

Wen-Ming Cong
Editor

Surgical Pathology of Hepatobiliary Tumors

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Foreword



China has a high incidence of hepatobiliary tumors at present and even in the forthcoming decades. With rapid development in the field of hepatic surgery, pathology should play a more supportive role in the improvement of clinical diagnosis and treatments. In order to greatly improve the long-term therapeutic effects of hepatocellular carcinoma (HCC), researchers and clinicians are making huge efforts of developing standardized individual clinic mode to diagnose and treat hepatic tumors, which would lead to more emphasis on the research and understanding of the pathobiological features of HCC. Now there is an increasing realization that exploration of clinic mode to treat HCC in the perspective of biological characterization is an optimal way to greatly improve the efficacy of early diagnosis and treatment, and the instructive function of HCC diagnosis and treatment standards on individualized treatment is limiting without the involvement of the pathobiological characterization of HCC.

This book *Surgical Pathology of Hepatobiliary Tumors*, based on the former edition published 15 years ago, was reedited by a group of experts with Professor Wen-Ming Cong as the editor in chief, who is the director of the Department of Pathology of Eastern Hepatobiliary Surgery Hospital (EHBH). In this book our experience in the pathological diagnosis of hepatobiliary tumors of more than 40,000 cases over 30 years in EHBH is summed up, and a new histological classification of hepatobiliary tumors termed as “Three Types and Six Subtypes” is advanced. Aiming to reveal the recent developments of surgical pathology of hepatobiliary in the perspective of pathobiology of tumors, this book contains descriptions of more than 100 tumors of the liver and intrahepatic bile duct, with updated information in picture-illustrated

composing style and broad clinical practicability and guidance. It is the most systemic and thorough reference book on pathological diagnosis of hepatobiliary tumors and will be greatly useful for clinicians, pathologists, and researchers of medical basis or other disciplines.

I wish to see close cooperation between liver cancer surgeons and the pathologists, innovative researches focusing on key clinical concerns and demands, and active exploration of new mode and methods of pathological diagnosis, further developing technology architecture of diagnostic pathology which is scientific, objective, and standardized, playing a more supportive basis role in improving clinical long-term curative effect of HCC. This book *Surgical Pathology of Hepatobiliary Tumors* is a beneficial exploration on the above facets and deserves my sincere congratulations on its publication. I should be very glad to recommend this book to my peers.

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Meng-Chao Wu

Preface



It has been 15 years since I drew the outline of the former edition of *Diagnostic Surgical Pathology of Hepatobiliary Tumors* when I was a visiting scholar of the Department of Pathology at the University of Pittsburgh Medical Center (UPMC) in 1999. As the first Chinese book on pathological diagnosis of hepatobiliary tumors, it has gained much attention and recognition and become one of the frequently used reference books due to its useful guide for improving the pathological diagnosis of hepatobiliary tumors. However, during the past 15 years, integration and mutual promotion of the molecular biology and molecular pathology of liver cancer have been witnessed, and new concepts such as heterogeneity, pathobiological features, molecular classification, and individualized treatment have emerged and been accepted as the basic guidance in modern clinical therapeutics of liver cancer. Furthermore, Chinese scholars have made innovative achievements in molecular pathology and histopathological diagnosis of liver cancer. With much experience in clinical pathological diagnosis and with new hepatic lesions, understanding, and concepts and methods put forward, we are ready to rewrite this book. Receiving much encouragement and support from my teacher, Professor Meng-Chao Wu, a world-famous Chinese hepatobiliary surgery scientist and surgeon, being considered as the “father of Chinese hepatobiliary surgery,” we finished the recompiling of the book after one year’s intense work and present it to everyone here.

