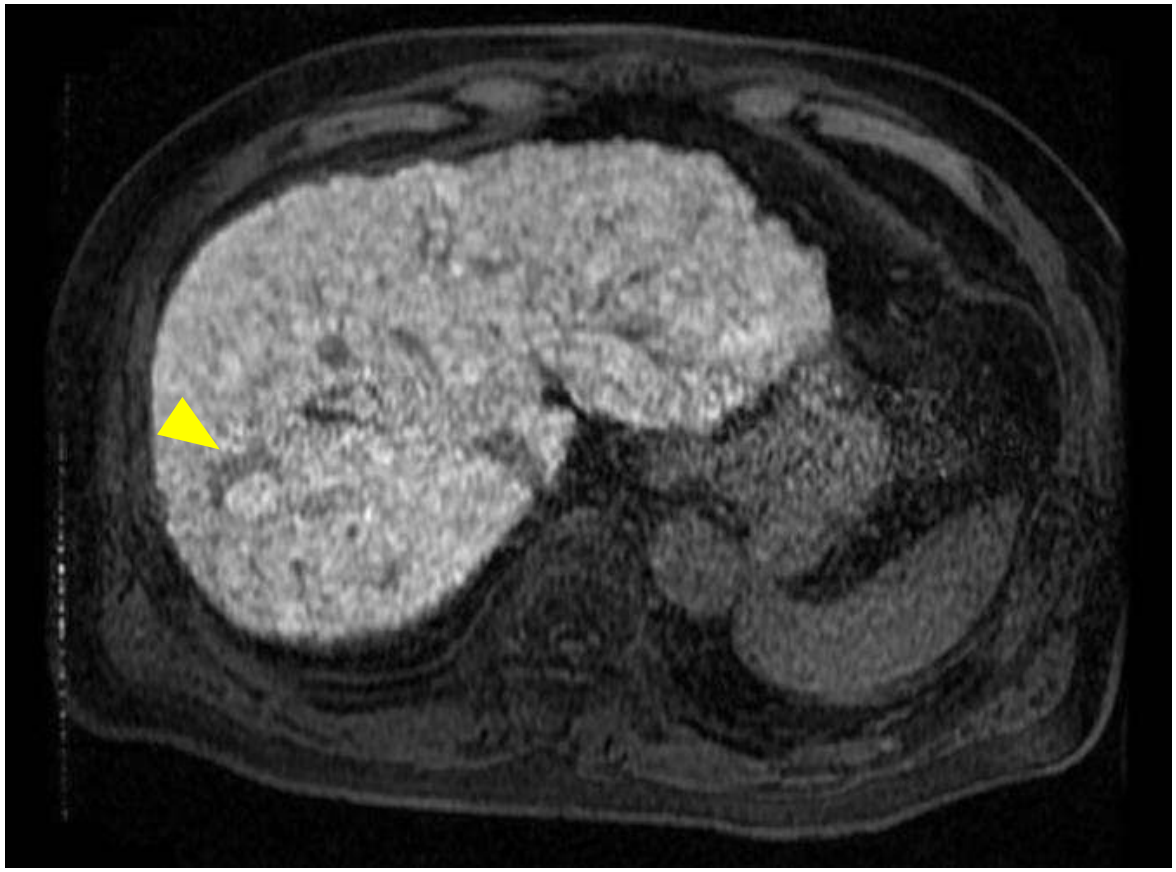
- Inflammation
  - AST, ALT, GGT, etc…
- Fibrosis
  - platelet count
  - serum markers: hyaluronic acid, type IV collagen
  - Transient Elastography (FibroScan®)
- Focal liver lesions
  - Imaging modalities
  - tumor markers

