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Proliferative index facilitates distinction between benign biliary lesions and intrahepatic cholangiocarcinoma☆

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Summary

Differentiation between benign and malignant lesions of the hepatic biliary tree may pose a diagnostic problem because well-differentiated intrahepatic cholangiocarcinoma may mimic biliary hamartoma, bile duct adenoma, or parenchymal extinction. We evaluated Ki-67 proliferative index and p53 status by immunohistochemical staining to aid in exclusion of cholangiocarcinoma. Fourteen biliary hamartomas, 21 bile duct adenomas, and 11 livers with parenchymal extinction were compared with 26 intrahepatic cholangiocarcinomas (16 well-differentiated and 10 moderately or poorly differentiated tumors). We found an increased proliferative index in intrahepatic cholangiocarcinomas compared with benign biliary lesions (average 23.0% in cholangiocarcinoma versus 1.4% in all benign biliary lesions, n = 26 versus n = 46, $P < .001$). No difference in average proliferative index was observed between well-differentiated and moderately/poorly differentiated cholangiocarcinomas (average 22.7% versus 23.3%, n = 16 versus n = 10, $P = .92$). Average proliferation indices of benign biliary lesions were uniformly low (biliary hamartoma, 1.2%; bile duct adenoma, 2%; parenchymal extinction, 0.5%). Most cholangiocarcinomas (23/26; 88.5%), but none of the benign lesions (0/46; 0%), had proliferative indices greater than 10%. Strong nuclear p53 immunohistochemical staining was only seen in cholangiocarcinomas (9/26; 34.6%) and not in benign biliary lesions (0/46; 0%), although many of the benign lesions showed weak to moderate staining. Immunohistochemical staining for Ki-67 facilitates distinction between benign and malignant lesions of the intrahepatic biliary tree, whereas p53 immunohistochemical staining is less helpful.

Keywords

Cholangiocarcinoma; Bile duct adenoma; Biliary hamartoma; Von Meyenburg complex; Ki-67; Mib1

☆Competing Interest: The authors declare no conflicts of interest.

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1. Introduction

Cholangiocarcinomas represent approximately 3% of all gastrointestinal tumors worldwide and 15% to 20% of primary liver malignancies [1–3]. Diagnosis of cholangiocarcinoma confers a dismal prognosis, even at an early stage, with 5-year survival of less than 5% [2,3]. The incidence of cholangiocarcinoma, particularly intrahepatic cholangiocarcinoma, has increased in the United States, as has its consequent mortality [3]. Benign biliary lesions may show overlapping morphologic features with small or early intrahepatic cholangiocarcinoma. Here we describe use of immunohistochemical staining for Ki-67 and, to a limited extent, p53 in distinguishing between intrahepatic cholangiocarcinoma and its benign mimics.

2. Materials and methods

2.1. Case selection

After approval by the University of California, San Francisco, Institutional Committee on Human Research, the liver specimens of 14 patients with biliary hamartomas (3 core biopsies, 2 wedge biopsies, 9 resections), 21 patients with bile duct adenomas (1 core biopsy, 19 resections, 1 autopsy), 11 patients with parenchymal extinction (5 core biopsies, 6 resections), and 26 patients with intrahepatic cholangiocarcinoma (3 core biopsies, 1 wedge biopsy, 22 resections) were retrieved from the files at the Department of Pathology, University of California, San Francisco (Table 1). All histologic slides of all patients were reviewed by R. M. G. and C. G. T. The diagnoses were confirmed according to most recent World Health Organization criteria. Demographic and follow-up data were extracted from the clinical records when possible.