The disciplines we stick to throughout our writing is emphasizing the integration of basic research, pathological diagnosis, and clinical practice, introducing recent developments and scientific achievements, focusing on the philosophy and mode of diagnosing liver cancer pathobiologically, and illustrating the theories, concepts, pathological features, and diagnostic techniques, in the aim of providing the readers with a reference book which helps improve the pathological theories and diagnosis of liver cancer. Therefore, we put emphasis on the new

concepts and knowledge in surgical pathology of hepatobiliary tumors. Based on our new histological classification of hepatobiliary tumors termed as “Three Types and Six Subtypes,” we described the histological classification of more than 100 entities of the liver and intrahepatic bile ducts in detail with a selection of over 600 pictures to illustrate the pathological features and biological behavior of these tumors. We have omitted the chapter “Pathological Diagnosis of Liver Transplantation,” the contents of which were demonstrated in our published book *Clinical Pathology of Liver Transplantation* in 2011. To elucidate the pathological features of hepatic tumors in children systematically, we added the chapter “Hepatic Tumors in Children.” It should be explained that tumors of the same type will be referred to in different parts of the book to maintain its integrity, because they can be seen in both adults and children. Besides, some tumors of the liver can also be seen in intrahepatic and extrahepatic bile ducts and gallbladder. A glossary of terms is included for the reader’s convenience. In particular, Professor Thung SN, who was the director of the Department of Pathology of Mount Sinai School of Medicine in New York, USA, was invited to write the chapter “Biopsy and Pathologic Diagnosis of Hepatic Tumor.” I hope this will be helpful for the improvement of the level of hepatic pathological diagnosis on small biopsy tissue samples.

I am particularly grateful to my supervisor, Professor Meng-Chao Wu, an Academician of the Chinese Academy of Sciences, for his precious advice on the compiling and his kindness to write the preface. Academician Meng-Chao Wu has been so kind and attentive to me and offering careful guidance on my learning, working, and research for the past several decades for which I’ve been grateful and respectful. Academician Meng-Chao Wu is a pioneer and chief founder of Chinese hepatic surgery and has devoted much attention to the development of our Department of Pathology. The establishment of the new Department of Pathology in the An-Ting new district of EHBH was brought into a new era under his support. Academician Meng-Chao Wu pointed out in the preface that “the instructive function of HCC diagnosis and treatment standards on individualized treatment is limiting without the involvement of the pathobiological characterization of HCC,” which makes us be more aware of the heavy responsibilities and glorious mission of pathologists, as tissue samples are the most important and direct carrier of biological features of liver cancer.

I would particularly thank the world-renowned expert in liver cancer and Academician of the Chinese Academy of Engineering, Professor Zhao-You Tang, who was invited to make a brilliant exposition on the fundamental roles of pathobiological characteristics in improving the level of diagnosis and treatment of hepatocellular carcinoma. Academician Tang begins his article with “pathology is a prerequisite for a cancer surgeon to make decisions, I am grateful for the contributions made by pathologists,” which allows us to deeply feel his profound understanding and ardent love of the subject of pathology. I am extremely honored that Academician Tang has been the Chairman of the dissertation committee for my both master’s and doctor’s degree theses, and I always have a deep respect for the care and guidance from him.

I would particularly thank the world-famous expert in liver cancer, Academician of the Chinese Academy of Engineering, Professor Hong-Yang Wang, who was invited to make a profound analysis and prediction on the development trend of the research on molecular biology of hepatocellular carcinoma. Academician Wang brilliantly pointed out that liver cancer molecular typing and individual treatment are the only way to overcome the liver cancer. Academician Wang led an Innovative Research Groups of the National Natural Science Foundation of China on liver cancer and significantly promotes the academic research level of hepatocellular carcinoma of China, and our pathology team also got a lot of concern and guidance from Academician Wang.

I would like to thank Professor Thung SN from the Department of Pathology of Mount Sinai School of Medicine in New York, USA, Professor Yuan Ji from the Department of Pathology of Shanghai Zhongshan Hospital, and Professor Xiang-Ru Wu from the Department of Pathology of Shanghai Xinhua Hospital, who are successful experts in hepatopathological study, and their preciseness and elaboration in writing represent the basic discipline of the book to explore the new diagnostic mode of pathobiological characteristics of liver cancer.

And I would also like to thank Hui Dong, Xin-Yuan Lu, You-Wen Qian, Qian Zhao, Yu-Yao Zhu, Long-Hai Feng, Sheng Xia, Guang-Zhi Jin, Zhi-hong Xian, and Hua Yu et al. who are all my colleagues for their hard work in data collection and sorting and technical support for the compiling of the book. Their meticulous statistical work on the archival data from the Department of Pathology over 30 years provides the readers with representative data of the Chinese population. Among them, Hui Dong, PhD; You-Wen Qian, PhD; and Yu-Yao Zhu, MS undertook the serious work on formatting the final manuscript, picture editing, and text proofreading.

