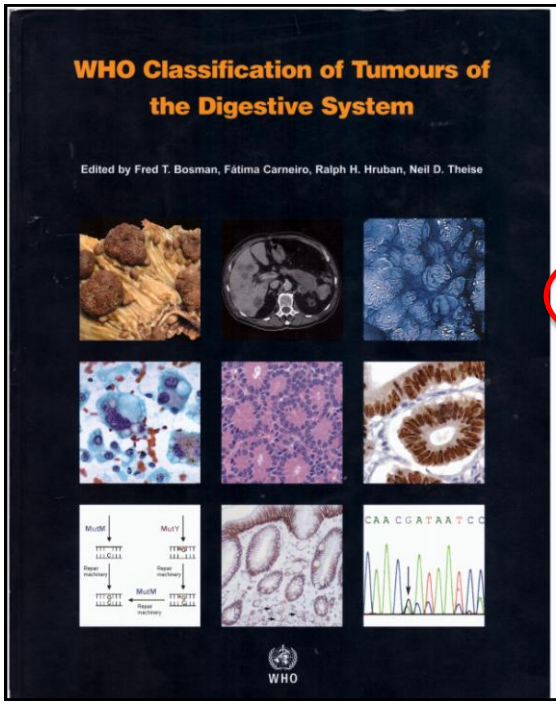
# Опухоли печени у взрослых: морфологические особенности и диагностика гепатоцеллюлярного рака

Дмитрий Валерьевич Калинин
кандидат медицинских наук
заведующий отделом патологической анатомии
ФГБУ "Институт хирургии им. А.В. Вишневского" МЗ РФ
г. Москва

Regular Member of the United States and Canadian Academy of Pathology (USCAP)
International fellow, College of American Pathologists (IFCAP)




World Health Organization Classification of Tumours

WHO OMS

International Agency for Research on Cancer (IARC)

*Malignancy-associated and premalignant lesions*

Large cell change (formerly "dysplasia")
Small cell change (formerly "dysplasia")
Dysplastic nodules
Low grade
High grade

*Malignant*

| | |
|---|---|
| Hepatocellular carcinoma | 8170/3 |
| Hepatocellular carcinoma, fibrolamellar variant | 8171/3 |
| Hepatoblastoma, epithelial variants | 8970/3 |
| Undifferentiated carcinoma | 8020/3 |

International Agency for Research on Cancer
Lyon, 2010

SPECIAL ARTICLE

HEPATOLOGY, February 2009

# Pathologic Diagnosis of Early Hepatocellular Carcinoma: A Report of the International Consensus Group for Hepatocellular Neoplasia

International Consensus Group for Hepatocellular Neoplasia

See Editorial on Page 355

Advances in imaging techniques and establishment of surveillance protocols for high-risk populations have led to the detection of small hepatic nodules in patients with chronic liver diseases, particularly those with cirrhosis or chronic hepatitis caused by hepatitis B or C viruses. These nodules, comprising a broad range of diagnostic entities—some benign and some with malignant potential—are currently defined histologically, and their clinical management often depends on the ability to make a reliable histologic diagnosis.

Evidence accumulated in the last two decades strongly favors the existence of a sequence of events in hepatic nodules that precedes the emergence of hepatocellular carcinoma (HCC),[1-10] and these lesions are recognized as precursors of HCC. However, from the beginning of their recognition, there has been considerable confusion concerning nomenclature and diagnostic approaches to these hepatic nodules. To clarify these issues, an International Working Party (IWP) of the World Congresses of Gastroenterology proposed a consensus nomenclature and diagnostic criteria for hepatocellular nodular lesions in 1995.[11] The IWP classified nodular lesions found in chronic liver disease into large regenerative nodule, low-grade dysplastic nodule (L-DN), high-grade dysplastic nodule (H-DN), and HCC; this nomenclature has been widely adopted. In addition, the IWP introduced the concept of dysplastic focus as a cluster of hepatocytes with features of early neoplasia (in particular small cell change or iron-free foci in a siderotic background) measuring less than 0.1 cm, and defined small HCC as a tumor measuring less than 2 cm.

More recent studies support the division of small HCC into two clinico-pathological groups that have been termed early HCC and progressed HCC. Early HCC has a vaguely nodular appearance and is well differentiated. Progressed HCC has a distinctly nodular pattern and is mostly moderately differentiated, often with evidence of microvascular invasion.[12] Early HCC has a longer time to recurrence and a higher 5-year survival rate compared with progressed HCC.[13]

Small lesions with malignant potential have only subtle differences from the surrounding parenchyma, making them difficult to assess reproducibly. Differences in the application of diagnostic criteria between Western and

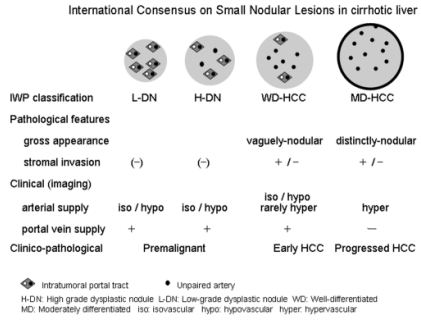



Fig. 5. Diagram summarizing clinical and pathological correlations. The cartoons in the top row show the anatomic changes that are found with the evolution of fully malignant HCC. Because early HCCs grow in a replacing pattern at the boundary, with tumor cells replacing the surrounding liver cell cords, they show a vaguely nodular appearance. When the tumors reach 1.5 to 2 cm in diameter, they tend to de-differentiate, becoming moderately differentiated and growing in an expansile fashion with formation of a fibrous capsule. Hypovascularity, hypervascularity, and isovascularity are understood to mean the signal intensity in the arterial phase of contrast-enhanced imaging relative to the nontumorous liver. Hypervascularity is related to the development of unpaired arteries, the absence of portal vein supply, and the distinctly nodular growth. The diagnosis must consider the context of the lesion, especially the presence of cirrhosis, the imaging findings, and the growth rate. In the appropriate context, a lesion with decreased portal vein supply without hypervascularity is suggestive of early HCC.

Hepatology. 1997, DOI: 10.1002/hep.510260607

## Large cell change (liver cell dysplasia) and hepatocellular carcinoma in cirrhosis: Matched case–control study, pathological analysis, and pathogenetic hypothesis

RG Lee; AC Tsamandas; AJ Demetris

Large cell change (LCC), characterized by cellular enlargement, nuclear pleomorphism and hyperchromasia, and multinucleation of hepatocytes, is a common lesion in cirrhotic livers, but its nature, significance, and pathogenesis remain uncertain. Therefore, we assessed the prognostic value of LCC as a marker of subsequent hepatocellular carcinoma (HCC) through a case-control study that compared pretransplant liver biopsy specimens from 37 cirrhotic liver transplant r
recipients without HCC, matched for sex, age (±5 yea
of the study and 7 (19%) of the control group biopsy
moderately increased risk of later HCC with an estim
a pathology review of 45 HCCs showed adjoining LCC
transition or a histogenetic association between the
rate by Ki-67 or proliferating cell nuclear antigen imn
showed a greater degree of apoptosis than normal h
reconcile these findings, we propose that LCC derive
of polyploidization. Such derangements, possibly cau
yield a population of enlarged liver cells with nuclear
minimal proliferation. According to this hypothesis, L
accompaniment of HCC but would not represent a d

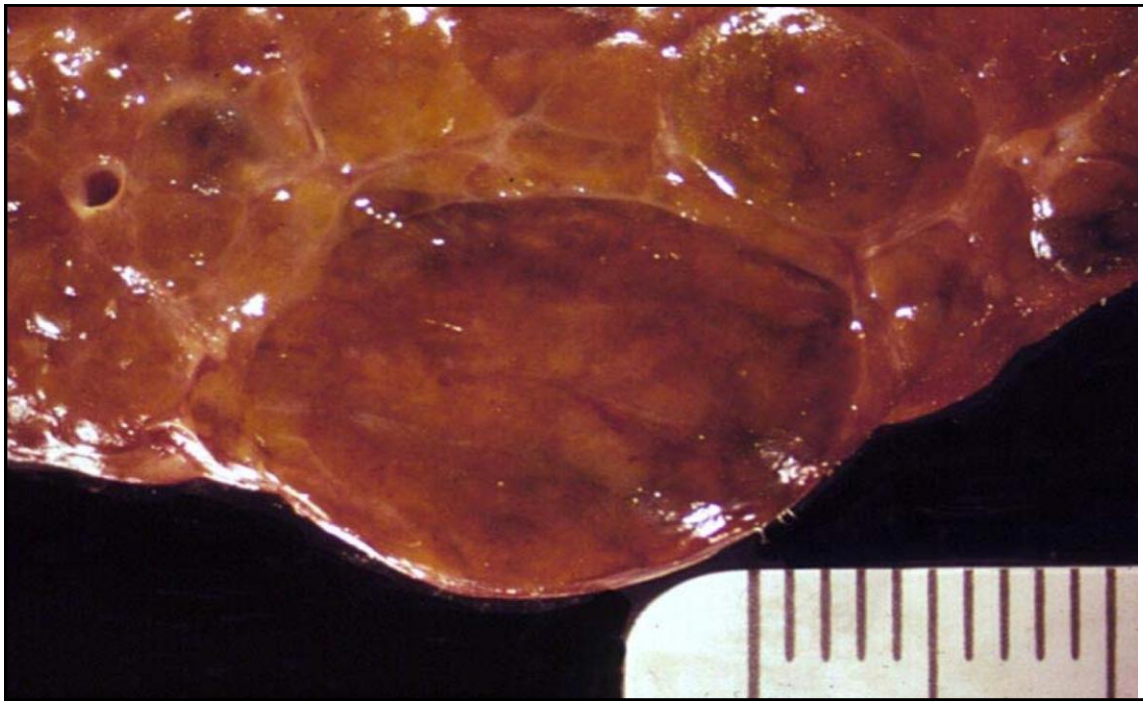
Oncology reports. 2010, PMID: 20372834

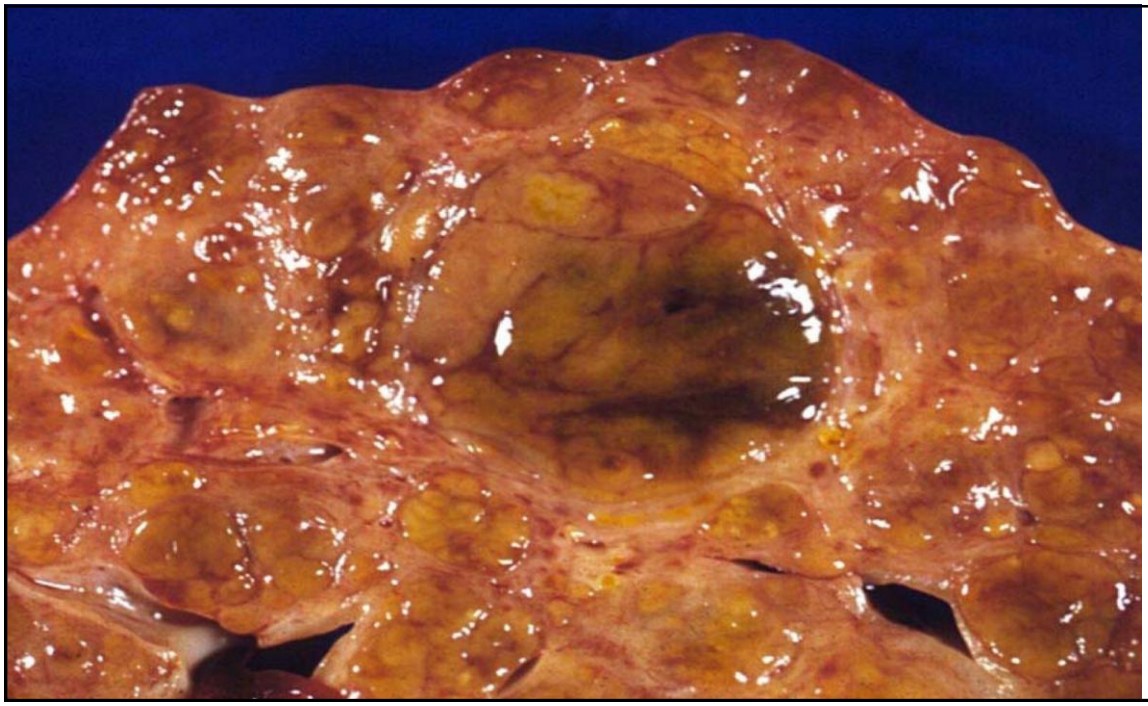
## The cytological characteristics of small cell change of dysplasia in small hepatic nodules.