FibsoScan® can stratify HCC risk

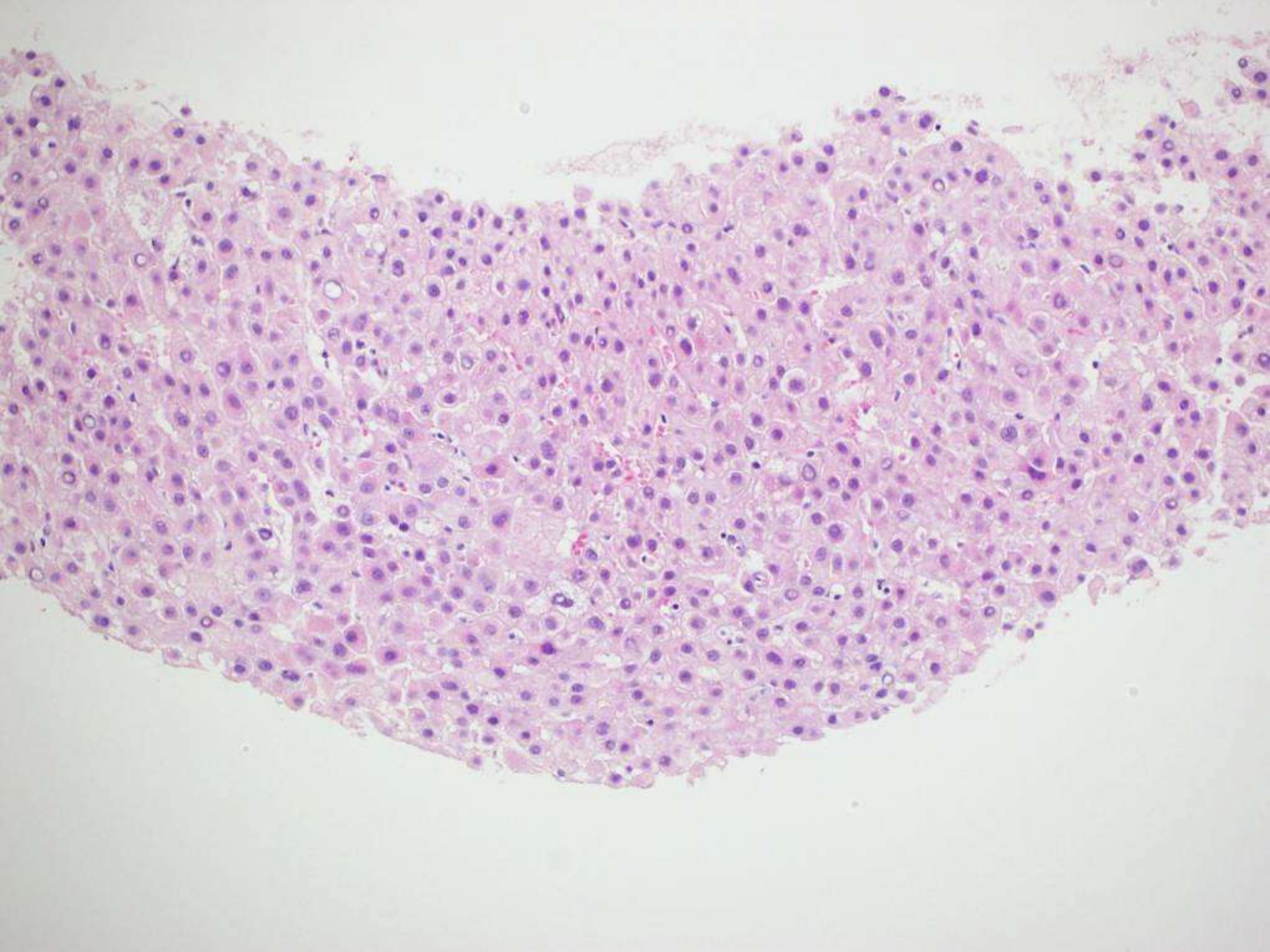


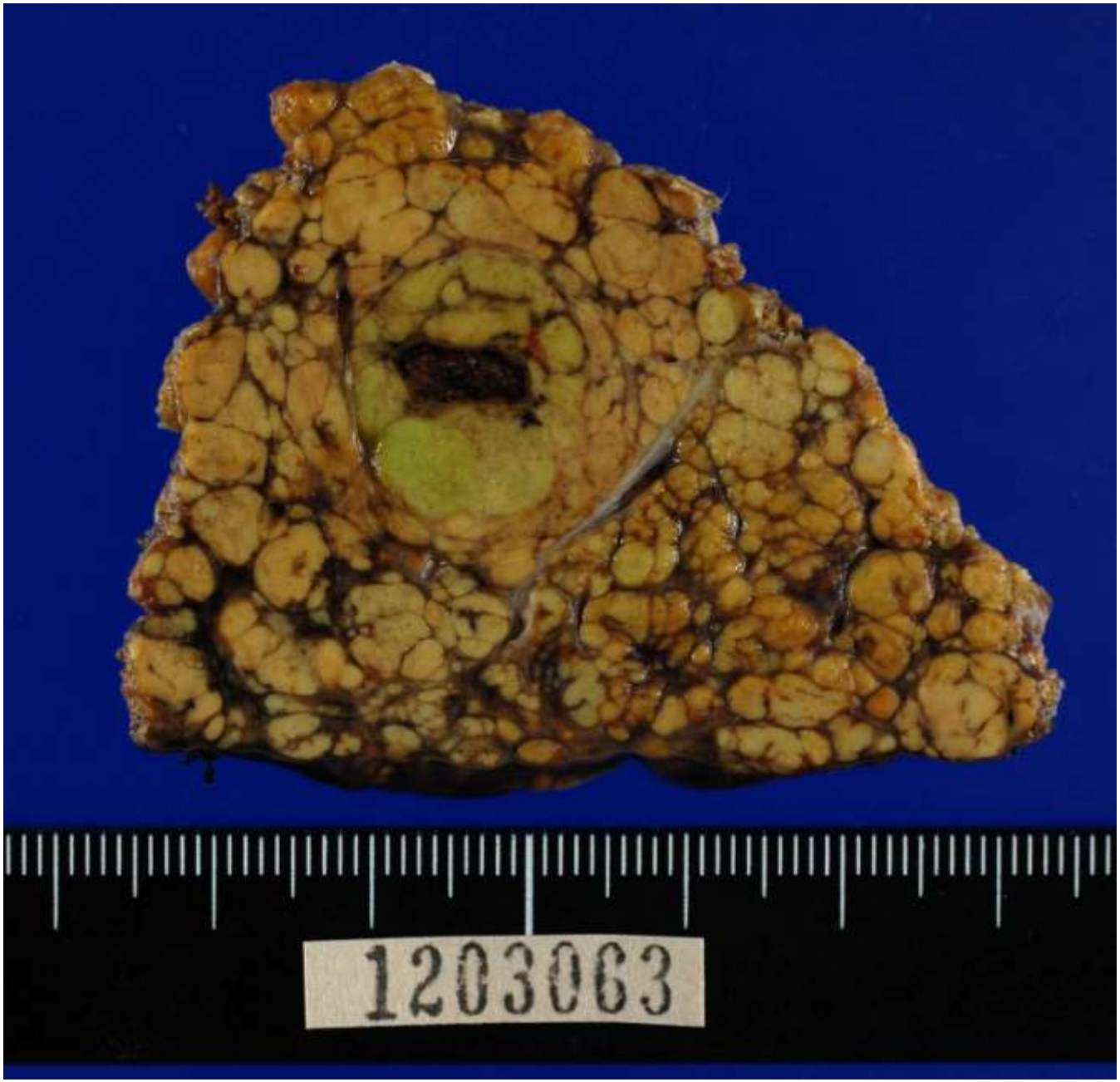
Masuzaki et al. Hepatology 2009;49:1954-61

EOB-MRI facilitate early diagnosis



Slow growing tumor in non-viral cirrhosis
