XXV CONGRESO NACIONAL DE ANATOMÍA PATOLÓGICA
Zaragoza, mayo 2011

CLUB DE PATOLOGÍA HEPATO-BILIAR
CASO SEMINARIO

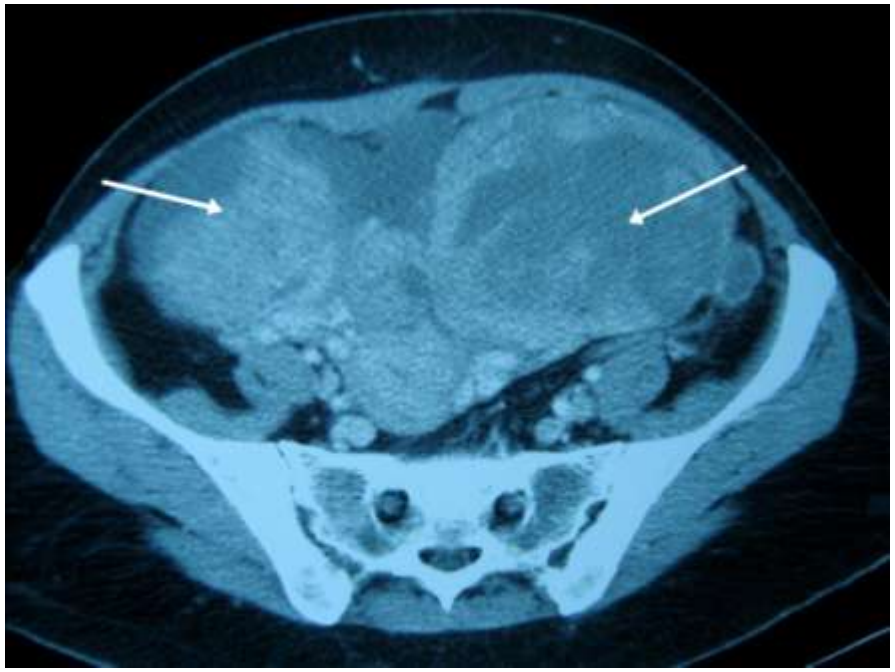
Dra. HELENA ALLENDE MONCLÚS
Dra. Mª ANGELES MONTERO

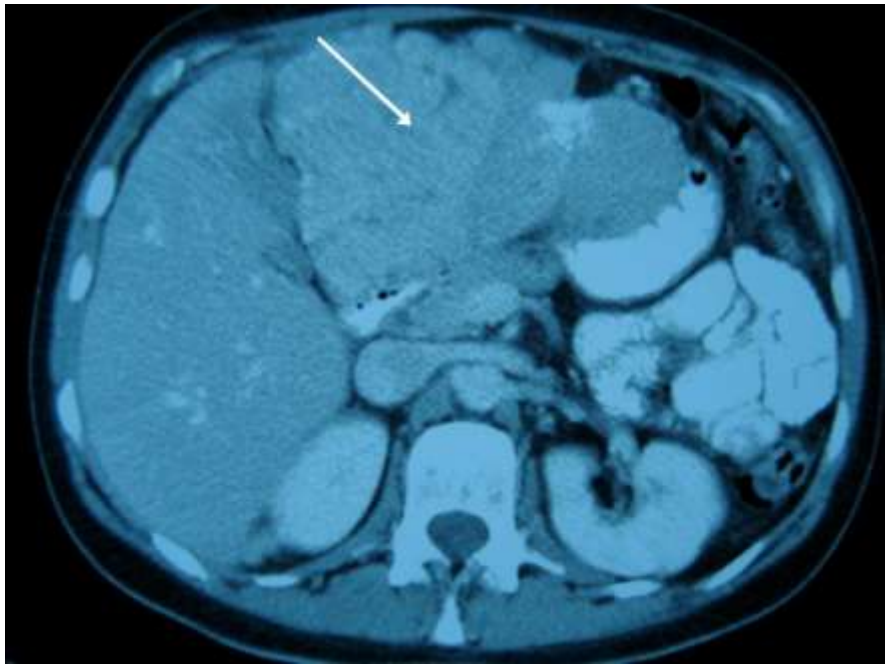
UAB
Universitat Autònoma de Barcelona

Vall d'Hebron
Hospital

CLÍNICA

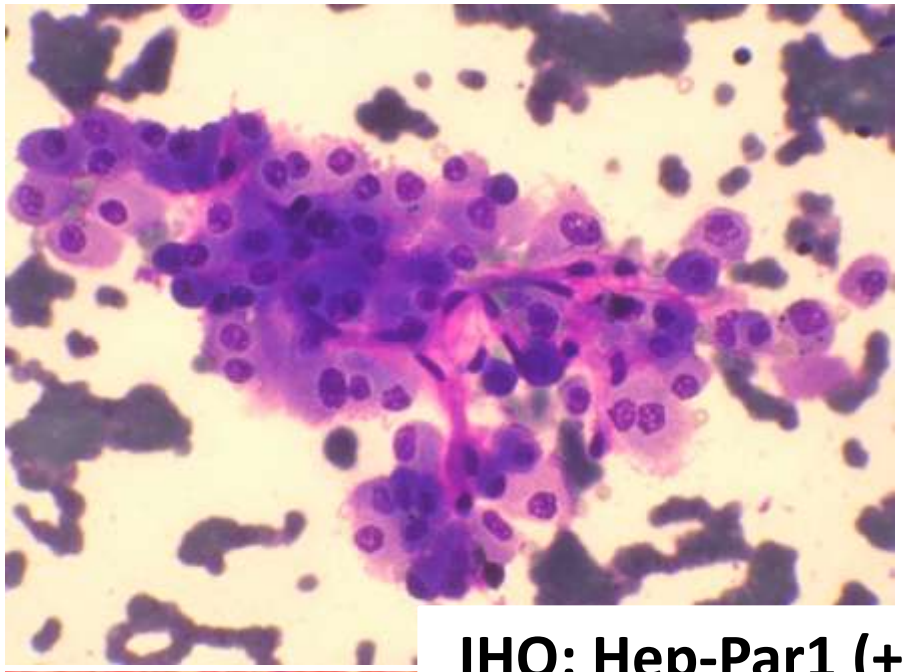
- **Paciente mujer de 47 años, sin antecedentes patológicos, que acude al hospital por disconfor y distensión abdominal de un año y medio de evolución.**
- **La RM pone de manifiesto dos grandes masas ováricas de 11.7 y 12.5 cm respectivamente, un gran tumor en lóbulo hepático izquierdo de 12x8 cm. Y adenopatias e implantes peritoneales.**
- **Marcadores tumorales: Ca125: 165 (N<35) y alfa-fetoproteína normal**
- **Marcadores virales hepáticos negativos y gastroscopia negativa.**

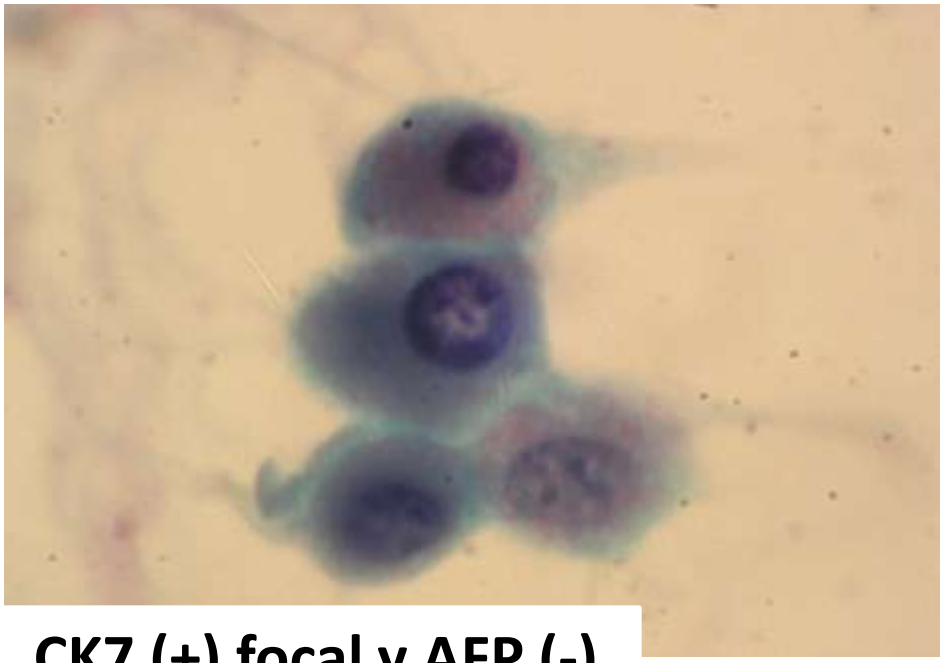




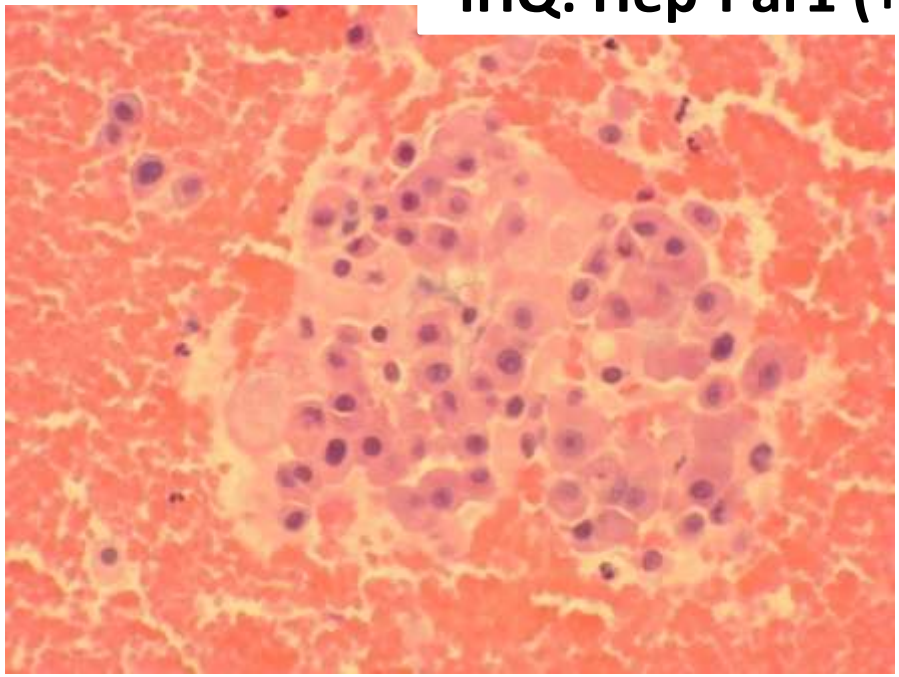
SE REALIZA PAAF DE LA MASA OVÁRICA IZQUIERDA

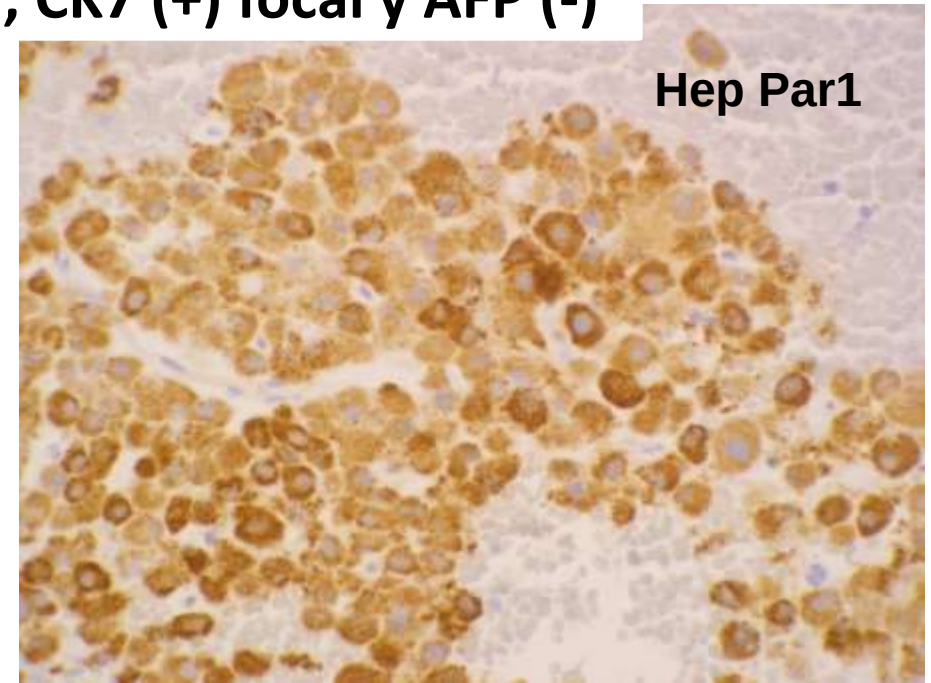
PAAF MASA OVÁRICA IZQUIERDA





IHQ: Hep-Par1 (+), CK7 (+) focal y AFP (-)





OPCIONES DIAGNÓSTICAS SEGÚN MORFOLOGÍA

1. TUMOR PRIMARIO OVÁRICO

- Tumor del seno endodérmico con áreas hepatoides
- Carcinoma hepatoide de ovario

Unilaterales, AFP elevada (IH+), infrecuentes, muy agresivos

2. METÁSTASIS DE ADENOCARCINOMA HEPATOIDE

Gastrointestinal (gastroscopia normal), ovario, páncreas, pulmón, riñón, útero, vejiga urinaria. AFP (IH+)

