Pancreatic Hepatoid Carcinoma: A Review of the Literature

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Introduction

Hepatoid carcinoma (HC) is a neoplasm exhibiting features of hepatocellular carcinoma (HCC) in terms of morphology and immunohistochemistry which grows outside the liver [1–3]. The first case was reported by Ishi- kura et al. [4] and concerned HC in the stomach. Since then, its occurrence has been described in gonadal yolk sac as well as in several non-germ cell origin primary sites, including esophagus, ampulla of Vater, colon, lung, gall-bladder, adrenal gland, kidney, urinary bladder, ovary, uterus, vagina, and testicle [1–16]. Microscopic ‘stigmata’ of those origins are typically detectable in tumor focal areas.

HC, much like HCC, is often associated with elevated serum α-fetoprotein (AFP) levels and usually presents in the pancreas. Treatment seems to be related to the association with other neoplasms, tumor extension at the time of diagnosis and the possibility to perform a radical resection. The common embryologic origin of the pancreas and liver, together with peculiar environmental factors, may explain the development of pancreatic HCs.

Key Words
Ectopic liver cancer · Pancreatic hepatoid carcinoma · Rare pancreatic neoplasm

Abstract

Background: Hepatoid carcinomas (HCs) are extrahepatic neoplasms exhibiting features of hepatocellular tumors in terms of morphology and immunohistochemistry. They have been described in several organs, most notably in the stomach and ovary. They can present in pure forms or in association with other morphological aspects, such as endocrine tumors or ductal adenocarcinomas. The aim of this review is to describe aspects of hepatoid adenocarcinoma of the pancreas with regard to epidemiology, diagnosis, and treatment. Methods: The PubMed database was searched for publications addressing hepatoid adenocarcinoma of the pancreas. We have searched for articles including the following keywords: ‘pancreatic hepatoid carcinoma’, ‘ectopic liver cancer’ and ‘rare pancreas neoplasm’ published to date. As references, we used case reports and review articles. Results: Pancreatic forms of HCs are extremely uncommon: only 22 cases have been reported. Conclusions: The possibility of an HC of the pancreas should be considered in the differential diagnosis of an uncommon pathological mass of the pancreas. Treatment seems to be related to the association with other neoplasms, tumor extension at the time of diagnosis and the possibility to perform a radical resection. The common embryologic origin of the pancreas and liver, together with peculiar environmental factors, may explain the development of pancreatic HCs.
elderly individuals [16]. Since the liver, pancreas and stomach all originate from the primitive embryonic foregut, it is likely that these organs retain a latent ability to produce AFP, or that the tumor cells differentiate into hepatic cells and intestinal mucosal cells. Recently, the absence in serum of the protein induced by vitamin K or elevated antagonist II (PIVKAI-II), which is used for early diagnosis of HCC, has been reported with HC [16, 17].

These tumors can present in pure forms or in association with other morphological aspects, such as endocrine tumors or ductal adenocarcinomas. This hepatoid differentiation within the pancreas can be explained by the common embryologic foregut derivation of the pancreas and liver. In this report, we describe the clinical, cytologic and histopathologic features of a pure pancreatic HC. We reviewed published literature on HC of the pancreas to interpret diagnostic, treatment and prognostic issues, as well as possible etiological hypotheses of this rare disease.