Defect in hepatobiliary phase of EOB-Gd-DTPA MRI

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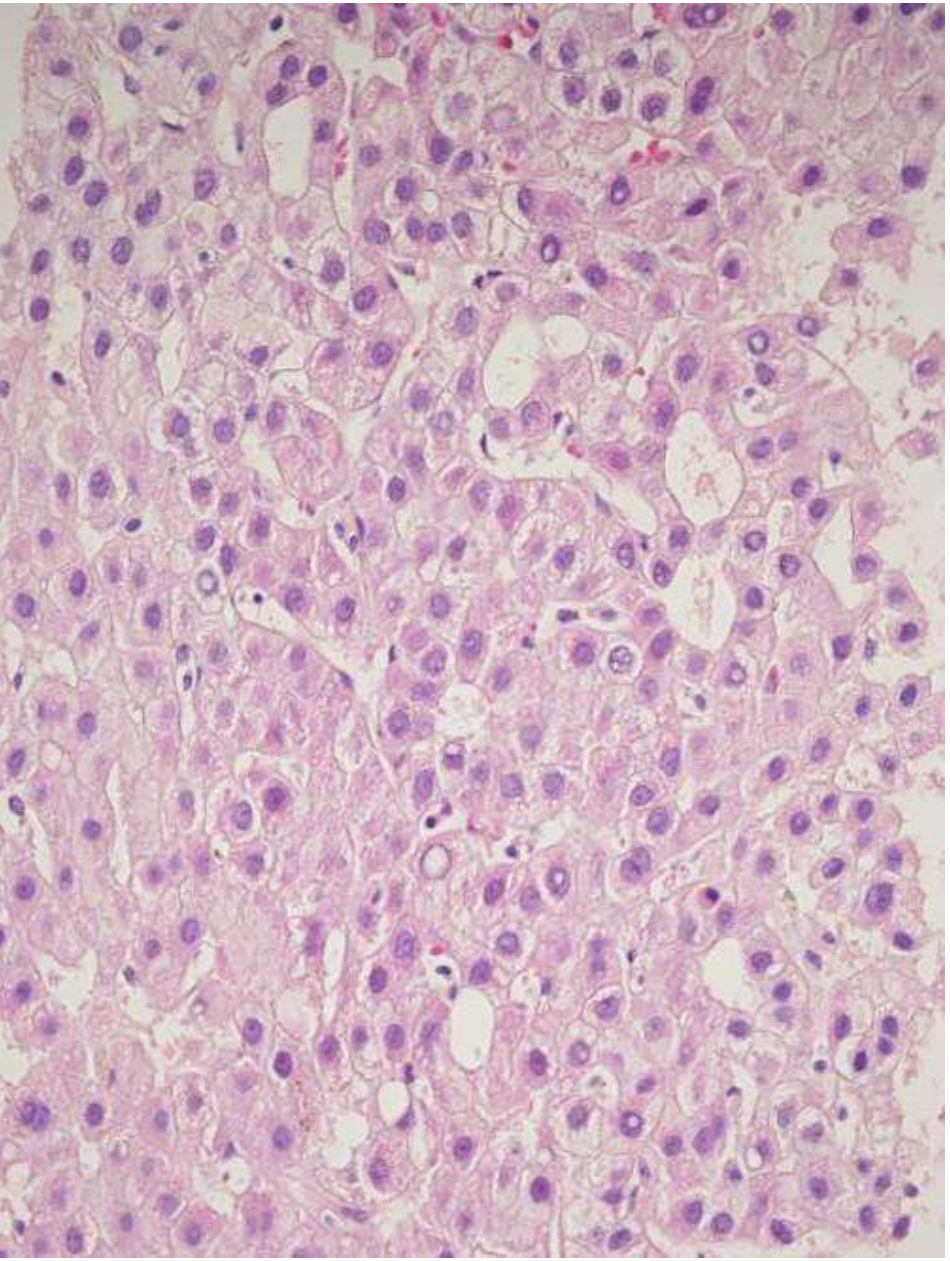
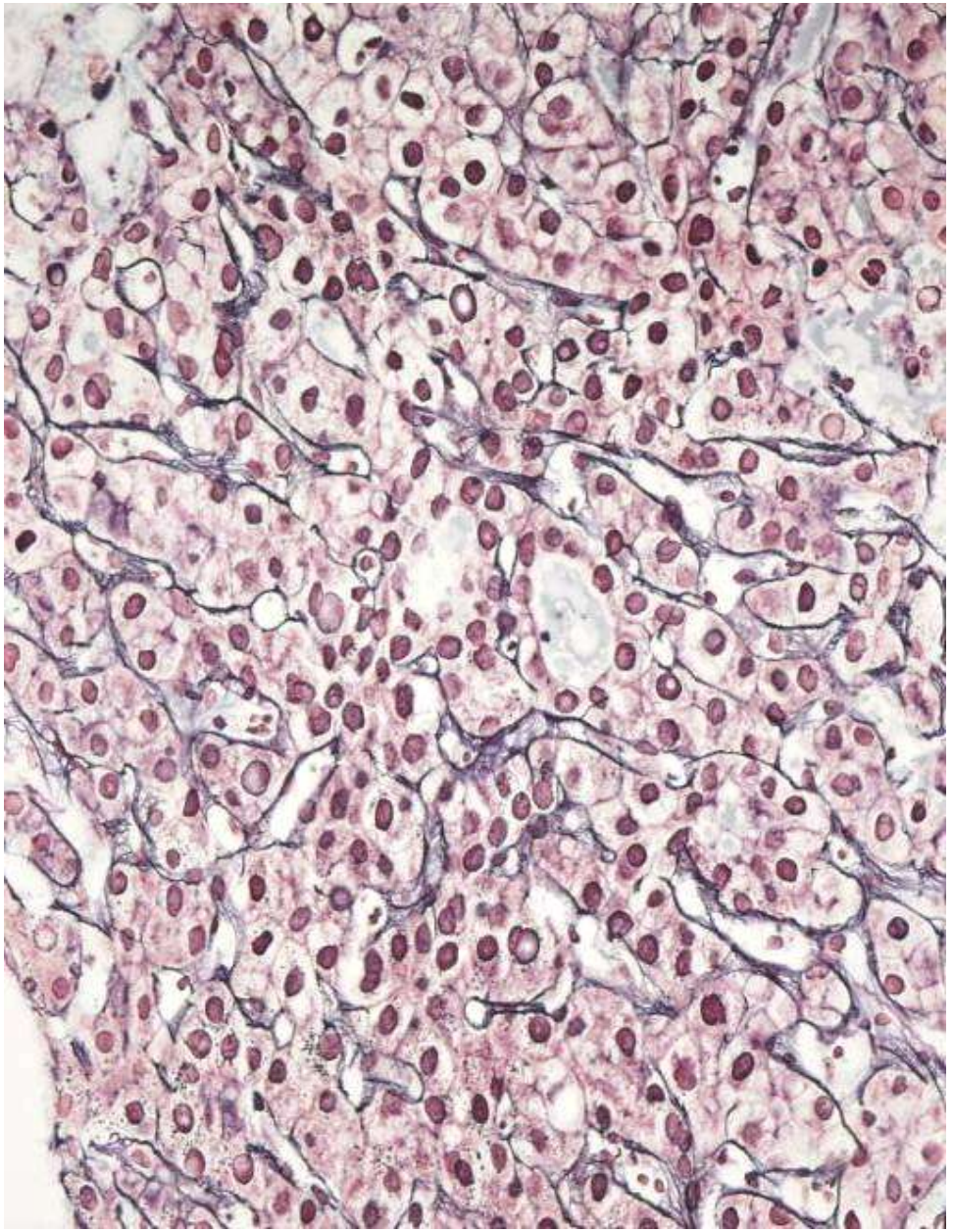
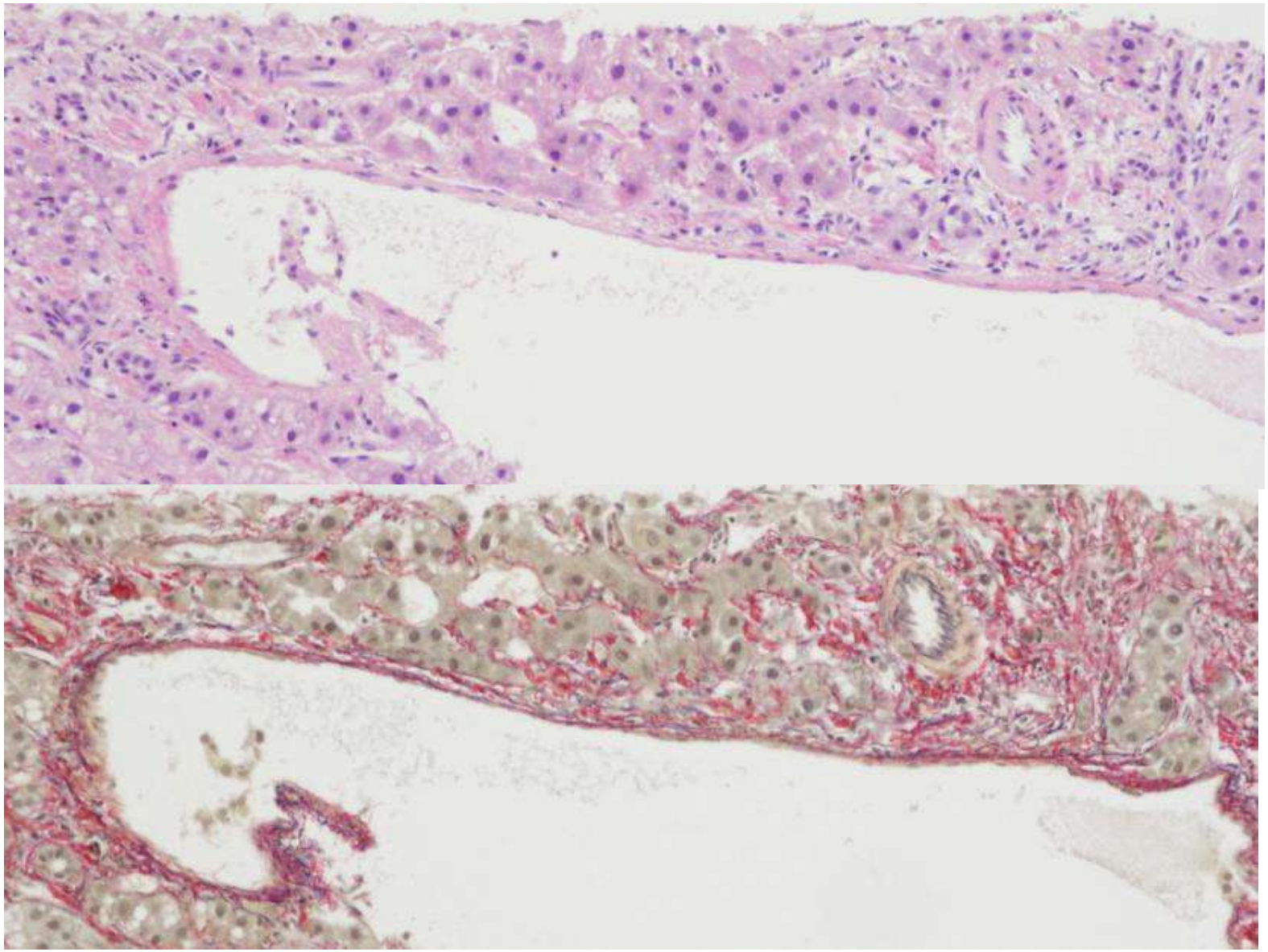