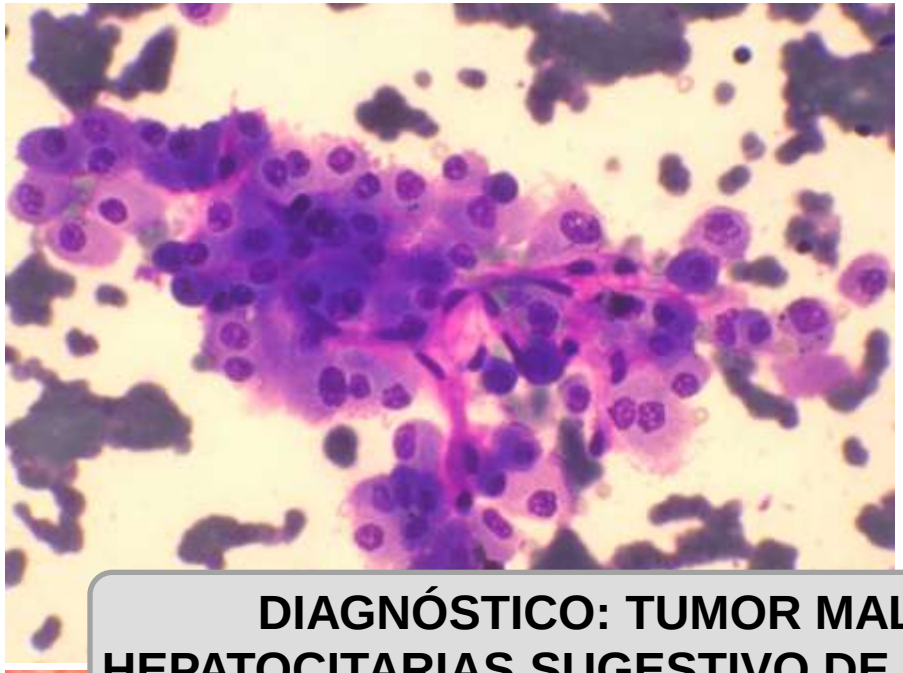
3. METÁSTASIS DE HEPATOCARCINOMA

Revisión de la TAC ⟶ tumor con imagen sugestiva de cicatriz central sobre hígado normal

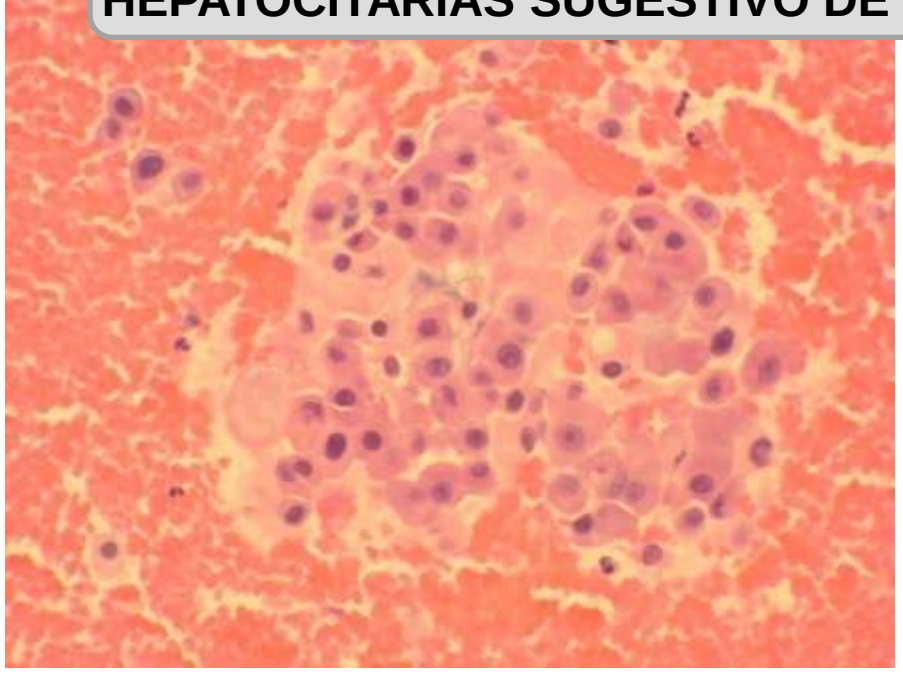
↓

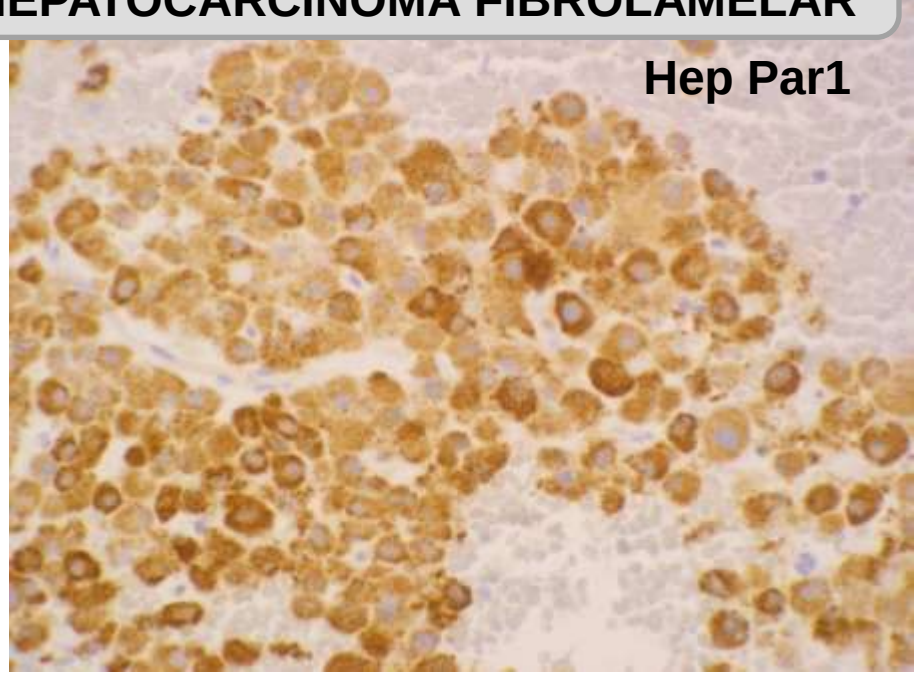
DIAGNÓSTICO

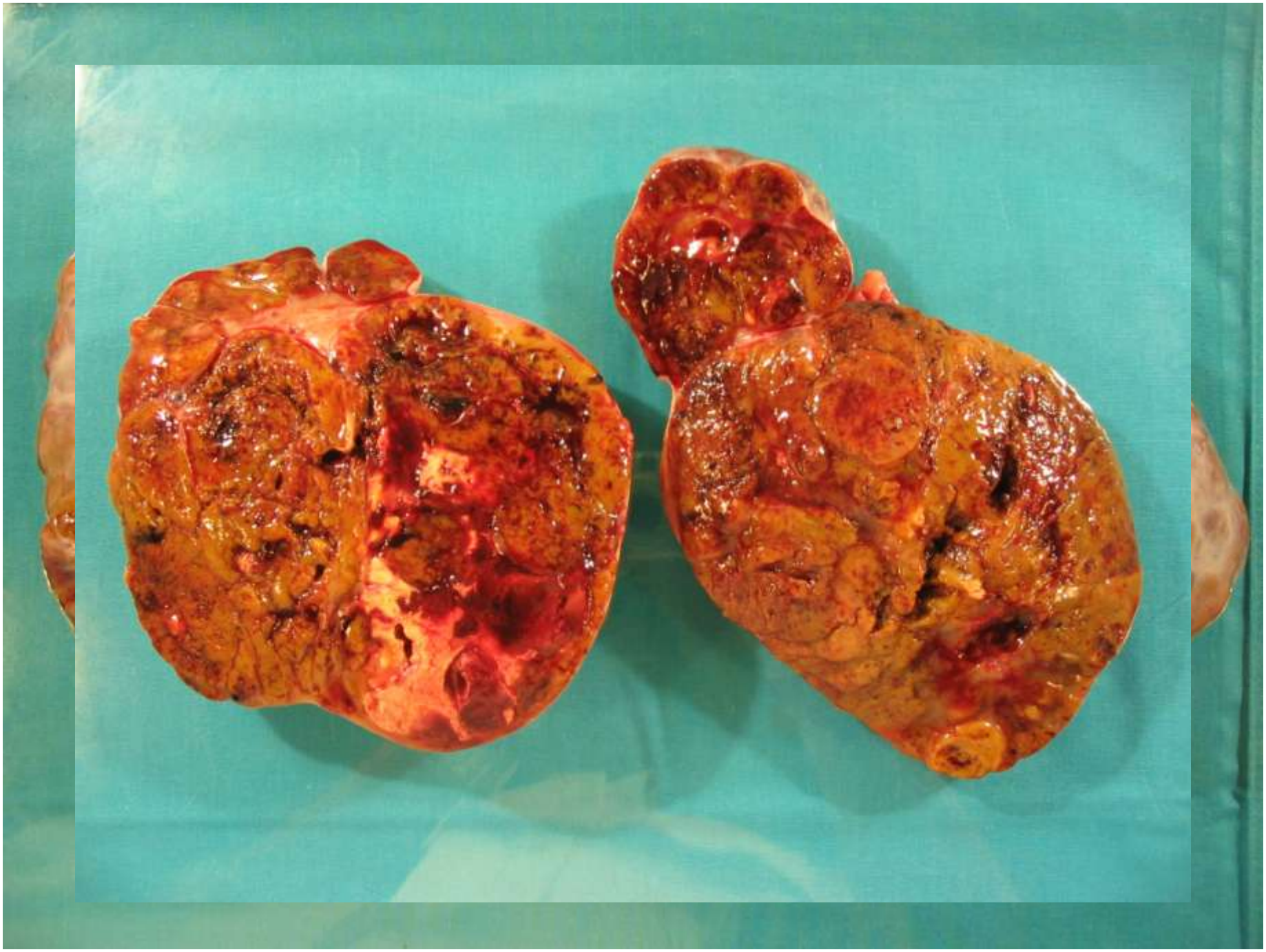
PAAF MASA OVÁRICA IZQUIERDA



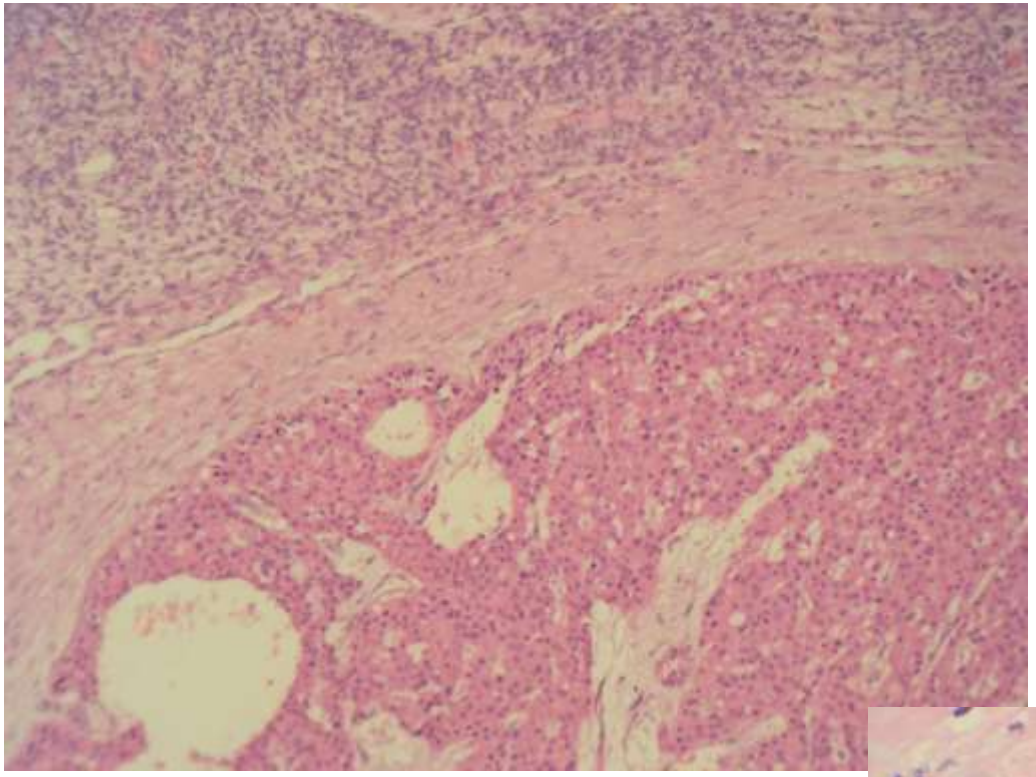
DIAGNÓSTICO: TUMOR MALIGNO CON CARACTERÍSTICAS HEPATOCITARIAS SUGESTIVO DE HEPATOCARCINOMA FIBROLAMELAR