Okki Chang; Yoshihiko Yano; Akira Masuzawa; Noriyuki Fukushima; Kazuhiro Teramura; Yoshitake Hayashi

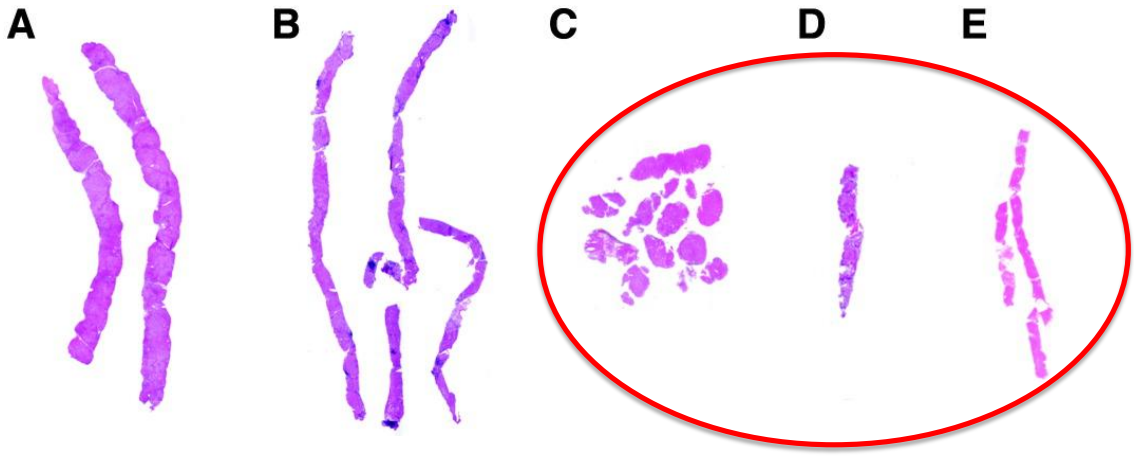
Small cell change of dysplasia (SCD) is characterized as an initial step in hepatocarcinogenesis. Histopathological diagnosis is an important diagnostic procedure for nodular lesions in the liver. However, the biopsied specimen is so small that it is sometimes difficult to differentiate between regenerative nodules, dysplastic nodules, and hepatocellular carcinoma even histologically. To examine the usefulness of cytology in the differential diagnosis of hepatic nodular lesions, the cellular characteristics of SCD were evaluated using Papanicolaou staining and a micrometer. Sixty-four histologically diagnosed small nodular lesions in the liver were analyzed retrospectively. All cases were histologically classified according to the Terminology of Nodular Hepatocellular Lesions by the International Working party: hepatocellular carcinoma (HCC) (n=17); low-grade dysplastic nodule (LGDN) (n=26); high-grade dysplastic nodule (HGDN) (n=6); large regenerative nodule: (n=15). SCD was noted in all of the histological categories, and the proportion of SCD tended to be higher in W-HCC than in dysplastic nodules. Although the cellular size was the smallest in HGDN, the nuclear size was the largest in well-differentiated HCC (W-HCC). The nuclear/cytoplasmic ratio was higher in HGDN and W-HCC than in other nodular lesions. Hyperchromasia in W-HCC was obviously stronger than that in other nodules. SCD was frequently found in HGDN and W-HCC. The present study showed that detailed cytological findings of SCD are useful for differentiating HGDN from LGDN, and HGDN from W-HCC.

| | Вид/тип образования | Микроскопические характеристики |
|---|---|---|
| | Диспластический фокус | Кластер гепатоцитов с мелкоклеточными изменениями, размерами менее 1 мм (ранее использовался термин мелкоклеточная дисплазия). |
| MRN | Макрорегенераторный узел | Регенераторный узел размерами более всех остальных цирротических узелков (более 5 мм); содержит несколько портальных трактов и выстланные синусоидами трабекулы гепатоцитов, шириной не более 2 клеток; без признаков дисплазии. |
| L-DN | Дисплатический узел низкой степени злокачественности | Отграниченное узкой фиброзной капсулой узловое образование с незначительным или умеренным увеличением клеточности; может содержать гепатоциты с крупноклеточными изменениями, однако без признаков архитектурной атипии; содержит несколько портальных трактов. |
| H-DN | Дисплатический узел высокой степени злокачественности | Явная цитологическая и архитектурная атипия, недостаточная для постановки диагноза ГЦР; резкое увеличение клеточности и мелкоклеточные изменения; может содержать несколько непарных артериол; не имеет признаков стромальной инвазии; небольшая протоковая реакция вдоль краёв узла по экспрессии CK7/19. |





# Liver biopsy



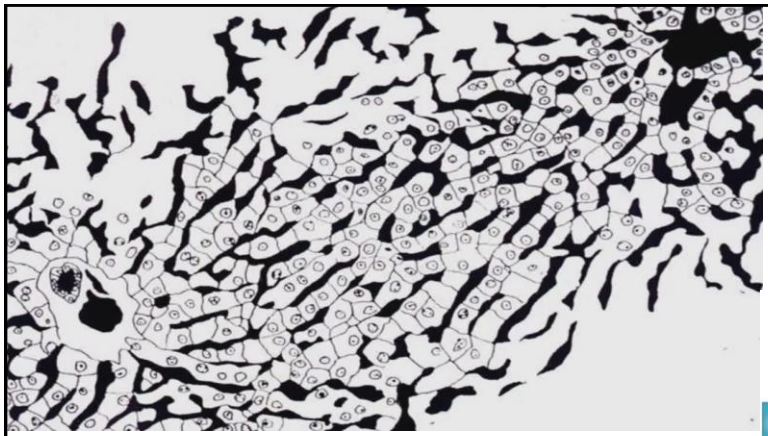

Hepatology
Volume 49, Issue 3, pages 1017-1044, 20 NOV 2008 DOI: 10.1002/hep.22742
http://onlinelibrary.wiley.com/doi/10.1002/hep.22742/full#fig1

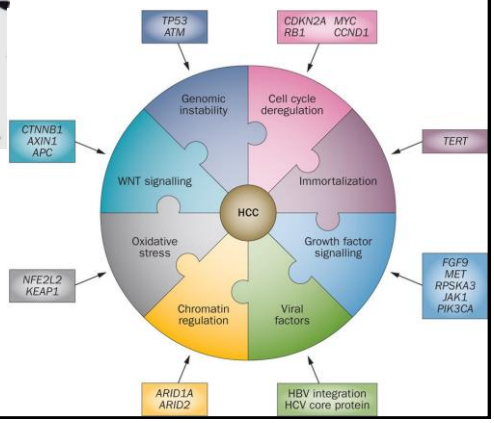
# Update on Precursor and Early Lesions of Hepatocellular Carcinomas

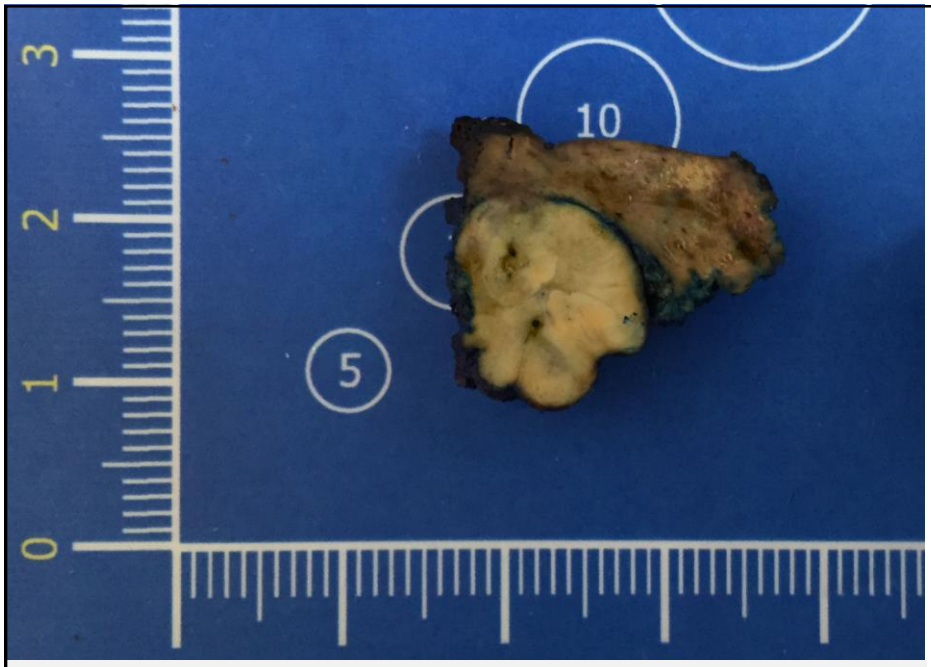
| | LRN | LGDN | HGDN | WD HCC |
|---|---|---|---|---|
| Cytologic features | | | | |
| Small cell change | − | − | + | + |
| Large cell change | ± | ± | ± | − |
| Clonelike foci (clear, fatty) | − | ± | + | + |
| Architectural features | | | | |
| Plate thickening ≥3 cells | − | − | − | + |
| Increased cell density compared with surroundings | − | − | 1.3 to 2 times | >2 times |
| Pseudoglands | − | − | ± | + |
| Nodule-in-nodule | − | − | − | ± |
| Portal tract | + | + | + | ± |
| Unpaired arteries and capillarized sinusoids[a] | − | ± | ± | + |
| Stromal invasion[b] | − | − | − | + |
| Reticulin framework | + | + | + | ± |
| Tumor markers | | | | |
| Glypican-3 | − | − | ± (9%) | + (69%) |
| Heat shock protein 70 | − | − | ± (5%) | + (78%) |
| Glutamine synthetase | − | − | ± (13%) | + (59%) |
| Positive in at least 2 of above 3 markers | − | − | − | + (72%) |

Abbreviations: −, absent; ±, may be present; +, usually present; ( ), % of positivity in resected specimen; HGDN, high-grade dysplastic nodule; LGDN, low-grade dysplastic nodule; LRN, large regenerative nodule; WD HCC, well-differentiated hepatocellular carcinoma.

[a] Immunohistochemical stain for CD34 is helpful.
[b] Immunohistochemical stain for keratin 7/19 is helpful.



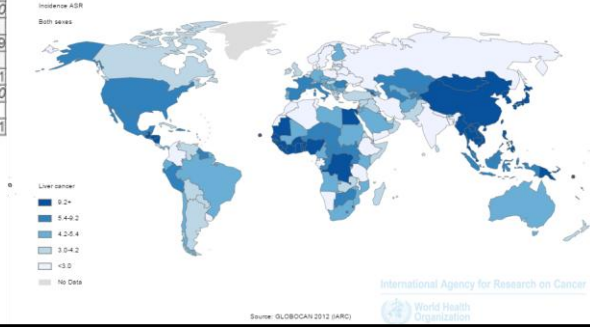





**Наблюдение 1**

## RUSSIAN FEDERATION - BOTH SEXES
## ESTIMATED INCIDENCE BY AGE

| Cancer | Total | 0-14 | 15-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75+ | Crude | ASR(W) | Cum.[0-74] | *ICD-10* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All cancers excl. non-melanoma skin cancer | 458382 | 13.2 | 43.1 | 151.1 | 257.5 | 413.0 | 627.5 | 867.3 | 1081.9 | 1197.8 | 1144.5 | 321.2 | **204.3** | **21.5** | *C00-97/C44* |
| Bladder | 13853 | 0.1 | 0.3 | 1.4 | 4.3 | 9.0 | 16.6 | 27.3 | 38.3 | 44.9 | 47.4 | 9.7 | **5.7** | **0.7** | *C67* |
| Brain, nervous system | 7377 | 2.4 | 2.7 | 5.0 | 6.5 | 8.0 | 9.7 | 10.4 | 10.4 | 9.6 | 6.7 | 5.2 | **4.3** | **0.4** | *C70-72* |
| Colorectum | 59928 | *0.0* | 1.3 | 8.6 | 20.1 | 39.7 | 72.4 | 114.4 | 161.0 | 196.1 | 204.2 | 42.0 | **24.5** | **3.0** | *C18-21* |
| Gallbladder | 3411 | *0.0* | 0.1 | 0.4 | 0.9 | 1.9 | 3.4 | 5.5 | 8.4 | 11.6 | 14.4 | 2.4 | **1.3** | **0.2** | *C23-24* |
| Hodgkin lymphoma | 2911 | 0.5 | 2.8 | 2.4 | 2.1 | 2.0 | 1.9 | 1.9 | 1.9 | 1.8 | 1.6 | 2.0 | **1.8** | **0.1** | *C81* |
| Kaposi sarcoma | 190 | - | 0.0 | *0.0* | *0.0* | *0.1* | 0.2 | 0.3 | 0.5 | *0.2* | 1.0 | 0.1 | **0.1** | **0.0** | *C46* |
| Kidney | 19313 | 1.2 | 1.0 | 7.1 | 14.9 | 23.5 | 32.9 | 39.1 | 42.5 | 41.8 | 34.8 | 13.5 | **8.9** | **1.0** | *C64-66* |
| Larynx | 6421 | - | 0.1 | 1.5 | 4.2 | 8.0 | 12.9 | 16.3 | 16.5 | 13.5 | 8.6 | 4.5 | **2.9** | **0.4** | *C32* |
| Leukaemia | 11773 | 4.5 | 1.9 | 3.7 | 6.1 | 9.3 | 14.2 | 19.5 | 23.9 | 25.8 | 26.2 | 8.2 | **6.3** | **0.6** | *C91-95* |
| Lip, oral cavity | 10240 | 0.1 | 0.6 | 3.0 | 6.2 | 10.9 | 15.5 | 21.9 | 23.9 | 25.0 | 23.0 | 7.2 | **4.5** | **0.5** | *C00-08* |
| **Liver** | **6812** | **0.2** | **0.3** | **1.2** | **2.7** | **5.2** | **8.7** | **12.7** | **16.7** | **20.2** | **21.8** | **4.8** | **2.9** | **0.3** | *C22* |
| Lung | 55805 | *0.0* | 1.0 | 9.1 | 25.1 | 52.1 | 88.3 | 126.3 | 153.5 | 157.2 | 131.6 | 39.1 | **24.0** | **3.0** | *C33-34* |
| Melanoma of skin | 8717 | 0.1 | 1.9 | 4.8 | 6.6 | 8.6 | 11.3 | 14.0 | 16.1 | 17.8 | 19.1 | 6.1 | **4.1** | **0.4** | *C43* |
| Multiple myeloma | 2738 | *0.0* | | | | | | | | | | | **.2** | **0.2** | *C88+C90* |
| Nasopharynx | 456 | - | | | | | | | | | | | **.2** | **0.0** | *C11* |
| Non-Hodgkin lymphoma | 7715 | 0.9 | | | | | | | | | | | **.8** | **0.4** | *C82-85,C96* |
| Oesophagus | 7263 | - | | | | | | | | | | | **.1** | **0.4** | *C15* |
| Other pharynx | 4104 | 0.1 | | | | | | | | | | | **.9** | **0.2** | *C09-10,C12-14* |
| Pancreas | 14512 | *0.0* | | | | | | | | | | | **.0** | **0.7** | *C25* |
| Stomach | 38417 | - | | | | | | | | | | | **.0** | **2.0** | *C16* |
| Thyroid | 10174 | 0.1 | | | | | | | | | | | **.2** | **0.5** | *C73* |