2.2. Immunohistochemistry

All formalin-fixed, paraffin-embedded tissue samples were routinely processed, and serial sections from representative paraffin blocks were used for hematoxylin-eosin staining and immunohistochemistry. Immunohistochemical analysis was performed using previously described techniques [4]. Briefly, 4-μm paraffin-embedded sections were heat-treated; deparaffinized; heated in citrate buffer; blocked for endogenous peroxidase, avidin, and biotin; and incubated with antibodies for either Ki-67 (Dako, Carpinteria, CA; clone MIB-1, 1:50) or p53 (Vector, Burlingame, CA; clone DO7, 1:100). Sections were subsequently washed and developed with the Vector Labs ABC kit. For all antibodies, the number of immunopositive and immunonegative cells was manually counted in a 1000-cell count (focusing on regions with the most positive cells), when available. All lesional cells were counted in cases with less than 1000 available lesional cells. For Ki-67, any degree of nuclear staining was scored as positive. For benign biliary proliferations and cholangiocarcinomas, the number of cases in which greater than 5% and greater than 10% of cells stained positive were tabulated for comparison (Table 2). For p53, nuclear staining was scored as positive, and the intensity of staining was further graded as weak (1+), moderate (2+), or strong (3+). For benign biliary proliferations and cholangiocarcinomas, the number of cases with greater than 1% strong nuclear staining is tabulated for comparison (Table 3).

Appropriate positive controls for Ki-67 and p53 were performed. Slides were scored by C. G. T. and reviewed by R. M. G. to reach consensus.

2.3. Statistical analysis

Statistical differences between groups were analyzed using Student *t* test and analysis of variance.

3. Results

3.1. Study populations

The study population demographics and pathologic features of the cases are summarized in Table 1. There was no significant difference in age of patients diagnosed as having benign biliary lesions compared with cholangiocarcinoma ($P = .30$; Table 1). The mean age was 59 years (range, 41–80 years) for biliary hamartoma, 55 years (range, 28–75 years) for bile duct adenoma, 55 years (range, 48–65 years) for parenchymal extinction, and 62 years (range, 38–85 years) for cholangiocarcinoma. Forty-three percent of the biliary hamartoma cases were in men (versus 52%of bile duct adenoma cases, 64% of parenchymal extinction cases, and 42% of cholangiocarcinoma cases).

3.2. Pathologic features

All biliary lesions, both benign and malignant, were intrahepatic. Well-differentiated, moderately differentiated, and poorly differentiated adenocarcinomas comprised 16, 8, and 2 of the cholangiocarcinomas in the study population, respectively. In comparison of cases in which size of the lesion was available, cholangiocarcinomas were significantly larger than the benign biliary lesions (5.3 cm versus 0.4 cm, n = 22 versus n = 38, $P < .001$).

3.3. Immunohistochemical results

The results of the immunohistochemical stains are summarized in Tables 2 and 3. Cholangiocarcinomas demonstrated significantly higher Ki-67 proliferation indices compared with benign lesions (23% versus 1.4%, $P < .001$; Table 2, Figs. 1 and 2). Well-differentiated cholangiocarcinomas showed a similar average proliferative index as moderately/poorly differentiated cholangiocarcinomas (22.7% versus 23.3%, n = 16 versus n = 10, $P = .92$). Indeed, the staining results were similar when comparing benign biliary lesions with only well-differentiated cholangiocarcinomas, which had significantly higher proliferation index relative to benign proliferations (22.7% versus 1.4%, respectively; $P < .001$). Most (23/26 cases; 88.5%) cholangiocarcinomas had proliferation indices greater than 10%. Two of these cases showed variability in Ki-67 staining such that some areas (up to 1000 tumor cells) were identified in which the proliferation index was less than 10% (2/23 cases [8.7%], 1 well-differentiated cholangiocarcinoma and 1 moderately differentiated cholangiocarcinoma). Of note, all 3 cholangiocarcinomas present in core biopsy specimens showed proliferation indices greater than 10%. In contrast, none of the benign biliary lesions (0/46 cases; 0%) had indices greater than 10% (100% specificity), including 9 core biopsy samples. Of the 3 patients with cholangiocarcinoma, with a proliferative index less than 10% (one each in the well-, moderately, and poorly differentiated categories), 2 (67%) had received embolic treatment of presumed hepatocellular carcinoma (based on imaging

findings; compared with only 1/23 cholangiocarcinomas with >10% proliferation index). Decreasing the Ki-67 cutoff to 5% raised the sensitivity for cholangiocarcinoma to 96% (25/26 positive cases), but 2 benign biliary lesions also had indices greater than 5% (2/46; specificity, 96%), including 1 bile duct adenoma (1/21) with a proliferation index of 7.5% and 1 biliary hamartoma (1/14) with a proliferation index of 5.2%. Of well-differentiated cholangiocarcinomas, 100% and 94% had proliferation indices greater than 5% and 10%, respectively. Both core biopsy samples of well-differentiated cholangiocarcinoma had proliferation indices greater than 10% (11.8% and 17.2%).

