Invasive Papillary Carcinomas of the Extrahepatic Bile Ducts: a Clinicopathologic and Immunohistochemical Study of 13 Cases

Mai P. Hoang, M.D., Linda A. Murakata, M.D., Nora Katabi, M.D., Donald E. Henson, M.D., Jorge Albores-Saavedra, M.D.

Division of Anatomic Pathology, The University of Texas Southwestern Medical Center (MPH, JA-S), Dallas; Division of Anatomic Pathology, Baylor Medical Center (NK), Dallas, Texas; Armed Forces Institute of Pathology (LAM), Washington, DC; and Division of Cancer Prevention, National Cancer Institute (DEH), Bethesda, Maryland

Carcinomas of the extrahepatic bile ducts are uncommon neoplasms that are morphologically heterogeneous and associated with a poor prognosis. We have previously shown that the noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts behave as *in situ* carcinomas and are associated with a better prognosis. We reviewed the clinical records of 13 patients with invasive papillary carcinomas of the extrahepatic bile ducts and analyzed the microscopic features and selected immunohistochemical reactivity (p53, Mib-1, and Dpc4) that might correlate with patient survival. In addition, we present the updated SEER (Surveillance, Epidemiology, and End Results) data of the National Cancer Institute for the invasive extrahepatic bile duct carcinomas compiled from 1975 to 1998. The 13 patients with papillary carcinoma had a male to female ratio of 1:1, and their ages ranged from 33 to 89 years. Painless jaundice and abdominal pain were the most common complaints. Five tumors were located in the distal portion, one in the mid portion, and six in the proximal portion of the common bile duct. One papillary carcinoma arose in the right hepatic duct. The Whipple procedure was performed in six patients, common bile duct resection in six, and right hepatic lobectomy in one. The cell phenotype of the papillary carcinomas was biliary in nine and intestinal in three. One tumor had both biliary and intestinal phenotypes. Four tumors dedifferentiated (two to undifferentiated small cell carcinomas, one to small [oat] cell carcinoma, and one to giant cell carcinoma). Two papillary carcinomas extended into the pancreas and three into the liver. Only one patient had lymph node metastases at presentation. Follow-up was available in 10 patients. Six patients died of disease from 2 weeks to 2 years and 1 month after surgery. Four patients are alive with no evidence of disease from 4 months to 8 years and 8 months after surgery. Of 174 invasive papillary carcinomas compiled by the SEER program, 71 were confined to the ductal wall, and 61 had regional lymph node metastases. Papillary carcinomas confined to the ductal wall have better 10-year relative survival rates than adenocarcinomas limited to the wall (21% versus 12%). Likewise papillary carcinomas with lymph node metastasis have better prognosis than adenocarcinoma with nodal metastases (10-y survival rate of 12% versus 5%). Currently, the histologic type and the stage of the disease are the most important prognostic factors in these papillary carcinomas. Separation of invasive and noninvasive or minimally invasive papillary carcinoma is critical in estimating the patient outcome. Our findings suggest that there is no correlation between p53, Ki-67, and Dpc4 expression in these tumors and survival of the patients.

KEY WORDS: Extrahepatic bile ducts, Immunohistochemistry, Papillary carcinoma.

Mod Pathol 2002;15(12):1251–1258

Papillary carcinoma is an uncommon neoplasm of the extrahepatic bile ducts. Among 143 cases of extrahepatic bile duct carcinomas reported by Albores-Saavedra *et al.* (1), there were six papillary carcinomas (4.1%). The carcinomas of the extrahepatic bile ducts collected by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 1981–1990 included

VOL. 15, NO. 12, P. 1251, 2002 Printed in the U.S.A.
Date of acceptance: August 15, 2002.
Address reprint requests to: Jorge Albores-Saavedra, M.D., Department of Pathology, Louisiana State University, Health Sciences Center, Shreveport, P.O. Box 33932, Shreveport, LA 71130.

DOI: 10.1097/01.MP.0000036450.61830.8E

79 cases of papillary carcinomas (6%; 2). Papillary carcinomas appear to have better prognosis than do other types of carcinoma of the extrahepatic bile ducts (2). This relatively good prognosis of papillary carcinomas is attributed to the exophytic nature of the tumors, their late invasion into the ductal wall, and their location. The exophytic nature of papillary carcinomas gives rise to obstructive symptoms sooner than in the case of conventional adenocarcinomas. In addition, tumors located in the distal third of the common bile duct can be resected by means of a pancreatoduodenectomy.