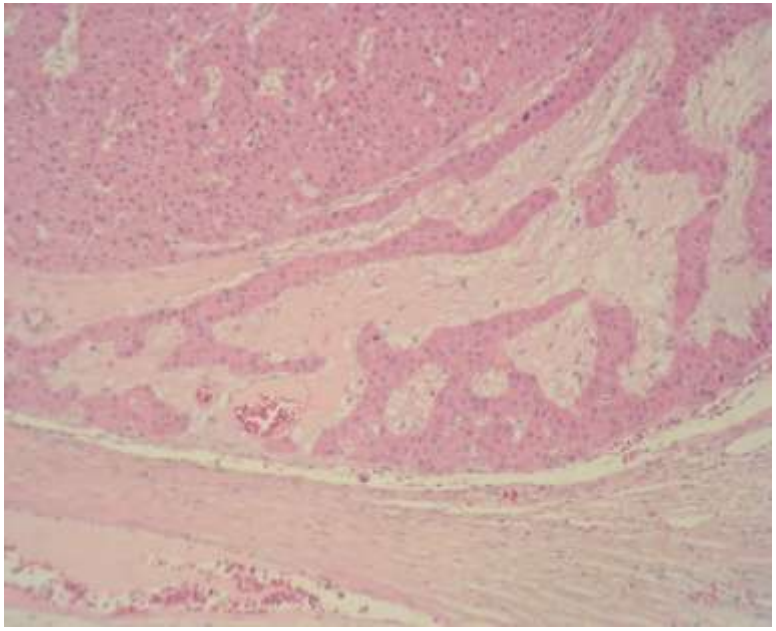


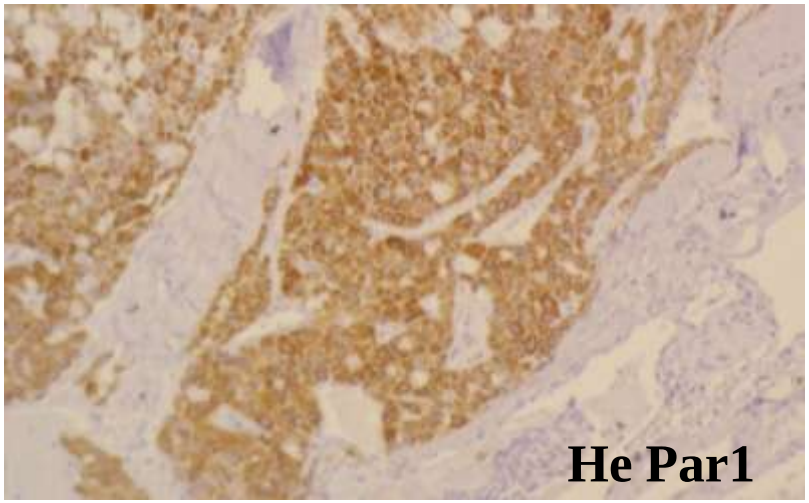


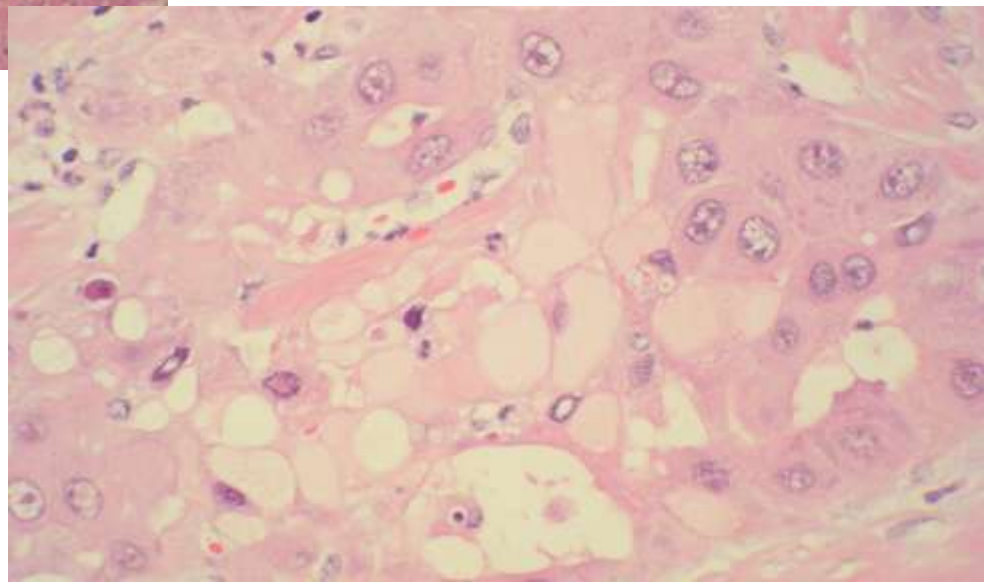


OVARIOS

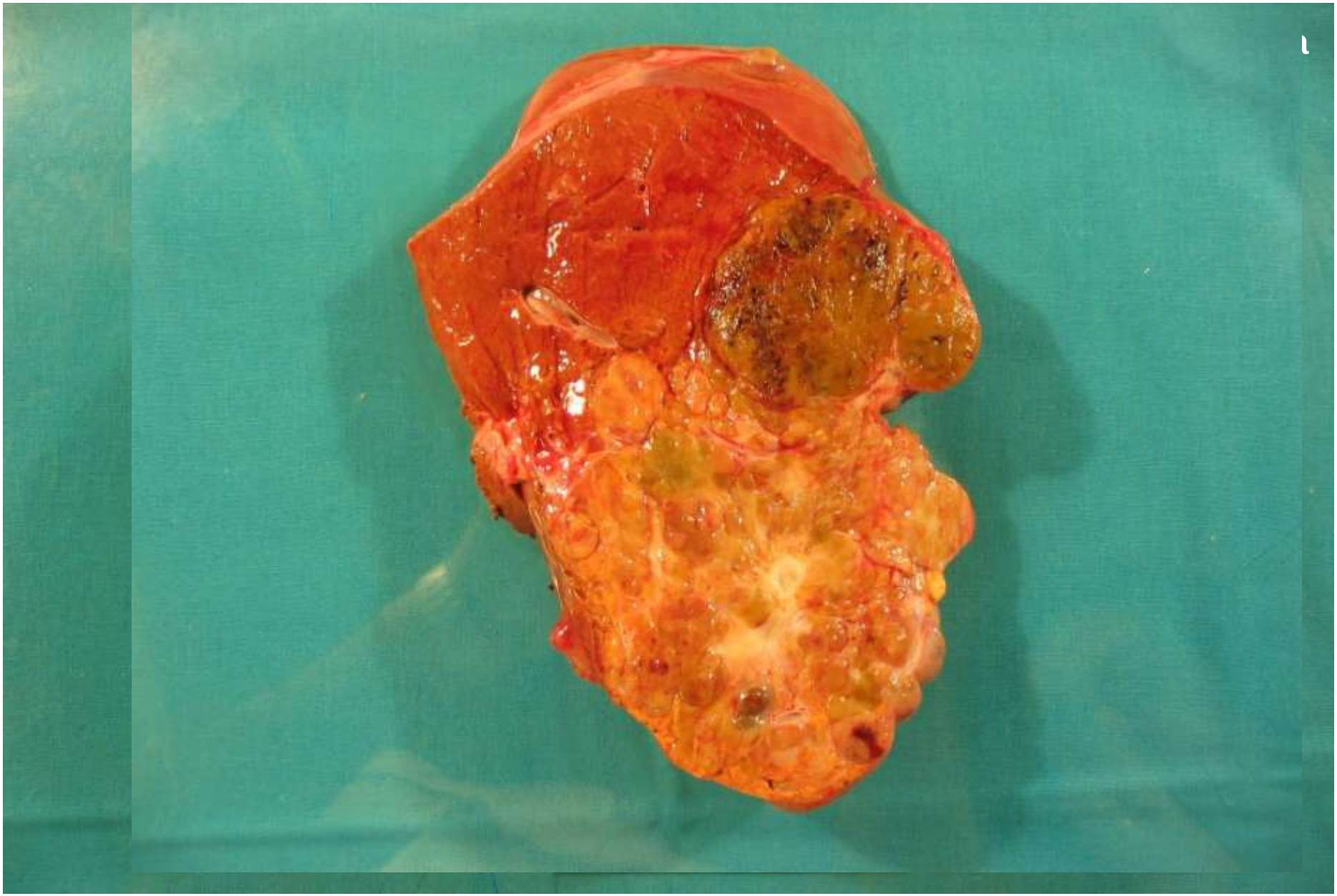




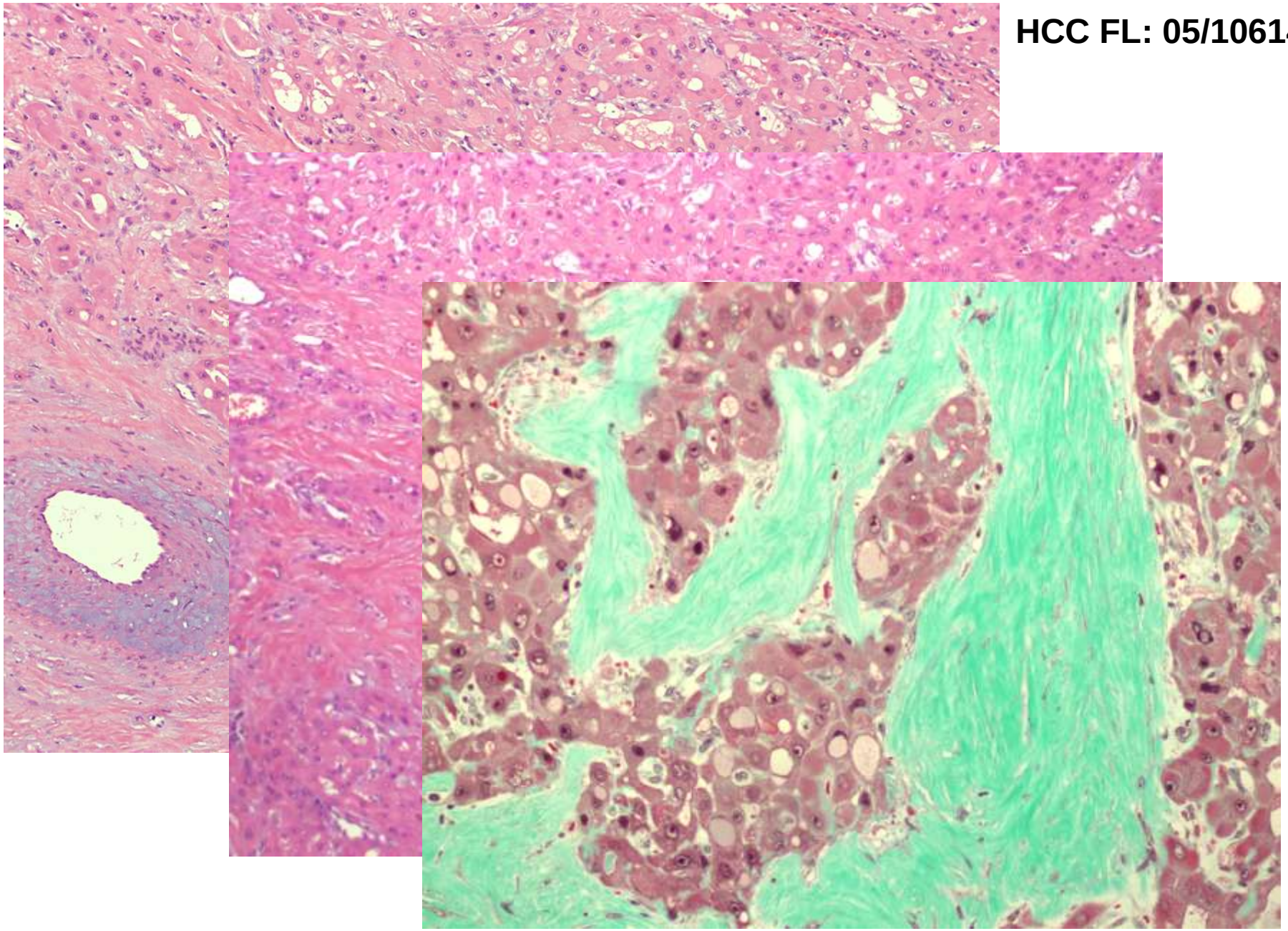


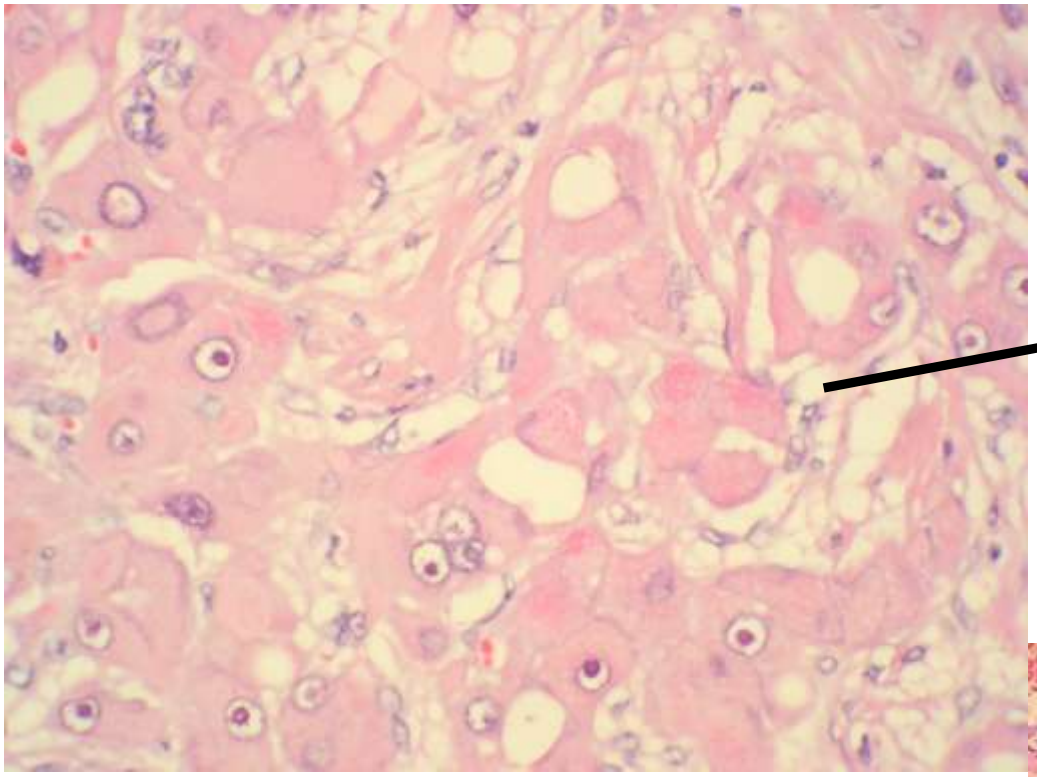


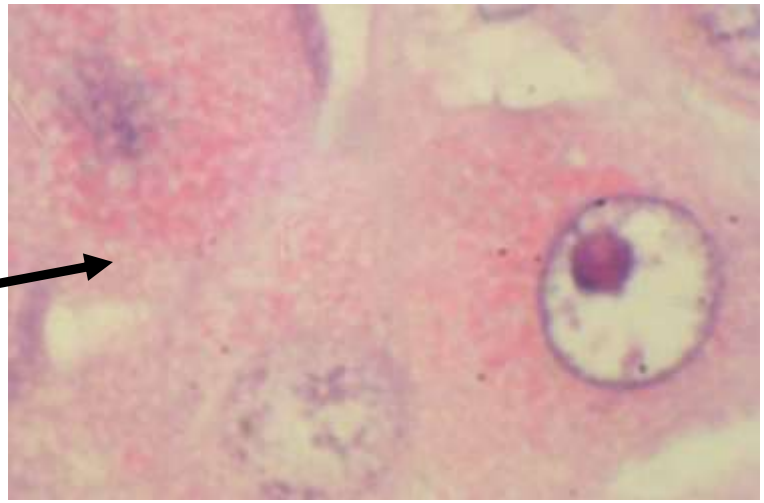
