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Review article

Pathogenesis of carcinoma of the papilla of Vater

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Abstract
Most adenomas and carcinomas of the small intestine and extrahepatic bile ducts arise in the region of the papilla of Vater. In familial adenomatous polyposis (FAP) it is the main location for carcinomas after proctocolectomy. In many cases symptoms due to stenosis lead to diagnosis at an early tumor stage. In about 80%, curative intended resection is possible. Operability is the most relevant prognostic factor. Most ampullary carcinomas resp. carcinomas of the papilla of Vater develop from adenomatous or flat dysplastic precursor lesions. They can be sited in the ampulloduodenal part of the papilla of Vater, which is lined by intestinal mucosa. They also can develop in deeper parts of the ampulla, which are lined by pancreaticobiliary duct mucosa. Intestinal-type adenocarcinoma and pancreaticobiliary-type adenocarcinoma represent the main histological types of ampullary carcinoma. Furthermore, there exist unusual types and undifferentiated carcinomas. Many carcinomas of intestinal type express the immunohistochemical marker profile of intestinal mucosa (keratin 7−, keratin 20+, MUC2+). Carcinomas of pancreaticobiliary type usually show the immunohistochemical profile of pancreaticobiliary duct mucosa (keratin 7+, keratin 20−, MUC2−). Even poorly differentiated carcinomas, as well as unusual histological types, may conserve the marker profile of the mucosa they developed from. These findings underline the concept of histogenetically different carcinomas of the papilla of Vater which develop either from intestinal- or from pancreaticobiliary-type mucosa of the papilla of Vater. Molecular alterations in ampullary carcinomas are similar to those of colorectal as well as pancreatic carcinomas, although they appear at different frequencies. In future studies, molecular alterations in ampullary carcinomas should be correlated closely with the different histologic tumor types. Consequently, the histologic classification should reflect the histogenesis of ampullary tumors from the two different types of papillary mucosa.

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Introduction

Carcinomas of the papilla of Vater are of special pathogenetic interest: this valve organ includes the border between two completely different types of mucosa (Fig. 1). The intestinal mucosa of the ampulloduodenum adjoins the mucosa of the ampullo-pancreatico-biliary duct resp. the common channel. This channel drains the ampullo-pancreatic duct segment coming from the main pancreatic duct and the ampullo-biliary duct segment coming from the choledochal duct. The periampullary region, including the papilla resp. ampulla of Vater, is exposed to three different juices. This region is a hot spot for adenomas and malignant tumors of the small intestine.[1]

The histopathology of ampullary carcinomas is of special classificatory interest. The very special situation of this border between two different types of mucosa should be reflected in the classification of these tumors, as has consequently been done by Kimura et al.[2] They subdivided these carcinomas into intestinal-type tumors and pancreaticobiliary-type tumors. The question of whether carcinomas from intestinal-type mucosa or pancreaticobiliary duct mucosa of the ampullary region develop under different molecular-pathologic conditions has not yet been answered. The possible prognostic and therapeutic implications of such a classification will have to be worked out in future. The diagnostic criteria and limitations of such a histogenetically based classification will be discussed in the following review.

The histopathology of ampullary carcinomas is of special diagnostic interest: the diagnosis is made on a few small biopsy specimens and is followed by consider-

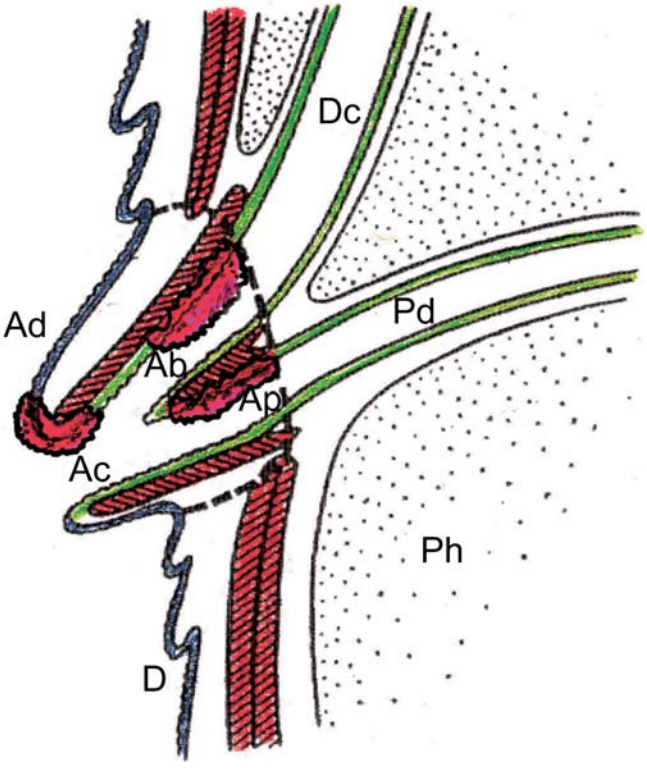

Fig. 1. Diagrammatic illustration of the papilla of Vater. Ampullo-biliary segment (*Ab*), ampullo-pancreatic segment (*Ap*), ampullo-pancreatico-biliary segment of the common channel (*Ac*), ampulloduodenum (*Ad*). Neighboring structures are the choledochal duct (*Dc*), pancreatic duct (*Pd*), pancreatic head (*Ph*), and duodenum (*D*). Different primary sites of neoplastic lesions are shown (*n*)