We have shown elsewhere that the noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts behave as *in situ* carcinomas and are associated with a better prognosis (3). In this study, we examined the clinical, morphologic, and immunohistochemical features of 13 papillary carcinomas of the extrahepatic bile ducts that invaded the full thickness of the wall or extended beyond the ductal wall. In addition, we present the updated SEER data for the invasive extrahepatic bile duct carcinomas compiled from 1975 to 1998.

MATERIALS AND METHODS

The surgical pathology files of the Armed Forces Institute of Pathology (AFIP), Washington, D.C.; and of the University of Texas Southwestern Medical Center, the North Texas Veterans Affairs Medical Center, and Baylor Medical Center, Dallas, Texas, were searched for invasive papillary carcinomas of the extrahepatic bile ducts. Twenty-nine cases were found. Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts and papillary carcinomas that arose in the ampulla of Vater were excluded. Papillary carcinomas in which only biopsy material was available and examples of biliary papillomatosis and villous adenoma were also excluded. Thirteen cases remained. Seven cases were accessioned in the AFIP files during a 31-year period between 1964 and 1995. Of the remaining six cases, two were retrieved from the University of Texas Southwestern Medical Center surgical pathology files, two from the Veterans Affairs North Texas Health Care Center, and two from the Pathology Department of Baylor Medical Center. These cases were accessioned from 1992 to 2001. Clinicopathologic data such as age, sex, site, tumor size, presence of lymph node and/or distant metastases, and follow-up were extracted from available pathology reports and clinical charts.

Routine hematoxylin and eosin–stained sections were available in all cases. The paraffin blocks and unstained slides were available in five and four tumors, respectively. Immunohistochemical studies were performed on an automated immunostainer (Ventana Bio Tek System, Tucson, AZ) using the standard avidin-biotin peroxidase complex technique and the heat-induced epitope retrieval buffer. The following primary antibodies were used: p53 (DO-7, 1:50 dilution, DAKO, Carpinteria, CA), MIB-1 (1:10 dilution, Bio Genex, San Ramon, CA), monoclonal carcinoembryonic antigen (CEA; 1:400 dilution, DAKO), cytokeratin 7 (1:40 dilution, DAKO), Dpc4 (MADR1 JV4–1, 1:400 dilution, Santa Cruz Biotechnology, Santa Cruz, CA), neuron-specific enolase (BBS/VI-HI4, 1:4000, DAKO), synaptophysin (1:100, DAKO), and chromogranin (DAK-A3, 1:700, DAKO). Positive and negative controls were included with each run.

The SEER Program of the National Cancer Institute surveys the incidence and mortality of cancer in the United States. The SEER program covers 9.6% of the population. It includes five states (Connecticut, Iowa, New Mexico, Utah, and Hawaii) and four large metropolitan areas, including Detroit, Michigan; the San Francisco–Oakland Bay area, California; Atlanta, Georgia; and Seattle, Washington. For this study, data were taken from 1975 to 1998. The histologic slides were not reviewed. The diagnosis was based on the pathology report submitted to the SEER program. Survival curves were calculated by the Kaplan-Meier method.

RESULTS

The clinicopathologic data of the 13 patients are summarized in Table 1. The male to female ratio was 1:1, and their ages ranged from 33 to 89 years (mean: 67 y; median: 69 y). None of the patients had associated risk factors such as ulcerative colitis or primary sclerosing cholangitis. Painless jaundice and abdominal pain were the most common complaints. The Whipple procedure was performed in 6 patients, common bile duct resection in 6, and right hepatic lobectomy in 1 patient. Follow-up was available in 10 patients. Three cases had a follow-up interval of <5 years. Six patients died of disease from 2 weeks to 2 years and 1 month after surgery. Four patients are alive with no evidence of disease from 4 months to 8 years and 8 months after surgery (40%).

Gross Findings

Five tumors were located in the distal portion, one in the mid portion, and six in the proximal portion of the common bile duct. One papillary carcinoma arose in the right hepatic duct. The tumors were polypoid or granular masses that projected into the bile duct lumen. Their sizes ranged from 0.8 to 3.5 cm (median, 1.5 cm).

TABLE 1. Clinicopathologic Data of 13 Patients with Invasive Papillary Carcinoma of the Extrahepatic Bile Ducts