Etiology and Cell Origin

Ectopic liver tissue is reported in several sites, such as the gallbladder, hepatic ligaments, omentum, retroperitoneum and thorax [18]. This suggests HC to be a tumor originating from ectopic pancreatic liver tissue [19, 20]. However, controversy still surrounds the etiology and the pathogenesis of HC of the pancreas. Early or late development of abnormalities on ectopic liver tissue may indeed occur, even though pancreatic liver tissue has never been described in the literature. Not even the 2 published papers supporting such hypothesis reported any ectopic normal liver tissue nearby the cancer area [19, 20]. Pancreas-to-liver ‘transdifferentiation’ has been assessed on animal models since 1991 [21], with many authors focusing on the histogenetic mechanism of hepatocyte differentiation in the pancreas of the rat model following copper depletion-repletion [22]. Complete hepatocyte function following the switch has also been described as the pancreas of adult mice contains hepatocyte progenitor cells capable of significant therapeutic liver reconstruction [22]. Several authors claim this would be the key event of the pancreatic development of HCs [23–26]. Another pathogenetic mechanism relies on the common origin of pancreatic and liver tissue from the posterior foregut endodermic cells, keeping at a certain point distinct differentiation pathways. Pancreatic multipotent cells normally suppress hepatocytic differentiation genes, which could be activated during tumor genesis or for particular environmental conditions [23]. As previously suggested by other authors, the presence of a common multipotent/stem cell in the coexistence of peculiar environmental conditions (e.g. production-specific cytokines by the intrapancreatic common bile duct) may be implicated in the hepatoid differentiation of pancreatic tumors. In this meaning, pancreatic HCs may be seen as a possibility in the wide spectrum of pancreatic pluriphenotypical differentiation.

Discussion and Review of the Literature

Epidemiology

The reported incidence of ectopic liver tissue in different organs ranges between 0.24 and 0.47% [18, 27]; however, the true incidence of HC of the pancreas is still not known since presentation is often silent until symptoms of compression, pain or bleeding occur, and it usually has an aggressive course [19, 49].

Patient Characteristics and Clinical Presentation

Table 1 summarizes patient characteristics and main features at presentation in hepatoid adenocarcinoma, as reported in the literature. Patients’ mean age was 52.9 years (range 21–80), about 15 years less than the age of patients with pancreatic ductal adenocarcinoma. Eight patients were female (36.4%), while 14 were male (63.6%). Generally, HC is associated with a very poor prognosis due to its aggressive course [34, 36]. The diagnosis is typically made incidentally, since lesions usually remain silent until symptoms of compression, pain or bleeding occur [19].

Table 2 outlines features characterizing the tumor in reported literature. There was no apparent predilection for location in the pancreas, and sizes ranged from 0.5 to 11 cm in the greatest dimension of tumor. Most cases were asymptomatic or incidentally discovered (31.3%), the most common presenting symptoms were pain, either back or epigastric (27.3%), followed by jaundice (18.2%), nausea/vomiting (18.2%) and weight loss (13.6%). Such data are comparable to those related to other pancreatic/peripancreatic malignant tumors. Of particular interest, 2 patients (9.1%) complained of clinical symptoms referable to a concomitant pancreatic neuroendocrine tumor (1 insulinoma and 1 glucagonoma, respectively), underlining the possible association of pancreatic HC with other pancreatic neoplasms. Elevated AFP serum levels might be present at time of diagnosis in all HCs, despite tumor primary site [7, 8, 11, 12, 28–33, 34]. Our review of pancreatic forms indeed reports a rate of 54.5% (12 out of
22 cases), bearing in mind that 3 papers did not report or did not assess AFP levels of their cases. However, AFP is not a specific marker: it can be elevated in acinar as well as in ductal, neuroendocrine and undifferentiated carcinomas of the pancreas [35] and, at the same time, it could be normal in the presence of an HCC. AFP serum level might therefore be more useful during the follow-up of surgically resected producing tumors. The radiological appearance of a diagnosed pancreatic HC is shown in figure 1, with an abdominal MRI revealing a 10-cm mass in the pancreatic head.

PIVKA-II, a tumor marker for HCC which was first described by Liebman in 1984, has become increasingly popular as a more specific and diagnostic serum marker than AFP [37–41]. Very rarely do malignant tumors other than HCC produce PIVKA-II, and it was discovered to be elevated in the case of HC of the pancreas [24]. Other tumor markers used for diagnosis include immunoreactivity with polyclonal antibodies against CEA, hepatocyte-specific Hep-Par1 antibody and albumin mRNA detected by in situ hybridization [28].