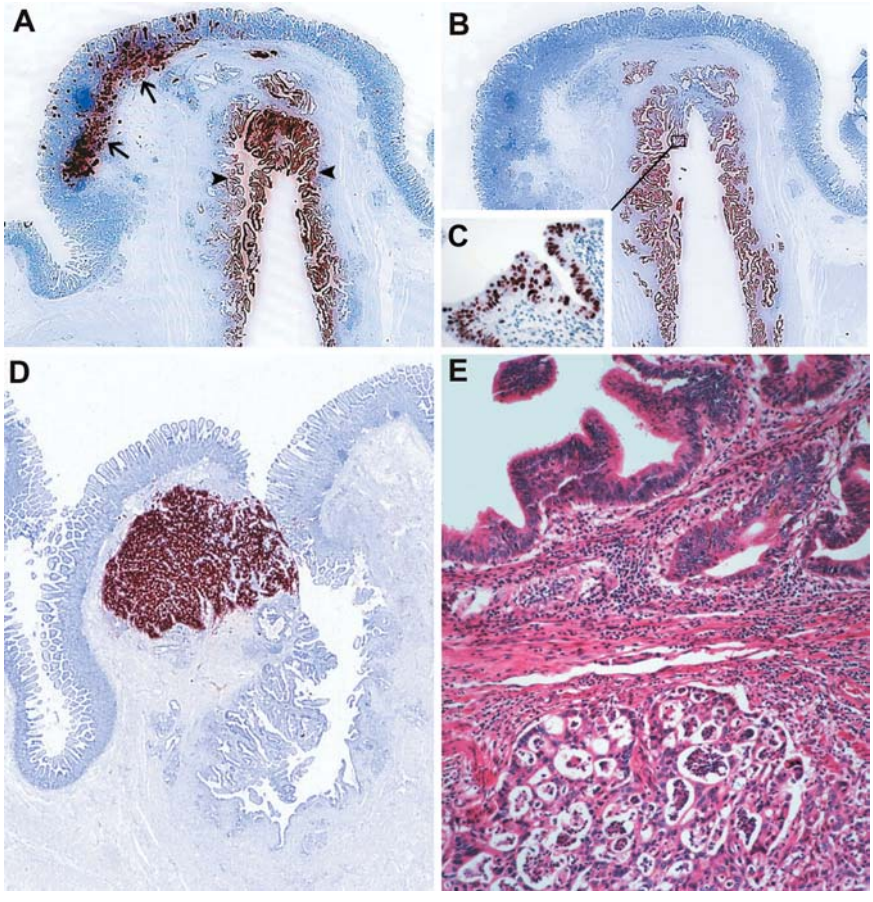

Fig. 2A,B,C. Undifferentiated carcinoma expresses apomucin MUCSA C (*arrows*) like its intraampullary precursor lesion (*arrowheads*; **A**), but without reaction to CK7-antibody, in contrast to the precursor lesion (**B**). Overexpression of p53 protein is seen in the intraampullary precursor lesion (**C**). (**D**, **E**) Intraampullary poorly differentiated adenocarcinoma, expresses apomucin 1, in contrast to the precursor lesion in the common channel (**D**). (**E**) Note border between in situ carcinoma (*upper part*) and invasive poorly differentiated carcinoma

able therapeutic implications. Inflammatory changes, fibrosis, regeneratory changes after endoscopic manipulation, hyperplasia, preneoplastic lesions close to carcinoma, and deeply sited carcinomas under protruded, non-neoplastic duodenal mucosa make the diagnosis difficult from biopsy material. One-third of the biopsy specimens — mostly taken to clear up a stenotic process — contain neoplastic tissue.[3] If an "adenomatous" process is found in a first series of biopsies, rebiopsies, excision biopsies, or operative specimens often will reveal a carcinomatous process (in one study[4] in 50%). The relation of the time and location of precarcinomatous lesions to invasive carcinoma plays a central role in histopathologic diagnosis.

Precursor lesions of ampullary carcinoma

Many ampullary carcinomas develop from preexisting adenomas or flat preneoplastic lesions. Residual adenomatous areas can be found in 30% to 91% of ampullary carcinomas,[5] The great frequency range of carcinoma-associated adenomatous lesions reflects the difficulties in the morphologic analysis of ampullary mucosal proliferations, especially from biopsies.