Rates based on less than 10 cases are *italicised*
Crude and age-standardised rates per 100,000.
Cumulative risk [0-74], percent.
GLOBOCAN 2012, IARC - 5.9.2015

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on day/month/year.

| *Malignancy-associated and premalignant lesions* | |
|---|---|
| Large cell change (formerly "dysplasia") | |
| Small cell change (formerly "dysplasia") | |
| Dysplastic nodules | |
| Low grade | |
| High grade | |
| *Malignant* | |
| Hepatocellular carcinoma | 8170/3 |
| Hepatocellular carcinoma, fibrolamellar variant | 8171/3 |
| Hepatoblastoma, epithelial variants | 8970/3 |
| Undifferentiated carcinoma | 8020/3 |

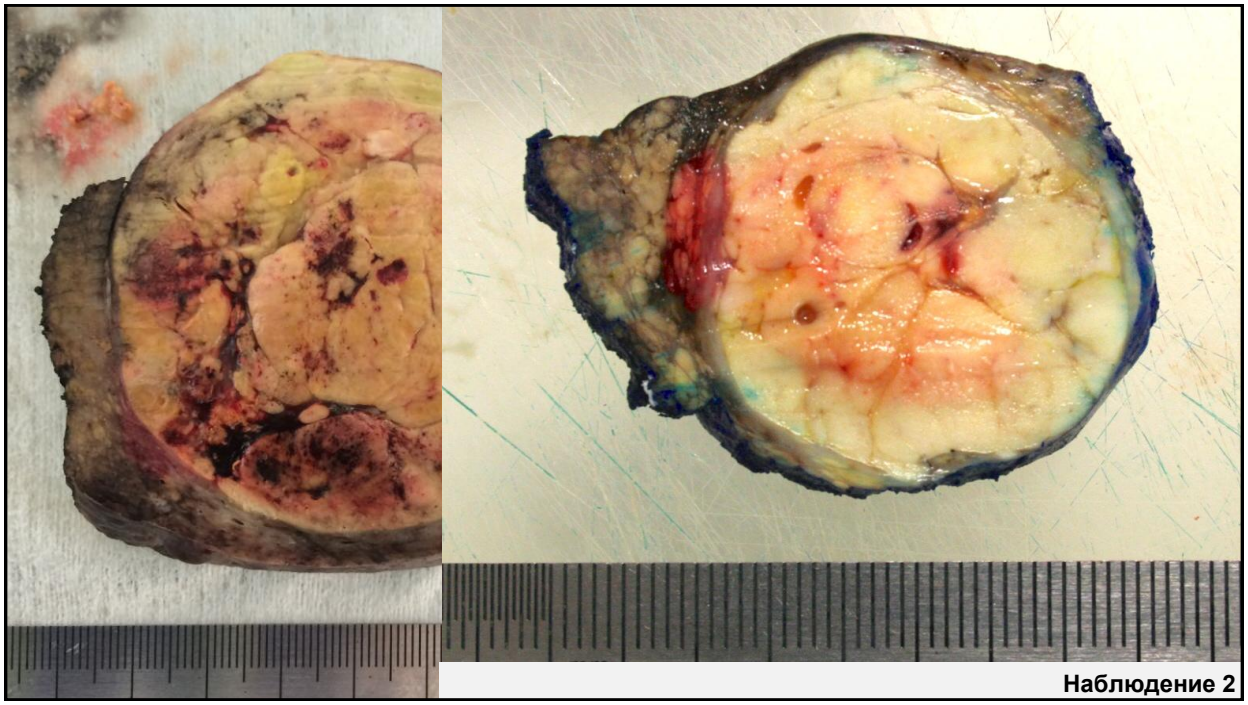
**Злокачественные гепатоцеллюлярные опухоли:**

гепатоцеллюлярный рак - М8170/3

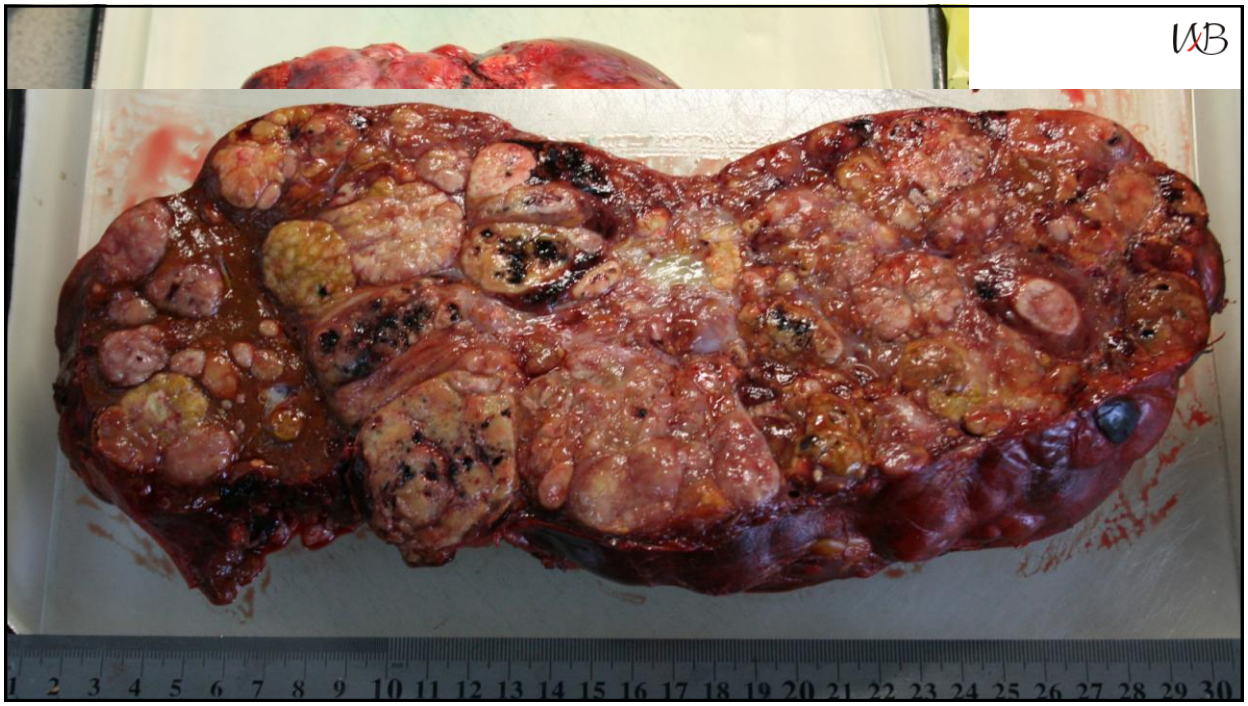
фиброламмелярный вариант гепатоцеллюлярного рака – М8171/3

Гепатобластома, эпителиальные варианты – М8970/3

Недифференцированная карцинома – М8020/3



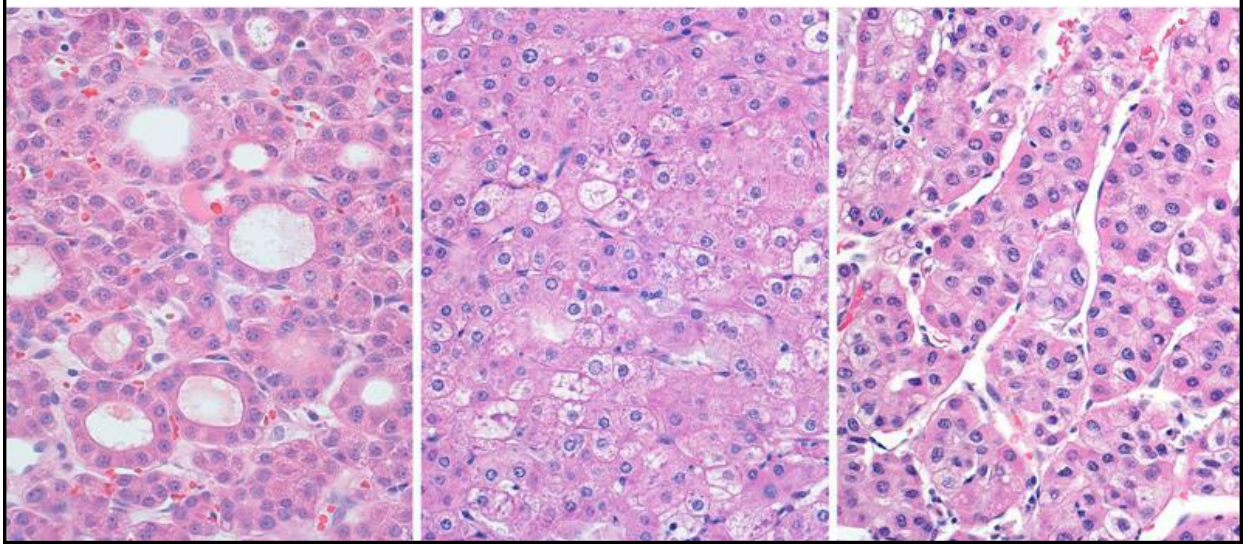
**Наблюдение 2**

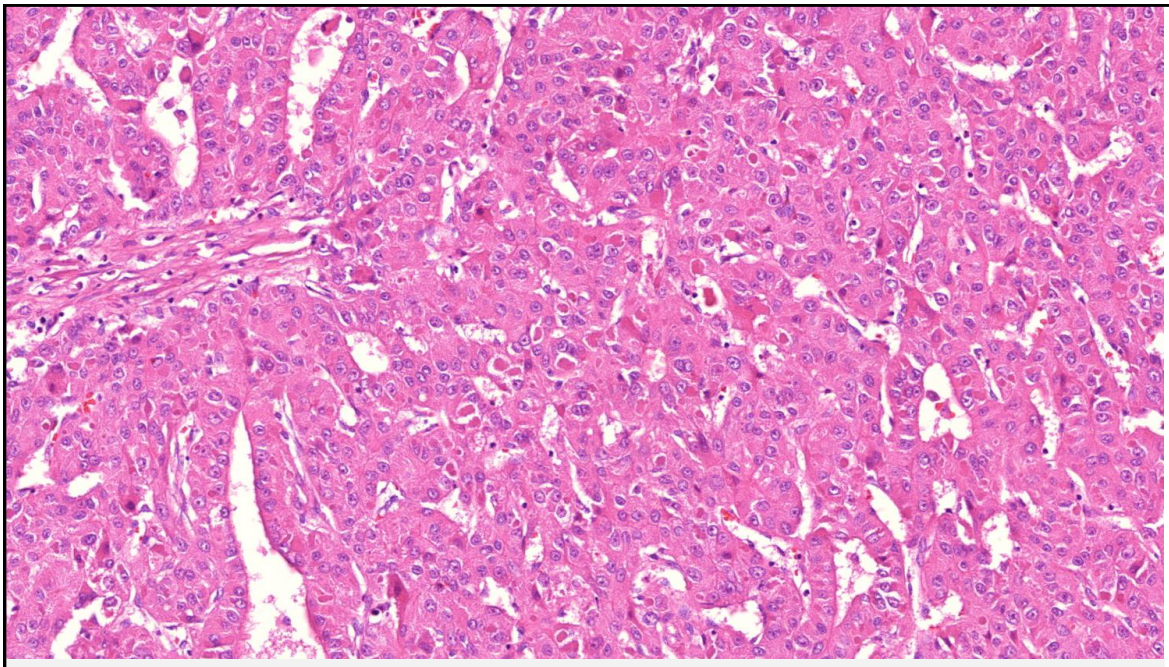


**Варианты структурной архитектуры гепатоцеллюлярного рака:**

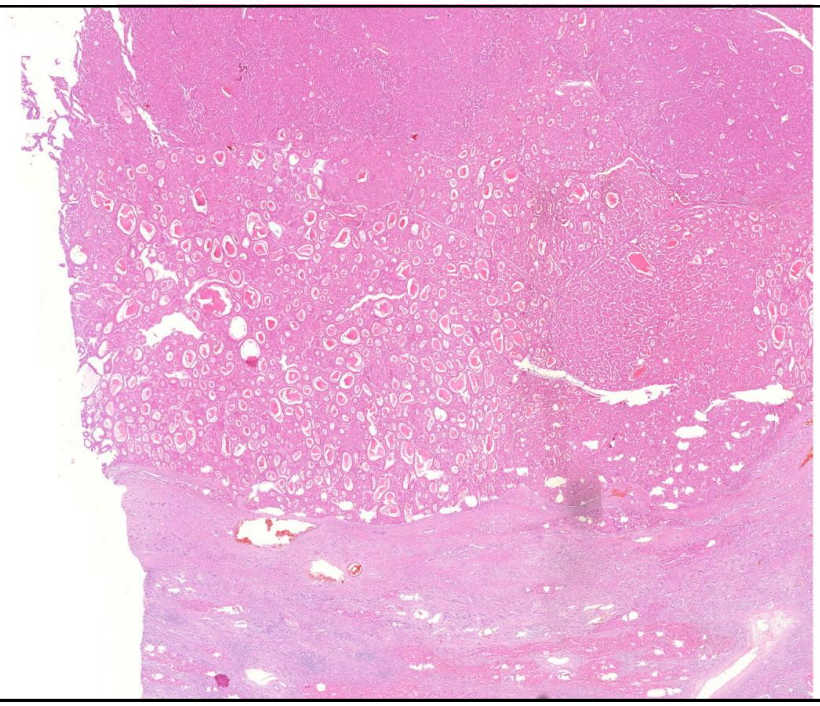
- солидный (компактный);
- трабекулярный;
- тубулярный;
- псевдопапиллярный;
- ацинарный (псевдожелезистый);
- скиррозный.