HE stain

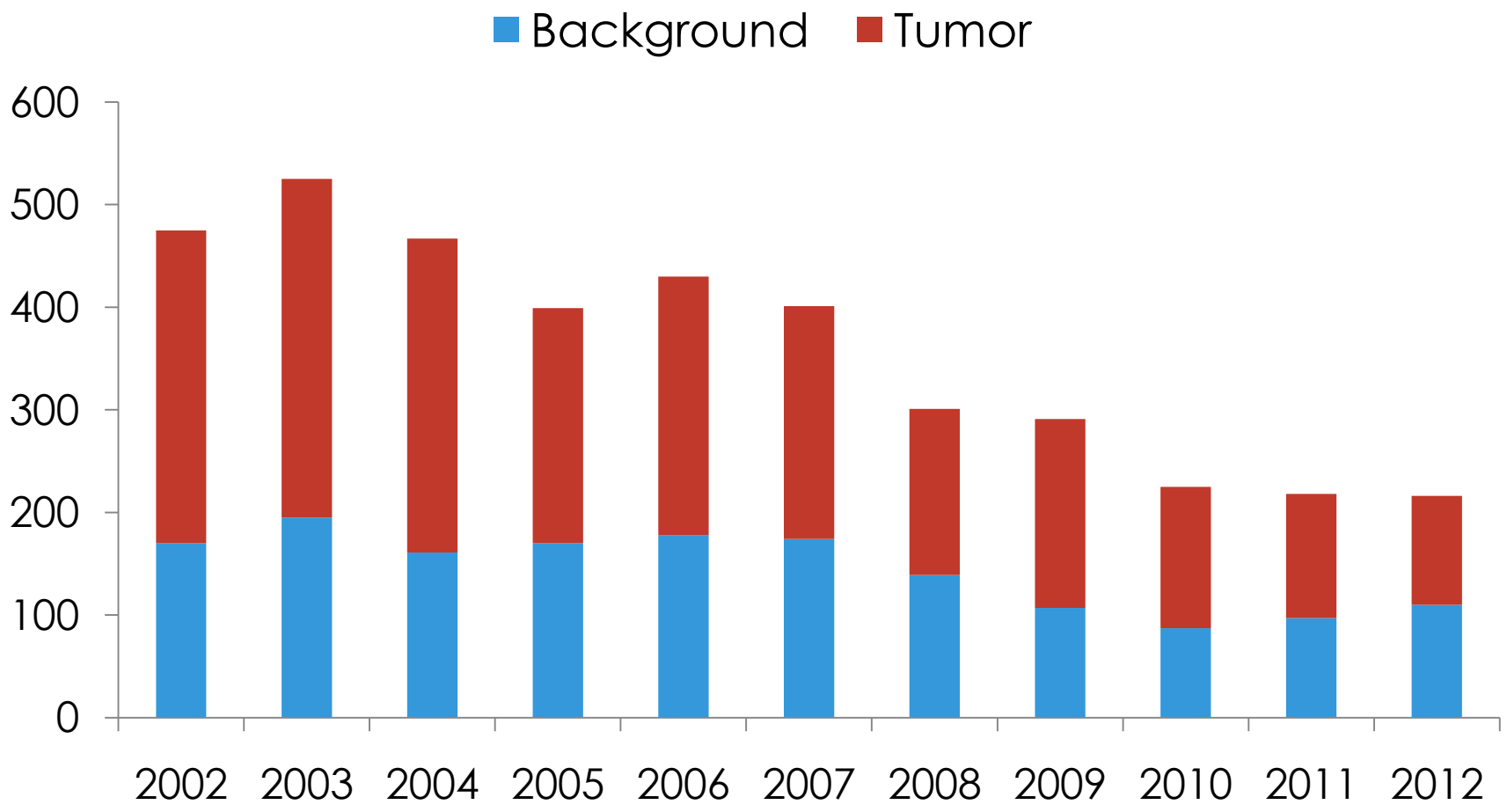


Silver stain



Stromal invasion

Number of Liver Biopsy @ UTH



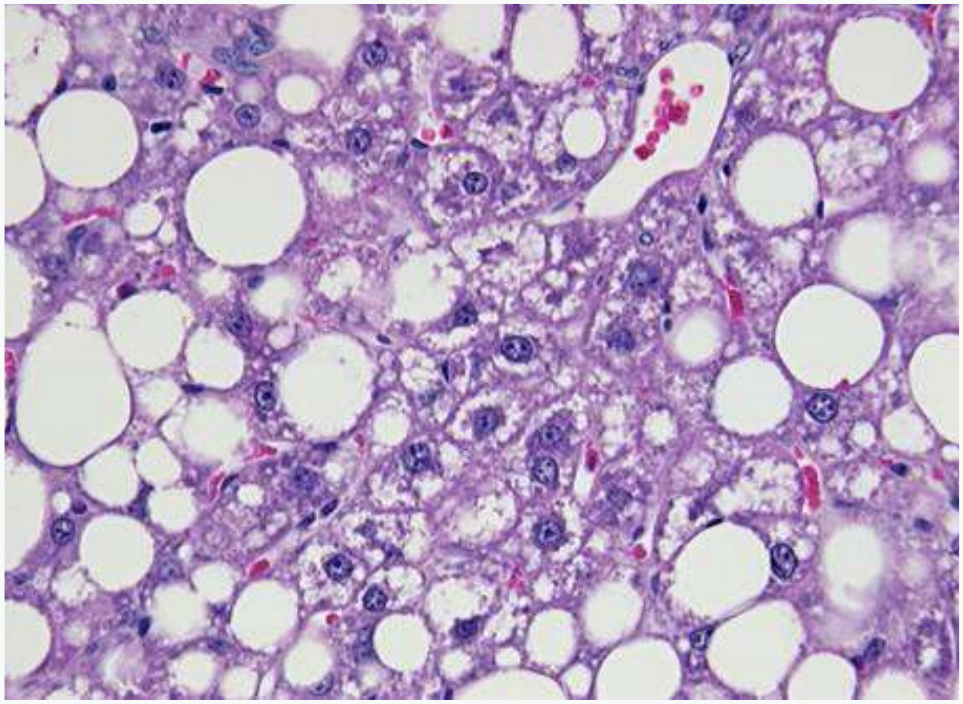
Liver Biopsy is still needed

What can we get from LB?

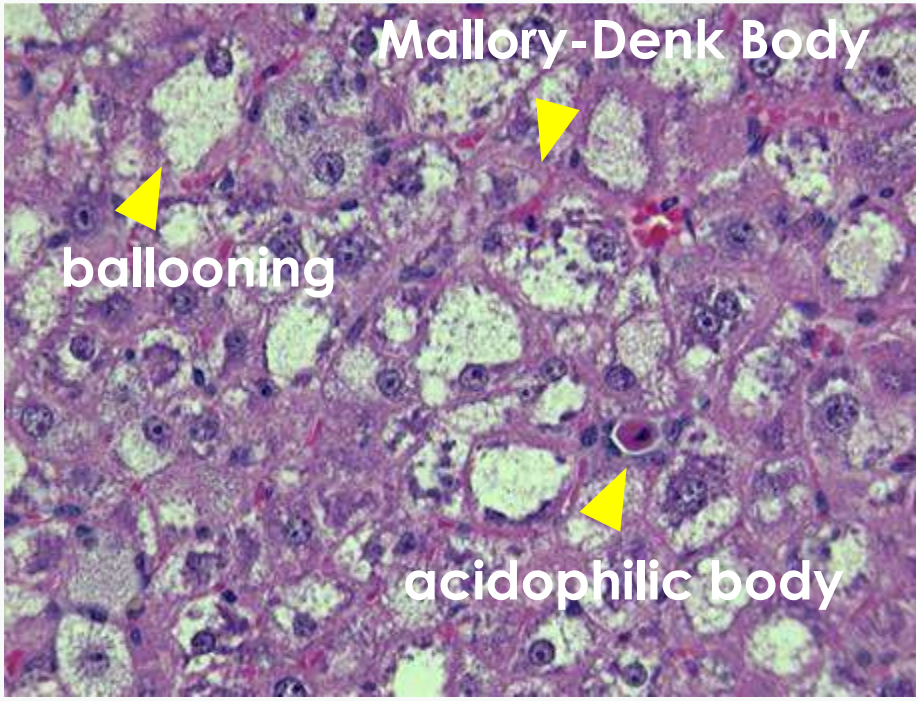
- Some chronic liver diseases still need LB for final diagnosis
  - non-alcoholic steatohepatitis (NASH)
  - AMA-negative PBC
- LB is needed to evaluate
  - minimal fibrosis/inflammation in CLD
- To differentiate small cholangioma and atypical HCC by imaging is difficult