More than 95% of benign ampullary neoplasms are adenomas of the intestinal type.[6] They have a tubular, or villous, or mixed tubulovillous pattern and resemble closely adenomas of the intestine. Most ampullary adenomas occur sporadically, at a mean age of 65 years.[4] They occur about 8 years earlier than ampullary carcinomas. The natural course of ampullary adenomas has been analyzed systematically only in cases associated with familial adenomatous polyposis (FAP). In one collective of 14 patients with FAP, there was no change in the grade of dysplasia and no progress to carcinoma at a mean follow-up time of 6.9 years.[7] In only 11% of 105 patients in another study, ampullary adenomas showed a progress in grade of dysplasia at a mean observation time of 4 years; however, 1 patient had developed an ampullary carcinoma.[8] The adenomas in both series had a tubular architecture with only minimal or moderate dysplasia. Remarkably, in 4 of 42 patients, a flat tubular adenoma was found histologically in biopsies from endoscopically nonsuspicious mucosa.[8] In contrast to polypoid ampullary adenomas, some precancerous lesions present as flat or micropapillary dysplasias or carcinoma in situ (Fig. 2).[6,9] These intraepithelial neoplasias often involve deeper parts of the ampullary mucosa, distal bile duct, and main pancreatic duct. Mostly they are associated with an invasive carcinoma.

Precursor lesions can arise from intestinal-type mucosa as well as from pancreatic duct-type ampullary mucosa which lines the common duct as well as the ampullo-pancreatic and ampullo-biliary segment of the papilla of Vater. These lesions may conserve the keratin types and type of apomucin of the mucosa they develop from and so can be differentiated from each other by immunohistochemical stainings[16] (see below). Carcinomas of the pancreaticobiliary type[11] and ulcerating carcinomas[12] often lack precursor lesions.

Carcinoma of the papilla of Vater

Predisposition and incidence

Most carcinomas of the papilla of Vater develop sporadically. Cigarette smoke is discussed to be a peristatic risk factor. Chronic infection by liver fluke is an important predisposition for this tumor type (for review, see reference[5]). In very young patients[13] and in ampullary carcinomas in twins,[14] a genetic predisposition has to be supposed. Ampullary carcinomas are not infrequently associated with other primary malignant tumors, especially carcinomas of the gastrointestinal tract.[1,5] Neurofibromatosis type I seems to be a predisposition not only for somatostatinomas of the papilla of Vater but also for ampullary carcinomas.[16] The finding of two ampullary carcinomas in 205 reported cases of Muir-Torre syndrome, a condition characterized by the association of multiple sebaceous tumors and kerato-acanthomas with internal malignancies, suggests a higher prevalence in this syndrome than in the general population.[17] In FAP, the ampullary region is the second hot spot for carcinomas after the colorectum. Ampullary carcinomas in FAP usually arise later than colorectal carcinomas, but at a mean age of 45 years, much earlier than that for sporadic ampullary carcinomas.[18,19] Single cases of carcinomas of the extrahepatic bile tract and the papilla of Vater were observed in families with hereditary nonpolyposis colorectal carcinoma (HNPCC).[20] However, the general incidence of ampullary malignancies in this familial cancer-predisposing disease is very low: only one extrahepatic cholangiocarcinoma, but not any ampullary carcinoma, developed in a collective of 252 patients from 22 HNPCC families during a 15-year observation time.[21] In our collective of 285 patients with HNPCC (collected and analyzed at the Department of Pathology and the Institute of Human Genetics of Bonn University) we found only one coincidental ampullary carcinoma.

Carcinomas of the papilla of Vater are uncommon, but they occur far more frequently than carcinomas of the small intestine outside the periampullary region.[1,6,10] Of 1545 carcinomas in the region of the head of the pancreas 8.3% were ampullary tumors.[5] The peak age incidence of sporadic carcinomas is in the seventh and eighth decades of life. Males appear to be more affected than females. The male-to-female ratio was found to be 1.48 to 1.[6]

Macroscopy

Ampullary carcinomas can be found predominantly at intraampullary or periampullary sites (Fig. 3), or they can be mixed intra/periampullary.[22] Yamaguchi and Enjoji[23] defined three macrotypes of ampullary carcinoma, based on their appearance from the duodenal aspect:

- Intramural protruding (intraampullary) type: polypoid tumors of the common channel without duodenal luminal component
- Extramural protruding (periampullary) type: polypoid tumors protruding through the papilla into the duodenum
- Ulcerating ampullary carcinomas

Ulcerating carcinomas are usually diagnosed at a higher tumor stage than protruding carcinomas. They tend to spread in a lymph- and hemangioinvasive manner and have affected lymph nodes more than twice as often as protruding carcinomas at the time of resection.[23,24] Interestingly, genetic alteration seems to influence the macroscopic growth pattern. Ulcerating carcinomas are associated more often with the overexpression of p53 protein than are polypoid carcinomas (67% versus 32%).[25]

Microscopic classification

Following a proposal of Kimura et al.,[2] Albores-Saavedra et al.[1] emphasize the intestinal type and the pancreaticobiliary type of carcinoma as the main histological types of carcinoma of the papilla of Vater (Table 1). Furthermore, these authors list unusual histological types, e.g. mucinous, signet-ring cell carcinomas, neuroendocrine, and undifferentiated carcinomas.[1] Intestinal-type carcinomas resemble carcinomas of the intestine, whereas pancreaticobiliary-type adenocarcinomas resemble carcinomas of the pancreas or extrahepatic bile ducts. In a collective from the Memorial Sloan-Kettering Cancer Center, the intestinal type of adenocarcinoma comprised 49% and the pancreaticobiliary type 21% of ampullary carcinomas (Table 2).[6] Kimura et al.[2] collected 38 pancreaticobiliary-type and 13 intestinal-type carcinomas. Also, in our collective, updated from reference,[10] the pancreaticobiliary type (44.8%) predominates over the intestinal type (26.9%) of adenocarcinoma. In the WHO classification, the intestinal type of adenocarcinoma is characterized as an "unusual variant" of tumors of the gallbladder and extrahepatic bile ducts including the ampullary region.[5] The considerable differencies in the frequencies of the different histological types of ampullary carcinomas make it obvious that there exists a not inconsiderable percentage of tumors that cannot be related definitively to the main types of ampullary adenocarcinoma by histologic criteria alone. This has to be considered if histologic classification is taken in account in therapeutic decisions.