Immunohistochemical staining for p53 highlighted more nuclei in cholangiocarcinomas than in benign lesions (14.6% versus 3.1%, $P < .001$; Table 3). However, there was overlap in the number of p53-positive nuclei between benign and malignant lesions, when any p53 nuclear staining intensity was scored as positive (Fig. 1). On the other hand, strong (3+) nuclear staining for p53 in greater than 1% of cells was seen exclusively in cholangiocarcinomas (9/26 cases, 35%sensitivity) and never (0/46, cases, 100% specificity) in any benign lesions (Fig. 1). Of well-differentiated cholangiocarcinomas, 6 of 16 cases had strong nuclear p53 staining in greater than 1% of cells (38% sensitivity).

4. Discussion

Diagnosis of intrahepatic cholangiocarcinoma requires distinction from benign mimics. Although benign biliary lesions are generally less than 2 cm, we have occasionally encountered larger benign lesions (in particular in the setting of parenchymal extinction), as well as small intrahepatic cholangiocarcinomas (<2 cm), or in some cases, we do not have a reliable size measurement at the time of biopsy. We commonly encounter liver mass biopsies in which an initial evaluation raised consideration for adenocarcinoma, namely, in the setting of bile duct adenoma, biliary hamartoma (von Meyenburg complex), or parenchymal extinction. All of these benign lesions may demonstrate mild cytologic/nuclear atypia, in some cases with an infiltrative border, which may raise concern for malignancy. In particular, a subset of bile duct adenomas may be associated with luminal blue mucin, which often raises alarm for adenocarcinoma, and parenchymal extinction can be associated with inflammation and stromal changes concerning for an invasive process. Whereas moderately to poorly differentiated cholangiocarcinomas characteristically show overt malignant changes such as anastomosing glandular growth, piling up of large cells, mucin production, atypical mitotic figures, lymphovascular invasion, and pronounced nuclear pleomorphism (which can allow for definitive diagnosis of adenocarcinoma (intrahepatic or metastatic) on frozen section evaluation), well-differentiated cholangiocarcinomas may be more subtle, with size and infiltrative growth representing the most helpful criteria for malignancy. A particular problem arises when a well-differentiated cholangiocarcinoma infiltrates into a benign biliary lesion. Accordingly, reliable ancillary testing is needed to better allow for distinction between well-differentiated intrahepatic cholangiocarcinomas and benign biliary lesions [5].

Recent efforts to characterize genetic alterations in intrahepatic cholangiocarcinomas with next-generation sequencing have revealed that they harbor a heterogeneous collection of mutations. The most common genetic alterations are *FGFR2-PPHLN1* fusions, which are

present in ~45% of tumors, and *IDH1* or *IDH2* mutations, which are in ~20% of cholangiocarcinomas [6,7]. Although the presence of these and other mutations may be specific for cholangiocarcinoma, over other intrahepatic malignancies, and may provide relevant guidance for therapeutic intervention, these tests are not sufficiently sensitive to differentiate between benign and malignant biliary lesions and are not readily available in many laboratories. In addition, tissue is often limited on an initial diagnostic biopsy.

Ki-67/Mib1 labels proliferating cell nuclei [8] and has been used in several diagnostic scenarios to aid in discrimination between malignant and benign lesions. For example, Ki-67 has been used for cervical biopsies to differentiate a high-grade intraepithelial lesion from normal or atrophic squamous epithelium [9], for lymph node biopsies when the differential includes metastatic melanoma versus a benign nevus cell aggregate [10], and for endometrial biopsies when there is difficulty differentiating between clear cell carcinoma and Arias-Stella reaction [11]. Tan et al [12] evaluated Ki-67 staining in extrahepatic cholangiocarcinoma and found a similar average proliferative index (~35%; they also did not identify p53 staining in benign biliary lesions). This study further describes an increased proliferative index (22.9%) in nonneoplastic extrahepatic bile ducts with inflammation [12]. However, the utility of using Ki-67/Mib1 proliferation index for differentiating intrahepatic cholangiocarcinoma from benign mimics was not established.