TUMOR HEPÁTICO

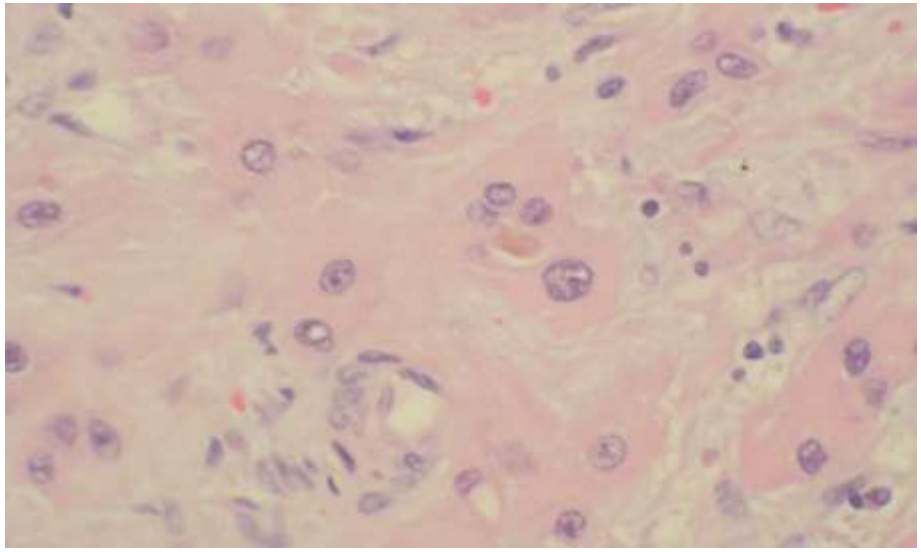


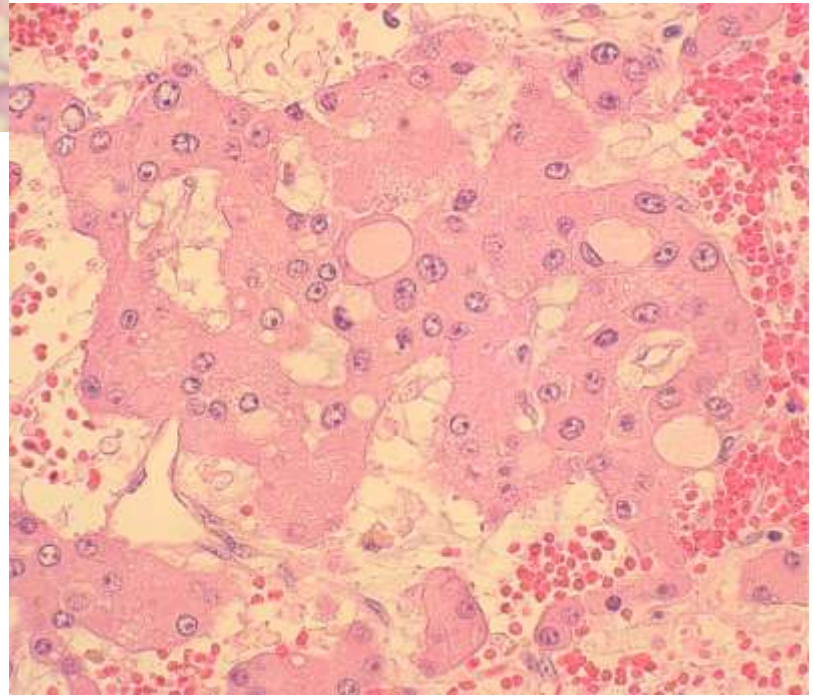
HCC FL: 05/10614

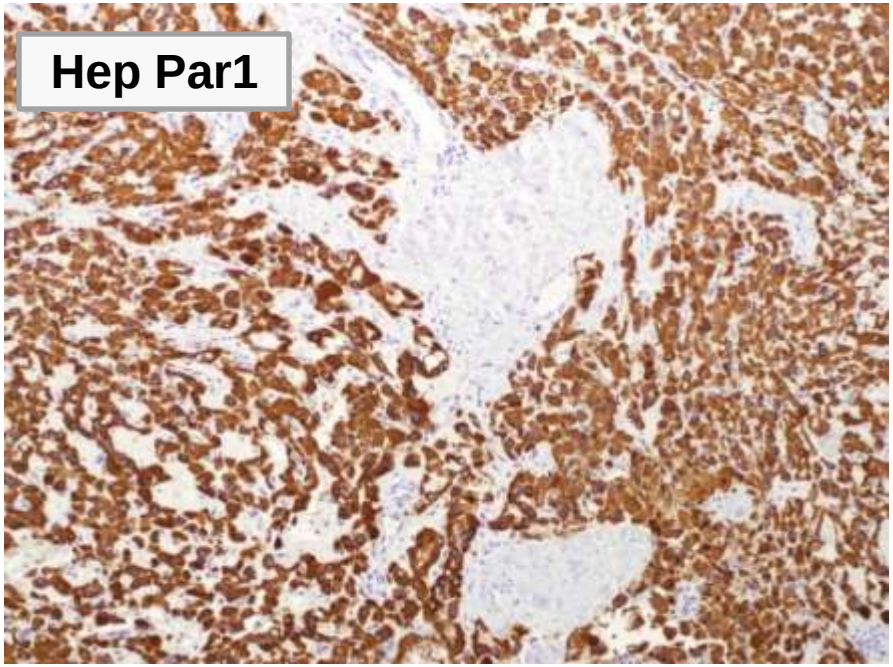


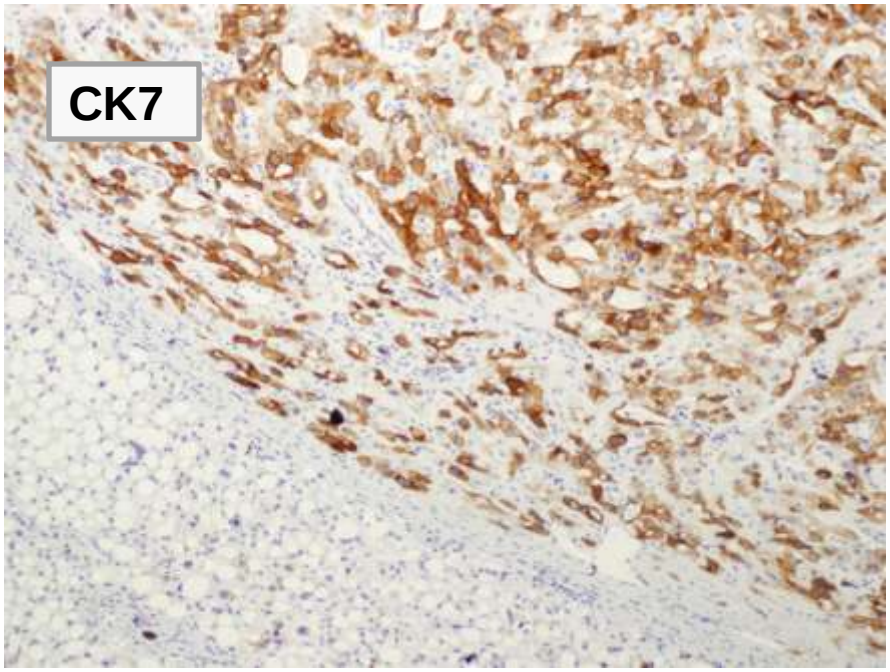


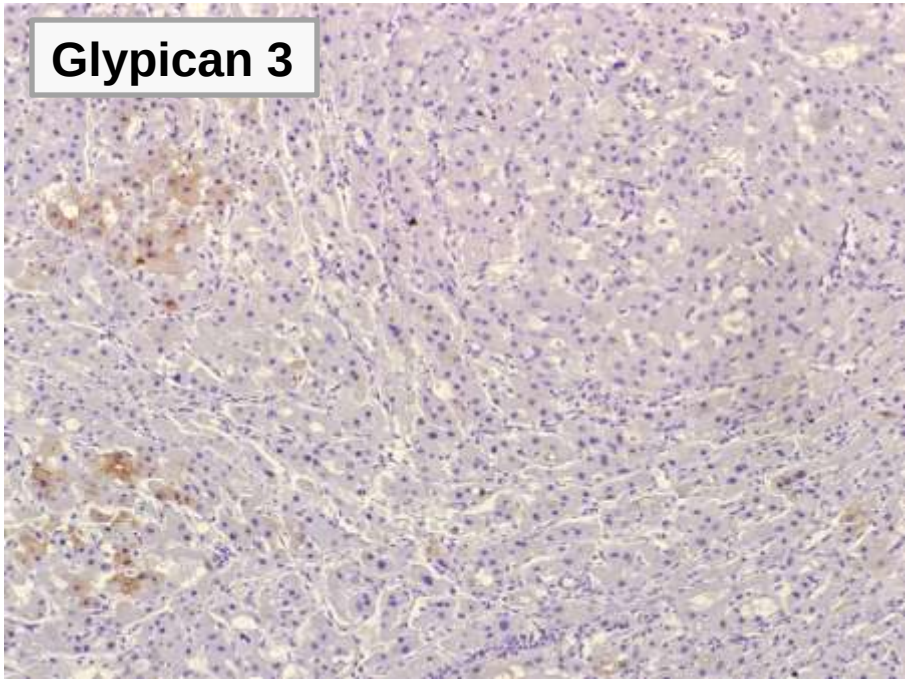


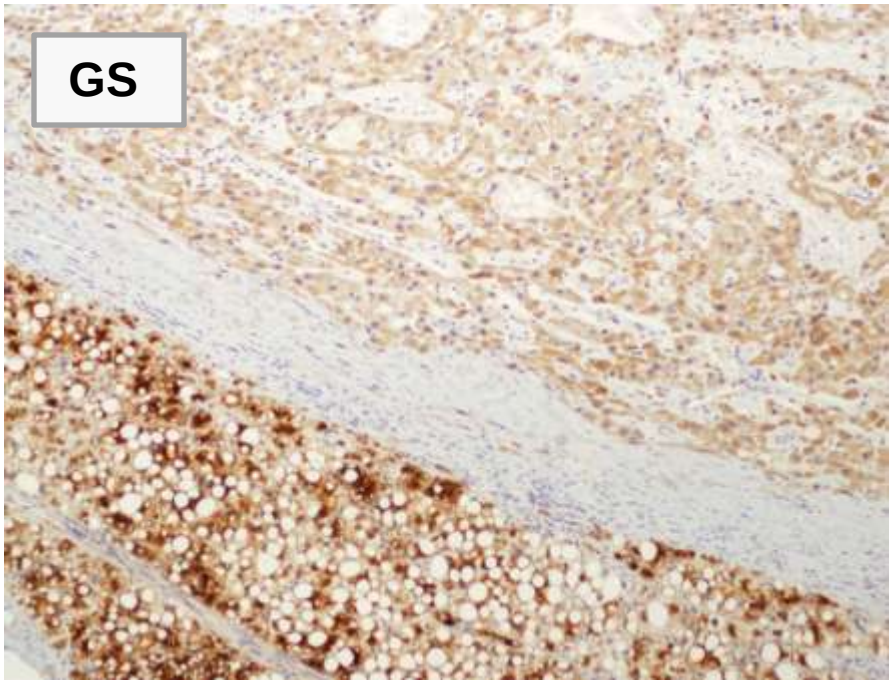