Differentiate NASH from Simple Steatosis

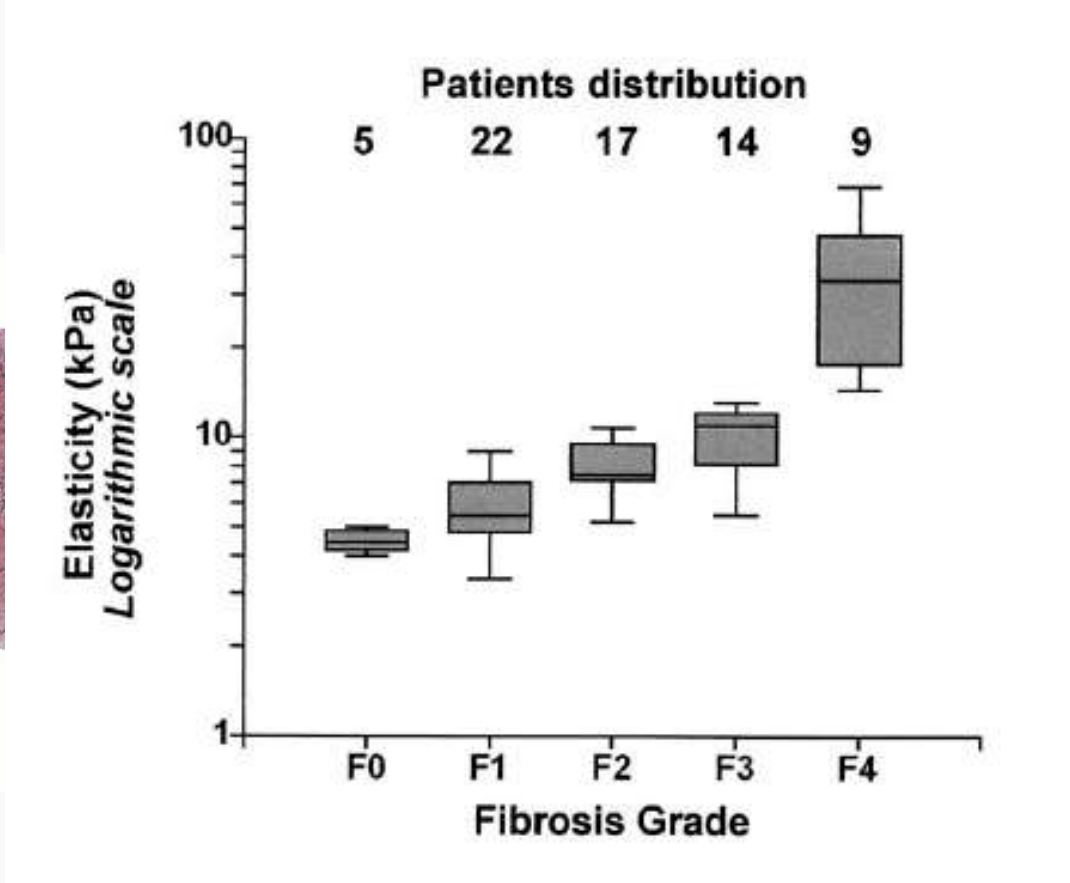
Simple Steatosis



NASH

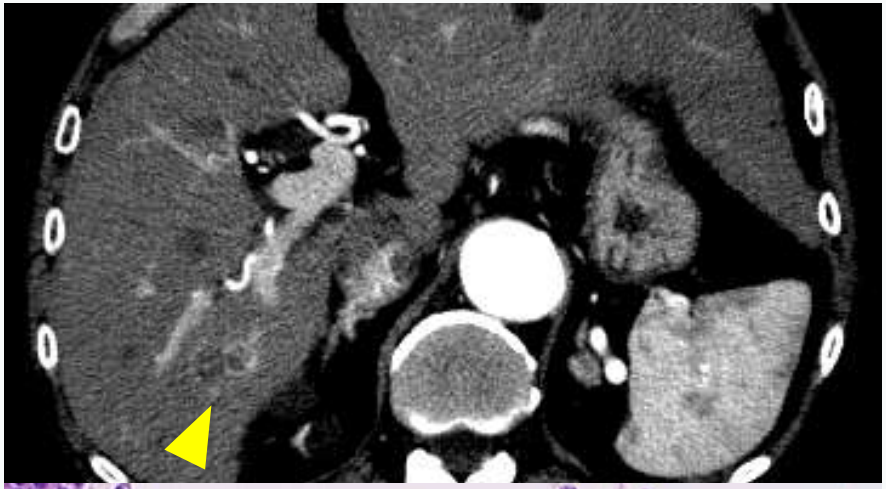


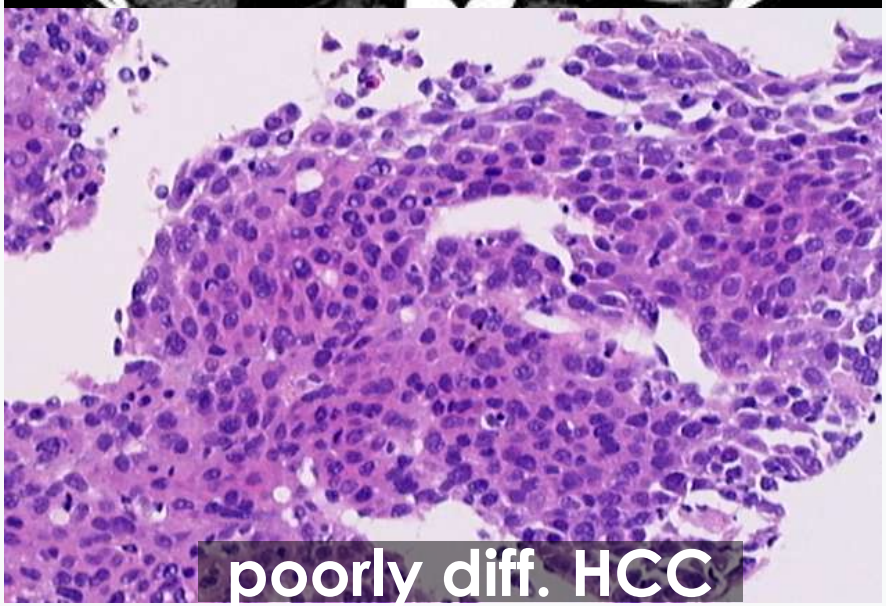
To detect minimal fibrosis

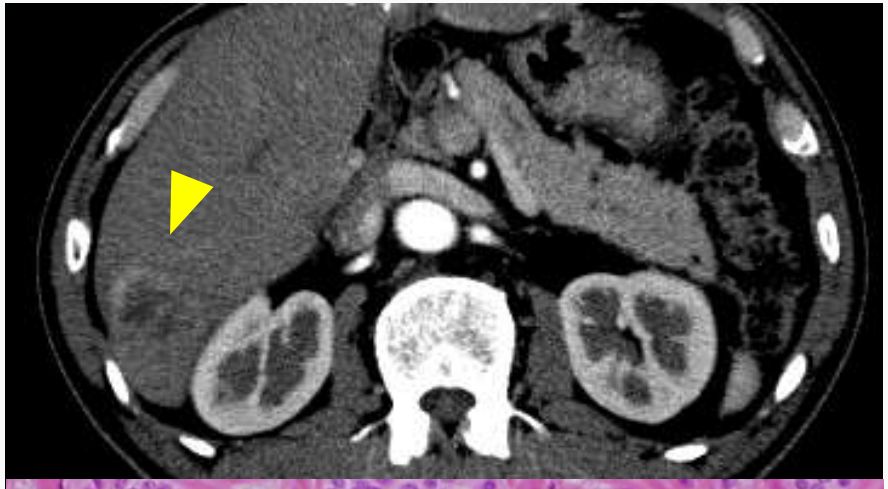


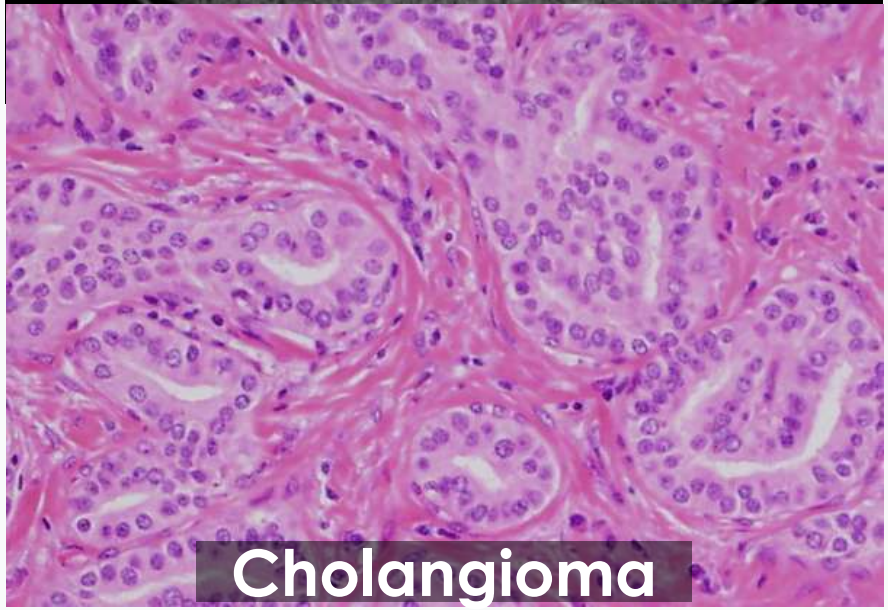
Sandrin et al. Ultrasound Med 2003

Atypical HCC vs. CCC





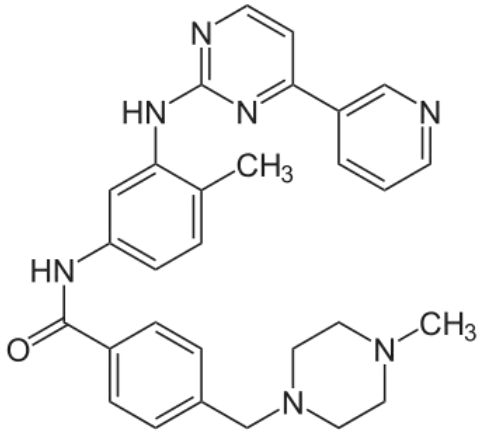




What will we get from LB?

The era of targeted therapy

- Imatinib opened a door into the era of targeted therapy.



Rationale of molecular targeted agents

- The reversal of only one or few genetic abnormalities sometimes can profoundly inhibit the growth of cancer cells.

Table 3 Clinical evidence of oncogene addiction.

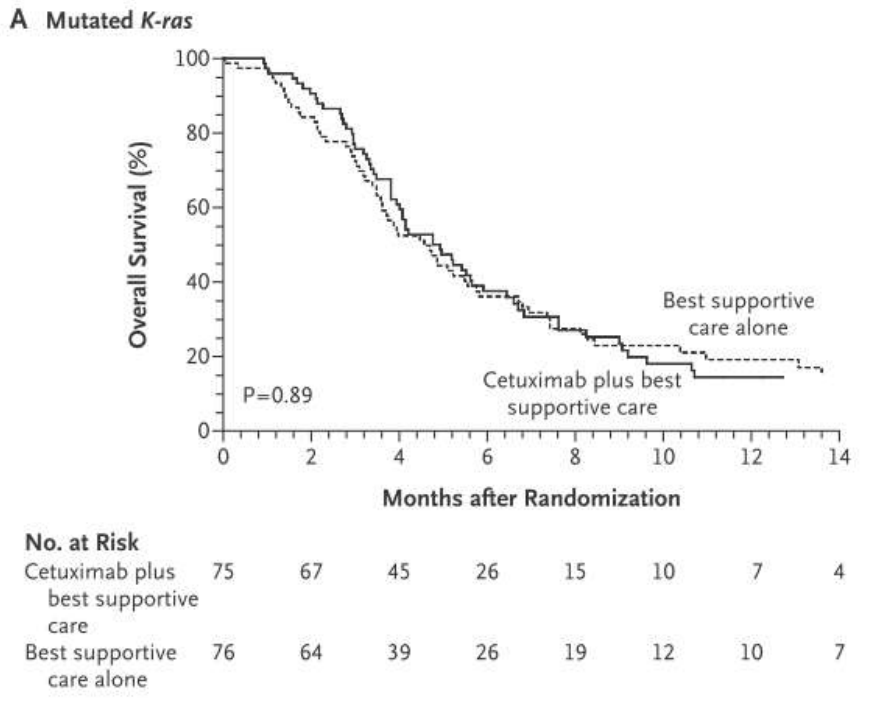
Target	Disease	Agent	Regimen	Reference
HER-2	Breast[a]	Trastuzumab	Combination	Slamon *et al.* (2001)[28,b], Piccart-Gebhart *et al.* (2005)[29,b]
EGFR	NSCLC[a]	Gefitinib, erlotinib	Monotherapy	Shepherd *et al.* (2005)[32,b], Taron *et al.* (2005)[35], Lynch *et al.* (2004)[36]
EGFR	Head and neck, colorectum[a]	Cetuximab	Combination	Baselga *et al.* (2005)[39], Cunningham *et al.* (2004)[40]
EGFR	Pancreas[a]	Erlotinib	Combination	Moore (2005)[34]
VEGF	Breast, colorectum[a], kidney	Bevacizumab	Combination	Miller *et al.* (2005)[41], Hurwitz *et al.* (2004)[42,b], Yang *et al.* (2003)[43]
VEGFR, B-Raf	Kidney[a]	Sorafenib	Monotherapy	Stadler (2005)[55]