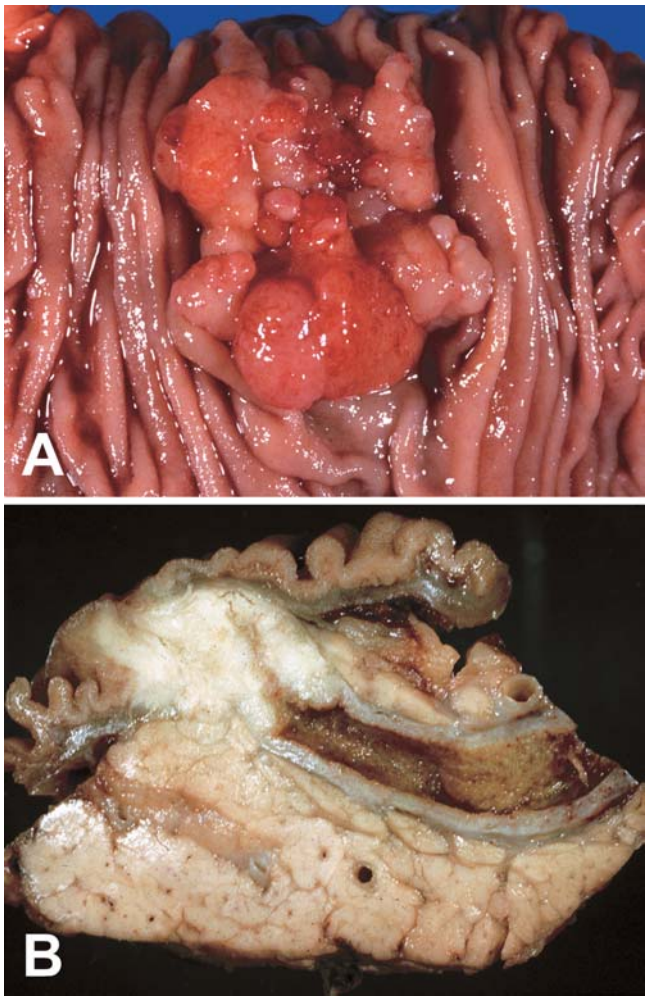

Fig. 3A,B. Macroscopic types of ampullary carcinoma. **A** Polypous periampullary carcinoma and **B** predominantly intraampullary carcinoma

Immunohistochemical characterization

Immunohistochemically, the different types of carcinomas can be characterized more objectively:[10,11] Pancreaticobiliary-type adenocarcinomas nearly always express keratin 7 and lack the intestinal apomucin MUC2. In a great majority of cases they are negative for keratin 20. This marker spectrum is according to both that of the normal pancreaticobiliary epithelium and that of the epithelium of the peripapillary glands of the papilla of Vater. Intestinal-type adenocarcinomas mostly contain keratin 20 and apomucin MUC2, and often lack keratin 7, similar to the characteristics of the intestinal epithelium (Fig. 4). Interestingly, also many

Table 1. Histological classification of tumors of the gallbladder and extrahepatic bile ducts (WHO, 2000),[1] and of benign and malignant tumors of the ampullary region (Albores-Saavedra et al.[6] 2000)

WHO histological classification, 2000[1]	Classification according to Albores-Saavedra et al.[6]
Adenoma	Adenoma
Tubular	Tubular
Papillary	Papillary
Tubulopapillary	Tubulopapillary
Papillomatosis (adenomatosis)	Flat carcinoma in situ
Intraepithelial neoplasia (dysplasia and carcinoma in situ)	Carcinoma
Carcinoma	Usual types
Adenocarcinoma	Intestinal-type adenocarcinoma
Papillary adenocarcinoma	Pancreaticobiliary-type adenocarcinoma
Adenocarcinoma, intestinal type	Unusual histological types
Adenocarcinoma, gastric-foveolar type	Papillary carcinoma (noninvasive)
Mucinous adenocarcinoma	Invasive papillary carcinoma
Clear-cell adenocarcinoma	Mucinous carcinoma
Signet-ring cell carcinoma	Signet-ring cell carcinoma
Adenosquamous carcinoma	Clear-cell carcinoma
Squamous cell carcinoma	Adenocarcinoma with hepatoid differentiation
Small-cell carcinoma	Adenosquamous carcinoma
Large-cell carcinoma	Small-cell carcinoma
Undifferentiated carcinoma	Large-cell neuroendocrine carcinoma
Biliary cystadenocarcinoma	Undifferentiated carcinoma