Case No.	Age (y)/Sex	Clinical Presentation	Surgical Procedure	Site	Size (cm)	Extent of Invasion	Lymph Node Status	Follow-Up, Time Status Postsurgery
1	68/M	Biliary obstruction	Whipple	Distal CBD	1.5	Into ductal wall	NA	NA
2	78/F	Epigastric pain	CBD resection	Proximal CBD	NA	Through ductal wall, extend to cystic duct	ND	NA
3	83/F	Jaundice	CBD resection	Proximal CBD	2.0	Through ductal wall, into liver	ND	DOD, 1 y, 11 mo
4	61/M	Painless jaundice	CBD resection	Proximal CBD	NA	Through ductal wall, extend to cystic duct	ND	DOD, 2 y, 1 mo
5	70/F	Jaundice, melena	CBD resection	Proximal CBD	NA	Through ductal wall, into liver	ND	NA
6	82/M	Biliary obstruction	CBD resection	mid CBD	0.8	Through ductal wall	ND	DOD, 1 y, 11 mo
7	51/M	Jaundice, abdominal pain	CBD resection	Proximal CBD	1.5	Into ductal wall	ND	DOD, 1 mo
8	33/F	Biliary obstruction	Whipple	Distal CBD	1.5	Through ductal wall, into pancreas	1/13	DOD, 2 y
9	70/F	Biliary obstruction	Whipple	Distal CBD	1.5	Through ductal wall, into duodenum	0/11	DOD, 0.5 mo
10	64/M	NA	Whipple	Distal CBD	NA	Through ductal wall	0/23	NED, 6 y, 5 mo
11	69/M	NA	Whipple	Proximal CBD	2.5	Through ductal wall	0/10	NED, 3 y
12	59/F	Painless jaundice	Right hepatic lobectomy	Rt hepatic duct	3.5	Into liver	0/1	NED, 4 mo
13	89/F	Painless jaundice	Whipple	Distal CBD	3.5	Into pancreas	0/19	NED, 8 y, 8 mo

M, male; F, female; CBD, common bile duct; NA, not available; ND, not done; DOD, died of disease; NED, no evidence of disease.

Histologic Findings

The noninvasive component of all tumors was characterized by exophytic proliferation of complex papillary structures with or without gland formation (Fig. 1). Papillary epithelial projections with fibrovascular cores of variable sizes were noted in all tumors. One neoplasm had a micropapillary architecture and was associated with extensive necrosis (Fig. 2). Regarding cell phenotype, nine tumors were of biliary type and three of intestinal type. One tumor had a combined pattern of intestinal and biliary. The columnar biliary-type cells lining the papillae were well to moderately differentiated and showed few mitotic figures. The columnar intestinal-type cells were taller, pseudostratified, and with elongated nuclei. Rarely were goblet cells admixed with the columnar cells. Both biliary-type and intestinal-type epithelia contained little or no mucin. Focal extracellular mucin (10%) was identified in only one case.

The invasive component was comprised predominantly of infiltrative glands that invaded the full thickness of the ductal wall. Four tumors dedifferentiated. At the base of two papillary carcinomas, there was an undifferentiated component characterized by a diffuse proliferation of uniform small ovoid neoplastic cells with vesicular nuclei, visible nucleoli, and eosinophilic cytoplasm (Fig. 1). Another tumor had cordlike or diffuse growth patterns and was composed of cells with scant cytoplasm, hyperchromatic nuclei, and ill-defined cell borders characteristic of small (oat) cell carcinoma (Fig. 1). In one additional case (Case 11), an anaplastic component characterized by pleomorphic giant cells was seen focally (Fig. 1). Three tumors showed an invasive papillary pattern similar to that of the noninvasive papillary component. Two tumors extended into the pancreas and three into the liver. Only one patient had lymph node metastasis at presentation.

Immunohistochemical Findings

Archival materials were available in 9 cases. The immunohistochemical results of these cases are summarized in Table 2. Strong cytoplasmic staining to monoclonal CEA was noted focally in six cases (6/9). The undifferentiated components in three cases were negative for CEA. Cytokeratin 7 strongly labeled the neoplastic cells (9/9) in all nine cases with available archival materials, with the exception of the undifferentiated component in one case (Fig. 2). Ki-67 immunolabeling were seen in nine of nine cases—high in eight cases (30–100%) and moderate in one case (10%; Fig. 2). Carcinomas showing >30% nuclear p53 labeling were considered positive (4). Nuclear immunolabeling for p53 was noted in four of eight cases, with the exception of the undifferentiated component in one case (Fig. 2). Loss of Dpc4 expression was noted in 5 of 8 cases (Fig. 2). When present, Dpc4 positivity was noted in the cytoplasm with focal nuclear staining only. Nonneoplastic intramural glands, pancreatic epithelium, stromal fibroblasts, and lymphoid aggregates, all of which expressed Dpc4 with a moderate to strong intensity, served as internal positive controls.