The immunohistochemical stain for p53, a tumor suppressor, has been shown to clearly identify certain primary malignancies in a few organs. The stain has been particularly reliable for high-grade serous carcinoma of the uterus and ovary [13] and somewhat useful in detecting urothelial carcinoma in situ of the bladder [14]. However, in other scenarios, such as in astrocytomas of the central nervous system, immunohistochemistry for p53 is less reliable in detecting abnormal p53 function [15], possibly due to a difference in baseline expression level in normal tissue and/or additional unknown factors. Mutations in *TP53* have been reported in ~30% of intrahepatic cholangiocarcinomas [16]. However, it has not been established whether immunohistochemical staining for p53 reliably identifies *TP53* mutation in intrahepatic cholangiocarcinoma. A case report using Ki-67 and p53 immunohistochemistry found these markers to distinguish a rare case of a “cholangiolocellular carcinoma” (a stem cell subtype of combined hepatocellular cholangiocarcinoma) from benign ductular reaction [17]. However, systematic evaluation of these markers to reliably distinguish malignant from benign intrahepatic lesions was not performed.

In this study, we demonstrate that Ki-67 and, to a limited extent, p53 are useful immunohistochemical markers in differentiating benign from malignant intrahepatic biliary lesions. We found a significant increase in the Ki-67 proliferation indices of intrahepatic cholangiocarcinomas when compared with benign biliary lesions. Immunohistochemical staining for p53 also showed diagnostic utility when strong positive staining was present, although this marker is not sensitive for detection of cholangiocarcinoma and only a minority of tumor cells show staining, in contrast to some other tumors where enumeration of p53-positive nuclei is useful [13]. We propose that these 2 commonly available immunohistochemical stains are useful in distinguishing benign from malignant biliary lesions, especially when there is limited tissue. We found that a 10% proliferation index was

a useful diagnostic threshold because only 3 cholangiocarcinomas had proliferation indices below this threshold. Two of these aberrant cases had received prior chemoembolic treatment of presumed hepatocellular carcinoma, which may have affected proliferation indices. Only a small subset (<10%) of cholangiocarcinoma cases had variable Ki-67 staining, to an extent that sampling could potentially result in a false-negative result; it follows that on a limited sample, the sensitivity for identification of cholangiocarcinoma, by Ki-67 staining index, may fall slightly in this subset of cases. Nevertheless, all 3 core biopsies of cholangiocarcinoma included in our study (including 2 well-differentiated cholangiocarcinomas) showed proliferation indices greater than 10%.

Several other immunohistochemical markers have been studied in cholangiocarcinoma, but these are primarily aimed at differentiating between various intrahepatic malignant processes (ie, differentiation of cholangiocarcinoma from hepatocellular carcinoma or metastatic adenocarcinoma) [18,19]. A recent study identified “significant increased expression” of 14-3-3Sigma and SerpinH1 proteins in intrahepatic cholangiocarcinoma, and the authors advocate use of immunohistochemical stains for these proteins, together with the Ki-67 proliferative index (with a 5% proliferative index cutoff), as part of a 3-stain panel for distinction between benign and malignant biliary lesions [20]. However, only moderately to poorly differentiated intrahepatic cholangiocarcinoma cases were studied [20] and immunohistochemical stains for 14-3-3Sigma and SerpinH1 are not widely available for clinical use (and require interpretation of stain intensity); in contrast, Ki-67 proliferative index alone was effective in identifying even well-differentiated cholangiocarcinoma in our study (using a cutoff of 10%), which is the most problematic diagnostic scenario.

p53 immunohistochemical staining was also highly specific for cholangiocarcinoma, but only when strong (3+) nuclear staining in more than 1% of cells was considered positive. Unfortunately, low sensitivity (35% in our study, which is similar to reported rates of *TP53* mutations in cholangiocarcinoma [16]) limits diagnostic utility. Accordingly, anything less than strong nuclear staining should not be used to differentiate benign from malignant lesions due to the poor specificity of weaker staining for malignancy. In addition, given the great variability in p53 staining in benign tissue, it is possible that other benign processes, such as a rare biliary adenofibroma [21,22], will have strong nuclear p53 staining.

In summary, using a 10% proliferation index cutoff provides excellent sensitivity and specificity for differentiating intrahepatic cholangiocarcinomas from benign biliary lesions. However, a low proliferation index (ie, 5%–10%) may not entirely exclude adenocarcinoma, especially in patients who have received chemoembolization directed at the lesion, and correlation with morphologic findings can provide the most accurate diagnosis.