## Варианты структурной архитектуры гепатоцеллюлярного рака





Наблюдение 4



**Цитологические варианты гепатоцеллюлярного рака:**
светлоклеточный;
веретеноклеточный;
плеоморфный;
с остеокластоподобными клетками.

**Редкие варианты гепатоцеллюлярного рака:**
богатый лимфоцитами гепатоцеллюлярный рак,
гепатоцеллюлярный рак с нейроэндокринной дифференцировкой.

**Все перечисленные архитектурные и цитологические характеристики необходимо отражать в патологоанатомическим диагнозе.**

## Степени злокачественности по Edmondson и Steiner:

Grade X – степень злокачественности не может быть определена;

Grade I – высокая степень дифференцировки (опухолевые клетки практически не отличаются от гиперплазированных гепатоцитов, злокачественный характер процесса устанавливается по наличию инвазивного/агрессивного роста);

Grade II – умеренная степень дифференцировки (клетки напоминают нормальные гепатоциты, но с более крупными и гиперхромными ядрами, обильной эозинофильной цитоплазмой, цитоплазма части атипичных гепатитов содержит желчный пигмент, в просвете ацинусов содержится желчь);

Grade III – низкая степень дифференцировки (опухолевые клетки имеют крупные гиперхромные ядра, с высоким ядерно-цитоплазматическим отношением; цитоплазма зернистая, желчного пигмента нет, отдельные группы клеток в сосудистых пространствах);

Grade IV – недифференцированная / анапластическая карцинома (резкая гиперхромазия ядер, диффузный рост, очаговое веретеноклеточное / мелкоклеточное строение).

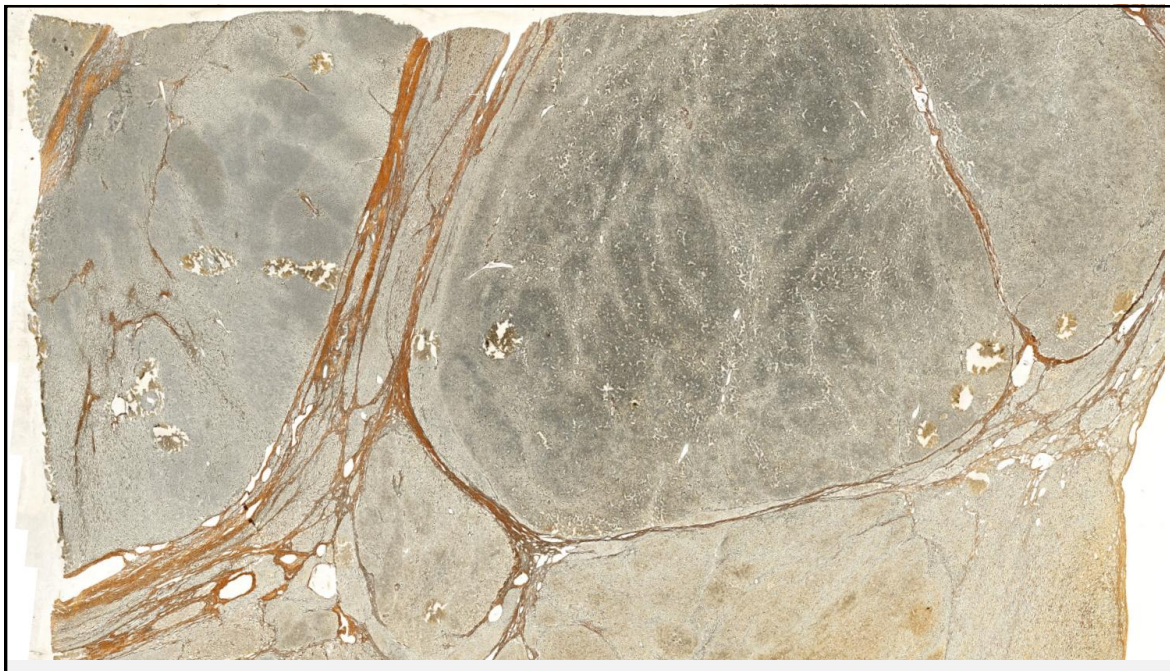
## Практический подход

**Grade 1:** опухоль – похожа на нормальную печени, мне нужны дополнительные окраски, чтобы удостовериться не рак ли это (лучше всего работает окраска на ретикулин, если доступно ИГХ – CD34 чтобы доказать эндотелизацию синусоидов или HSP70, чтобы доказать присутствие молекулярный аномалий в опухоли, Ki67 и Glypican-3)

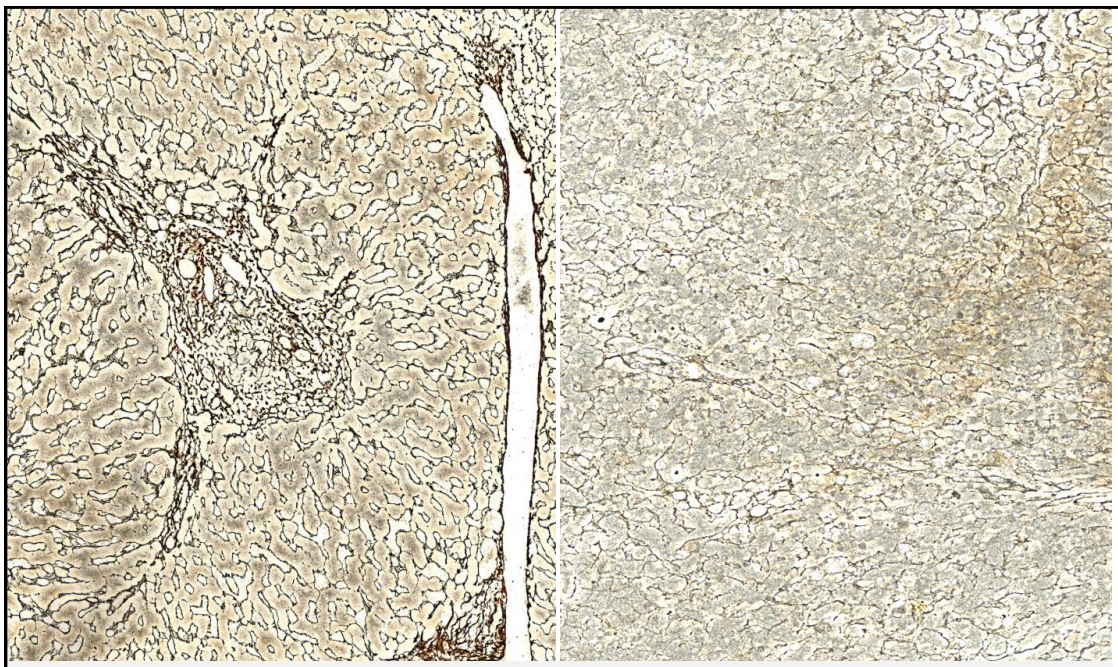
**Grade 2:** точно рак, по срезам окрашенным гематоксилином и эозином довольно хорошо видно что опухоль гепатоцеллюлярная - надо сделать ИГХ только, чтобы подтвердить гепатоцеллюлярную дифференцировку (достаточно 1 маркера)

**Grade 3:** ясно что это рак, но по препаратам, окрашенным гематоксилином и эозином я понятия не имею какой

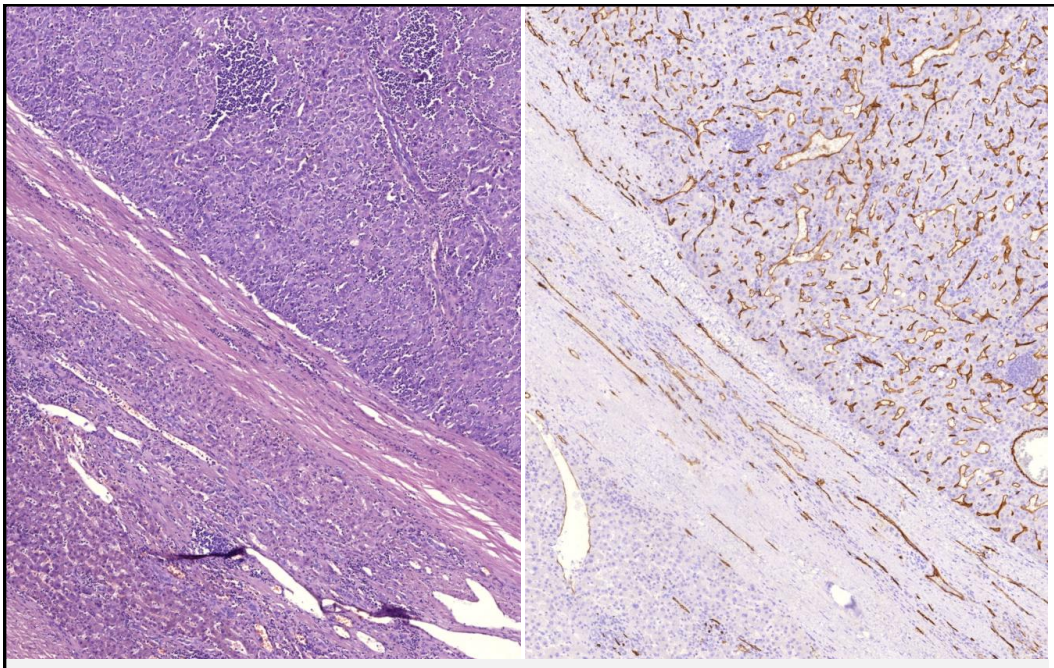
- ИГХ нужно доказать гепатоцеллюлярную дифференцировку
- В этой ситуации лучше использовать широкую панель первичных антител (Hep Par 1; Glypican-3; Arginase-1; CD10 или pCEA; AFP; Albumin ISH)



Окраска ретикулярных волокон по Гомори . Наблюдение 5



Окраска ретикулярных волокон по Гомори. Наблюдение 5



H&E и CD34 (клон QBEnd/10, Cell Marque). Наблюдение 6

# Comparison of 5 Immunohistochemical Markers of Hepatocellular Differentiation for the Diagnosis of Hepatocellular Carcinoma

*Thuy Nguyen, MD; Daniel Phillips, MD; Dhanpat Jain, MD; Michael Torbenson, MD; Tsung-Teh Wu, MD, PhD; Matthew M. Yeh, MD, PhD; Sanjay Kakar, MD*

• ***Context.***—Several immunohistochemical markers are available to establish the diagnosis of hepatocellular carcinoma. Judicious selection is essential to achieve a reliable diagnosis in limited tissue provided by liver biopsy.

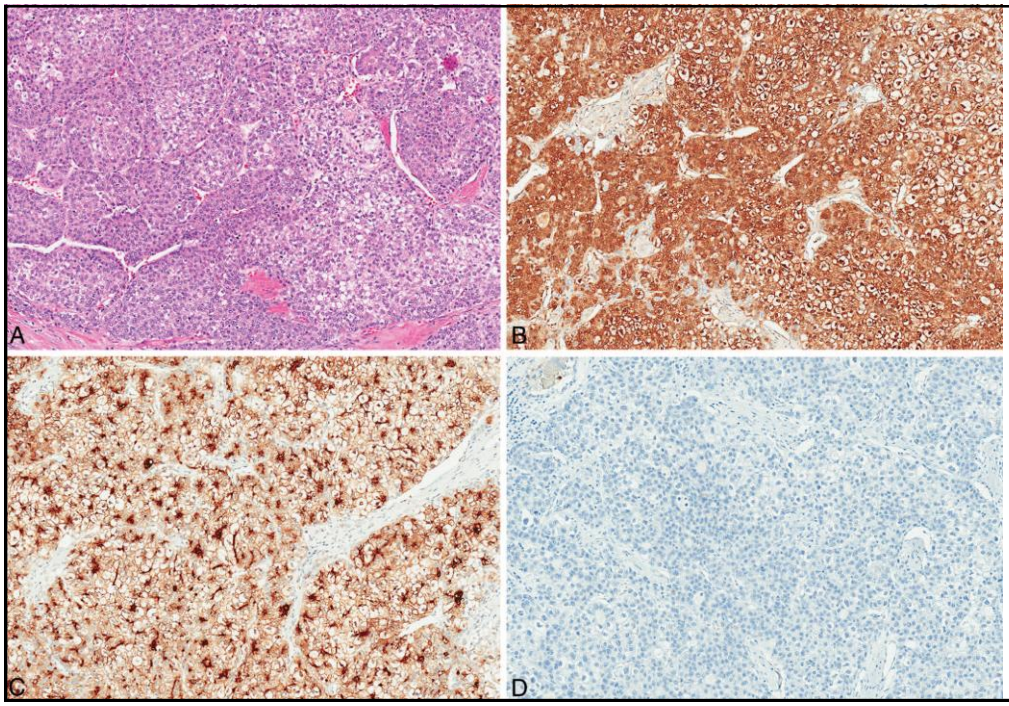
***Objective.***—To compare the efficacy of 5 hepatocellular markers for the diagnosis of hepatocellular carcinoma across various levels of differentiations.

***Design.***—Immunohistochemistry for hepatocyte paraffin antigen 1 (Hep Par 1), polyclonal carcinoembryonic antigen (CEA), glypican-3, arginase-1, and bile salt export pump transporter was performed in 79 hepatocellular carcinomas, yielding 93 observations (13 well-differentiated [14%], 41 moderately differentiated [44%], and 39 poorly differentiated [42%] tumors).