The neoplastic cells of the small cell carcinoma component of one tumor showed immunoreactiv-

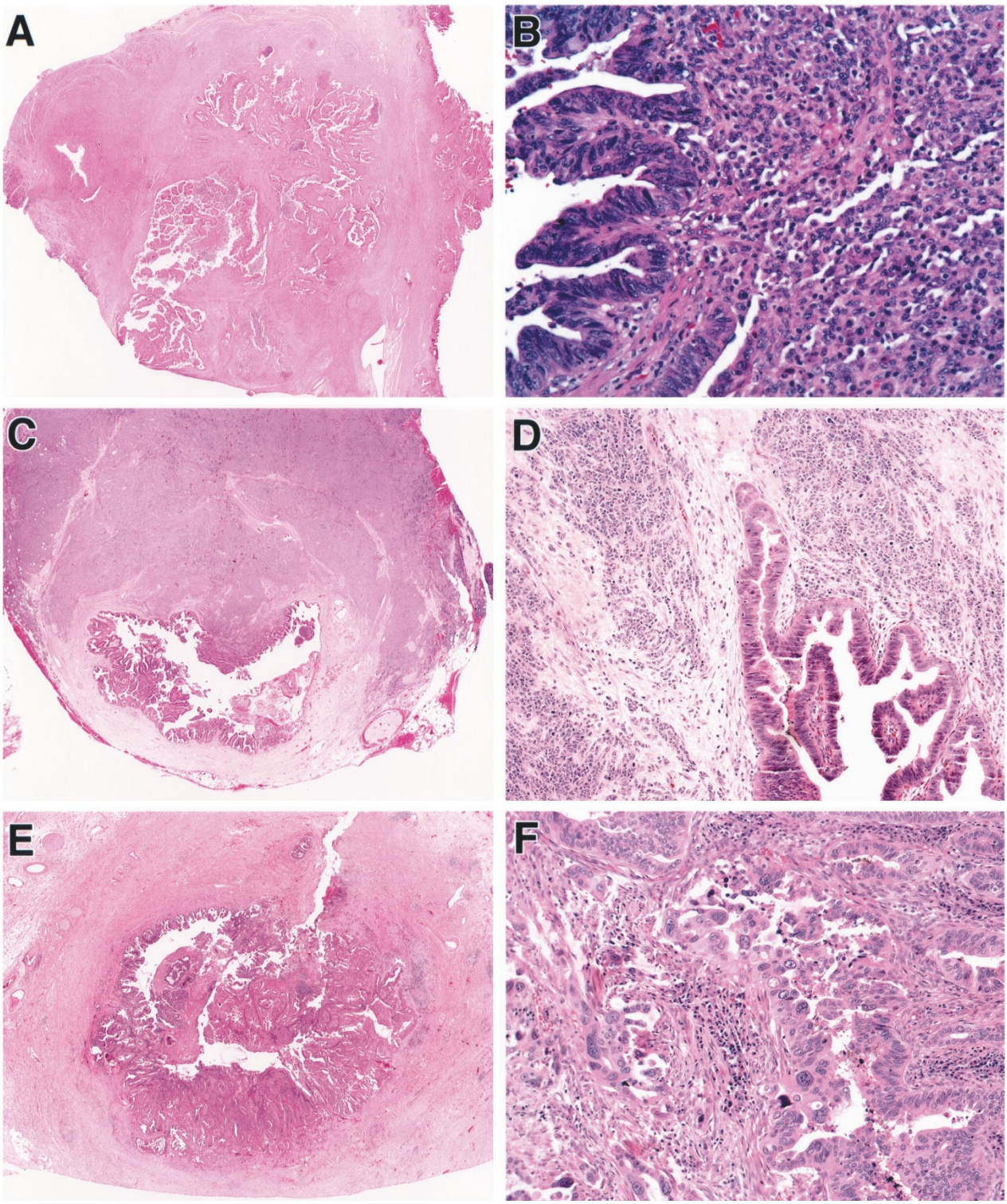

FIGURE 1. (**A, C, E**) The tumors are characterized by exophytic and intraluminal proliferation of complex papillary structures and an underlying invasive component. At the base of the papillary carcinoma, there is an undifferentiated component in one case (**B**) as well as a small (oat) cell carcinoma in another (**D**). (**F**) An anaplastic component characterized by pleomorphic giant cells is seen in glands adjacent to the papillary carcinoma.

ity for neuron-specific enolase and synaptophysin but were negative for chromogranin.