In the light of pathological diversity of hepatobiliary tumors, there is controversy about some concepts and understanding, and studies on liver cancer cover a wide research area with rapid developments of clinical diagnosis and treatment, which altogether bring a great challenge to the writing of the book. Despite our efforts to perfect the book, there may still be some omissions and inadequacies. We would appreciate it very much if readers will kindly point out our errors for future revision of this book.

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My View on the Biological Features and Surgical Treatment of Liver Cancer

1

Zhao-You Tang

Pathology is the prerequisite for oncology surgeons to make decisions. I can only feel grateful for the contribution made by my fellow pathologists. Having the honor to write a passage for the introduction to this monograph, I am even more overwhelmed. After all, I'm only a clinician, not a basic research fellow. Fortunately there are the two words "my view" in my title. Therefore this passage will just be my personal opinions from the clinical perspective for the reference of those engaged in the same pursuit.

In 2012 the article "Two Hundred Years of Cancer Research" [1] by DeVita and Rosenberg was published on *The New England Journal of Medicine*, in which the "cellular origin of cancer" put forward by Virchow in 1863 has laid the "pathological foundation" for modern oncology and become the gold standard for cancer diagnosis and the basis for treatment decisions, and Watson et al. discovered the double helix structure of DNA in 1953, EGF and its EDNR in 1979, p53 anti-oncogene in 1981, etc., all these initiating the research of molecular biology and suggesting that the context of cancer research has been gradually transformed from "pathology" to "pathology-biology." The establishment of the "pathological foundation" of cancer has focused the attention of the great cancer-fighting army on one thing, i.e., employing all available means to eliminate pathologically confirmed tumors, which leads to the development of tumor-eliminating treatments such as surgery, radiotherapy, chemotherapy, interventional therapy (e.g., TACE), and local treatment, hence the substantial progress of curative effect in cancer treatment.

As an oncology surgeon, I've realized the distinct differences of liver cancer from the pathological and biological perspectives. For example, in terms of diagnosis, the former focuses on appearance and answers questions of whether it is

cancer or what cancer it is, while the latter focuses on biological features, i.e., how is its degree of malignancy. In terms of treatment, the former is about eliminating tumor, while the latter is aimed at decreasing the potentiality of cancer invasion and metastasis and improving the body's cancer-fighting ability. In terms of means of application, the former has surgery, radiotherapy, chemotherapy, local treatment, interventional therapy, the latest VEGF-targeted molecular targeted curative agent, etc., while the latter emphasizes biological treatment like differentiation inducing therapy and immunotherapy. In terms of prognostic indicator, the former values biological features of morphologic correlation like degree of differentiation, while the latter values biological features of molecular correlation like prognostic molecular predictor. In terms of efficacy evaluation, the former values the effective rate for tumor (complete remission, partial remission, etc.), while the latter values overall survival rate and quality of life.

Now that there is still a long way to go before cancer is conquered, this transformation of context gives us new ideas from the clinical perspective. It is expected that in the future trend of cancer treatment, tumor elimination will still be the most important goal of treatment. Nevertheless, besides the elimination of primary tumor, another important goal will be the modification of residual tumor to decrease its degree of malignancy and the modification of body to increase its cancer-fighting ability. In this way, "transforming the bad" or "surviving with tumor" becomes another "end point" of treatment.

1.1 Surgical Treatment in the Pathological Context

Surgical treatment plays a decisive role in improving the curative effect of liver cancer in the twentieth century. In the 1950s, the regular hepatectomy of liver cancer for the first time improved the curative effect for liver cancer substantially. Started in the 1960s and confirmed in the 1990s, the

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liver cancer treatment method liver transplantation made part of unresectable relatively small liver cancer treatable, thus extending the benefits to more liver cancer patients. In the 1970s, alpha fetoprotein was used for screening, and the curative effect of resection was doubled through early detection, early diagnosis, and early treatment, especially the local resection of small liver cancer (≤ 5 cm). In the 1980s, thanks to combined therapy such as surgical hepatic artery ligation, intubation infusion chemotherapy, and radiotherapy, resection after downstaging (reduction) made radical cure possible for a small number of patients with unresectable liver cancer. The rise of local treatment like TACE and radiofrequency ablation has obviously extended the benefits to more patients, among which some were cured after resection of reduced tumor. All of these efforts are aimed at “tumor elimination.” During the past half century, the survival rate of inpatients at the Liver Cancer Research Institute of Zhongshan Hospital, Fudan University (hereinafter referred to as this Institute) has indeed experienced improvement every 10 years, which is attributable to surgical treatment, especially the resection of small liver cancer.