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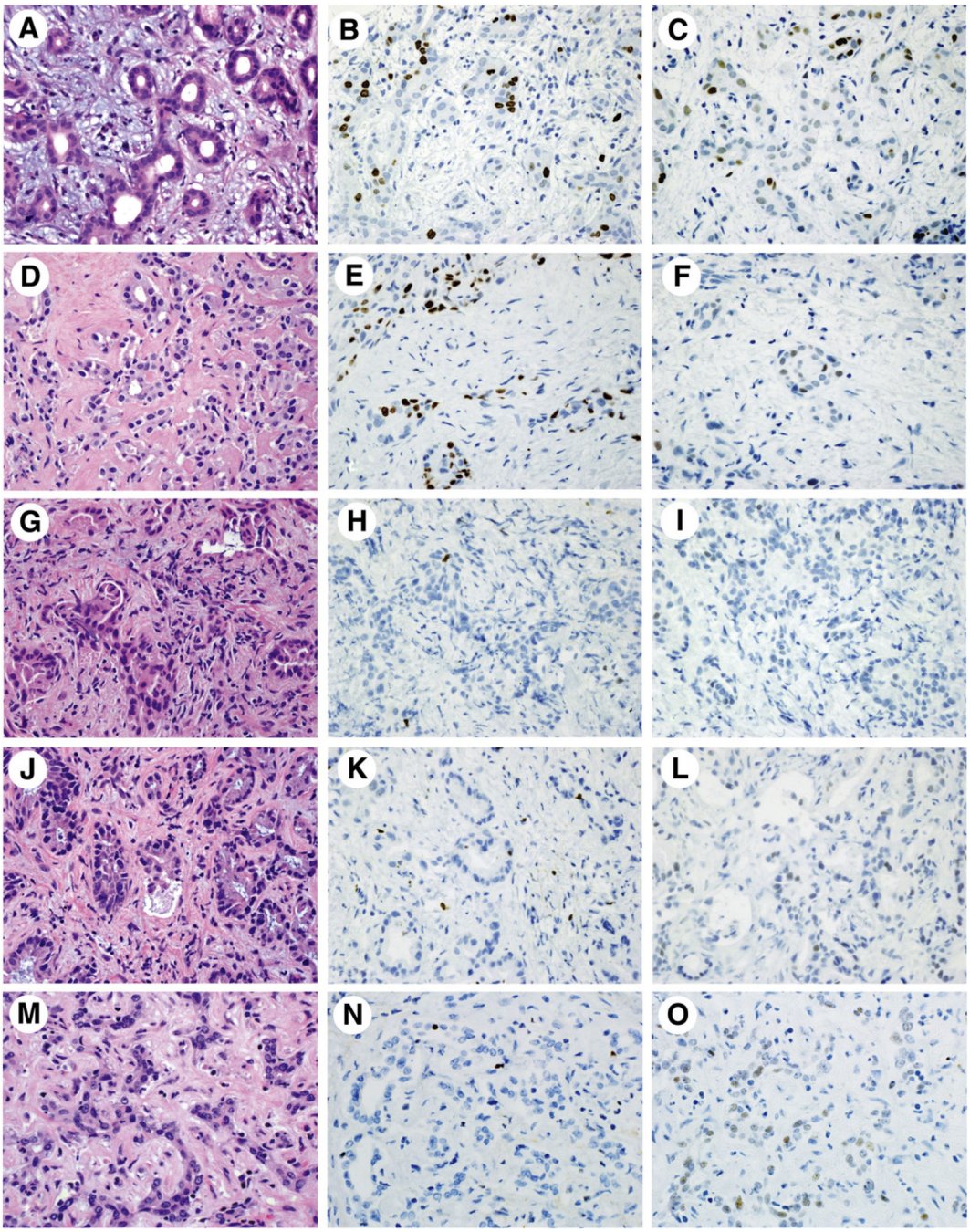

Fig. 1.