***Results.***—Arginase-1 and Hep Par 1 had the highest sensitivity for well-differentiated hepatocellular carcinoma, whereas arginase-1 and glypican-3 had the highest sensitivity for poorly differentiated hepatocellular carcinoma. When staining of more than 50% of the tumor was considered a positive result, arginase-1 remained the most sensitive marker for all differentiations, whereas sensitivity for Hep Par 1 in poorly differentiated hepatocellular carcinoma dropped to 30% and that of glypican-3 in well-differentiated hepatocellular carcinoma was 15%. The addition of Hep Par 1 and/or polyclonal CEA to arginase-1 did not lead to an increase in sensitivity for any differentiation. The combined use of arginase-1 and glypican-3 yielded 100% sensitivity for poorly differentiated hepatocellular carcinoma.

***Conclusion.***—Arginase-1 was the most sensitive marker in all differentiations of hepatocellular carcinoma. Glypican-3 had high sensitivity for poorly differentiated cases and its combined use with arginase-1 enabled identification of nearly all cases of poorly differentiated hepatocellular carcinoma. Although bile salt export pump transporter has good overall sensitivity, it has a limited role in establishing hepatocellular differentiation when added to a panel of arginase-1 with either glypican-3 or Hep Par 1.

(*Arch Pathol Lab Med.* 2015;139:1028–1034; doi: 10.5858/arpa.2014-0479-OA)




**H&E (A)**
**Arginase-1 (B)**
**Glypican-3 (C)**
**Hep Par 1 (D)**

**Table 2. Immunohistochemical Markers in Hepatocellular Carcinoma With 5%[a] Staining Considered Positive**

| Differentiation | Arginase-1, No. (%) | Glypican-3, No. (%) | Hep Par-1, No. (%) | pCEA, No. (%) | BSEP, No. (%) |
|---|---|---|---|---|---|
| Well, n = 13 | 13 (100) | 8 (62) | 13 (100) | 12 (92) | 12 (92) |
| Moderately, n = 41 | 41 (100) | 33 (80) | 40 (98) | 36 (88) | 37 (95)[b] |
| Poorly, n = 39 | 38 (97) | 33 (85) | 25 (64) | 21 (54) | 14 (45)[c] |

Abbreviations: BSEP, bile salt export pump; Hep Par-1, hepatocyte paraffin antigen 1; pCEA, polyclonal carcinoembryonic antigen.

[a] Staining in 5% or more of the tumor cells was considered positive.
[b] BSEP results were not available in every case; n = 39.
[c] BSEP results were not available in every case; n = 31.

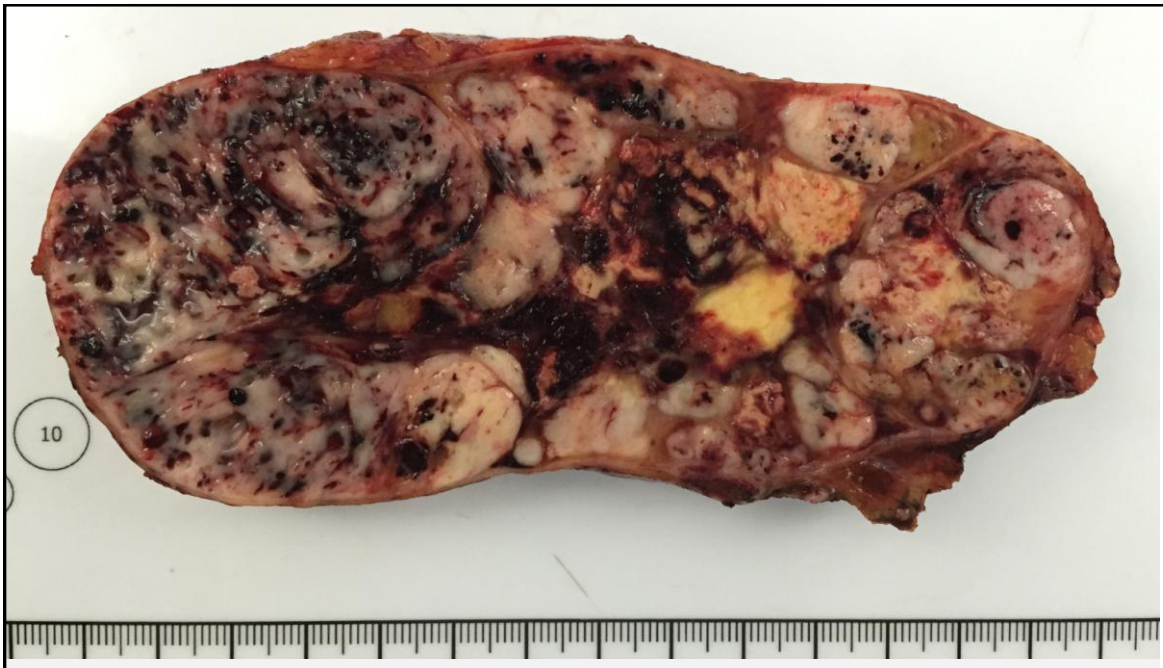
**Table 3. Immunohistochemical Markers in Hepatocellular Carcinoma With 50%[a] Staining Considered Positive**

| Differentiation | Arginase-1, No. (%) | Glypican-3, No. (%) | Hep Par-1, No. (%) | pCEA, No. (%) | BSEP, No. (%) |
|---|---|---|---|---|---|
| Well, n = 13 | 13 (100) | 2 (15) | 13 (100) | 10 (77) | 9 (69) |
| Moderately, n = 41 | 40 (98) | 24 (58) | 34 (83) | 26 (63) | 28 (72)[b] |
| Poorly, n = 35 | 34 (88) | 29 (74) | 12 (30) | 7 (18) | 6 (6)[c] |

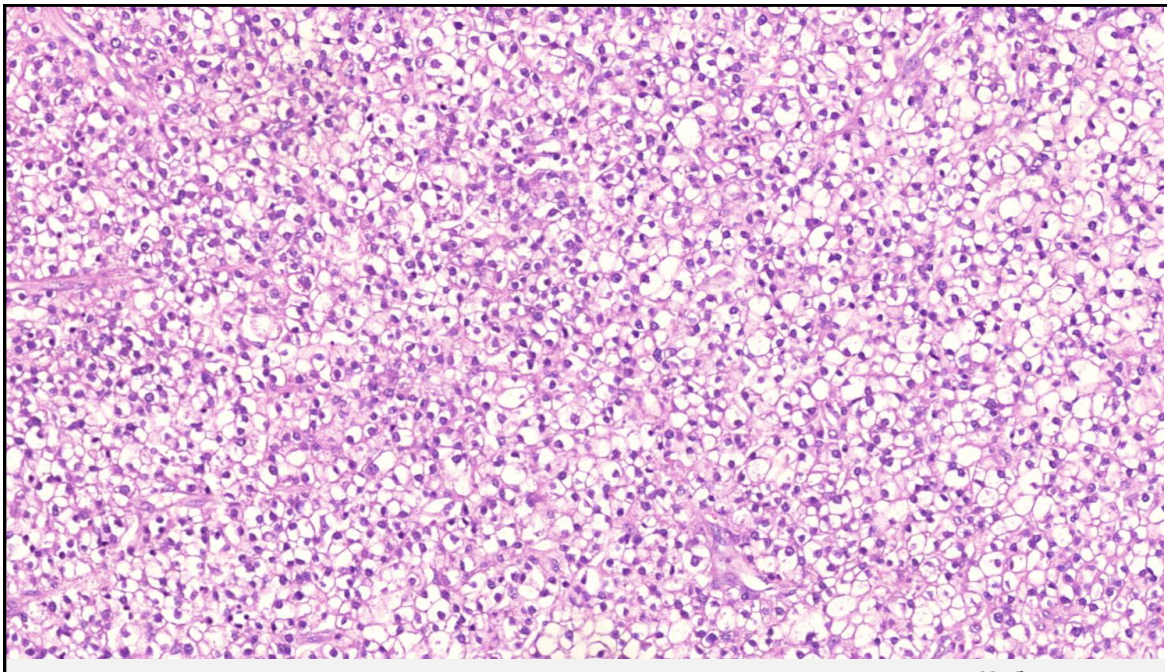
**Table 4. Sensitivity of Different Combinations of Immunohistochemical Markers in Hepatocellular Carcinoma**

| Differentiation | Hep Par-1$^+$ and/or Glypican-3$^+$, No. (%) | | Hep Par-1$^+$ and/or Arginase-1$^+$, No. (%) | | Glypican-3$^+$ and/or Arginase-1$^+$, No. (%) | |
|---|---|---|---|---|---|---|
| **Tumor cells staining, %** | **≥5** | **≥50** | **≥5** | **≥50** | **≥5** | **≥50** |
| Well, n = 13 | 13 (100) | 13 (100) | 13 (100) | 13 (100) | 13 (100) | 13 (100) |
| Moderately, n = 41 | 41 (100) | 40 (98) | 41 (100) | 40 (98) | 41 (100) | 41 (100) |
| Poorly, n = 39 | 36 (97) | 34 (87) | 37 (97) | 34 (88) | 39 (100) | 37 (95) |

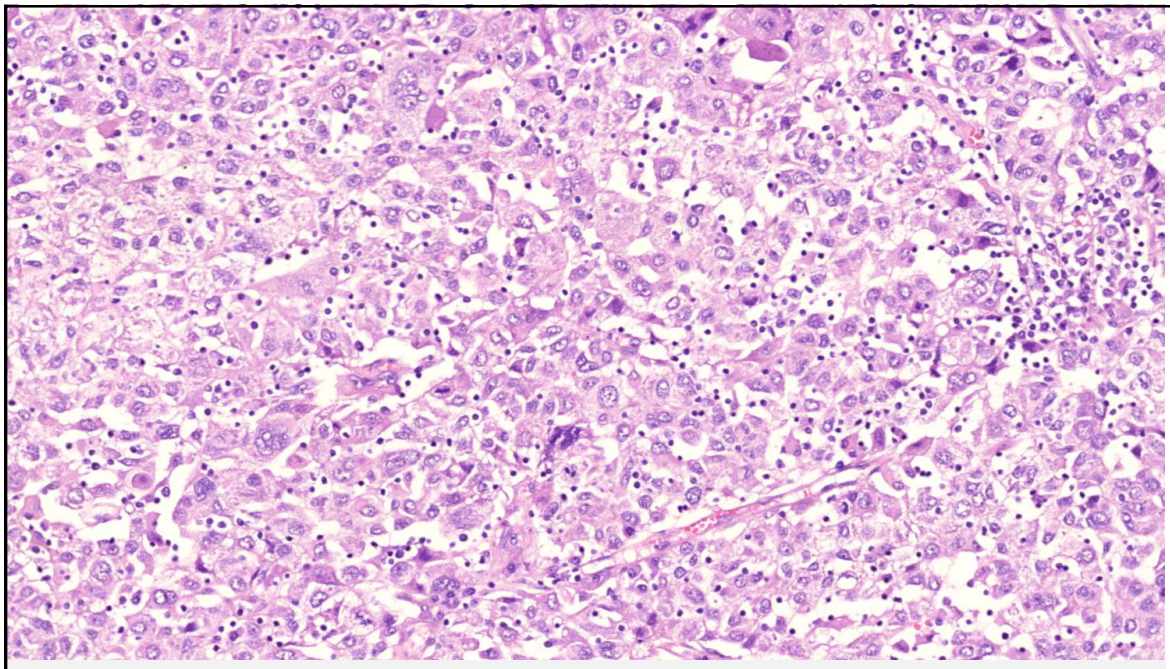
Abbreviation: Hep Par-1, hepatocyte paraffin antigen 1.