In the “pathological context,” efforts during the past half century are mainly aimed toward “eliminating tumors as many as possible,” which include:

1. Surgery-related: researches on improving resection rate, decreasing operative mortality rate, resection of tumor along its edges, operation method in strict accordance with intrahepatic anatomy, reducing tumor spread during operation, etc.
2. Liver transplantation to treat liver cancer, which is also mainly for the purpose of eliminating tumor even more completely
3. Preoperative and postoperative treatment-related: researches on how to further eliminate residual cancer, such as postoperative radiotherapy, chemotherapy, application of TACE, and application of molecular targeted curative agent sorafenib

However, even though all these efforts have improved curative effect to a certain extent, none of them can solve the problem completely, the greatest bottleneck being postoperative cancer metastasis and recurrence.

Apparently, the metastasis of cancer originates from the cancer cells left behind. And there are two possibilities for the recurrence of cancer: metastatic tumor and another primary tumor, the latter of which falls into the category of cancer prevention. Therefore, the main barrier to improving the curative effect of surgical treatment for liver cancer is cancer metastasis. The most obvious evidence is that in about 40 years, despite the growth of cases of small liver cancer

resection at this Institute by hundreds of times, the five-year survival rate is still wandering below 60%.

1.2 Biological Hallmarks of Cancer

The “biological hallmarks of cancer” is a very comprehensive issue, and it would be quite difficult to summarize in one passage. In 2011 the article “Hallmarks of Cancer: The Next Generation” by Hanahan was published in *Cell*, which may provide a brief summary of the biological hallmarks of cancer [2]. Including a few upcoming hallmarks, ten hallmarks are listed: (1) sustaining proliferative signaling, (2) evading growth suppressors, (3) resisting cell death, (4) enabling replicative immortality, (5) inducing angiogenesis, (6) activating invasion and metastasis, (7) reprogramming of energy metabolism, (8) avoiding immune destruction, (9) tumor promoting inflammation, and (10) genome instability and mutation. Among which, based on my understanding, the former six hallmarks are related to cancer cells, while the latter four involve the whole body, e.g., metabolic regulation, immune function, inflammation-triggered cancer, genetic mutation, and instability. Therefore, cancer originates from cells. However, instead of simple cytopathic effect, this process involves the whole body which is under the influence of external environment and heredity.

From the clinical perspective, I believe “activating invasion and metastasis” is of the uttermost importance among the abovementioned ten hallmarks of cancer. This is the major biological feature that makes cancer different from benign tumor. Without the potentiality for invasion and metastasis, cancer will become benign tumor, while most of the other hallmarks serve the feature of “invasion and metastasis.”

Since the understanding of the biological hallmarks of cancer invasion and metastasis has been updated significantly in recent years, proper adjustment should be made in the surgical treatment of liver cancer. (1) It was once believed that the enhancement of the potentiality for cancer metastasis is the result of clone screening during cancer progression. Now it is believed that cancer metastasis is a systemic issue; apart from targeting at metastasis, cancer treatment should also attach importance to systemic intervention, which may change the potentiality for cancer metastasis. As mentioned above, four out of the ten cancer hallmarks of the next generation are related to systemic regulation. It is also pointed out in literature that general conditions and intrahepatic tumor control are risk factors of extrahepatic metastasis [3], which also signifies that the prevention of cancer metastasis requires systemic intervention. (2) It was understood that cancer metastasis is a phenomenon of advanced-stage cancer.