SEER Data

From 1975 to 1998, clinicopathologic data of 3534 invasive carcinomas of the extrahepatic bile duct carcinomas were reviewed. There were 174 invasive papillary carcinomas that comprised 4.9% of the total number of cases. Of these 174 tumors, 71 were confined to the ductal wall, 69 had regional node metastases, and 16 had distant metastases. Eighteen tumors were unstaged. The

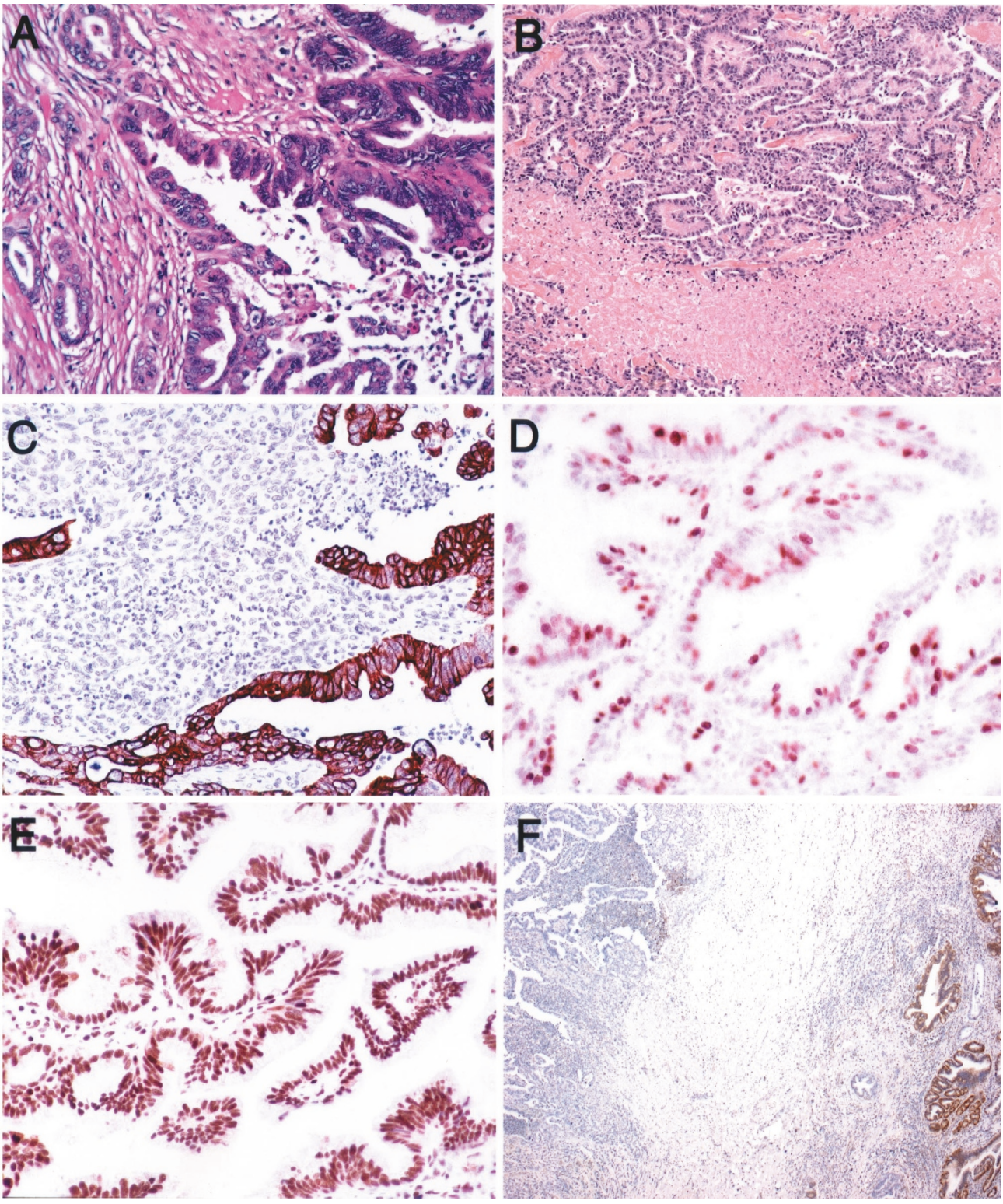

FIGURE 2. (**A**) Beneath the noninvasive papillary component, infiltrating small neoplastic glands are seen. (**B**) A micropapillary carcinoma is seen associated with extensive necrosis. (**C**) There is strong cytokeratin 7 immunoreactivity in the papillary component, whereas the adjacent undifferentiated component is negative. (**D**) Nuclear Ki-67 staining in the invasive papillary carcinoma. (**E**) Nuclear p53 expression in the noninvasive papillary carcinoma. (**F**) Loss of Dpc4 expression is noted in the tumor cells, whereas cytoplasmic and nuclear Dpc4 expression is seen in the adjacent non-neoplastic epithelium.