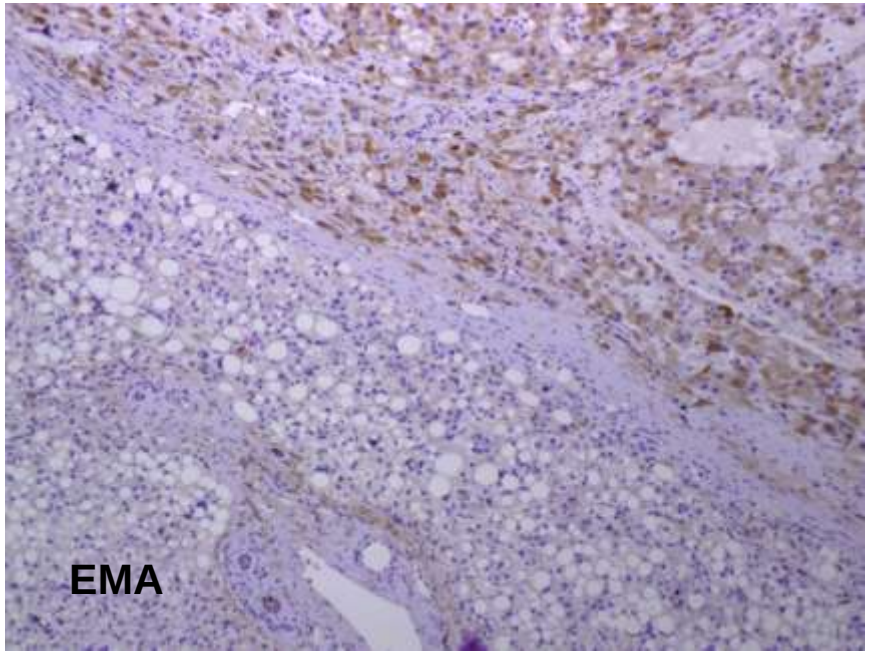


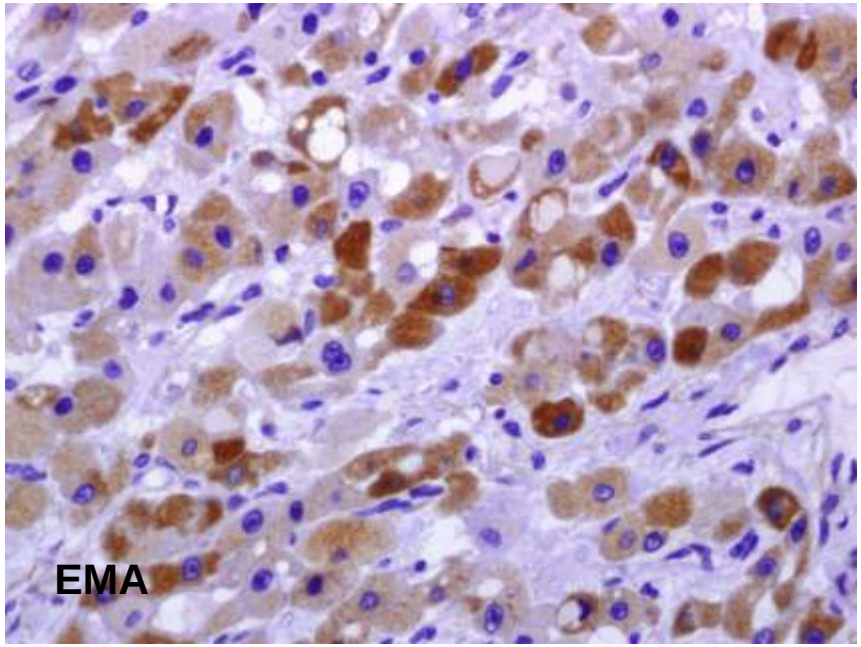

Hep Par1


CK7


Glypican 3


GS


EMA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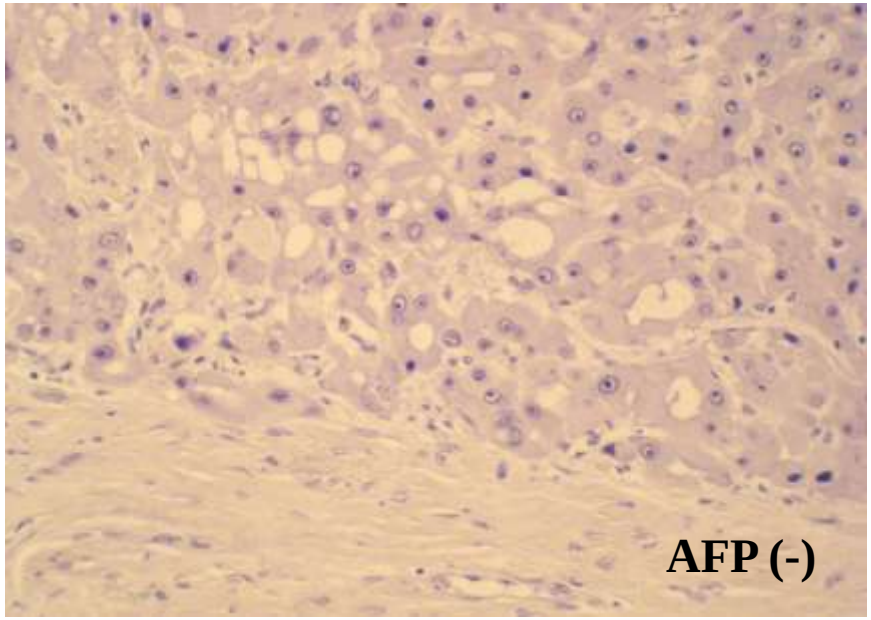
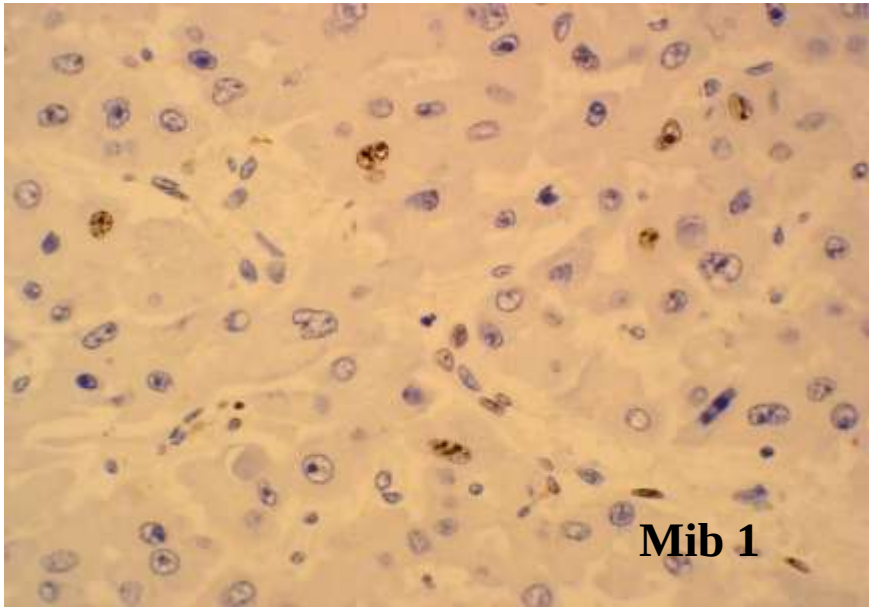
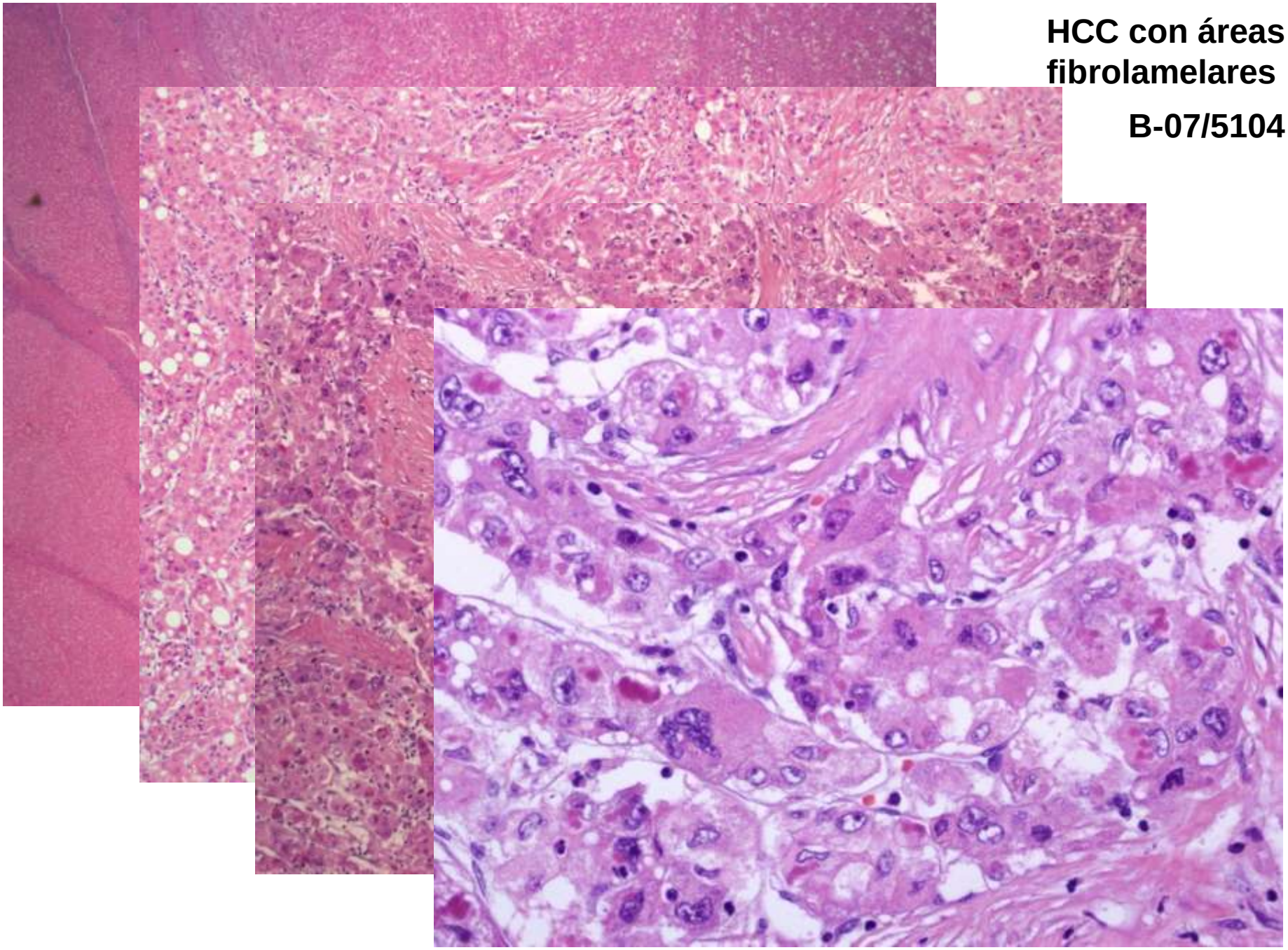

AFP (-)