Morphologic and immunohistochemical features of benign and malignant biliary lesions. Well-differentiated intrahepatic cholangiocarcinoma (A–C and D–F, 2 cases) may show overlapping histologic features with biliary hamartoma (G–I), bile duct adenoma (J–L), or parenchymal extinction (M–O). Ki-67 proliferation indices (second column) are increased in 2 cholangiocarcinomas (B and E) compared with benign lesions (H, K, and N). Immunohistochemical stain for p53 (third column) shows strong staining in one positive cholangiocarcinoma (C), whereas the staining intensity is weak to moderate in the benign

lesions (I, L, and O) as well as in a different cholangiocarcinoma (F), which was scored as negative. Original magnification ×400.

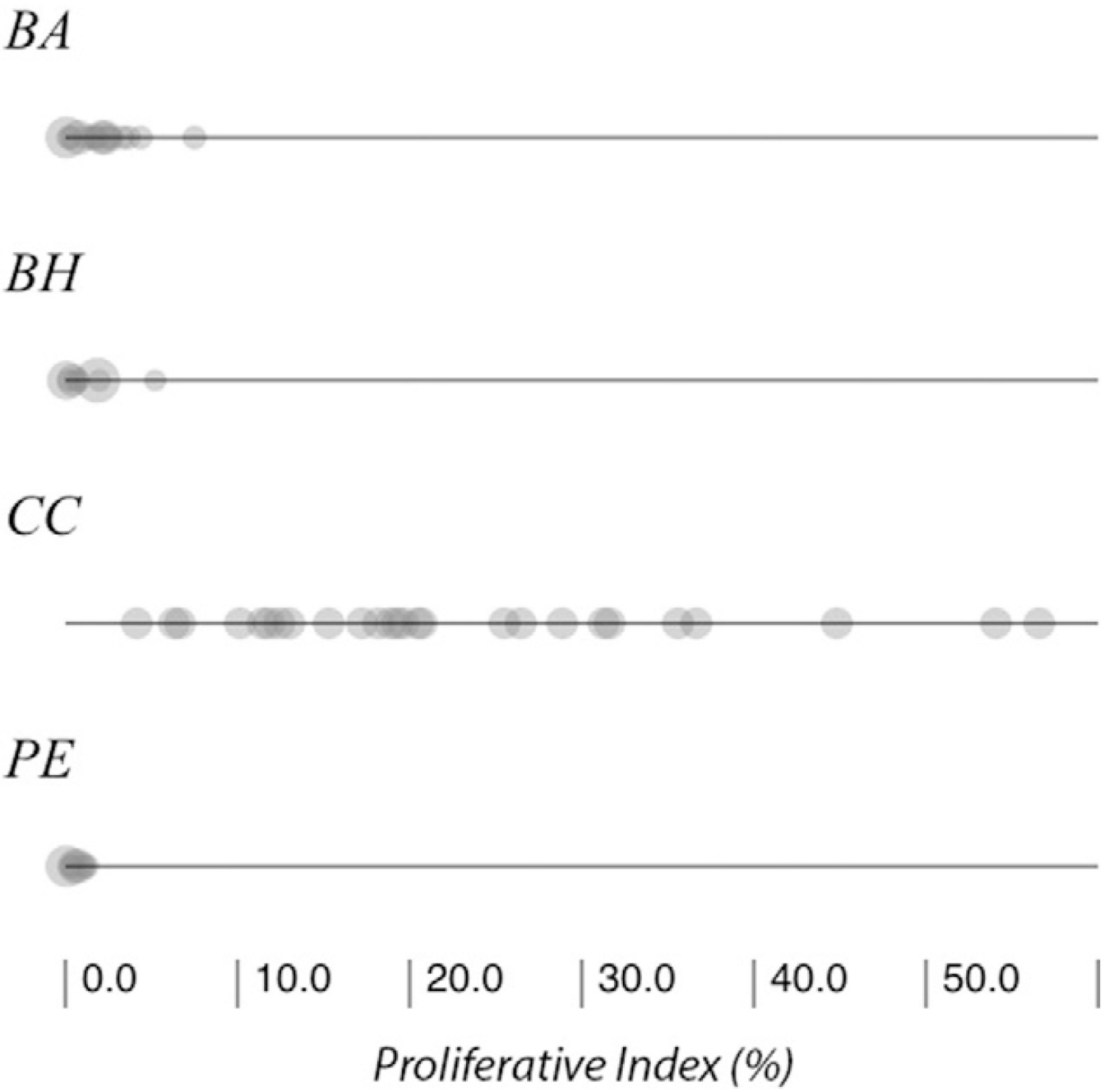

Fig. 2.