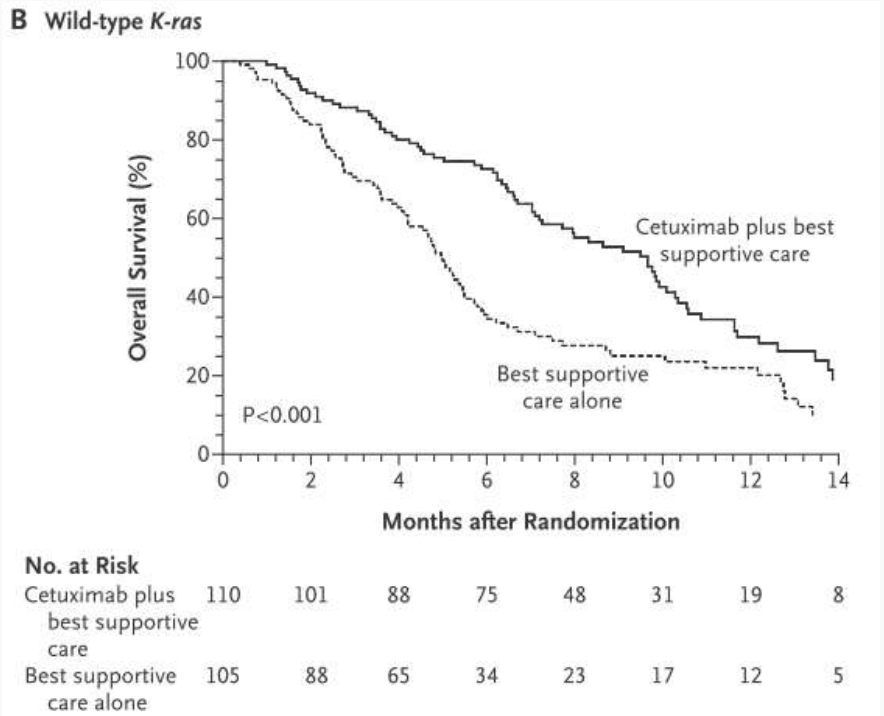
Treatment regimen indicates agent alone (monotherapy) or in combination with cytotoxic agents (combination). [a]FDA-approved; [b]Phase III evidence demonstrates improved disease-free or overall survival rates. Abbreviations: NSCLC, non-small-cell lung cancer; VEGFR, vascular endothelial growth factor receptor.

Oncogenic addiction

Weinstein et al. Nature Clin Pract Oncol 2006

Effort to find biomarkers

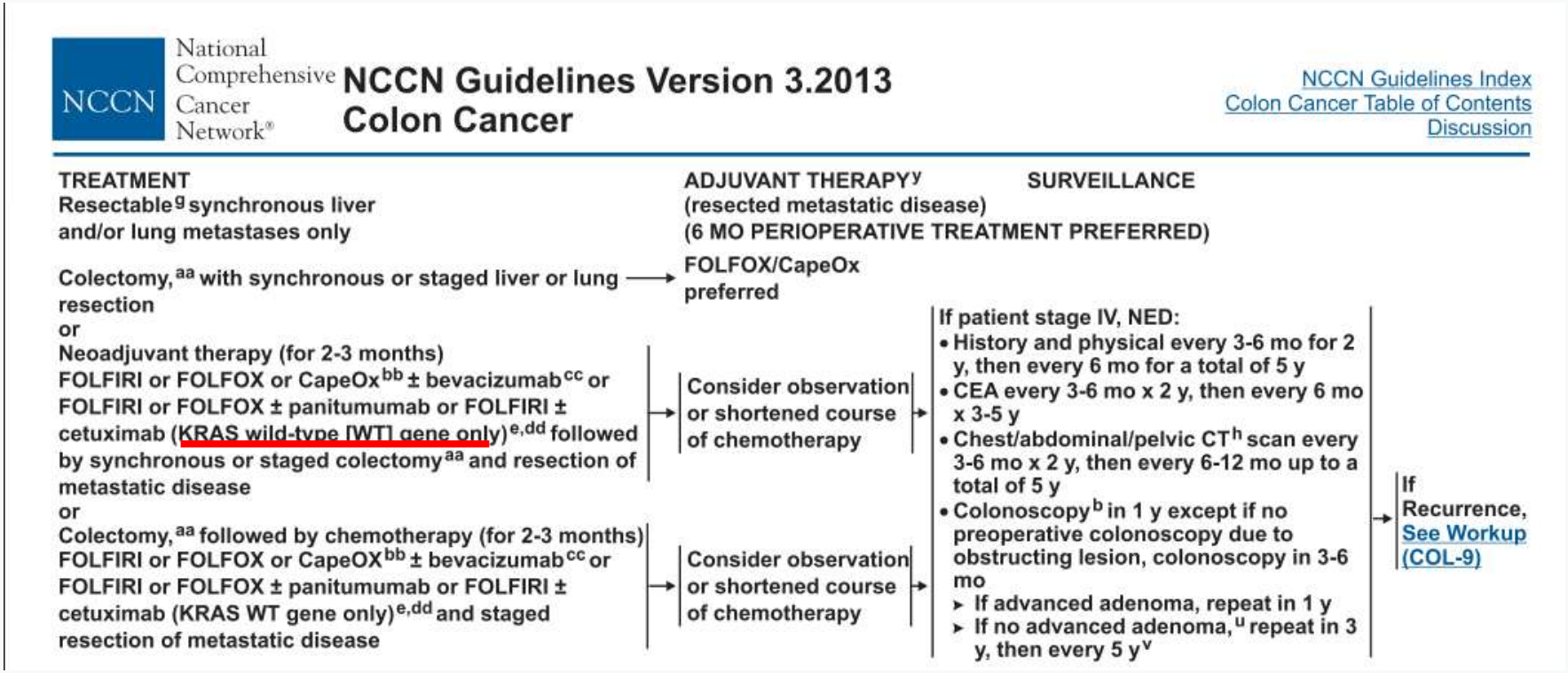




Cetuximab, a monoclonal antibody to EGFR, is only effective in those without *K-ras* mutation.

Christos S, et al. NEJM 2008

KRAS exam is included in daily practice



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2013
Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

TREATMENT
Resectable[g] synchronous liver and/or lung metastases only

Colectomy,[aa] with synchronous or staged liver or lung resection
or
Neoadjuvant therapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOx[bb] ± bevacizumab[cc] or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS wild-type [WT] gene only)[e,dd] followed by synchronous or staged colectomy[aa] and resection of metastatic disease
or
Colectomy,[aa] followed by chemotherapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOX[bb] ± bevacizumab[cc] or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± cetuximab (KRAS WT gene only)[e,dd] and staged resection of metastatic disease

ADJUVANT THERAPY[y]
(resected metastatic disease)
(6 MO PERIOPERATIVE TREATMENT PREFERRED)

FOLFOX/CapeOx preferred

Consider observation or shortened course of chemotherapy

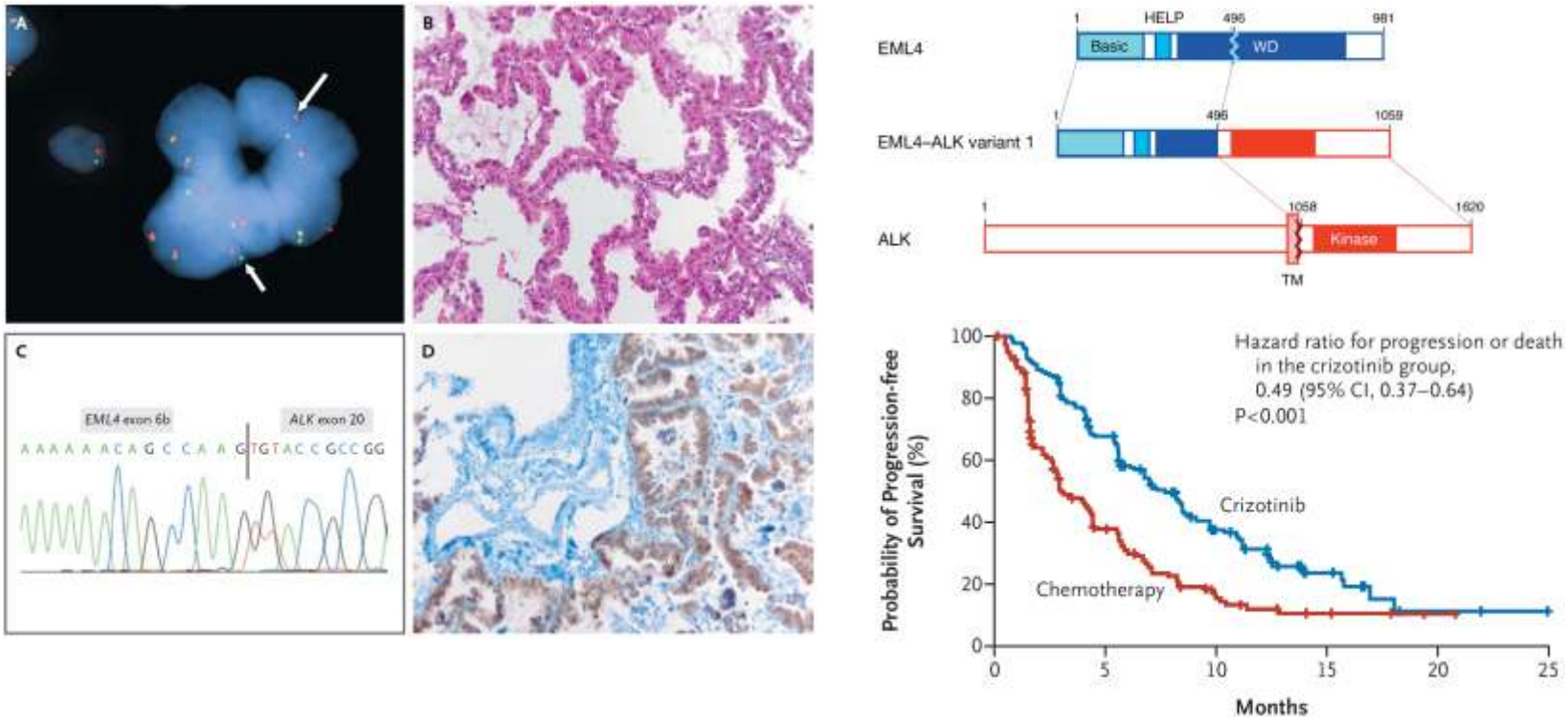
Consider observation or shortened course of chemotherapy

