Expert consensus on the scheme of pathological diagnosis of primary liver cancer

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Submitted May 29, 2012. Accepted for publication Jun 29, 2012.
DOI: 10.3978/j.issn.2304-3865.2012.06.02
Scan to your mobile device or view this article at: http://www.thecco.net/article/view/960/1242

Primary liver cancer is highly prevalent in China. The continued advances in the surgical diagnosis and treatment for liver cancer have facilitated the rapid development of clinicopathological diagnosis of liver cancer in China, a country with remarkable advantages in the amount and type of pathological specimens of liver cancer. Meanwhile, to develop tailored treatment schemes for patients and improve the long-term therapeutic effectiveness, clinically new requirements have been proposed for the information contained in a pathology report for liver cancer. Although up to ten thousands of liver cancer cases have been diagnosed in some Chinese medical institutions, the pathological diagnosis of liver cancer still develops in an unbalanced manner, with diverse content and various formats in a pathology report, which is far from being able to meet the clinical demands of individualized precise treatment. On January 17, 2010, the Chinese Society of Liver Cancer (CSLC), Chinese Society of Clinical Oncology (CSCO), Liver Cancer Group, Chinese Society of Hepatology, and Chinese Pathological Group of Hepatobiliary Tumors and Liver Transplantation co-sponsored a consensus conference on the scheme of pathological diagnosis of primary liver cancer in Shanghai, China. The chief officers of the sponsoring societies and the exports who attended the meeting discussed issues related with the standardized pathological diagnosis of primary liver cancer and shared their experiences in the research and application of immunopathological and molecular pathological diagnosis of liver tumors. They presented many constructive opinions and recommendations for the standardized pathological diagnosis of primary liver cancer from the perspectives of clinical diagnosis and treatment and described new methods that that had been adopted by some foreign hospitals for the pathological diagnosis of liver tumors. Based on the discussions of the speakers, a preliminary draft of the consensus paper was proposed and then revised after extensive consultations. This document reflects a collective consensus on this topic and provides instructive information for clinical practices. Nevertheless, it will be constantly revised and upgraded in the future to meet the "real-world" demands on the pathological diagnosis of liver tumors.

1. Contents of a pathology report

A primary liver cancer refers to the malignant tumor originate from hepatocytes or intrahepatic biliary epithelial cells, with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) being the most common forms. However, most information in this scheme is also applicable for other types of liver tumor. Liver cancer occupies an important place in the routine practice of hepatic surgery, during which the pathological diagnosis is critical for the establishment of clinical treatment scheme and the improvement of health care level. Therefore, a pathology report should not only pay attention to the accuracy of pathological diagnosis but also systematically describe the main pathological and biological features that may influence the patient's prognosis. The information provided by a pathology report should assist the clinicians to determine the nature, metastasis potential, and surgical outcome of a liver cancer.

1.1 Key information required for gross description (1-2)

(I) Specimen type: partially resected liver tissue, resected liver specimen during liver transplantation, and tissues obtained through liver wedge biopsy, core needle biopsy, or fine-needle aspiration biopsy. (II) Tumor morphology: size, number, color, necrsosis/bleeding, integrity of capsule, and existence of naked-eye visible tumor embolus. (III) Lesions at liver tissues adjacent to a tumor: the existence of satellite nodules, type of cirrhosis, shortest distance between the surgical margin and the tumor, and existence of cancer tissue at the resection margins. (IV) Large size of tumor or special morphological appearance should be weighed with photo evidences.

The morphologic typing of HCC can be based on the "Five Types and Six Subtypes" discribed by Liver Cancer Pathology Research Group of China in 1979. To make the tumor size-based typing being more parallel with the current diagnosis and treatment capabilities for liver cancers in China, it is recommended that a liver tumor with a maximum diameter of ≤1.0 cm is defined as minute HCC, 1.1-3.0 cm as small HCC, 3.1-5.0 cm as middle HCC, 5.1-10.0 cm as large liver carcinoma, and >10.0 cm as large HCC. The diffuse liver cancer refers to the condition where the whole liver is scatteredly distributed with small tumor foci (similiar to cirrhotic nodules). The morphologic types of ICC can be divided into four types: mass-forming type, nodule-infiltrative type, periductal infiltrating type, and intraductal growing type.