Endocrine tumors and related neoplasms are left out of this comparison

Table 2. Frequency of the main histological types of carcinomas of papilla of Vater in different studies

Authors/study	No. of cases	Intestinal type (%)	Pancreaticobiliary type (%)	Other types (%)
Kimura et al.[2]	51	25	75	
Matsubayashi et al.[11]	52	58	42	
Memorial Sloan Kettering Cancer Center[6]	140	49	21	30
WHO classification[1]		Unusual		
Fischer and Zhou update of[10]	55	23	44	24

Table 3. Histological types and expression of keratin 7, keratin 20, and of intestinal apomucin MUC2 in carcinomas of the papilla of Vater (own cases) (update of[10])

Histological type (AFIP)	No. of cases	CK7+ CK20−	CK7− CK20+	CK7+ CK20+	CK7− CK20−	Muc2 (+/−)
Intestinal	**15**	0	**10**	3	2	8/7
Pancreaticobiliary	**24**	**21**	0	2	1	**0/24**
Adenocarcinoma	5	4	—	1	0	0/5
Mucinous	3	—	1	1	1	**3/0**
Signet-ring cell	3	—	3	—	–	**3/0**
Papillary	4	3	0	—	1	**0/4**
Papillary, non-invasive	1	1	—	—	—	0/1
Total	55	29	14	7	5	14/41
Muc 2 (+/−)	14/41	**0/29**	12/2	1/6	1/4	

Antibody staining in more than 10% of tumor cells was defined as a positive reaction

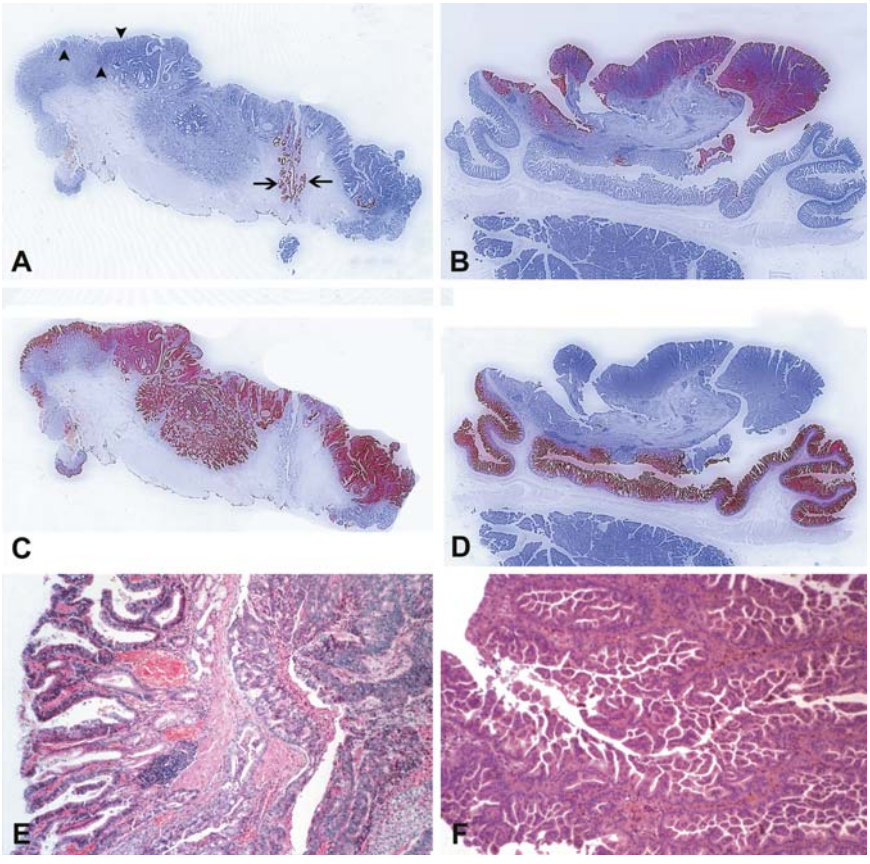

Fig. 4A,C,E. Periampullary carcinoma of intestinal type without reaction to CK7-antibody, in contrast to the ampullary mucosa (**A**), stained by CK20-antibody, similarly to intestinal mucosa (**C**), and consisting of complex cribriform glands (**E**). (**B**, **D**, **F**) Non-invasive papillary carcinoma stained by CK7-antibody (**B**), but without reaction to CK20-antibody, similarly to pancreaticobiliary duct mucosa (**D**), and consisting of complex branching papillae and secondary micropapillae (**F**)

unusual carcinomas of the papillary region can be related to the intestinal type or pancreaticobiliary type of mucosa. In our collective, most poorly differentiated carcinomas, as well as most papillary carcinomas, showed the immunohistochemical pattern of pancreaticobiliary duct mucosa (Fig. 4, Table 3). All mucinous and signet-ring cell type carcinomas in our collective expressed intestinal apomucin MUC2. The signet-ring type carcinomas reflected the keratin profile of the intestinal epithelium. Some carcinomas which reacted negatively for keratins and apomucin 2 developed from precursor lesions with a line specific marker pattern for intestinal or pancreaticobiliary duct mucosa (Fig. 2).[10]