5- and 10-year survival rates of invasive papillary carcinoma and adenocarcinoma of the extrahepatic bile ducts are summarized in Figure 3. Invasive papillary carcinomas confined to the ductal wall have better 10-year relative survival (21%) rates than do invasive adenocarcinomas (12%;

TABLE 2. Histologic Type and Immunohistochemical Results of 13 Invasive Papillary Carcinomas of the Extrahepatic Bile Ducts

Case No.	Tumor Type	Monoclonal CEA	Cytokeratin 7	Ki-67	p53[a]	Dpc4
1	Intestinal	−	++++	++	−	ND
2	Biliary	ND	ND	ND	ND	ND
3	Biliary	−	++++	+	−	−
4	Biliary	ND	ND	ND	ND	ND
5	Biliary	+	++++	++	++	−
6	Intestinal	−	+++	++++	ND	++
	SCC Component	−	−	++++	ND	++++
7	Biliary	ND	ND	ND	ND	ND
8	Biliary	++++	++++	++	++++	−
	UD Component	−	+++	++	++++	−
9	Intestinal	ND	ND	ND	ND	ND
10	Intestinal/biliary	+++	++++	++	−	−
11	Biliary	++	++++	++++	++++	++++
12	Biliary	+	++	++++	−	−
	UD Component	−	++	++++	−	−
13	Biliary	+	++++	+++	++++	++++

CEA, carcinoembryonic antigen; SCC, small cell carcinoma; UD, undifferentiated; +, 5–25%; ++, 26–50%; +++, 51–75%; ++++, 76–100%.
[a] <30%: negative for p53.

Fig. 3). Likewise, papillary carcinomas with lymph node metastasis have better prognosis (10-year survival rate of 12%) than do adenocarcinomas with nodal metastasis (10-year survival rate of 5%).

DISCUSSION

Papillary carcinomas represent 4–5% of all malignant epithelial tumors of the extrahepatic bile ducts (1). The most common clinical presentation of the patients in this series was painless jaundice, followed by abdominal pain and weight loss, similar to that of patients with conventional adenocarcinomas. Papillary carcinomas of the extrahepatic bile ducts can be classified as invasive and noninvasive. This separation is important, because noninvasive and minimally invasive papillary carcinomas behave as *in situ* carcinomas (3). In contrast, in this small series of invasive papillary carcinoma, 60% of the patients died as a result of the tumor, but one patient has been followed for only 4 months. Most likely, with longer follow-up, the number of surviving patients would have decreased. Invasion of the full thickness of the ductal wall and beyond appears to be the most significant prognostic factor. Other factors probably play a role in the outcome of patients with papillary carcinomas of the extrahepatic bile ducts, such as the presence of undifferentiated carcinoma or small cell carcinoma at the base of the tumors, location, and lymph node metastasis. In our series, two of the three patients who had these high-grade undifferentiated or small cell carcinomas at the base of the papillary carcinomas died as a result of the tumors. The updated SEER data affirms that papillary carcinomas, even those with regional metastasis, have better prognosis than do other types of extrahepatic bile duct carcinomas. The 5-year and 10-year relative survival rates for 71 patients with invasive papillary carcinomas confined to the ductal wall are 28% and 21%, in comparison to 18% and 12% for those with conventional adenocarcinomas, respectively. Microscopically, the biliary type is more common than the intestinal type in both the noninvasive and invasive papillary carcinomas (3), but this cell phenotype appears to have no prognostic implications.

All of our tumors were strongly positive for CK7, thus confirming the previous observations of Rullier *et al.* (5). This antibody lacks specificity but is useful in distinguishing extrahepatic bile duct carcinomas, intestinal type, from the exceedingly rare metastatic colorectal carcinomas, especially on biopsy specimens.

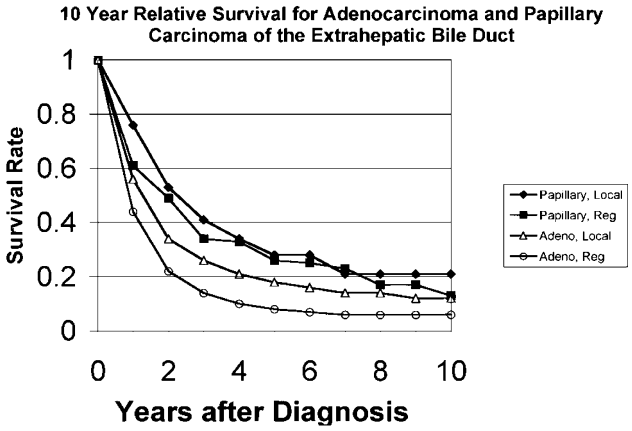

FIGURE 3. There were 71 cases of localized invasive papillary carcinomas of the extrahepatic bile ducts, 69 cases of invasive papillary carcinomas with regional metastases, 478 cases of localized invasive adenocarcinomas, and 982 cases of invasive adenocarcinomas with regional metastases. These cases were collected by the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute from 1975 to 1998.