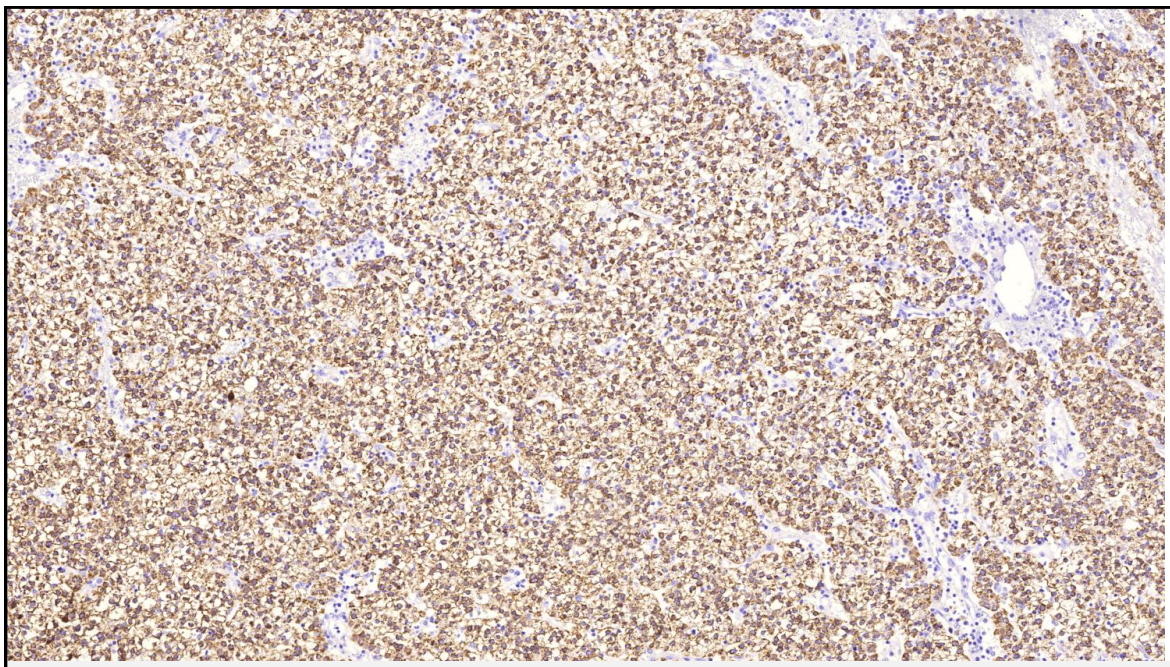

Наблюдение 7



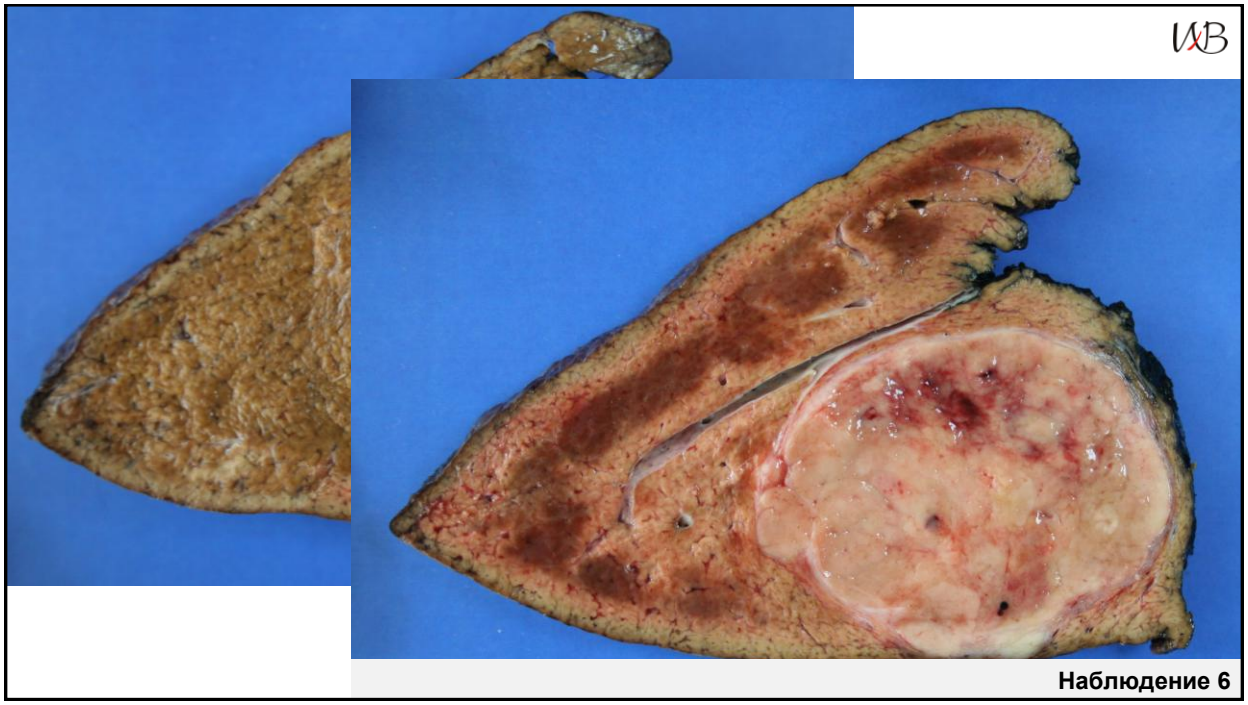
Наблюдение 7



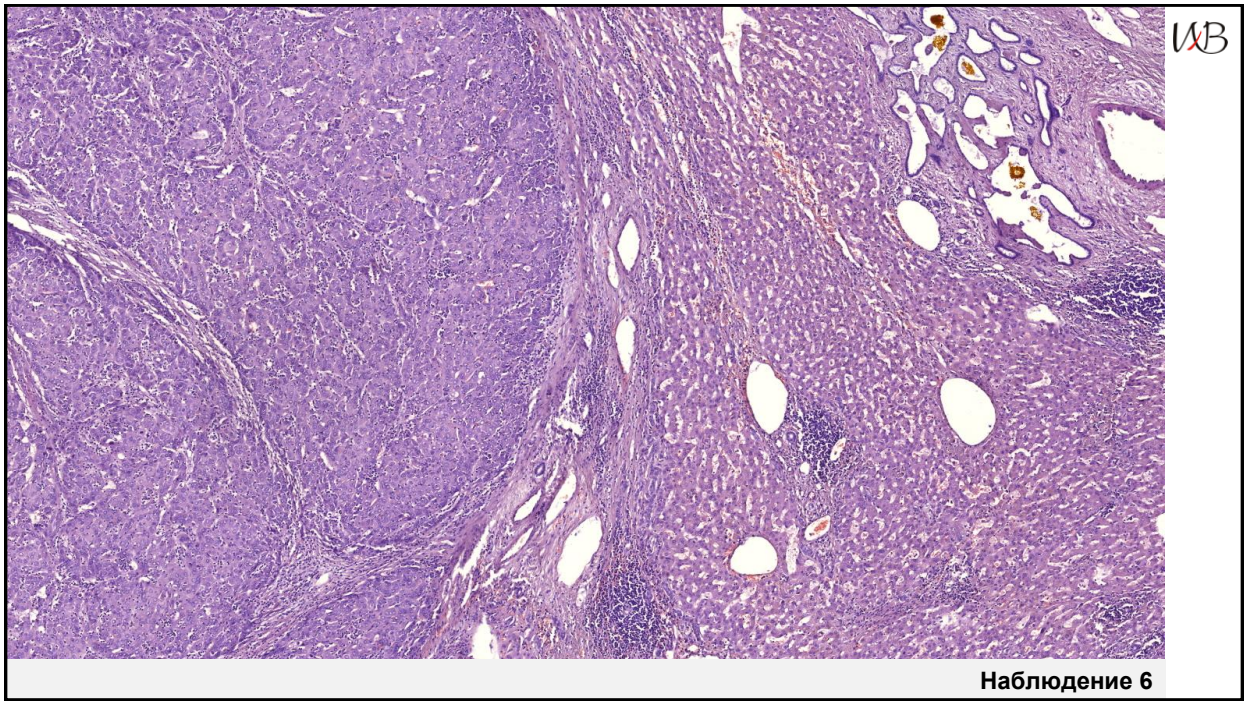
Наблюдение 7



Hep Par 1 (клон OCH1E5, Cell Marque). Наблюдение 7



Наблюдение 6



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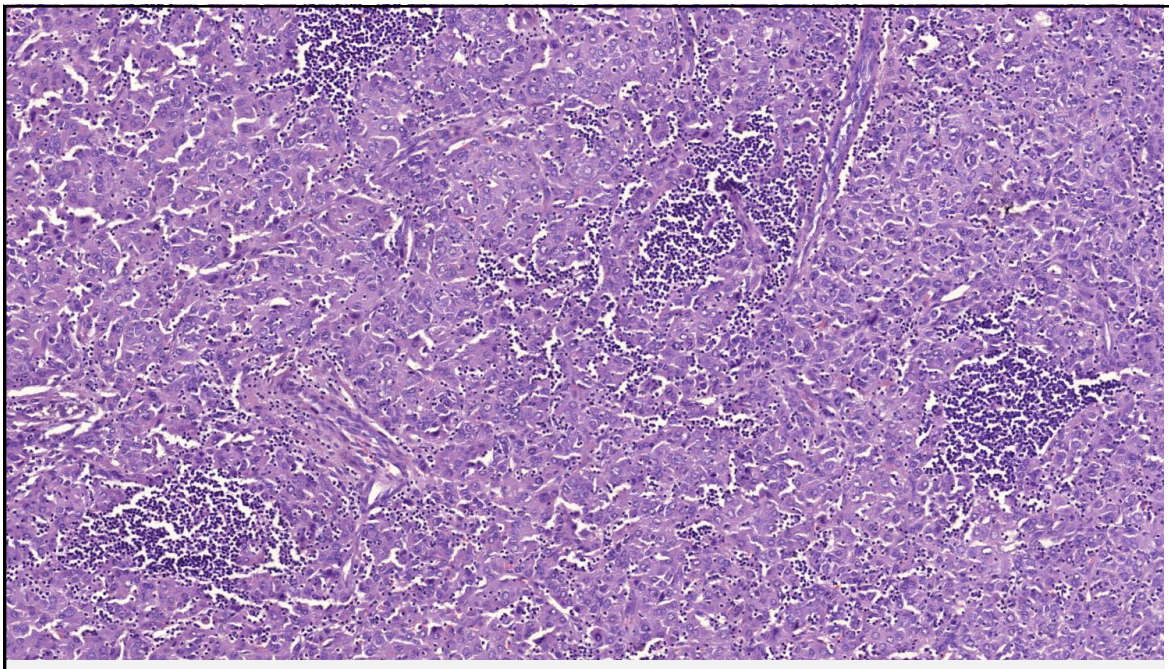


**Наблюдение 6**

## Фиброламмелярный вариант гепатоцеллюлярного рака

**Эпидемиология:**
около 5% всех типов гепатоцеллюлярного рака и около 30% всех типов гепатоцеллюлярного рака у подростков и молодых совершеннолетних
М=Ж
в настоящее время нет инфорации о возможных этиологических агентах

**Клинические особенности:** средний возраст пациентов - 26 лет
самый молодой описанный пацент: 4 года;
самые старые 60 +

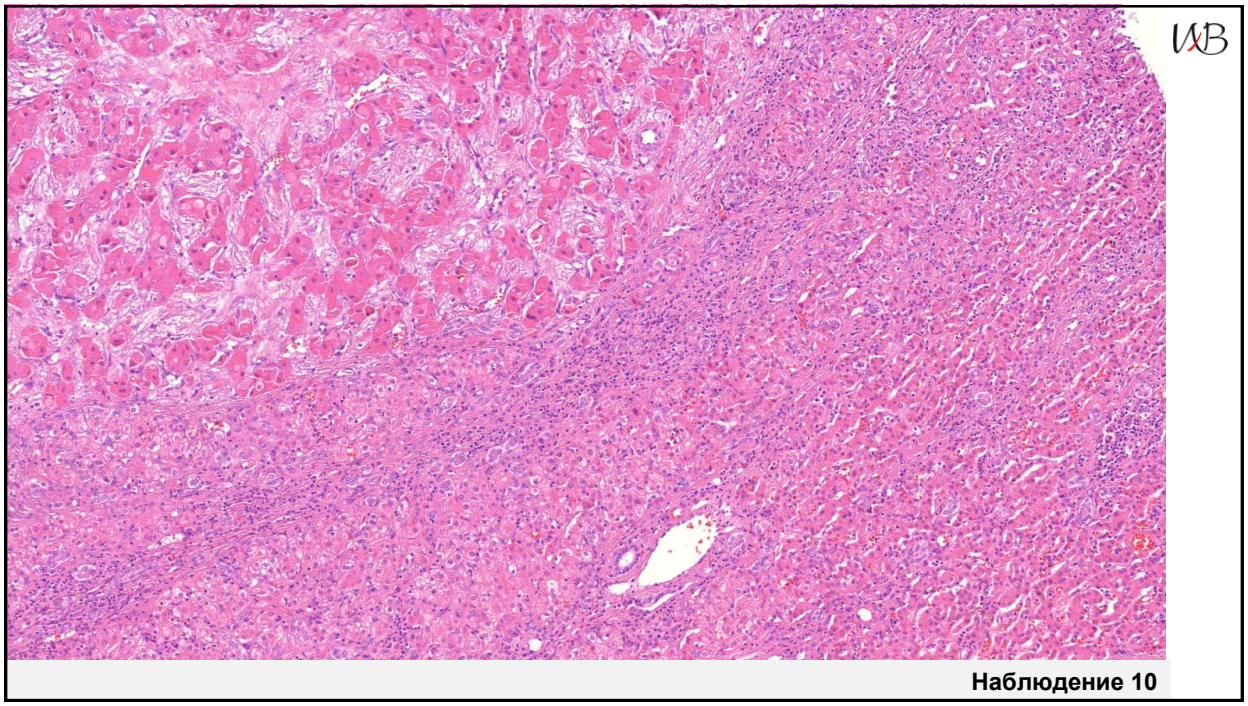
**Клинические проявления:** боль в животе, анорексия, усталость

Никаких фоновых печени заболеваний печени

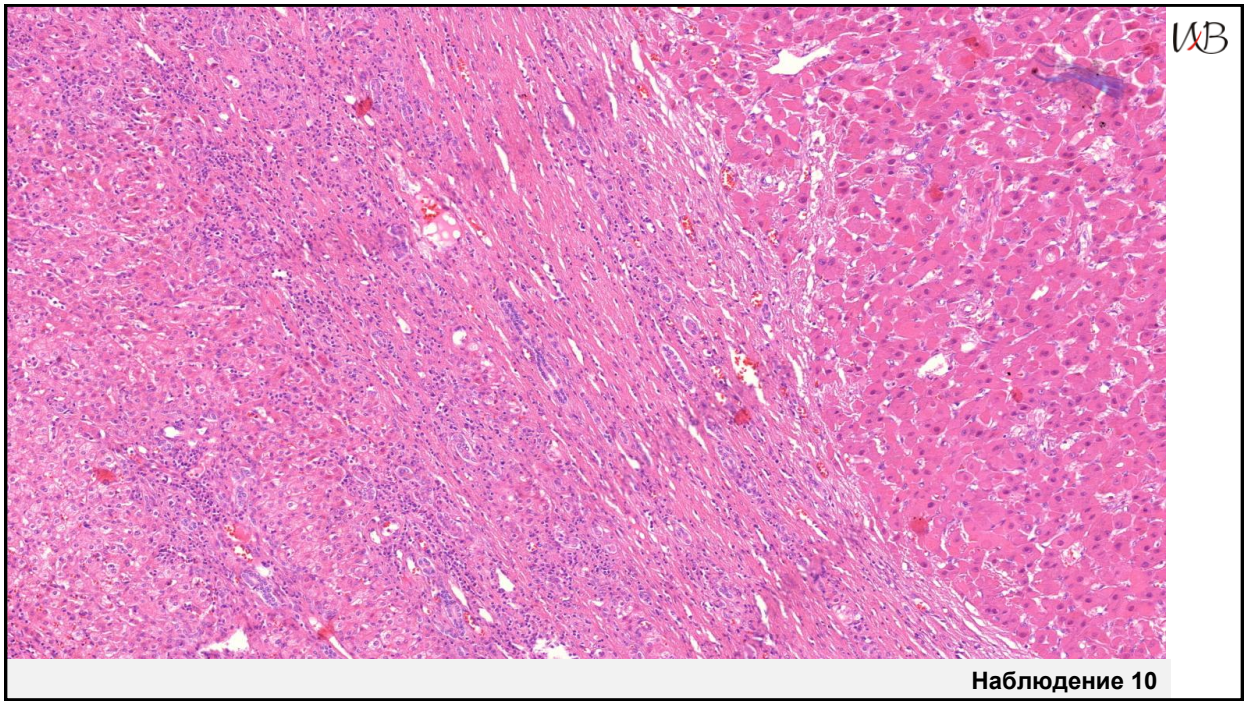
**Серологические особенности:**
аФП - отрицательный (если положительный, вероятно не ФГЦР)