Histogenesis of carcinomas of the papilla of Vater

The strikingly correlated expression pattern of two unrelated types of immunohistochemical markers (keratins and apomucin 2) in pancreaticobiliary duct epithelium as well as in pancreaticobiliary-type carcinomas (CK 7+, CK 20−, MUC2−) versus intestinal epithelium and intestinal-type adenocarcinomas (CK 7−, CK 20+, MUC2+) indicates that these different tumor types develop from two different types of mucosa. A recent topologic analysis of very small ampullary carcinomas underlines this histogenetic concept: non-invasive precursor lesions of intestinal-type carcinomas consistently involved the ampulloduodenal part of the papilla or were limited to this region. Intramucosal parts of pancreaticobiliary carcinomas often skipped the ampulloduodenum. Apparently they arose in the deeper parts of Vater's papilla.[10,11]

Interestingly, a relevant part of carcinomas of the papilla of Vater express the apomucin MUC 5AC. showing metaplastic gastric and foveolar changes.[10,11] These tumors often bear K-*ras*-mutations on codon 12. The intramucosal parts of these carcinomas are found significantly more often in the ampulloduodenum and the ampullopancreatic duct than in the ampullobiliary part of the papilla (see Fig. 1). Therefore, one may speculate that pancreatic juice may have an influence on the development and morphology of these carcinomas.[11]

Only two studies have attended to the association of intrapancreatic precursor lesions with ampullary carcinomas. In one study, intraductal neoplasias in large pancreatic ducts were found in 22% of resected ampullary carcinomas.[26] In another series of resection specimens, 2 of 5 ampullary adenomas and 7 of 17 ampullary ad-

enocarcinomas were associated with high-grade pancreatic intraepithelial neoplasias PanIN.[27] Unfortunately, the exact histologic type of the carcinomas was not reported. Thus, the question of whether, especially, the pancreaticobiliary type of carcinoma of the papilla is related to PanIN remains unanswered.

Prognosis and clinical aspects

Size, stage, and operability are the most important prognostic factors. Because ampullary carcinomas become symptomatic relatively early due to biliary obstruction and subsequent persistent icterus, about 80% to 90% of these tumors can be treated by surgery. This is the only potentially curative treatment. The 5-year survival rate after resection of ampullary carcinoma is 21% to 61%, with a mean of 40%. If the tumor is limited to the mucosa or the sphincter of Oddi, the survival rate is 85% (for review see references 6 and 10). *Nodal stage* influences the prognosis: the nodes close to the superior mesenteric artery are a critical station, because they drain directly into the paraaortal nodes.[24] Ulcerative *macrotype* and low *grade of differentiation* are associated with a worse course.[23,24] Carcinomas without precursor lesions are associated with a significantly shorter 5-year survival than carcinomas with precarcinomatous lesions.[12] The influence of the *histologic tumor type* on prognosis cannot be estimated conclusively. Resected tumors of pancreaticobiliary type seem to have a tendentially[6] or significantly[2] worse prognosis than intestinal-type carcinomas. The more aggressive local spread and significantly more frequent involvement of lymph nodes were reported to be responsible for the worse prognosis of pancreaticobiliary-type carcinomas in the series of Kimura et al.[2] Comparing the intestinal and pancreaticobiliary types of adenocarcinomas, we could not find significant differences in survival times in our German collective (publication in review process).

Molecular-pathologic findings

Ampullary carcinomas and ductal pancreatic carcinomas share similar molecular alterations in K-*ras* (mostly point mutations), *p53*, *DPC4* (mutations and loss of heterozygosity [LOH]), and *p16* (mutations, methylation, LOH). So pancreatic duct carcinoma and at least a subgroup of ampullary carcinomas seem to have common molecular pathways related to tumorigenesis and, possibly progression of malignancy.[28] However, the frequency of K-*ras* mutations (24%–47%)[28–32] is considerably lower than that in ductal pancreatic carcinomas (around 80%) and corresponds roughly to that in colorectal carcinomas.[30,33] In ampullary carcinomas and in colorectal carcinomas, K-*ras* aspartate 13-mutations were detected more frequently than in pancreatic carcinomas.[30] Molecular alterations of the cell cycle-modulating p53 protein can be found in about 60% of ampullary carcinomas.[28] The expression of the cyclin-dependent kinase (CDK-) inhibitor p21/Waf 1-protein appears to be independent of the expression of p53.[32] Other modulators of the cell cycle have been shown to be expressed at lower levels (p16, p21, p27) or overexpressed (cyclin D1, cyclin E), in different amounts, in ampullary carcinomas,[34] showing that deregulation of the G1/S transition is a common event in these tumors. Even adenomas may show K-*ras* mutations[29,30] and may show the immunohistochemical overexpression of p53.[25,35] Especially, non-invasive tumor areas of p53-positive ampullary carcinomas nearly always express this suppressor protein.[36] These findings support the concept of an adenoma-carcinoma sequence in the development of most ampullary carcinomas.