Distribution of Ki-67 staining indices in benign and malignant biliary lesions. Most (88.5%) intrahepatic cholangiocarcinomas show a Ki-67 proliferative index greater than 10%, whereas none of the benign biliary lesions show a Ki-67 proliferation index greater than 10%. Abbreviations: BA, biliary adenoma; BH, biliary hamartoma; CC, cholangiocarcinoma; PE, parenchymal extinction.

Table 1

Demographics of studied cases

	No. of cases	Sex (% male)	Average age (y)	*vs* WD CC (*P*)	Size (range)[a]	*vs* WD CC (*P*)
Biliary hamartoma	14	42.9	58.9	.90	0.2 (0.1–0.4)	<.001
Bile duct adenoma	21	52.4	55.2	.31	0.5 (0.1–1.8)	<.001
Parenchymal extinction	11	63.6	54.7	.18	0.2 (0.15–1.8)	<.001
All benign lesions	46	52.2	56.2	.30	0.4 (0.1–1.8)	<.001
WD cholangiocarcinoma	16	37.5	59.4	n/a	4.3 (0.9–9)	n/a
MD/PD cholangiocarcinoma	10	50	66.5	.13	6.7 (0.9–9.8)	.08
All cholangiocarcinomas	26	42.3	62.2	.61	5.3 (0.9–9.8)	.45

Abbreviations: n/a, not applicable; WD, well-differentiated; CC, cholangiocarcinoma; MD/PD, moderately/poorly differentiated cholangiocarcinomas.

[a]Sizes (cm) were available for 14, 19, 5, 13, and 9 of the biliary hamartomas, bile duct adenomas, parenchymal extinctions, WD cholangiocarcinomas, and MD/PD, respectively.

Table 2

Summary of Ki-67 proliferative index in biliary hamartoma, bile duct adenoma, parenchymal extinction, and intrahepatic cholangiocarcinoma

	No. of cases	Average (%)	Range (%)	*vs* WD CC (*P*)	% of cases >5%	% of cases >10%
Biliary hamartoma	14	1.2	0–5.2	<.001	7.1	0.0
Bile duct adenoma	21	2.0	0.1–7.5	<.001	4.8	0.0
Parenchymal extinction	11	0.5	0–1	<.001	0.0	0.0
All benign lesions	46	1.4	0–7.5	<.001	4.3	0.0
WD cholangiocarcinoma	16	22.7	6.6–56.6	n/a	100.0	93.8
MD/PD cholangiocarcinoma	10	23.3	4.1–54.1	.92	90.0	80.0
All cholangiocarcinomas	26	23.0	4.1–56.6	.95	96.2	88.5

Abbreviations: n/a, not applicable; WD, well-differentiated; CC, cholangiocarcinoma; MD/PD, moderately/poorly differentiated cholangiocarcinomas.

Table 3

Summary of p53 immunohistochemical staining in biliary hamartoma, bile duct adenoma, parenchymal extinction, and intrahepatic cholangiocarcinoma

	n	Average (% cells; any staining)	Range (% cells; any staining)	*vs* WD CC (*P*)	Average (% cells; strong staining)	Range (%; strong staining)	*vs* WD CC (*P*)	% of cases >1% strong staining
Biliary hamartoma	14	1.2	0–6.1	.001	0.0	0–0.3	.011	0.0
Biliary adenoma	21	4.7	0–14.3	.02	0.0	0.00	.002	0.0
Parenchymal extinction	11	2.3	0–15	.011	0.0	0.00	.024	0.0
All benign lesions	46	3.1	0–15	<.001	0.0	0–0.3	<.001	0.0
WD cholangiocarcinoma	16	11.5	0.2–40	n/a	0.8	0–3.9	n/a	37.5
MD/PD cholangiocarcinoma	10	19.5	0.5–69.9	.2	1.6	0–10.5	.36	30.0
All cholangiocarcinomas	26	14.6	0.2–69.9	.48	1.1	0–10.5	.62	34.6

Abbreviations: n/a, not applicable; WD, well-differentiated; CC, cholangiocarcinoma; MD/PD, moderately/poorly differentiated cholangiocarcinomas.