**Особенности морфологии:**
большие эозинофильные клетки заметные ядрышки
ламмелярный (чешуйчатый) внутриопухолевый фиброз
бледные тела и гиалиновые тела

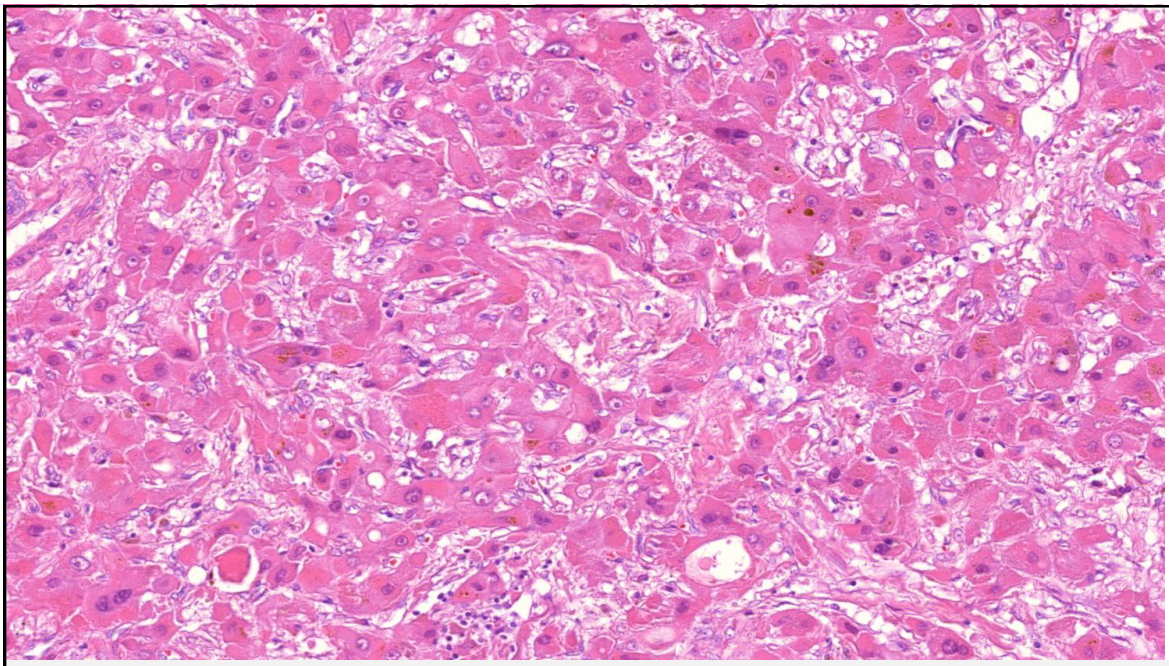
**Клиническое течение** – столь же агрессивный как типичный ГЦР,
средняя 5-летняя выживаемость:в случае резектабельных опухолей - 76%, нерезектабельных - 0%.



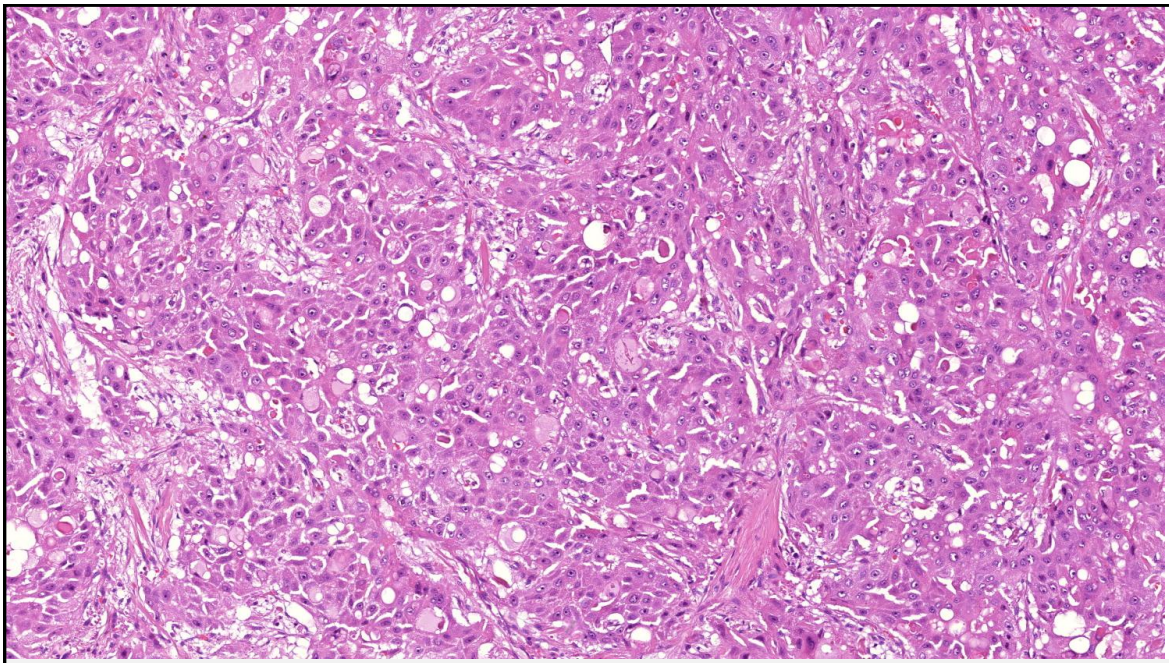
**Наблюдение 10**



**Наблюдение 10**



Наблюдение 10



Метастаз первичной опухоли в лимфатические узлы средостения через 3 года (наб. 10)

## Фиброламмелярный вариант гепатоцеллюлярного рака

- HepPar: 100%
- Glypican 3: 50%
- CK7: 100%
- CK5/6: 100%
- CK19: 20%
- CD68: 100%
- Chromogranin: 5%
- AFP: 0%

Подтверждение гепатоцеллюлярной дифференцировки в случае псевдожелезистого строение опухоли

Подтверждение фиброламмелярного варианта

## Comprehensive Variant List

1. Biphenotypic (hepatocellular and cholangiocarcinoma)
2. Cirrhotomimetic
3. Clear cell hepatocellular carcinoma
4. GCSFP hepatocellular carcinoma
5. Lymphocyte rich hepatocellular carcinoma
6. Mucin producing hepatocellular carcinoma
7. Sarcomatoid hepatocellular carcinoma
8. Scirrhous hepatocellular carcinoma
9. Steatohepatitic hepatocellular carcinoma
10. Stem cell/progenitor hepatocellular carcinoma
11. CAP hepatocellular carcinoma
12. Macrotrabecular hepatocellular carcinoma

**Дифференциальный диагноз между гепатоцеллюлярным раком и опухолевыми образованиями печени, имитирующих гепатоцеллюлярный рак**

- Почечноклеточный светлоклеточный рак – PAX-2, RCC, CD10
- Адренокортикальный рак – melan A, Inhibin $\alpha$, calretenin
- Меланома – HMB-45, S100
- Ангиомиолипома, эпителиоидный вариант – HMB-45, aSMA
- Гастроинтестинальная опухоль, эпителиоидный вариант – CD117

- Холангиоцеллюлярный рак – муцины, CK19, CEA (цитоплазматическое окрашивание)
- Нейроэндокринные опухоли - Syn, ChrA, CD56
- Аденокарцинома легкого – TTF1 (ядерное окрашивание!), Napsin A
- Рак молочной железы – маммоглобин, ER, PR, GCDF-15, GATA3

Surg Pathol Clin. 2013 Jun;6(2):333-65. doi: 10.1016/j.path.2013.03.005. Epub 2013 May 4.
**Diagnostic Approach to Hepatic Mass Lesions and Role of Immunohistochemistry. Marginean EC, Gown AM, Jain D.**

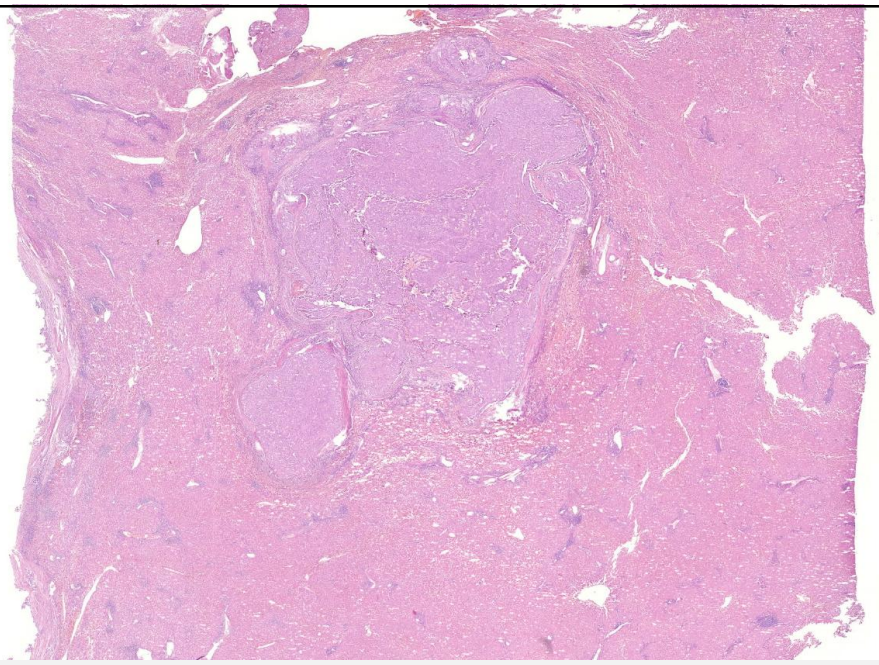
*Table 4*
**IHC markers useful in the workup of hepatocytic lesions: usefulness and pitfalls**

| | | Hepatocellular Carcinoma |
|---|---|---|
| **IHC Marker** | **Staining Pattern** | **Pitfalls** |
| HepPar-1 | Cytoplasmic, granular | Low sensitivity or absent in poorly differentiated and scirrhous HCC<br>Patchy staining in biopsies<br>Can be positive in gastric hepatoid, esophageal, lung, pancreatic, urothelial, adrenocortical, colorectal, and uterine cervical carcinomas |
| Arg1 | Cytoplasmic and nuclear | May show minimal, patchy positivity in pancreatic carcinomas |
| GPC3 | Cytoplasmic | Low sensitivity in well-differentiated HCC and in biopsies (<50%)<br>Can be positive in melanoma, lung squamous carcinoma, germ cell tumors, and gastric hepatoid carcinomas<br>Sometimes membranous or canalicular staining |
| GS | Cytoplasmic | Diffusely positive in β-catenin–activated HA-focal expression in HGDN<br>Typical maplike pattern in FNH |
| α Fetoprotein | Cytoplasmic | Low sensitivity (25%–50%)<br>Patchy staining<br>Positive also in germ cell tumors |
| pCEA | Canalicular | Distinction between cytoplasmic staining in adenocarcinoma and canalicular pattern in HCC can be difficult<br>Sensitivity in poorly differentiated HCC is low (25%–50%) |
| CD10 | Canalicular | Low sensitivity (<50%)<br>Does not differentiate between benign and malignant hepatocytic lesions<br>Can show a membranous pattern staining |
| CD34 | Sinusoidal | Can show incomplete staining in HGDN, HA, and FNH |
| Heat shock protein 70 | Cytoplasmic and nuclear | Patchy staining in HCC |