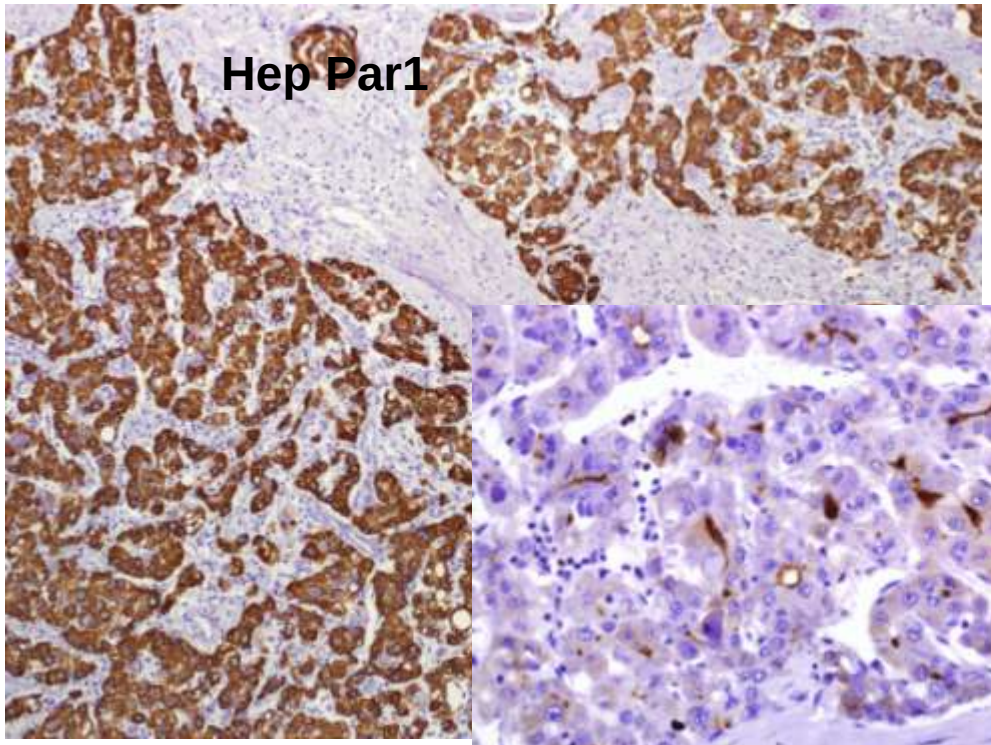

Mib 1

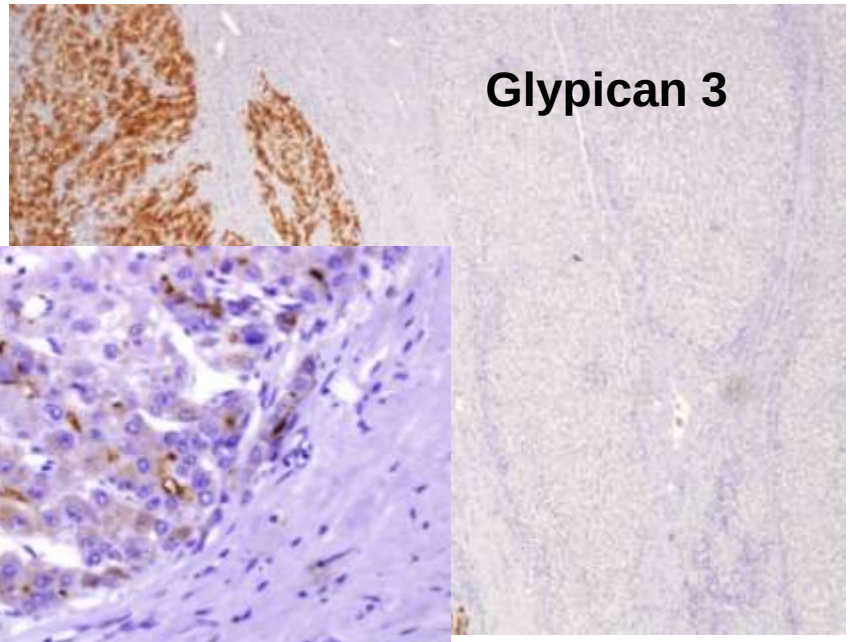


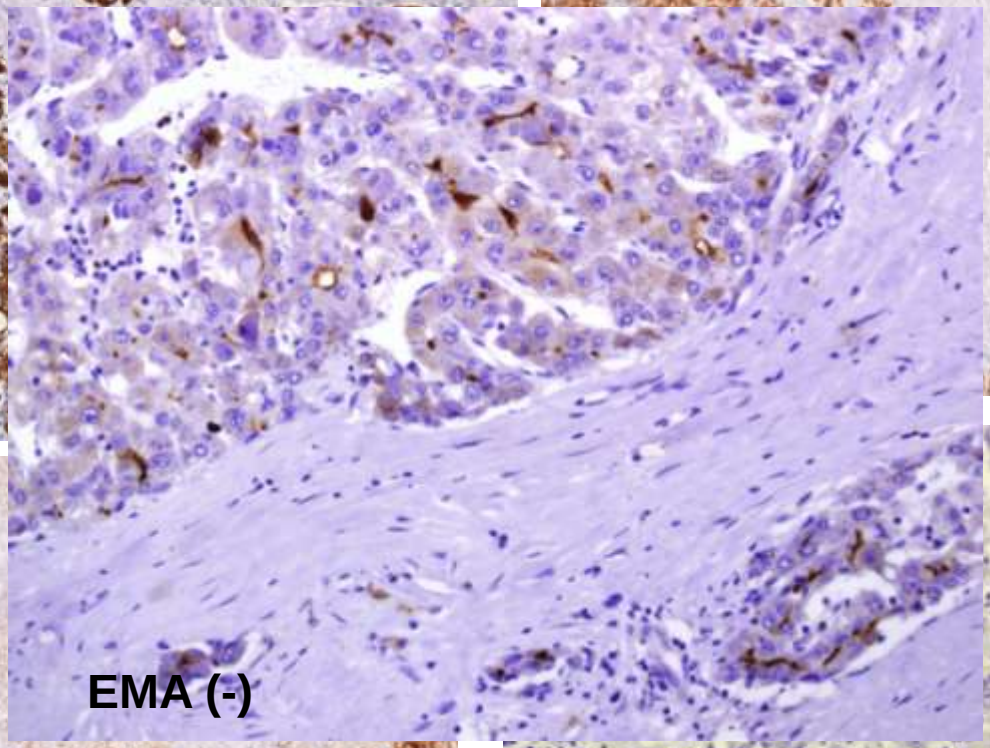
HCC con áreas fibrolamelares

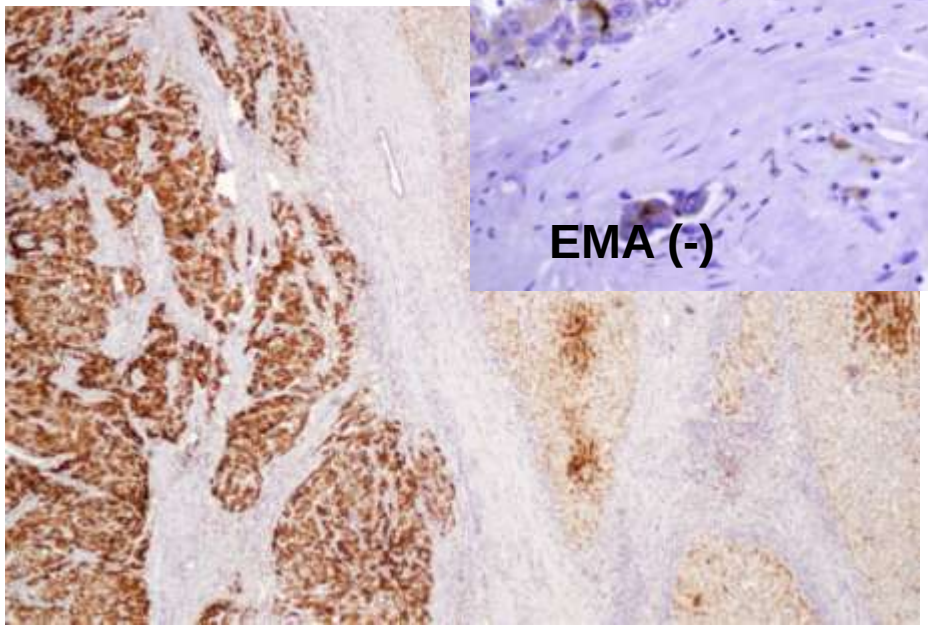
B-07/5104

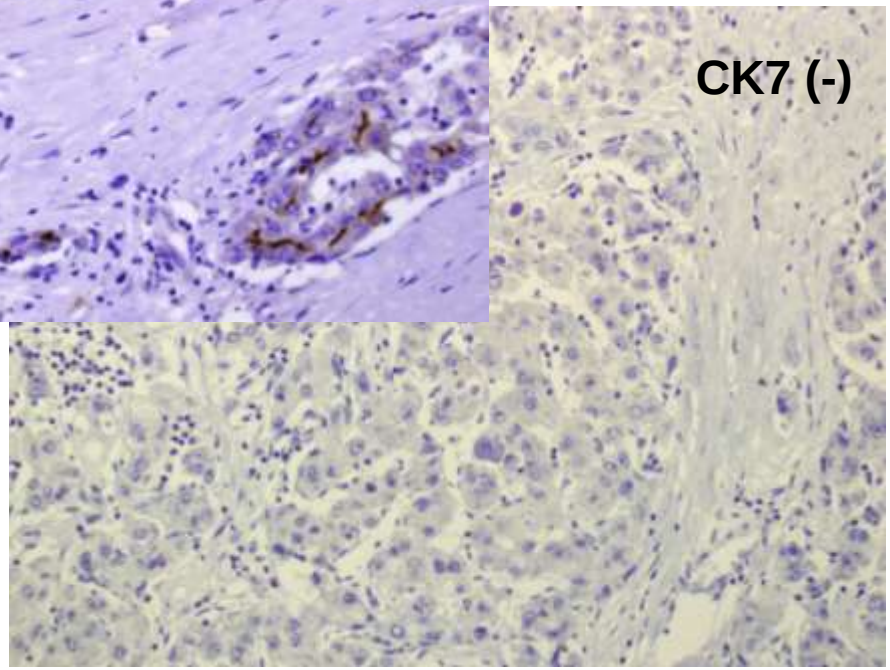
HCC con áreas FL: B-07/5104











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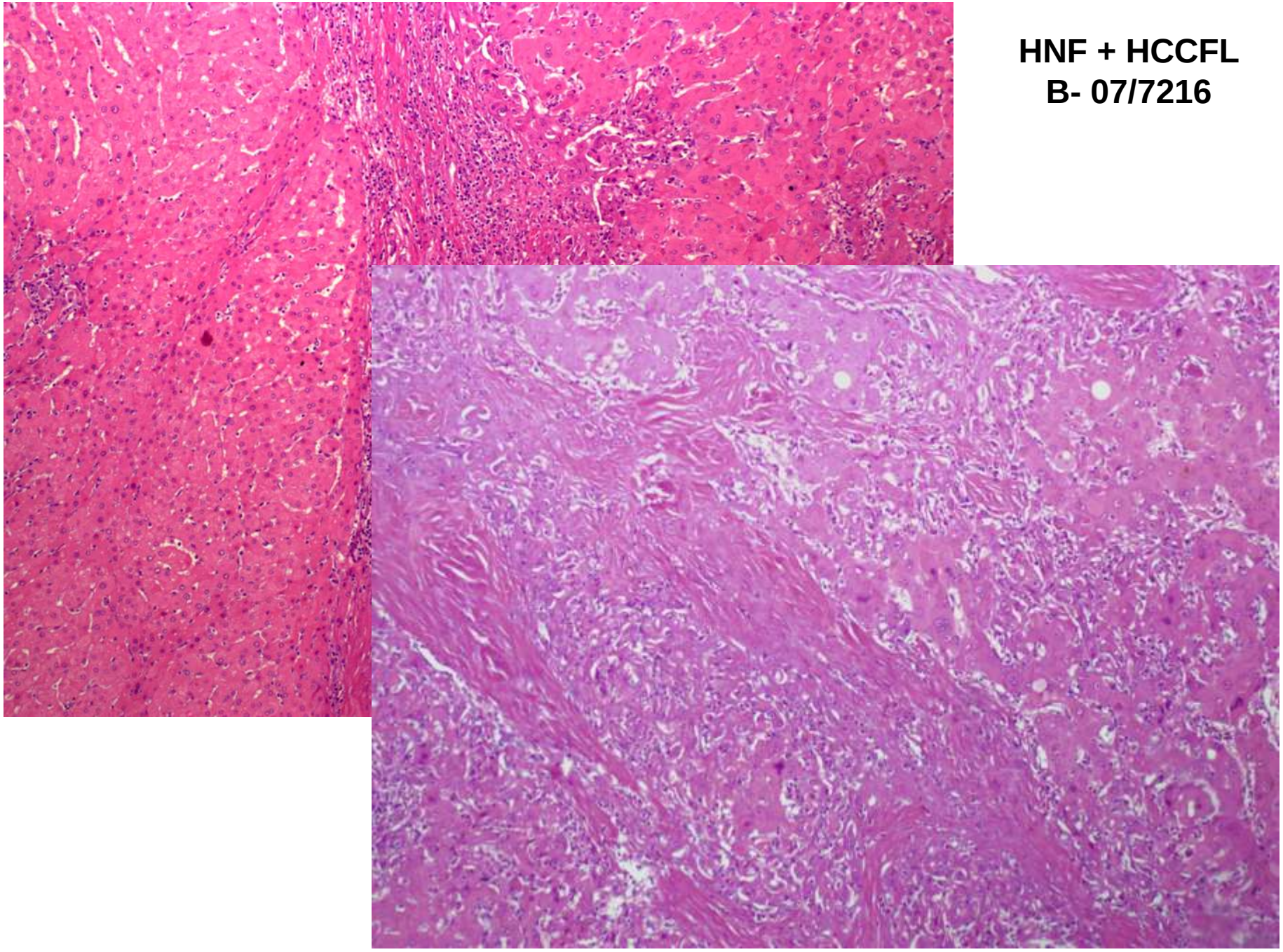
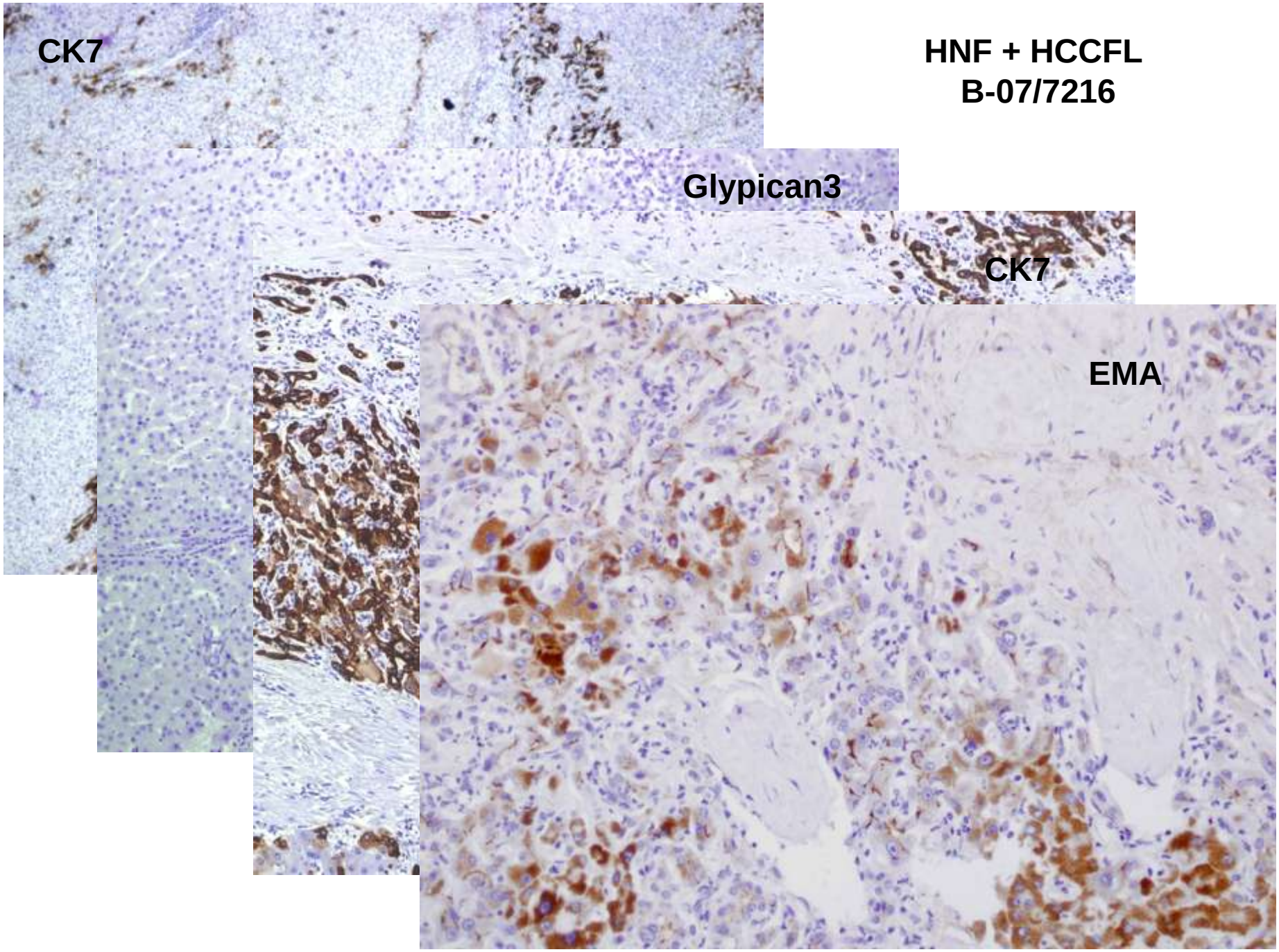
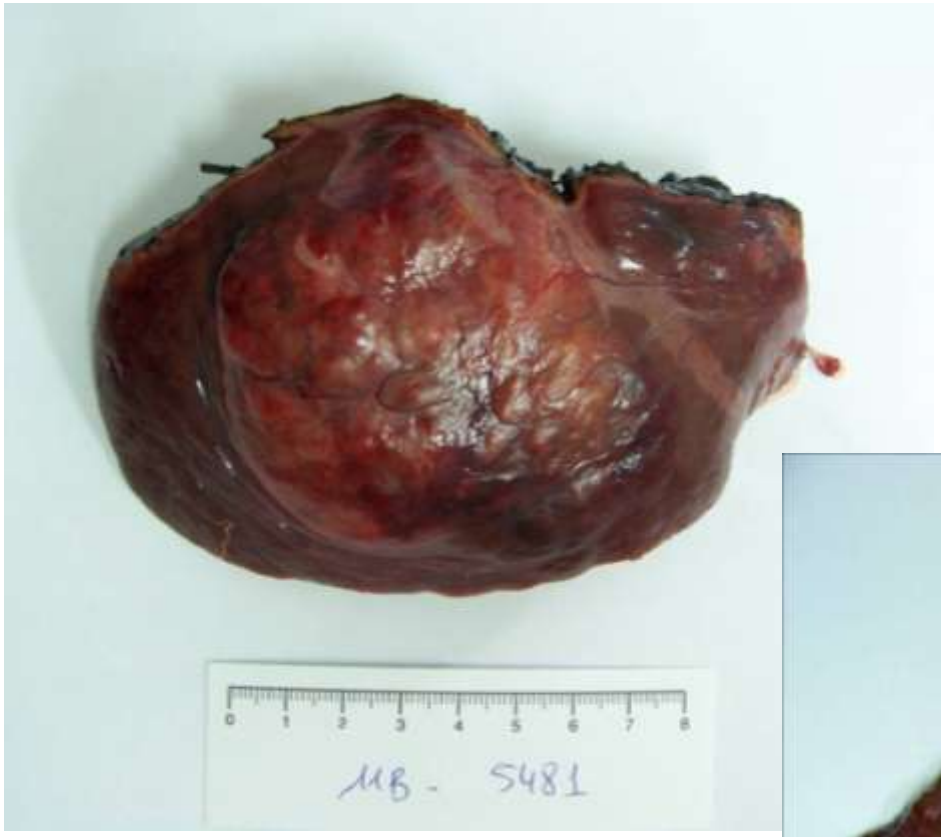


