

Organ-specific concept and controversy for premalignant lesions and carcinogenesis of gallbladder cancer

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Abstract: An analysis of premalignant lesions, risk factors and models of carcinogenesis of gallbladder cancer (GBC) involves the concept of organ specificity. In GBC, the dysplasia-carcinoma sequence and metaplasia-dysplasia-carcinoma sequence are considered to be more important models of carcinogenesis than the adenoma-carcinoma sequence. Cholecystectomy is recommended for gallbladder polyps ≥ 1.0 cm, and all pre-invasive adenomas and papillary neoplasms ≥ 1.0 cm are defined as intracholecystic papillary-tubular neoplasms (ICPTNs). Although adenomyomatosis (ADM) and xanthogranulomatous cholecystitis (XGC) are controversial lesions, a knowledge of their clinicopathological features would help clinicians to manage gallbladder lesions associated with ADM or XGC.

Keywords: Gallbladder cancer (GBC); premalignant lesion; adenoma; intracholecystic papillary-tubular neoplasms (ICPTNs); adenomyomatosis (ADM); xanthogranulomatous cholecystitis (XGC)

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Gallbladder cancer (GBC) is generally considered to be a rare malignant neoplasm, and there has been no definitive definition to date of its premalignant lesions, risk factors or models of carcinogenesis. Barreto *et al.* recently reviewed models of the pathways of carcinogenesis of GBC (1). Step-wise development via adenoma/dysplasia to carcinoma is the most classical model of GBC carcinogenesis. Adenoma of the gallbladder typically presents as well-demarcated polypoid lesions. It is classified into three histological subtypes: the pyloric gland type, the intestinal type and the foveolar type (2). Pyloric gland-type adenoma is the most common variant. In colorectal cancer, the adenoma-carcinoma sequence proposed by Fearon and Vogelstein (3) is widely accepted as a major model of carcinogenesis, while in GBC, the malignant transformation of adenoma or the co-existence of adenoma with GBC is very rare (4). Therefore, the dysplasia-carcinoma sequence (5) or the metaplasia-dysplasia-carcinoma sequence (6) is considered to be more important models of gallbladder carcinogenesis than the adenoma-carcinoma sequence. Generally, a

pathological diagnosis of dysplasia depends primarily on nuclear atypia, and a diagnosis of metaplasia depends primarily on features of cytoplasm.

The decision for or against surgical intervention is important in the clinical management of gallbladder polyps, and pathologists agree that, after cholecystectomy, routine pathological examination or extensive pathological examination of whole sections of the resected gallbladder is important. A consensus meeting of the Americas Hepato-Pancreato-Biliary Association (AHPBA) recommends surgery for gallbladder polyps ≥ 1.0 cm because polyps of this size are more frequently associated with cancer than smaller ones. The AHPBA also recommends extensive pathological examination of the remaining whole gallbladder when high-grade dysplasia is pathologically found in the polyp because carcinomatous changes frequently occur in the background gallbladder in that situation (7). Adsay *et al.* propose the term “intracholecystic papillary-tubular neoplasms” (ICPTNs) for all pre-invasive adenomas and papillary neoplasms of the gallbladder that are ≥ 1.0 cm,

regardless of the phenotype of tumor cells (8). By definition, ICPTNs embrace all subtypes of adenomas and intracystic papillary neoplasms in the WHO-2010 classification (2). Although intracholecystic papillary-tubular neoplasm was originally abbreviated as “ICPN” (8), “ICPTN” was used in the report on the AHPBA consensus meeting (7), probably to clearly distinguish “ICPTNs” from “intracystic papillary neoplasms”.

Adenomyomatosis (ADM) and xanthogranulomatous cholecystitis (XGC) are controversial lesions. Although ADM is not generally considered a premalignant lesion, previous studies and case reports suggest the malignant potential of ADM, and segmental-type ADM is known to have an increased risk of carcinogenesis (9-12). It is difficult to prove whether a cancer truly arose from rokitansky-aschoff sinus (RAS) or surface *in situ* cancer extended into RAS. In addition, as the carcinogenesis of GBC correlates with the presence of gallstones and/or inflammation, the accompanying gallstones and/or inflammation tend to be considered responsible for the carcinogenesis rather than the presence of ADM itself. Although the malignant potential of ADM remains unclear, the clinician should keep in mind that a diagnosis of early GBC is very difficult in the context of preceding ADM (13). Actually, in our previous series of invasive GBCs, approximately 25% were grossly associated with ADM and all of these cases were diagnosed at the advanced (\geq T2) stage (14).

As XGC often coexists with GBC, the malignant potential of XGC is disputed. One study suggests the malignant potential of XGC for its upregulated oncogenes (BCL-2, c-Myc) (15), while another study suggests the inflammatory nature of XGC through the expression of p53, proliferating cell nuclear antigen (PCNA) and beta-catenin (16). It is of clinical importance that XGC often mimics GBC and rarely involves adjacent organs (17). Therefore, clinicians should include XGC among the possible differential diagnoses of masses in the liver hilum.

In summary, a thorough understanding of precancerous lesions of the gallbladder, adenoma, dysplasia, and ICPTNs requires organ specificity. Although ADM and XGC remain controversial, a knowledge of their clinicopathological features would help clinicians to better manage gallbladder lesions associated with ADM or XGC.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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