1.2. Key information required for light microscopic description (2-5)

A light microscopic description should include information required in literatures published by World Health Organization and other institutions as follows: (I) The common histologic types of HCC include thin trabecular type, thick trabecular type, pseudoglandular type, and compact type, *et al*., (II) The cellular morphologies of HCC include clear cell type, fat-rich type, spindle cell type, undifferentiated type, and many other cell types. (III) The differentiation of HCC can be divided into four levels: well differentiated, moderately differentiated, poorly differentiated, and undifferentiated; however, the classical Edmondson-Steiner's grading system is also useful. (IV) Adenocarcinoma is the most common type of ICC, while many other specific histological and cytological types can also be found. (V) Combined hepatocellular and cholangiocarcinoma (cHCC-CC): the co-existence of both hepatocellular and cholangiocellular components in the same tumor nodule. (VI) Tumor growth patterns: they may include invasion into surrounding normal liver tissue, invasion into tumor capsule, development of satellite nodules, intrahepatic metastasis, and forming of tumor thrombi in the microvascular system. (VII) Lesions in the surrounding liver tissues: histological studies may be performed based on the National Protocol for Viral Hepatitis Prevention and Control of China (2000), in which inflammation grade(G) and fibrosis stage(S) were classified from G1 to G4 and S0 to S4, respectively. Alternatively, the lesions may be assessed according to other internationally recognized scoring systems such as Knodell's histologic activity index (HAI).

1.3. Key information required for the description of precancerous lesions (2-4)

The precancerous lesions of HCC usually occur after chronic viral hepatitis or cirrhosis. They may include: (I) Low-grade dysplastic nodule (LGDN); (II) High-grade dysplastic nodule (HGDN); (III) Nodule in nodule: early-stage cancer foci inside HGDN; (IV) Dysplastic foci: lesions (≤1.0 mm in diameter) formed by atypical hyperplastic hepatocytes; and (V) Hepatocellular changes (atypical hyperplasia): they can be classified as small cell change and large cell change. The precancerous lesions of ICC may include: (I) Biliary intraepithelial neoplasias: they can be classified as low grade and high grade; and (II) Intra-ductal papillary neoplasm: they can be classified as low grade and borderline tumors or high grade tumors.

1.4 Key information required for a pathologic diagnosis

Pathologic diagnosis provides an overall summary for the nature, tissue origin, differentiation level, biological behaviors, and key test results. Remarks may be added, when necessary, to further explain key biological behaviors that may affect the invasion, metastasis, and prognosis of tumors and/or highlight lesions that require further differential diagnosis.

2. Sampling areas and sample size

(I) Tumor tissue: 2-4 blocks; or, whole tumor tissue for small liver cancer <3.0 cm in diameter. (II) Borderline area between the tumor nodule and surrounding tissues: 2 blocks; (III) Surgical resection margin: 2 sblocks; (IV) Liver tissue adjacent to the tumor (>1.0 cm in distance): 2 blocks; and (V) Tumor emboli and satellite nodules: 2 blocks each, with a size of (1.0-2.0) cm × 1.0 cm × 0.2 cm.

3. Basic requirements for liver biopsy (6-7)

For ultrasound- or CT-guided liver biopsy, a 16G needle is recommended. Typically, one section is taken at both the tumor and its adjacent liver tissue for comparison, with ≥6 serial sections mounted on one slide. An ideal liver biopsy tissue sample should be a circular cylinder with equal diameter of 1.5-2.0 cm.

4. Specimen fixation

Parallel cutting planes spaced 1.0 cm are made along the coronal plane. Tissues for routine pathologic examinations are fixed in 10% neutral buffered formalin (4% formaldehyde) for 8-12 h. The fixation of liver biopsy specimens usually lasts 1-2 h.

5. Accessory diagnostic markers (2,8)

Accessory diagnostic markers may be selected based on the specific conditions of the patient and the available resources of a laboratory.

5.1. Diagnostic markers (2,8)

5.1.1. For HCC

(I) Hepatocyte specific antigen Hep Par 1 (however, it can not characterize the nature of a positive liver cell); (II) Polyclonal carcinembryonic antigen (pCEA) (however, it can not characterize the nature a positive liver cell); (III) glypican-3 (GPC-3) (it is positive for liver cancer cells and negative for liver tissue adjacent to a tumor); (IV) CD34 (shows a diffuse pattern of microvessel staining in hepatic sinusoid); (V) Alpha-fetoprotein (AFP); (VI) HBsAg; and (VII) HBcAg. Dual-phenotype HCC (DPHCC) that is also positive for bile duct cell markers is generally believed to be more malignant.

5.1.2. For ICC

(I) Cytokeratin (CK) 19/CK7; (II) Mucoprotein-1 (MUC-1); and (III) Aquaporin-1 (AQP-1). However, these markers can also be positive in non-tumor bile duct epithelial cells.

5.1.3. For HCC/ICC mixed tumor

The above mentioned tumor markers can be positively expressed by HCC and ICC tumor cells, respectively.

5.2. Markers of cell proliferation

These markers include: (I) Ki-67 proliferation index (assessed by point counting 500 to 1,000 cells, and is reported as percent positive cells): Low level ≤5% of tumor cells, middle level 5-10%, and high level >10% of tumor cells; (II) p53; and (III) Others.