In FAP, ampullary carcinomas are mostly associated with a germline mutation in the adenomatous polyposis coli (*APC*) gene on chromosome 5q-. Somatic alterations in the *APC* gene were found in 17% of European patients[37] and in 47% of a Japanese tumor collective[31] independent of FAP. The two groups also differed in the mutation pattern of the *p53* gene. Peristatic and genetic factors could be responsible for these differences between these two collectives of tumors from far different geographic regions. Other chromosome 5 allelic losses in sporadic ampullary adenomas and carcinomas were found recently in loci differing from that of *APC*, but corresponding to those in gastric carcinomas.[38] The same working group published a 20% rate of ampullary carcinomas with high levels of microsatellite instability (MSI-H). These tumors had a significantly better course[39] than MS stable carcinomas. The two patient groups did not differ with respect to individual or familial predisposition for malignancies.[39] In a recent analysis, 8 out of 22 adenomas and 9 out of 32 ampullary carcinomas were categorized as microsatellite instability-low (MSI-L), with MSI in one to three of nine dinucleotide markers.[40] All 93 ampullary neoplasms investigated by immunohistochemistry were found to express the mismatch repair proteins hMLH1 and hMSH2. MSI does not play an important role in the carcinogenesis of ampullary carcinoma.[40]

Carcinomas of the papilla of Vater share molecular pathologic analogies with colorectal carcinomas as well as pancreatic carcinomas. In future, these molecular findings should be correlated more closely with the different histologic and immunohistologic types of ampullary carcinoma, as defined above. Characterization of these tumors, based on histopathology, immunohistochemistry, and topologic relation to both types of ampullary mucosa, as well as molecular anomalies, may help to elucidate their etiology, and to define different risk profiles.