Most extrahepatic bile duct carcinomas, as well as dysplastic lesions, express CEA (6). Although CEA immunostain is not essential for diagnosis, it can be useful in delineating the extent of tumor infiltration and in distinguishing hyperplastic intramural glands from neoplastic ones, because normal glands are CEA negative. In addition, monitoring biliary CEA levels may be of importance in the management as well as in the detection of extrahepatic bile duct carcinomas (7).

There was no significant difference in the staining for Ki-67, p53, or Dpc4 between the papillary component and the undifferentiated counterpart. However, lack of CEA expression is a common feature of the undifferentiated component. The *p53* gene is one of the most commonly altered tumor suppressor genes in human cancer (8). The *p53* gene is located on the short arm of chromosome 17 (17p13), and it encodes for a nuclear phosphatase that plays an important role in cellular responses to DNA damage (9). Expression of p53 protein has been reported in 38–66% of invasive adenocarcinomas of the extrahepatic bile ducts (10, 11). Fifty percent of the papillary tumors in this series express p53 protein, and this finding is accordance with previous published results. Although Argani *et al.* (12) and Diamantis *et al.* (13) found a higher percentage of distal extrahepatic bile duct carcinomas expressed p53 than the proximal ones; we were unable to confirm their findings. Although our results indicate that p53 is not a useful prognostic marker for extrahepatic bile duct carcinomas, other authors have shown an association between p53 expression and survival in extrahepatic bile duct carcinoma (11, 13, 14). The reason for this discrepancy is unclear but may be due to the small number of tumors and to the inclusion of different histologic types of tumors in most series, or to different criteria for positive staining.

The Ki-67 antigen is expressed in active parts of the cell cycle (G1, S, G2, and M phases; 15). The correlation between MIB-1 and prognosis remains unconfirmed. Our study and that of Suto *et al.* (14) demonstrated no correlation between Ki-67 expression and survival. Larger series are needed to settle this issue.

Recent studies suggest that *DPC4* (deleted in pancreatic carcinoma, locus 4; *MADH4, SMAD4*) gene, a tumor-suppressor gene on the long arm of chromosome 18, is frequently inactivated in pancreatic and bile duct carcinomas (12, 16–19). In contrast, inactivation of the *DPC4* gene appears to be infrequent in other tumor types, such as carcinomas of the breast, lung, and colon (20). Inactivation occurs by mutation in one *DPC4* allele, coupled with loss of the other allele (loss of heterozygosity), or by deletion of both alleles (homozygous deletion; 9). The Dpc4 protein plays a critical role in transmitting growth-suppressive signals from transforming growth factor beta (21). In a series of 32 biliary tract carcinomas, 16% had point mutation in the *DPC4* gene by single-strand conformational analysis (16). Rijiken *et al.* (22) studied 14 distal common bile duct carcinomas by comparative genomic hybridization and found that the most frequent site of loss was at the long arm of chromosome 18, which housed the *DPC4* locus. Similarly, 60% of our invasive common bile duct papillary carcinomas showed loss of Dpc4 expression, thus confirming the findings of Argani *et al.* (12) that 55% of their distal bile duct carcinomas had loss of Dpc4 expression. We examined only one carcinoma that arose in the right hepatic duct and therefore are unable to confirm the lower loss of Dpc4 expression in these tumors.

We have shown that invasive papillary carcinomas have worse prognosis than noninvasive and minimally invasive papillary carcinomas but better prognosis than invasive adenocarcinomas arising in the extrahepatic bile ducts. Currently, the histologic type and the stage of disease are the most important prognostic factors in these invasive papillary tumors. Our findings suggest that there is no association between p53 and Ki-67 reactivity and Dpc4 lack of expression in these tumors and the survival of the patients.

REFERENCES

1. Albores-Saavedra J, Henson DE, Klimstra D. Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. 3rd ed, Fascicle 27. Washington, DC: Armed Forces Institute of Pathology; 2000.
2. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the extrahepatic bile ducts. Histologic types, stage of disease and survival rates. Cancer 1992;70:1498–501.
3. Albores-Saavedra J, Murakata L, Krueger JE, Henson DE. Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. Cancer 2000;89:508–15.
4. Baas IO, Mulder JR, Offerhaus GJA, Vogelstein B, Hamilton SR. An evaluation of six antibodies for immunohistochemistry of mutant p53 gene product in archival colorectal neoplasms. J Pathol 1994;172:5–12.
5. Rullier A, Le Bail B, Fawaz R, Blanc JF, Sahic J, Bioulac-Sage P. Cytokeratin 7 and 20 expression in cholangiocarcinomas varies from that in colorectal carcinoma metastasis. Am J Surg Pathol 2000;24:870–6.
6. Maxwell P, Davis RI, Sloan JM. Carcinoembryonic antigen (CEA) in benign and malignant epithelium of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. J Pathol 1993;170:73–6.
7. Nakeeb A, Lipsett PA, Lillemoe KD, Fox-Talbot MK, Coleman J, Cameron JL, *et al.* Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. Am J Surg 1996;171:147–52.
8. Levine AJ, Momand J, Finlay CA. The *p53* tumor suppressor gene. Nature 1991;351:453–6.
9. Hruban RH, Offerhaus GJA, Kern SE, Goggins M, Wilentz RE, Yeo CJ. Tumor-suppressor genes in pancreatic cancer. J Hepatobiliary Pancreatic Surg 1998;5:383–91.