5.3. Molecular biological markers (9,10)

Research on the molecular typing of liver cancers has advanced in recent years. It has been reported that molecular markers such as insulin-like growth factor 2 mRNA binding protein 3 (IMP3), oesteopontin (OPN), Stathmin protein, and microRNAs are associated with the invasion and metastatis potentials of liver cancer cells as well as with the prognosis. However, their actual significances require further evaluation. The clonal origins of the multinodular and postoperative recurrent HCC may be detected by analysing the loss of heterozygosity (LOH) of microstaellites, so as to understand whether the origin of the tumor is monoclonal (intrahepatic metastasis in nature) or polyclonal (newly developed HCC in nature), which will be helpful for clinicians to make proper diagnosis and treatment decisions for each individual case. Meanwhile, screening for the molecular targets of anticancer drugs has increasingly became a routine examination item, and its role in the research and application of the molecular pathology of liver cancer may be promising.

5.4. Special staining

Masson trichromal staining or van Gieson (VG) staining can display the proliferation of collagen. Reticular fiber staining can display the completeness of the reticular framework of hepatic plates and the hepatic lobules, and thus increase the accuracies in assessing the the reconstruction of the adjacent liver tissue and the level of hepatic fibrosis.

6. Appendix: An example of a pathology report of liver cancer

6.1. Gross

(I) A gray tumor of 2.6 cm × 2.2 cm, accompanied with focal necrosis/bleeding, is present at the cut surface of a 5.0 cm × 4.5 cm × 4.2 cm specimen resected from the right liver lobe. The surrounding fibrous capsule is intact. The adjacent liver tissue shows micronodular cirrhosis, while no tumor embolus or satellite nodule is found. The minimum distance from tumor to surgical cut margin is 1.0 cm, and there is no exposure of tumor on the cut margin. (II) A gray tumor nodule (1.0 cm in diameter) is present at the cut surface of a 3.0 cm × 2.0 cm × 2.2 cm specimen resected from the left liver lobe. It has no obvious capsule but has a well-defined margin with the surrounding liver tissue.

6.2. Microscopic findings

(I) The tumor in the right liver lobe is composed of polygon-shaped cells, having irregular trabecular structure. These cells have abundant acidophilic cytoplasm and round nucleus, with minimal atypia. The majority of the tumor mass is surrounded by capsule, along with the infiltration of many lymphocytes. Migration presents between some cancer tissues and the surrounding liver tissues, microvessel cancer emboli occasionally are found inside the capsules, and no invasion to the adjacent liver tissues or vessels is observed. The surrounding liver tissues have pseudolobular structure, associated with inflammation in portal tract, in which, a dysplastic focus formed by large cell change shows the expansion extrusion on the surrounding liver tissue, causing the adipose degeneration of a few hepatocytes. No tumor cell is found on the resection margins. (II) The tumor at the left liver lobe shows pseudoglandular structure; the tumor cells are small and cube-shaped, with moderate atypia. The tumor has no surrounding capsule. Migration of tumor cells into the surrounding liver tissue is found, with a well-defined border.

6.3. Immunohistochemical results

Hep Par1: positive; GPC-3: positive; HBsAg: positive; HBcAg: positive; CD34 shows diffuse distribution in microvessels; CK19: negative in pseudonodular area; and Ki-67 proliferation index: ≤5%.

6.4. Results of molecular pathological determinations

Microsatellite analysis for LOH at 10 high frequencies was performed for both left and right hepatic lobes. It is found that two tumor nodules exhibited 4 (40%) differential expression patterns of microsatellite LOH, suggesting that these two nodules originate from different tumor cell clones (A molecular pathology reporat may be attached if necessary).

6.5. Pathologic diagnosis

(I) Small hepatocellular carcinoma (of right liver lobe), trabecular pattern, grade II; (II) Small hepatocellular carcinoma (of left liver lobe), pseudonodular type, grade II; (III) Micronodular cirrhosis following hepatitis B, active; and (IV) A dysplastic focus at the adjacent liver tissues.

Note: (I) Analyses of microsatellite LOH show that the two tumor nodules in this case are double primary tumors with multicentric origins. (II) A dysplastic focus is found at the cirrhotic liver tissues adjacent to the tumors, suggesting the presence of precancerous lesions, which should be closely followed-up by clinicians.

Acknowledgments

Special thanks to Profs. Meng-chao Wu, Zhao-you Tang, Jia Fan, Sheng-long Ye, and Shu-kui Qin, who initiated and organized the development of this consensus scheme and provided many valuable comments and advice for this document.

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cong WM, Hu XQ, Sun YT, Tan YS, Ji XL, Yun JP, Zhu HG, Guo H, Wang RA, Liu SX, Yin HL, Wang X, Li ZS, Ji Y, on behave of Chinese Society of Liver Cancer (CSLC), Chinese Society of Clinical Oncology (CSCO), Liver Cancer Group, Chinese Society of Hepatology, and Chinese Pathological Group of Hepatobiliary Tumors and Liver Transplantation. Expert consensus on the scheme of pathological diagnosis of primary liver cancer. Chin Clin Oncol 2012;1:12. DOI: 10.3978/j.issn.2304-3865.2012.06.02