HNF + HCCFL
B- 07/7216


CK7
HNF + HCCFL
B-07/7216
Glypican3
CK7
EMA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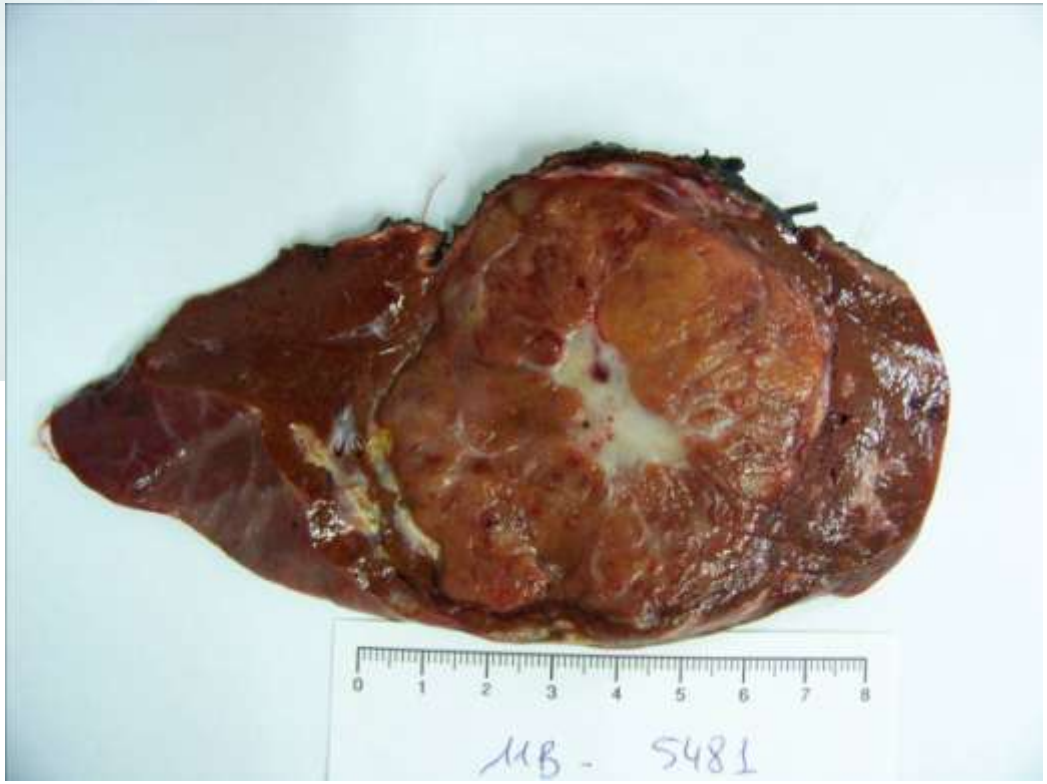
11B - 5481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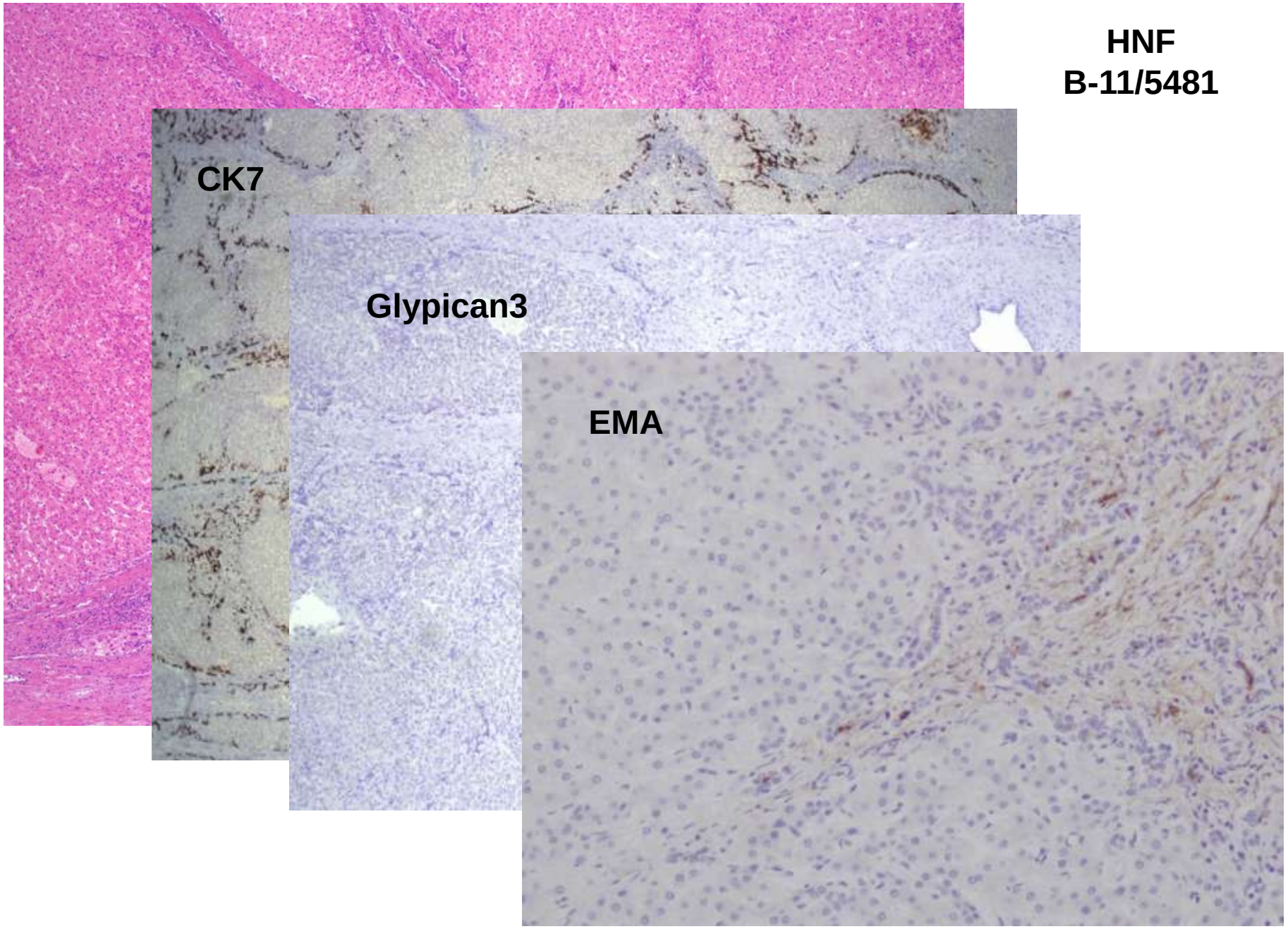
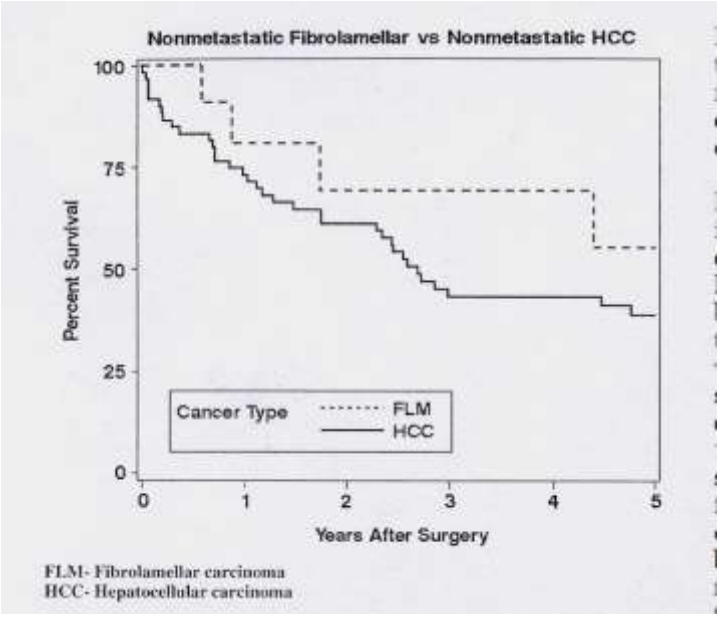
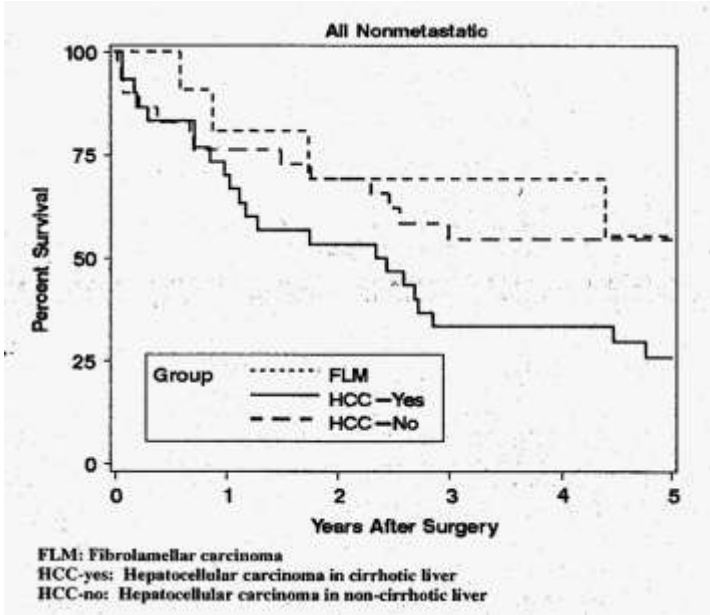

HNF
B-11/5481
CK7
Glypican3
EMA

Hepatocarcinoma fibrolamelar

- **Variante infrecuente del HCC (1-9%).**
- **Jóvenes entre 20-40 años, hígado sano.**
- **Dolor y hepatomegalia**
- **Masa única heterogénea con cicatriz central (20-60%). Calcificación (35-55%)**
- **AFP normal**
- **Mejor pronóstico**





Supervivencia del HC fibrolamelar a los cinco años: 45-60 %. Mortalidad global: 60 %
La ausencia de cirrosis hepática , y no otras características clínico patológicas, supone mejor pronóstico (comparable al del carcinoma hepatocelular convencional sobre hígado no cirrótico). Kakar S, Burgart LJ, Batts KP et al: Modern Pathology 2005;18:1417-1423

Modern Pathology (2008) 21, 1011–1018

www.modernpathology.org

Utility and limitations of glypican-3 expression for the diagnosis of hepatocellular carcinoma at both ends of the differentiation spectrum

Nafis Shafizadeh[1], Linda D Ferrell[1] and Sanjay Kakar[1,2]

[1]*Department of Anatomic Pathology, University of California, San Francisco, CA, USA and* [2]*Department of Anatomic Pathology, Veteran Affairs Medical Center, San Francisco, CA, USA*

Table 1 GPC-3 staining results in benign and malignant hepatocellular lesions

Liver lesions	*GPC-3 staining*[a]	
	Total positive	*Diffuse positive*
Benign hepatocellular lesions		
Cirrhotic nodules ($n=35$)	4 (11)	0 (0)
Macroregenerative nodule ($n=10$)	0 (0)	0 (0)
Hepatic adenoma ($n=8$)	0 (0)	0 (0)
Borderline and malignant lesions		
High-grade dysplastic nodule ($n=7$)	3 (43)	0 (0)
Extremely well-differentiated HCC ($n=10$)	5 (50)	2 (20)
HCC, well differentiated ($n=16$)[b]	9 (56)	5 (31)
HCC, moderately differentiated ($n=18$)	15 (83)	10 (56)
HCC, poorly differentiated ($n=24$)	22 (89)	20 (83)
Fibrolamellar HCC ($n=11$)	7 (64)	4 (36)

HCC, hepatocellular carcinoma.
[a]Figures in parenthesis reflect percentages.
[b]Includes extremely well-differentiated HCC.