Now it is understood that cancer metastasis doesn't manifest advanced stage of cancer, and prevention should start early. In our cooperation with the Americans, the comparison of small and big liver cancer reveals only seven genetic differences, while 153 genetic differences are discovered in the comparison of liver cancer with and without metastasis, suggesting that the genetic change of cancer metastasis occurs during the stage of primary tumor, and even small liver cancer can have strong metastatic potential [4]. This also explains why sometimes the recurrence and metastasis of small liver cancer happens very fast after resection and suggests the importance of early intervention. (3) It was once believed that metastasis is possible for all cancer cells. Now it's believed that it's just the cancer stem cells. For example, the EpCAM-positive liver cancer cells are stem-like cells; therefore, cancer stem cells are an important target of the anti-metastasis research [5]. I discovered that treatment with oxaliplatin in nude mouse model for human liver cancer can upregulate stem cell markers (e.g., EpCAM and CD90), while the "Song You Yin" containing five kinds of traditional Chinese medicine can downregulate those markers, reduce metastasis, and prolong survival time [6]. (4) It was once believed that cancer metastasis is in the nature of cancer cells, while now it is believed that immune inflammatory microenvironment is a key factor for cancer metastasis. During our collaboration with the Americans, it was discovered that 17 genes related to immunity and inflammation (not related to cancer metastasis) in the microenvironment around cancer can predict metastasis [7]. In 1889, Paget put forward the "seed and soil" theory of cancer metastasis, emphasizing that seed needs the right soil for growth. However, the discovery in the twenty-first century suggests that the performance of seed can also be influenced by different soils. Existing literature shows that the interaction between cancer stem cells and the microenvironment results in metastasis [8]. This Institute also finds that "Song You Yin" can improve microenvironment and inhibit cancer metastasis through downregulating the cytokines secreted by activated hepatic stellate cells [9]. Thus, a new field of intervention was discovered in anti-metastasis research. (5) It was usually believed that cancer cells could only become more malignant. Now it has been noticed that the potentiality for cancer metastasis can be bidirectional, i.e., it can either become worse or better. Therefore, "transforming the bad" is an important direction of research. It has always been believed that the metastasis potential of cancer gets increasingly enhanced during its development through clone screening, and the latest research also suggests that various cancer-killing therapies promote metastasis of residual cancer. However, differentiation inducing therapy and some Chinese medicine treatment can reduce the potential for metastasis.

All of these new ideas suggest the anti-metastasis research should not only be targeted at cancer cells, especially cancer stem cells, but also microenvironment, which is under the regulation of the whole body. Therefore, besides tumor elimination therapy, researchers should also focus on differentiation inducer, anti-inflammatory agent, immunotherapeutic agent, matrix metalloproteinase, fat metabolism, and other measures of systemic intervention. For instance, for cancer stem cells, the guiding principle of elimination and modification at the same time from the biological property point of view is more comprehensive than simple elimination advocated in the past. Above is the common problem of cancer metastasis. Despite the "individuality" of the biological hallmarks of liver cancer, their "commonness" is the most important. Therefore, the above analysis and statement is also suitable for liver cancer.

1.3 Outlook for Surgical Treatment in the Context of Pathology-Biology

For the past century, we have made every attempt to eliminate liver cancer once it's been confirmed by pathology. Since the 1990s, the development of molecular biology and systems biology has made us realize that similar to other cancers, liver cancer is not only local lesion but also systemic lesion. In addition to tumor elimination, goals of the clinical treatment of liver cancer should also include modification of tumor and body in the hope of transforming the bad residual cancer or reducing its invasion and metastasis potential and increasing the body's cancer-fighting ability so as to achieve "surviving with cancer." Since it's been proven that even the most radical surgical resection cannot ensure, there are no circulating tumor cells (CTC) left behind. Furthermore, as to the various existing therapies, we should not only recognize their efficacy and side reaction but also notice the "opposite effect" [10] and take countermeasures. This is a shortcut to improving the efficacy of tumor elimination therapy. I believe the conceptual change will broaden the perspective of liver cancer surgery research significantly.

It is expected that in the twenty-first century to improve the efficacy of liver cancer surgery, the goal will be changed from simple elimination of tumor to modification of tumor and body on the basis of elimination of as many tumors as possible. There are multiple ways to improve the efficacy of liver cancer surgery, some of which can promote efficacy significantly, such as early diagnosis and treatment, while others are less impressive, such as researches on distal and proximal resection in liver cancer surgery, surgical indications and complications, etc. Some can improve efficacy substantially, like the research on new therapy; and some improve efficacy