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References

1. Albores-Saavedra J, Menck HR, Scoazec JC, Soehendra N, Wittekind C, Sriram PVJ, Sripa B (2000) Tumours of the gallbladder and extrahepatic bile ducts. In: Hamilton SR, Aaltonen LA (eds) WHO classification of tumours. Pathology and genetics of the digestive system. IARC, Lyon, pp 203–218
2. Kimura W, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, Esaki Y (1994) Different clinicpathologic findings in two histologic types of carcinoma of papilla of Vater. Jpn J Cancer Res 85:161–166
3. Komorowski RA, Beggs BK, Geenan JE, Venu P (1991) Assessment of ampulla of Vater pathology. Am J Surg Pathol 15:1188–1196
4. Stolte M, Pscherer C (1996) Adenoma-carcinoma sequence in the papilla of Vater. Scand J Gastroenterol 31:376–382
5. Fischer HP, Zhou H (2000) Pathologie der Papilla Vateri. In: Doerr W, Seifert G, Uehlinger E (eds) Spezielle Pathologische Anatomie: Pathologie der Leber und der Gallenwege, 2nd edn. Springer, Berlin Heidelberg New York Tokyo, pp 1219–1257
6. Albores-Saavedra J, Henson DE, Klimstra DS (2000) Tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. In: Rosai J, Sobin LH (eds) Atlas of tumor pathology, third series. Fascicle 27. Armed Forces Institute of Pathology, Washington, DC
7. Noda Y, Watanabe H, Iida M, Narisawa R, Kurosaki I, Iwafuchi M, Satoh M, Ajioka Y (1992) Histologic follow-up of ampullary adenomas in patients with familial adenomatosis coli. Cancer 70:1825–1833
8. Burke CA, Beck GJ, Church JM, van Stolk RU (1999) The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. Gastrointest Endosc 49:358–364
9. Kimura W, Ohtsubo K (1988) Incidence, sites of origin, and immunohistochemical and histochemical characteristics of atypical epithelium and minute carcinoma of the papilla of Vater. Cancer 61:1394–1402
10. Fischer HP, Zhou H (2003) Pathogenese und Histopathologie von Adenomen und Karzinomen der Papilla Vateri. Übersicht und eigene Befunde Pathologe 24:196–203
11. Matsubayashi H, Watanabe H, Yamaguchi T, Ajioka Y, Nishikura K, Kijima H, Saito T (1999) Differences in mucus and K-ras mutation in relation to phenotypes of tumors of the papilla of vater. Cancer 86:596–607
12. Yamauchi H, Nitta A, Namiki T (1993) carcinoma of the papilla of Vater accompanied by non-invasive adenomatous component (NAC). Tohoku J Exp Med 170:147–156
13. Andiran F, Tanyel FC, Kale G, Akhan O, Akcoren Z, Hicsonmez A (1997) Obstructive jaundice resulting from adenocarcinoma of the Vater's ampulla. Rev Enferm Dig 85:391–393
14. Austin JC, Organ CH, Williams GR, Pitha JV (1988) Vaterian cancer in siblings. Ann Surg 207:644–661
15. Eriguchi N, Aoyagi S, Tamae T, Nishimura K, Hamada S, Kawabata M, Kodama T, Jimi A (2001) Carcinoma of the ampulla of Vater associated with other organ malignancies. Kurume Med J 48:255–259
16. Costi R, Caruana P, Sarli L, Violi V, Roncoroni L, Bordi C (2001) Ampullary adenocarcinoma in neurofibromatosis type 1. Case report and literature review. Mod Pathol 14:1169–1174
17. Matthews JJ, Roberts R, O'Reilly DA, Schick S, Kingsnorth AN (2002) Muir-Torre syndrome: a case for surveillance of the ampulla of Vater. Dig Surg 19:65–66
18. Galle TS, Juel K, Bülow S (1999) Causes of death in familial adenomatous polyposis. Scand J Gastroenterol 34:808–812
19. Iwama T, Mishima Y, Utsunomiya J (1993) The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 217:101–108
20. Mecklin JP, Jävinen HJ, Virolainen M (1992) The association between cholangiocarcinoma and hereditary nonpolyposis colorectal carcinoma. Cancer 69:1112–1114
21. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, de la Chapelle A, Mecklin JP (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118:829–834
22. Cubilla AL, Fitzgerald PJ (1980) Surgical pathology: aspects of cancer of the ampulla-head of pancreas region. Monogr Pathol 21:67–81
23. Yamaguchi K, Enjoji M (1987) Carcinoma of the ampulla of Vater. Cancer 59:506–515
24. Kayahara M, Nagakawa T, Ohta T, Kitagawa H, Miyazaki I (1997) Surgical strategy for carcinoma of the papilla of Vater on the basis of lymphatic spread and mode of recurrence. Surgery 121:611–617
25. Younes M, Riley S, Genta RM, Mosharaf M, Mody DR (2000) p53 Protein accumulation in tumors of the ampulla of Vater. Cancer 76:1150–1154
26. Liu TH, Chen J, Zeng XJ (1983) Histogenesis of pancreatic head and ampullary region carcinoma. Chin Med J 96:167–174
27. Agoff SN, Crispin DA, Bronner MP, Dail DH, Hawes SE, Haggitt RC (2001) Neoplasms of the ampulla of Vater with concurrent pancreatic intraductal neoplasia: a histological and molecular study. Mod Pathol 14:139–146
28. Moore PS, Orlandini S, Zamboni G, Capelli P, Rigaud G, Falconi M, Bassi C, Lemoine NR, Scarpa A (2001) Pancreatic tumours: molecular pathways implicated in ductal cancer are involved in ampullary but not in exocrine nonductal or endocrine tumorigenesis. Br J Cancer 84:253–262
29. Chung CH, Wilentz RE, Polak MM, Ramsoekh TB, Noorduyn LA, Gouma DJ, Huibregtse K, Offerhaus GJA, Siebos RJC (1996) Clinical significance of K-ras oncogene activation in ampullary neoplasms. Clin Pathol 49:460–464
30. Howe JR, Klimstra DS, Cordon-Cardo C, Paty PB, Park PY, Brennan MF (1997) K-ras mutation in adenomas and carcinomas of the ampulla of vater. Clin Cancer Res 3:129–133
31. Imai Y, Oda H, Tsurutani N, Nakatsuru Y, Inoue T, Ishikawa T (1997) Frequent somatic mutations of the APC and p53 genes in sporadic ampullary carcinomas. Jpn J Cancer Res 88:846–854
32. Zhao B, Kimura W, Futakawa N, Muto T, Kubota K, Harihara Y, Takayama T, Makuuchi M (1999) p53 and p21/Waf1 protein expression and K-ras codon 12 mutation in carcinoma of the papilla of Vater. Am J Gastroenterol 94:2128–2134
33. Finklestein SD, Sayegh, R, Christensen S, Swalsky PA (1993) Genotypic classification of colorectal adenocarcinoma. Cancer 71:3827–3838
34. Li X, Hui AM, Shi YZ, Sun L, Takayama T, Makuuchi M (2002) Deregulation of G1/S transition is a common event in carcinoma of the ampulla of Vater. Hepatogastroenterology 49:1239–1244
35. Park SH, Kim Y, Park YH, Kim S, Kim YT, Kim,WH (2000) Clinicopathologic correlation of p53 protein overexpression in adenoma and carcinoma of the ampulla of Vater World J Surg 24:54–59
36. Takashima M, Ueki T, Nagai E, Yao T, Yamaguchi K, Tanaka M, Tsuneyoshi M (2000) Carcinoma of the ampulla of Vater associated with or without adenoma: a clinicopathologic analysis of 198

cases with Reference to p53 and Ki-67 immunohistochemical expressions. Mod Pathol 13:1300–1307
37. Achille A, Scupoli MT, Magalini A, Zamboni G, Romanelli MG, Orlandini S, Biasi MO, Lemoine NR, Accola RS, Scarpa A (1996) APC gene mutations and allelic losses in sporadic ampullary tumours: evidence of genetic difference from tumours associated with familial adenomatous polyposis. Int J Cancer 68:305–312
38. Achille A, Baron A, Zamboni G, Di Pace C, Orlandini S, Scarpa A (1998) Chromosome 5 allelic losses are early events in tumours of the papilla of Vater and occur at sites similar to those of gastric cancer. Br J Cancer 78:1653–1660
39. Achille A, Biasi MO, Zamboni G, Bogina G, Iacono C, Talamini G, Capella G, Scarpa A (1997) Cancers of the papilla of Vater: mutator phenotype is associated with good prognosis. Clin Cancer Res 3:1841–1847
40. Park S, Kim SW, Kim SH, Darwish NS, Kim WH (2003) Lack of microsatellite instability in neoplasms of ampulla of Vater. Pathol Int 53:667–670