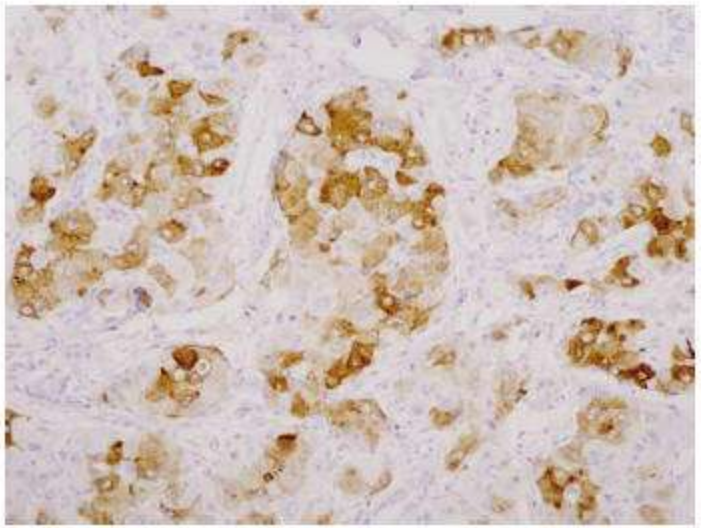


Figure 5 Diffuse cytoplasmic expression of glypican-3 in fibrolamellar hepatocellular carcinoma (× 200).

MODERN PATHOLOGY (2010) 23, 1180–1190

Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation

Stephen C Ward[1,3], Jiaoti Huang[1,4], Satish K Tickoo[1], Swan N Thung[2], Marc Ladanyi[1] and David S Klimstra[1]

[1]*Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA and* [2]*The Lillian and Henry M. Stratton-Hans Popper Department of Pathology, The Mount Sinai Medical Center, New York, NY, USA*

Table 3 Results of immunohistochemical stains with pCEA, HepPar1, and anti-AFP, and *in situ* hybridization with an albumin mRNA probe

		HepPar	*pCEA*[a]	*AFP*	*Albumin mRNA probe*	
	n	*% Positive (% FP)*	*% Positive (% FP)*	*% Positive (% FP)*	*Anti-sense*	*Sense*
Hepatocellular carcinoma	10	100 (0)	0 (80)	0 (40)	100	0
Fibrolamellar carcinoma	9	100 (0)	11 (78)	0 (0)	100	0

[a]Only canalicular staining pattern is considered true staining.

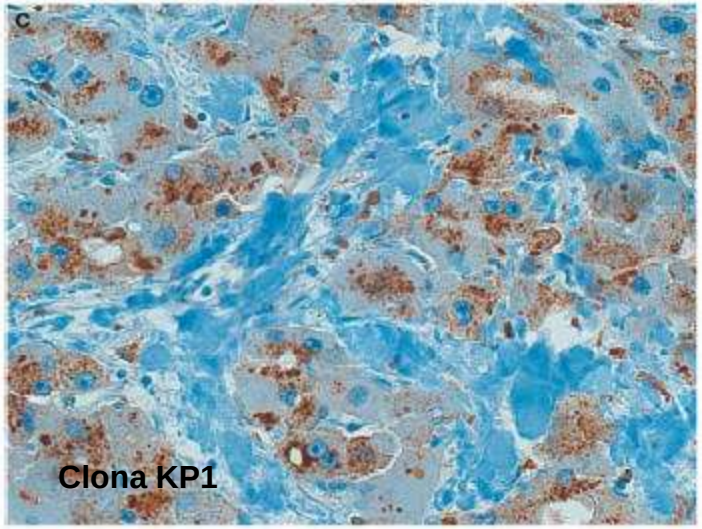
Table 4 Results of immunohistochemical stains for p53, glypican-3, and markers associated with biliary differentiation

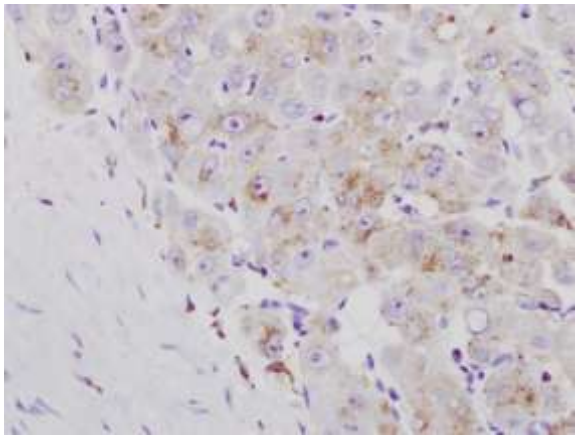
	n	*p53 % Positive (% FP)*	*Glypican-3 % Positive (% FP)*	*CD10 % Positive (% FP)*	*CK7 % Positive (% FP)*	*EMA % Positive (% FP)*	*B72.3 % Positive (% FP)*	*mCEA % Positive (% FP)*	*EpCAM % Positive (% FP)*	*CK19 % Positive (%FP)*	*CA19-9 % Positive (% FP)*
HCC	50	38 (18)	39 (0)*	30 (6)	28 (32)	28 (6)	0 (2)	0 (0)	0 (0)*	10 (4)	2 (4)
FLC	22	23 (14)	59 (0)	32 (5)	100 (0)	100 (0)	23 (23)	9 (0)	14 (5)	23 (0)	0 (9)
P-value		NS	NS	NS	<0.0001	<0.0001	<0.0001	<0.01	<0.01	NS	NS

MODERN PATHOLOGY (2011) 24, 390–395

Fibrolamellar carcinomas are positive for CD68

Hillary M Ross[1], Hubert DJ Daniel[1], Perumal Vivekanandan[1], Rajesh Kannangai[1], Matthew M Yeh[2], Tsung-Teh Wu[3], Hala R Makhlouf[4] and Michael Torbenson[1]





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Clona: PG-M1

Table 2 Accuracy indices of CD68 staining as a marker for the diagnosis of fibrolamellar carcinoma in a primary liver carcinoma[a]

Performance characteristics	*Value (%)*
Sensitivity	95.6
Specificity	80.3
Positive predictive value	62.9
Negative predictive value	98.1

[a]Calculated using 23 cases with primary fibrolamellar carcinoma and 66 cases with typical hepatocellular carcinoma.

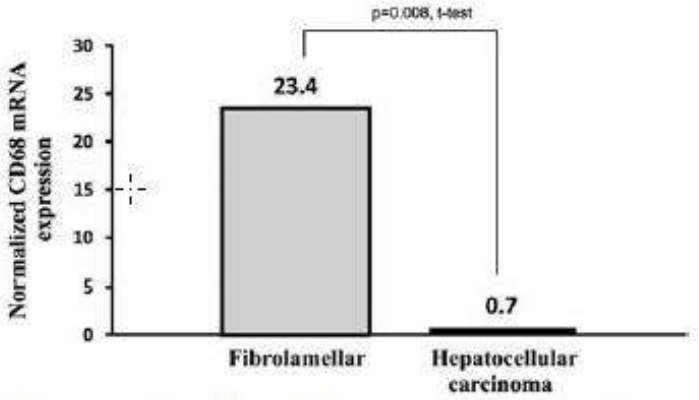

Figure 3 Fibrolamellar carcinomas ($N=7$) showed significantly more expression of CD68 than typical hepatocellular carcinomas ($N=6$). The typical hepatocellular carcinomas arose in livers with cirrhosis and chronic hepatitis C.

HEPATOCARCINOMA FIBROLAMELAR
ESTUDIO INMUNOHISTOQUÍMICO

- **M. de epitelio biliar: CK7, EMA**
- **M. de hepatocito: HepPar1, Glypican 3 (< sensibilidad que el HCC)**
- **Células progenitoras hepáticas: CK19, EpCAM**
- **pCEA y CD10 (+) con patrón canalicular**
- **AFP (-)**
- **CD68 (+)**

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Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation

Stephen C Ward[1,3], Jiaoti Huang[1,4], Satish K Tickoo[1], Swan N Thung[2], Marc Ladanyi[1] and David S Klimstra[1]

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Fibrolamellar Hepatocellular Carcinoma: An Immunohistochemical Comparison With Conventional Hepatocellular Carcinoma

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www.ijcep.com /IJCEP1010004

Original Article

Cell cycle biology of fibrolamellar hepatocellular carcinoma

Sadhna Dhingra[1], Wei Li[1], Dongfeng Tan[2], Maryam Zenali[2], Haizeng Zhang[2], Robert E. Brown[1]

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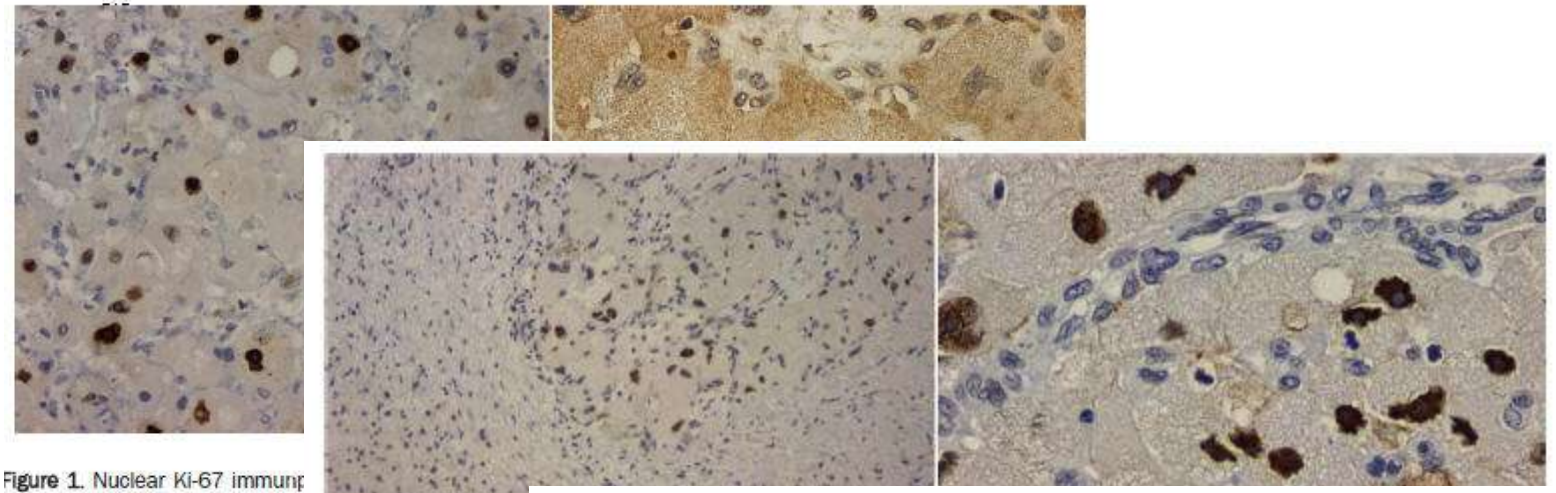

Figure 1. Nuclear Ki-67 immunop
nuclear percentage of 29.8% (A)
with background cytoplasmic sta

Figure 2. Intense nu
expression in adjace
of p16INK4 with spa

Table 2. Nuclear cell cycle analytes and expression frequency in seven (7) cases of fibrolamellar hepatocellular carcinoma

Analyte	Cell cycle phase	Expression frequency
Ki-67	G1, S,G2, M phase	7/7*
p16INK4	CDKI(Inhibits G1 to S phase)	7/7 (100%)
p27Kip1	CDKI(Inhibits G1 to S phase)	1/7(14%)
Skp2	S phase (Promotes G1 to S phase)	0/7 (0%)
Mitotic Index**	M phase	0-1 mitotic figures /10 hpf

* Ki-67 (proliferation index) with average nuclear percentage range of 1 to 29.8% among the 7 cases (median at 5.5 %). ** Mitotic index range of 0 to 1 mitotic figures per ten high power fields in each of 7 cases.

Modern Pathology (2009) 22, 134–141

www.modernpathology.org

Chromosomal changes in fibrolamellar hepatocellular carcinoma detected by array comparative genomic hybridization

Sanjay Kakar[1,2], Xin Chen[3], Coral Ho[3], Lawrence J Burgart[4], Vaibhav Sahai[5], Somkid Dachrut[6], Annoel Yabes[1], Dhanpat Jain[7] and Linda D Ferrell[1]

(*P* = 0.1). In conclusion, fibrolamellar carcinomas show fewer chromosomal abnormalities compared with those reported in literature for conventional hepatocellular carcinoma. The most common abnormalities occur in chromosomes 7 and 8. Fibrolamellar carcinomas with chromosomal changes appear to behave more aggressively compared with cases with no cytogenetic abnormalities. The favorable outcome in some fibrolamellar carcinomas may be due to absent or low number of cytogenetic aberrations.
Modern Pathology (2009) **22**, 134–141; doi:10.1038/modpathol.2008.178; published online 7 November 2008

Mod Pathol. 2010 June ; 23(6): 790–798. doi:10.1038/modpathol.2010.51.

Mitochondrial Mutations in Hepatocellular Carcinomas and Fibrolamellar Carcinomas

Perumal Vivekanandan, Ph.D.[1], **Hubert Daniel, Ph.D.**[1], **Matthew M. Yeh, M.D., Ph.D.**[2], and **Michael Torbenson, M.D.**[1]

In conclusion, control region deletions are associated with lower mitochondrial DNA levels and their recurrent presence in hepatocellular carcinoma suggests a potential oncogenic role. In contrast, somatic mutations in the coding region do not adequately explain the variation in tumor mitochondrial DNA numbers. Furthermore, most control region single base pair mutations are not oncogenic because they are also present as polymorphisms in the general population. These observations are expanded and reinforced by analysis of fibrolamellar carcinomas, which do have not consistent patterns of mitochondrial DNA changes despite their mitochondrial abnormalities.

HEPATOCARCINOMA FIBROLAMELAR

PUNTOS FUERTES

- **Tumoración hepática única en pacientes jóvenes sin hepatopatía de base**
- **Rx: Lesión hipervascular con frecuente cicatriz central hipoecoica e hipodensa.**
- **Microscópicamente : Componente bifásico con hepatocitos oncocitarios y fibrosis de disposición lamelar**
- **El HCC FL puede presentar áreas de HNF**
- **Los HCC pueden presentar áreas fibrolamelares**
- **IH más prevalente: HepPar1(+), Glypican-3 (+/-) CK7 (+). EMA (+) pCEA (+) CD68 (+) AFP (-)**
- **La edad del paciente y la ausencia de cirrosis le confieren mejor pronóstico que el HCC convencional y por ello ser más agresivo en el tratamiento quirúrgico.**