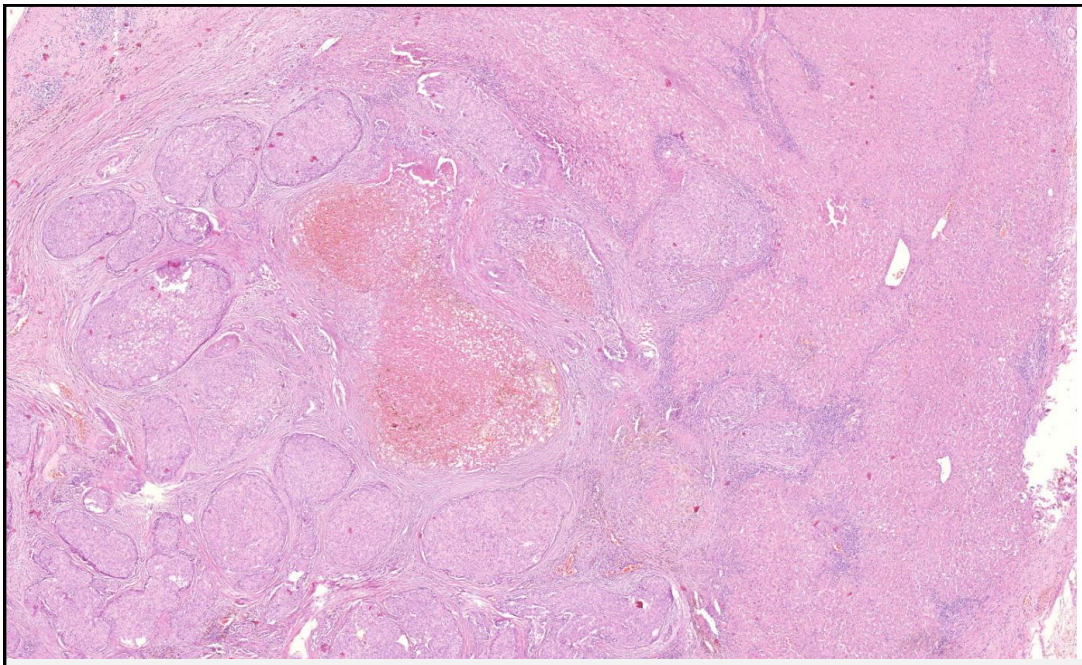
*Table 5*
**Most commonly used IHC stains in the differential diagnosis of hepatic metastatic carcinomas of unknown primary and tumors of unclear lineage**

| Tumor Type | MOC31 | HepPar-1, GPC3, or Arg1 | Pertinent Positive Markers |
|---|---|---|---|
| HCC | – | + | pCEA[a], CD34[b], CD10[a], villin[a], GS, AFP |
| CC | + | – | CK7, CK19, CD5, CK 8/18, CK20 (40%), pCEA (cytoplasmic), CDX2 |
| Colorectal adenocarcinoma | + | – | CK20, CDX2, villin, MUC2 |
| Pancreatic adenocarcinoma | + | – | CK8/18, CK17, CK19, CK7, IMP3, MUC1, MUC4, MUC5AC, MUC2 (intestinal type), CA19-9 |
| Lung adenocarcinoma | + | – | CK7, TTF1, napsin A, surfactant A, MUC1 |
| Squamous cell carcinoma | + | – | p63, p40, CK5/6 |
| Neuroendocrine tumors | + | – | CD56, synaptophysin, chromogranin, TTF1, AE1/3 |
| Endometrium carcinoma | + | – | CK7, ER, PR, β-catenin, vimentin, Pax8, CA125, CD138 |
| Ovarian serous | + | – | CK7, Pax8, CA125, ER, PR, WT1, mesothelin, vimentin, MUC1 |
| Ovarian mucinous carcinoma | + | – | CK7, CK20, Pax8, CDX2, mCEA, E-cadherin |
| Prostate adenocarcinoma | + | – | AMACR (not specific for prostate), PSA, PAP, AE1/3, NKX3.1, ERG (Ets-related gene) |
| Renal clear cell carcinoma | + | – | RCC, vimentin, EMA, CD10, Pax8, Pax2 |
| Renal chromophobe carcinoma | + | – | CD117, CK7, E-cadherin, Pax8, EMA |
| Renal papillary carcinoma | + | – | CK7, RCC, Pax8, AMACR, Pax2, RCC, EMA |
| Malignant Melanoma | – | – | S100, HMB45, Melan A, MART1, tyrosinase |
| Adrenal gland carcinoma | – | – | AE1/3, Melan A, calretinin, inhibin, CD56 |
| Testicular seminomatous tumors | ± | – | CD117, OCT3/4, PLAP, SALL4 |
| Testicular nonseminomatous (germ cell tumors) | ± | – | AE1/3, CD30, CK8/18/CAM5.2, CD10, PLAP (60%), HCG, SALL4 |
| Bladder transitional carcinoma | + | – | CK7, CK20, CK5, p63, GATA3, E-cadherin, uroplakin III |
| Vascular tumors | – | – | CD31, CD34, FLI-1, ERG |
| AML | – | – | HMB45, Melan A, MART1, actin HHF-35, CD68, TFE3 (transcription factor E3)[77] |

[a] Canalicular.
[b] Sinusoidal.



Наблюдение 8



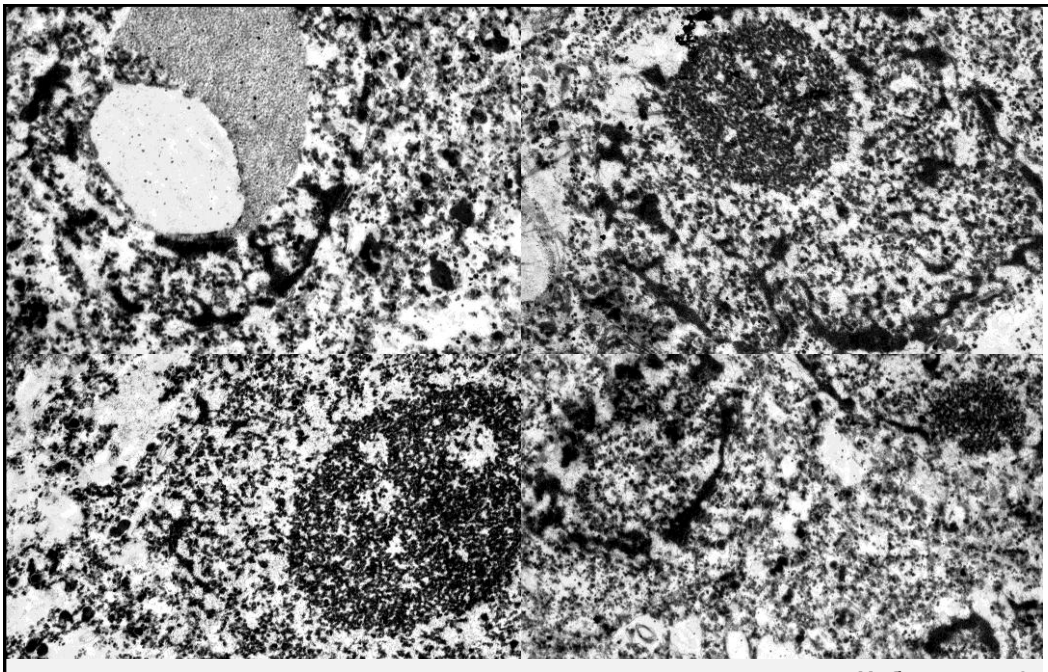
Наблюдение 8

**При иммуногистохимическом исследовании клетки опухоли обнаруживают экспрессию:**
**пан-цитокератин (клон AE1/AE3) – диффузную цитоплазматическую;**
**S100P (клон 16/f5) – диффузную цитоплазматическую;**
**beta-Catenin (клон 14) – мембранную;**
**Arginase-1 (клон SP156) – очаговую цитоплазматическую.**

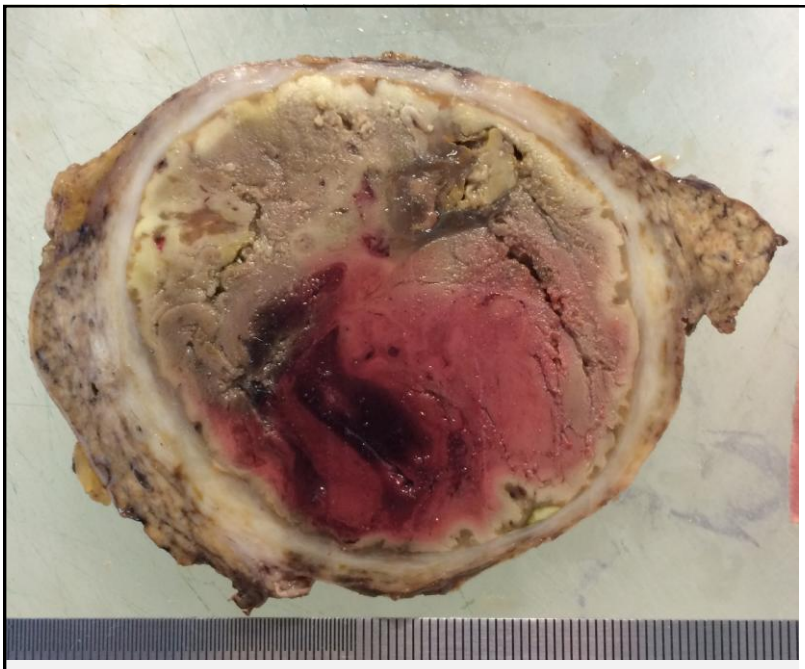
**Клетки опухоли негативны к**
**Hepatocyte (клон OCH1E5, DAKO),**
**HepPar1 (клон OCH1E5, CellMarque),**
**Glutamine Synthetase (клон GS-6),**
**Glypican-3 (клон 1G12),**
**Melan A (клон A103),**
**Melanoma Coctail (клон A103 + HMB-45 + T311),**
**CD56 (клон 123C3),**
**Chromogranin A (клон DAK-A3),**
**TTF-1 (клон 8G7G3/1),**
**CD34 (клон QBEnd/10),**
**CD10 (клон 56C6),**
**CEA (клон CEA31),**
**Vimentin (клон V9),**
**CK 7 (клон OV-TL 12/30),**
**CK 19 (клон A53-B/A2.26)**

**В одном из срезов к структуре опухоли обнаруживаются замурованные островки ткани печени, экспрессирующие HepPar1 (клон OCH1E5, CellMarque), Glutamine Synthetase (клон GS-6), Arginase-1 (клон SP156).**

**Наблюдение 8**

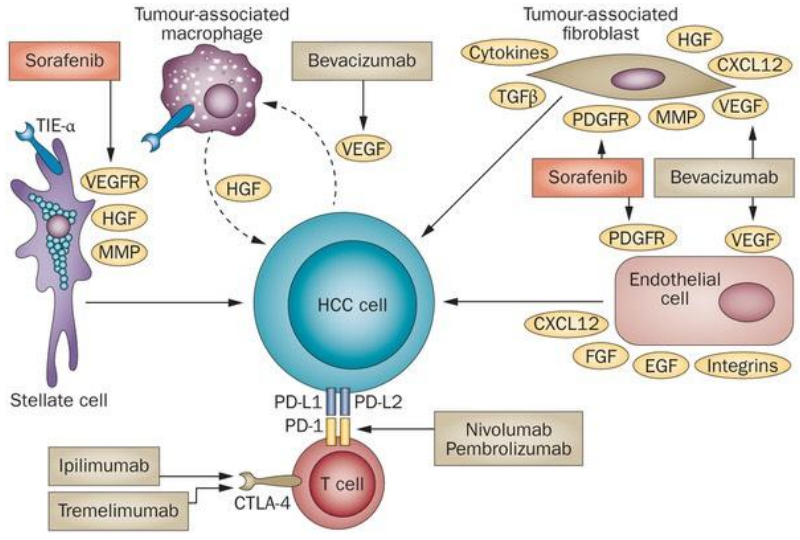


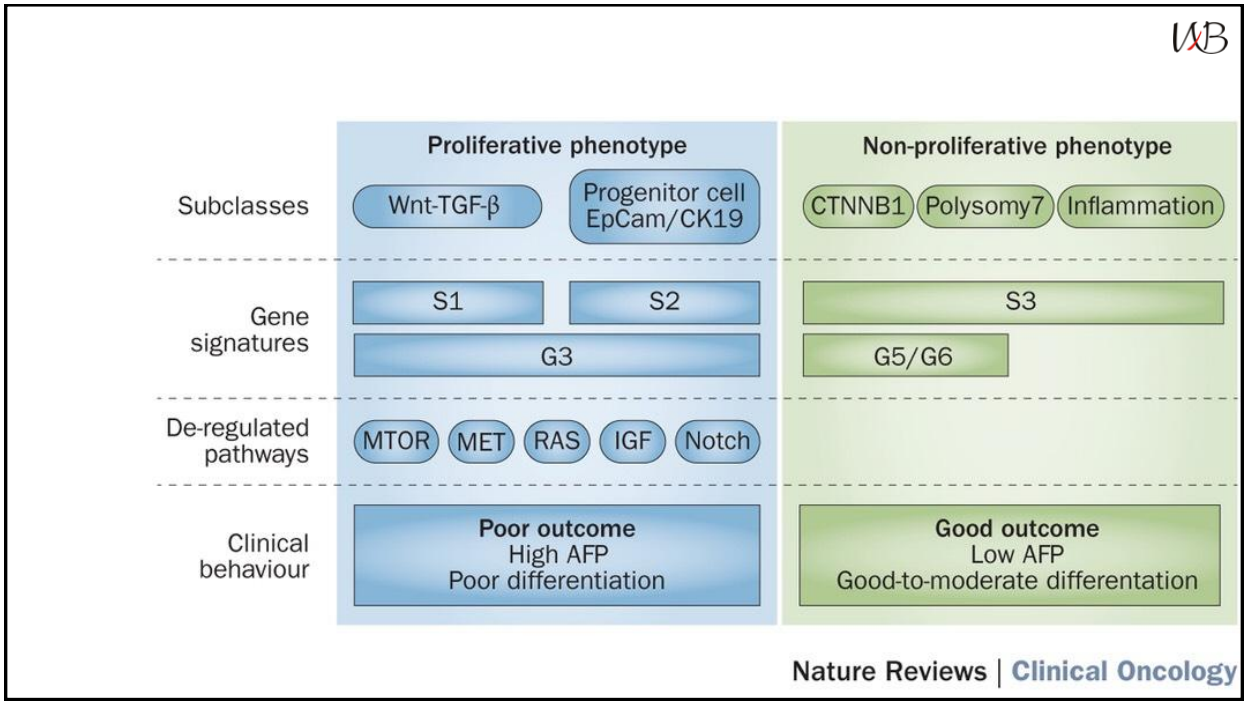
**Наблюдение 8**



**Наблюдение 9**

**Advances in targeted therapies for hepatocellular carcinoma in the genomic era**
Josep M. Llovet, Augusto Villanueva, Anja Lachenmayer & Richard S. Finn
*Nature Reviews Clinical Oncology 12, 408–424 (2015) doi:10.1038/nrclinonc.2015.103*






# Спасибо за внимание!

COLLEGE of AMERICAN PATHOLOGISTS

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