SURVEILLANCE

If patient stage IV, NED:
- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3-6 mo x 2 y, then every 6 mo x 3-5 y
- Chest/abdominal/pelvic CT[h] scan every 3-6 mo x 2 y, then every 6-12 mo up to a total of 5 y
- Colonoscopy[b] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[u] repeat in 3 y, then every 5 y[v]

If Recurrence, See Workup (COL-9)

Development of test kit in parallel with anti-cancer agents



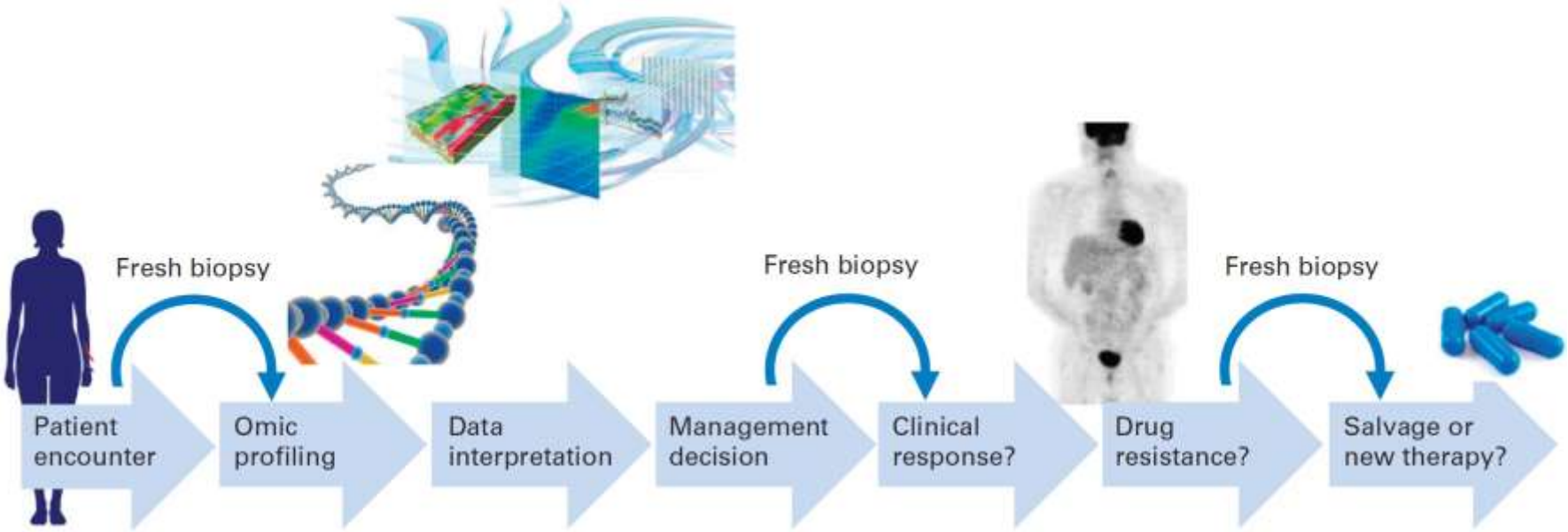
Crizotinib (ALK inhibitor) kills ALK-positive lung cancer