10. Teh M, Wee A, Raju GC. An immunohistochemical study of p53 protein in gallbladder and extrahepatic bile duct/ampullary carcinomas. Cancer 1994;74:1542–5.
11. Washington K, Gotffried MR. Expression of p53 in adenocarcinoma of the gallbladder and bile ducts. Liver 1996;16:99–104.
12. Argani P, Shaukat A, Kaushal M, Wilentz RE, Su GH, Sohn TA, *et al*. Differing rates of loss of Dpc4 expression and of p53 overexpression among carcinomas of the proximal and distal bile ducts: evidence for a biologic distinction. Cancer 2001;91:1332–41.
13. Diamantis I, Karamitopoulou E, Perentes E, Zimmerman A. P53 protein immunoreactivity in extrahepatic bile duct and gallbladder cancer: correlation with tumor grade and survival. Hepatology 1995;22:774–9.
14. Suto T, Sugai T, Nakamura D-I, Funato O, Nitta H, Sasaki R, *et al*. Assessment of the expression of p53, MIB-1 (Ki-67 antigen), and argyrophilic nucleolar organizer regions in carcinoma of the extrahepatic bile duct. Cancer 1998;82:79–85.
15. Gerdes J, Lemke H, Baisch H, Wacker HH, Schwab U, Stein H. Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 1984;133:1710–5.
16. Hahn SA, Bartsch D, Schroers A, Galehdari H, Becker M, Ramaswamy A, *et al*. Mutations of the *DPC4/Smad4* gene in biliary tract carcinoma. Cancer Res 1998;58:1124–6.
17. Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, *et al*. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science 1996;271:350–3.
18. Schutte M. *DPC4/SMAD4* gene alterations in human cancer and their functional implications. Annu Oncol 1999; 10(Suppl 4):56–9.
19. Schutte M, Hruban RH, Hedrick L, Cho KR, Nadasky GM, Weinstein CL, *et al*. *DPC4* gene in various tumor types. Cancer Res 1996;56:2527–30.
20. Riggins GJ, Kinzler KW, Vogelstein B, Thiagalingam S. Frequency of Smad gene mutations in human cancers. Cancer Res 1997;57:2578–80.
21. Zhou S, Buckhaults P, Zawel L, Bunz F, Riggins G, Dai JL, *et al*. Targeted deletion of Smad4 shows it is required for transforming growth factor b and activin signaling in colorectal cancer cells. Proc Natl Acad Sci U S A 1998;95:2412–6.
22. Rijiken AM, Hu J, Perlman E, Morsberger LA, Long P, Kern SE, *et al*. Genomic alterations in distal bile duct carcinoma by comparative genomic hybridization and karyotype analysis. Genes Chromosomes Cancer 1999;26: 185–91.

Book Review

McKee GT: Cytopathology of the Breast, 312 pp, New York, Oxford University Press, 2002 ($172.00).

Breast cytopathology is a field of diagnostic pathology that has developed most rapidly during the past 10 years. Fine needle aspiration of breast has its established role as a diagnostic tool. It is truly "visually pleasing and diagnostically satisfying," if everything is done right.

This book is a valuable addition to several already existing books and chapters dealing with breast cytopathology. It contains 16 chapters covering all aspects of breast cytology, including normal breast, non-neoplastic lesions, neoplastic lesions, male breast lesions, and nipple cytology. The prognostic markers are discussed in the last chapter. Cytological features in each category are described in detail. A summary of cytological features under each topic, along with the tables, are features to be found most useful by practicing pathologists. Pitfalls in each diagnostic category also are discussed. The histology and cytology illustrations are full and in color; most are of high quality. Only a few cytology pictures are suboptimal, partly due to the three-dimensional nature of cytology specimens, which are difficult to photograph at high magnification.

I also liked the format. It has the size of a handbook. It should serve well to the residents, fellows, and pathologists in practice who deal with breast cytopathology.

Fang Fan
University of Kansas Medical Center
Kansas City, Kansas