Molecular biomarker-informed personalized treatment

Soda, Nature 2007, Kwak, NEJM 2010, Shaw, NEJM 2013

By courtesy of Dr. Hoshida

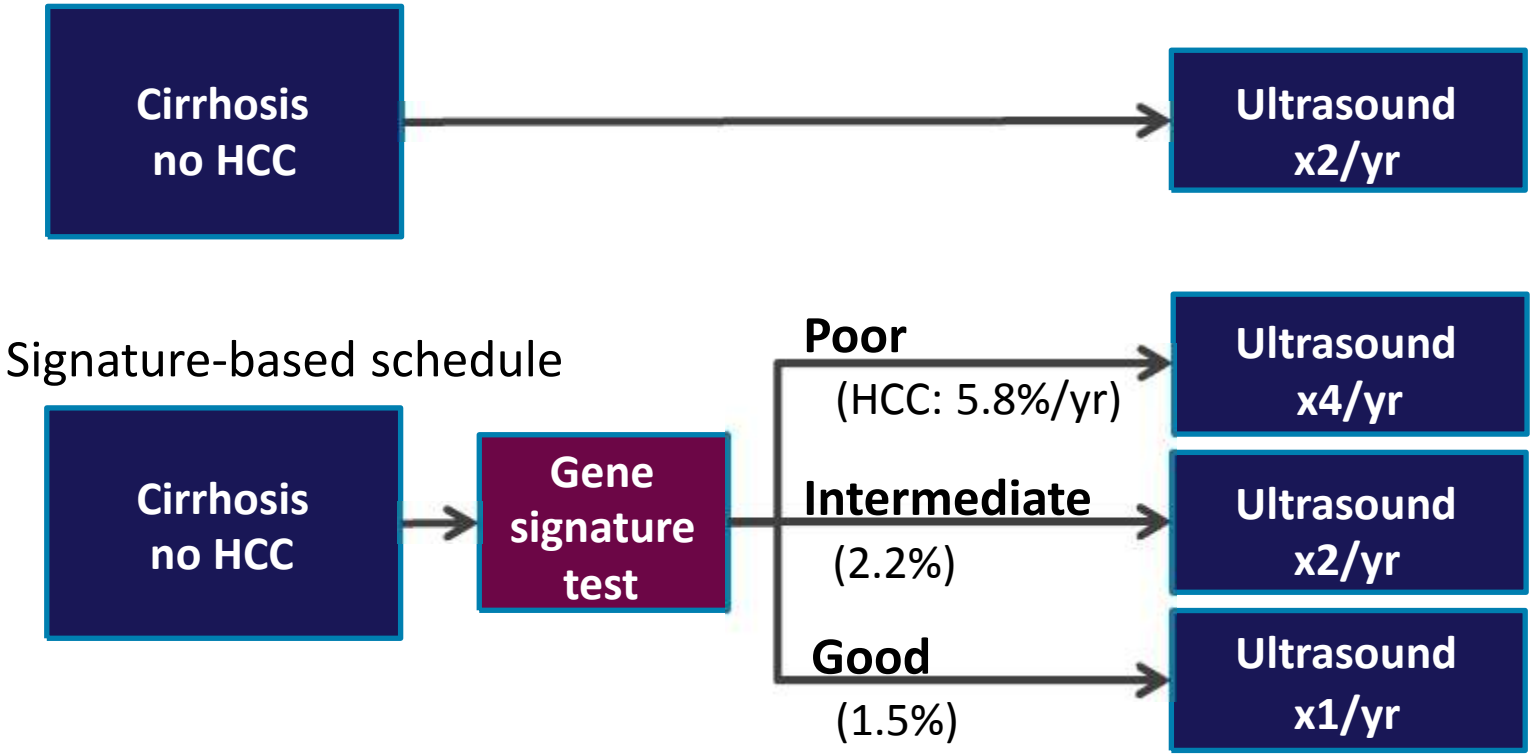
Biopsy-informed personalized oncology



Biopsy is critical especially during development of therapeutic strategy

Garraway, JCO 2013
By courtesy of Dr. Hoshida

Genome-based personalized HCC surveillance



Medical care cost ↓

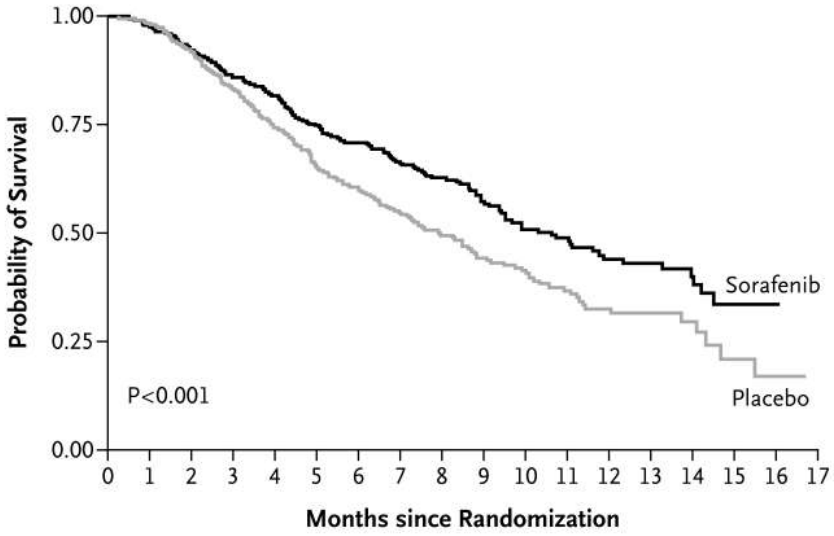
Life expectancy ↑

Andersson, Clin Gastro Hepatol 2008, Hoshida, Gastro 2013

Problems to be solved

Sorafenib

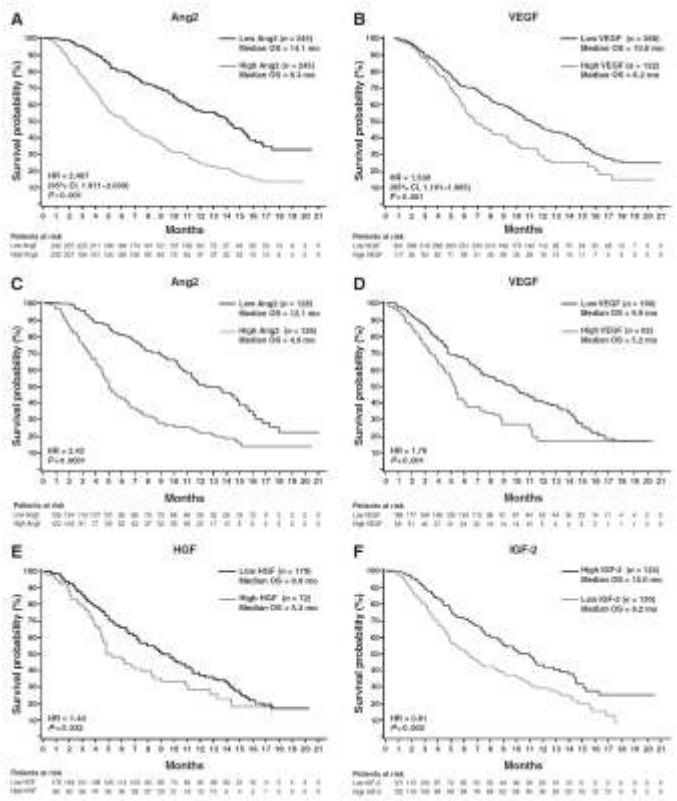
- Seven years after imatinib, sorafenib, a multikinase inhibitor, was first (and still only) approved as a molecular targeted drug for HCC.



Llovet et al. NEJM 2008

No established predictive biomarkererarkers for sorafenib response

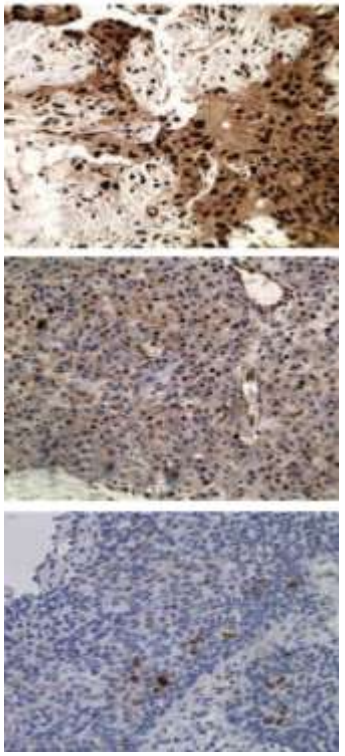
Plasma protein



Blood cell RNA

Gene Symbol
KIAA0102
EIF2C1
CAP350
LOC144363
DNM1L
ARP5
TNFAIP2
FLJ34443
PTP4A1
—
—
NAT1
DSCR2
CL640
S100A8
MIC1
C20orf16

Tissue staining



pERK

Abou Alfa, JCO 2006, Llovet, CCR 2012

No major mutations found in HCC

Table 1 Significantly mutated genes and their mutation frequency in the validation set

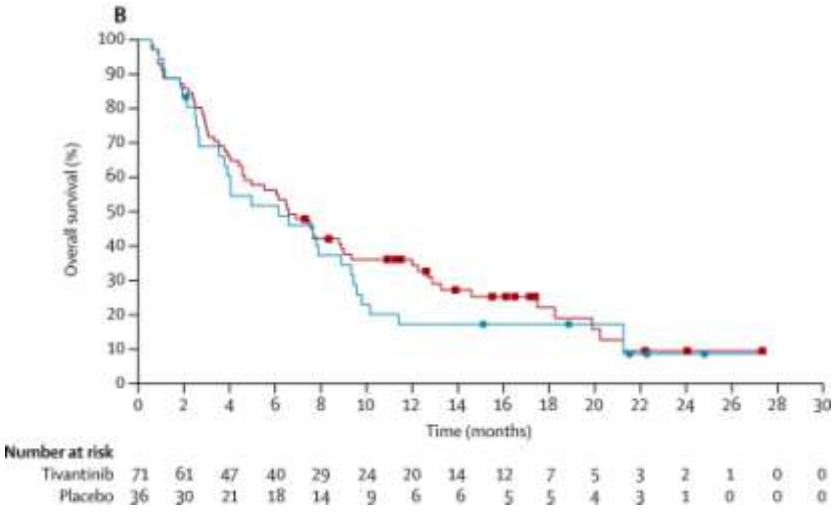
Gene	Chr.	Start	End	CDS length (bp)	Coding indel	Missense	Nonsense	Splice site	Total	*P* value	*q* value	Frequency in validation set
TP53	17	7,572,927	7,579,912	1,218	0	11	0	3	14	0	0	NA
ERRFI1	1	8,073,270	8,075,679	1,397	1	0	2	0	3	0.00020	0.0034	3.1% (2/65)
ZIC3	X	136,648,851	136,652,229	1,412	0	3	0	0	3	0.00050	0.0041	3.3% (4/120)
CTNNB1	3	41,265,560	41,280,833	2,398	0	3	0	0	3	0.0015	0.0071	NA
GXYLT1	12	42,481,588	42,538,448	1,351	0	3	0	0	3	0.0013	0.0071	0.8% (1/120)
OTOP1	4	4,190,530	4,228,591	1,859	1	2	0	0	3	0.0015	0.0071	0.8% (1/120)
ALB	4	74,270,045	74,286,015	1,882	3	0	0	0	3	0.0022	0.0089	3.3% (4/120)
ATM	11	108,098,352	108,236,235	9,415	1	4	0	0	5	0.0037	0.013	5.0% (6/120)
ZNF226	19	44,674,234	44,681,827	2,424	1	1	1	0	3	0.0043	0.014	3.3% (4/120)
USP25	21	17,102,713	17,250,794	3,260	1	2	0	0	3	0.0051	0.015	0% (0/120)
WWP1	8	87,386,280	87,479,122	2,857	2	1	0	0	3	0.0060	0.016	7.7% (5/65)
IGSF10	3	151,154,477	151,176,497	7,892	0	4	0	0	4	0.0091	0.023	3.3% (4/120)
ARID1A	1	27,022,895	27,107,247	6,934	2	1	0	0	3	0.011	0.026	10% (12/120)
UBR3	2	170,684,018	170,938,353	5,819	0	3	0	0	3	0.018	0.041	0.8% (1/120)
BAZ2B	2	160,176,776	160,335,230	6,643	0	3	0	0	3	0.024	0.050	1.6% (2/120)

Significantly mutated genes with more than two mutations are shown. Chr., chromosome.

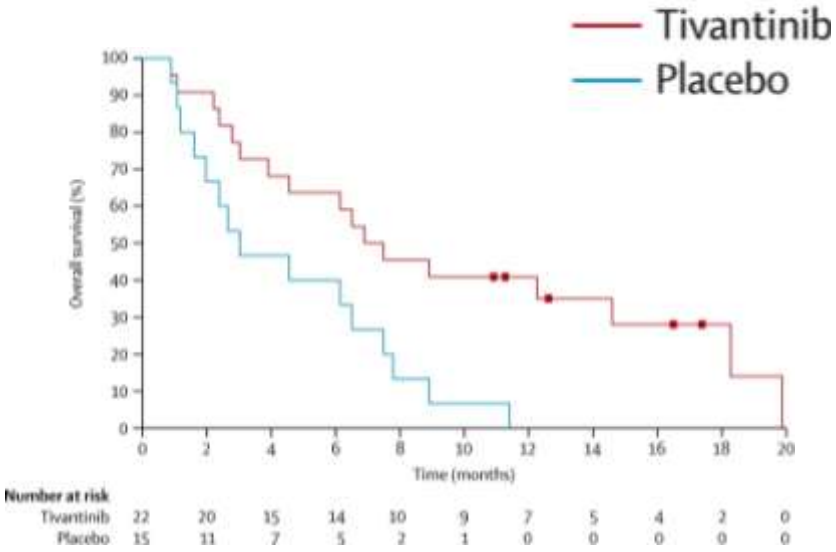
Fujimoto et al. Nat Gent 2012

Tivantinib as second-line

- Survival could be divided by MET expression



All patients



MET-high subgroup

Santoro et al. Lancet Oncol 2013

Conclusion

- The understanding of molecular mechanism of cancer sheds a new light on liver biopsy
- However “tailored medicine” is still far from clinical practice in HCC
- Further studies are needed for the development in this field

Thank you for your attention !