### Table 1. Patient characteristics and main features at presentation of hepatoid adenocarcinoma of the pancreas in the literature

<table>
<thead>
<tr>
<th>Case</th>
<th>First author</th>
<th>Ref.</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Serum AFP levels at diagnosis</th>
<th>CEA</th>
<th>Location (pancreas)</th>
<th>Size, cm</th>
<th>Other component</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hruban</td>
<td>36</td>
<td>1987</td>
<td>53</td>
<td>F</td>
<td>subcutaneous fat necrosis</td>
<td>normal</td>
<td>N/A</td>
<td>tail</td>
<td>1</td>
<td>acinar</td>
</tr>
<tr>
<td>2</td>
<td>Gardiner</td>
<td>2</td>
<td>1992</td>
<td>61</td>
<td>F</td>
<td>jaundice and fatigue</td>
<td>elevated</td>
<td>elevated</td>
<td>head</td>
<td>N/A</td>
<td>ductal adenocarcinoma</td>
</tr>
<tr>
<td>3</td>
<td>Tanno</td>
<td>23</td>
<td>1999</td>
<td>65</td>
<td>F</td>
<td>epigastric and back pain, anorexia, weight loss</td>
<td>elevated</td>
<td>elevated</td>
<td>body-tail</td>
<td>6×5</td>
<td>ductal adenocarcinoma</td>
</tr>
<tr>
<td>4</td>
<td>Yano</td>
<td>34</td>
<td>1999</td>
<td>57</td>
<td>M</td>
<td>jaundice, epigastric pain, vomiting and fever</td>
<td>elevated</td>
<td>elevated</td>
<td>head</td>
<td>9×7×5</td>
<td>ductal adenocarcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Paner</td>
<td>33</td>
<td>2000</td>
<td>57</td>
<td>M</td>
<td>vomiting, diarrhea, weight loss, skin rash</td>
<td>elevated</td>
<td>elevated</td>
<td>tail</td>
<td>6×4×3.5</td>
<td>glucagonoma</td>
</tr>
<tr>
<td>6</td>
<td>Paner</td>
<td>33</td>
<td>2000</td>
<td>28</td>
<td>M</td>
<td>abdominal and back pain</td>
<td>elevated</td>
<td>elevated</td>
<td>multifocal</td>
<td>8×8×6</td>
<td>ductal adenocarcinoma</td>
</tr>
<tr>
<td>7</td>
<td>Lam</td>
<td>30</td>
<td>2001</td>
<td>64</td>
<td>F</td>
<td>hypoglycemia and recurrent episodes of nocturnal sweating</td>
<td>elevated</td>
<td>N/A</td>
<td>tail</td>
<td>7×4×4</td>
<td>insulinoma</td>
</tr>
<tr>
<td>8</td>
<td>Cuilliere</td>
<td>46</td>
<td>2002</td>
<td>70</td>
<td>M</td>
<td>incidental (asymptomatic)</td>
<td>normal</td>
<td>N/A</td>
<td>body</td>
<td>3</td>
<td>serious microcystic adenoma</td>
</tr>
<tr>
<td>9</td>
<td>Hughes</td>
<td>11</td>
<td>2004</td>
<td>51</td>
<td>M</td>
<td>gastrointestinal bleeding</td>
<td>normal</td>
<td>normal</td>
<td>tail</td>
<td>6×5.5×5.5</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>Matsueda</td>
<td>24</td>
<td>2006</td>
<td>49</td>
<td>F</td>
<td>weight loss</td>
<td>elevated</td>
<td>normal</td>
<td>widespread</td>
<td>N/A</td>
<td>no</td>
</tr>
<tr>
<td>11</td>
<td>Shih</td>
<td>43</td>
<td>2006</td>
<td>32</td>
<td>M</td>
<td>incidental (asymptomatic)</td>
<td>normal</td>
<td>elevated</td>
<td>tail</td>
<td>7</td>
<td>no</td>
</tr>
<tr>
<td>12</td>
<td>Oh</td>
<td>25</td>
<td>2006</td>
<td>21</td>
<td>M</td>
<td>incidental (asymptomatic)</td>
<td>elevated</td>
<td>N/A</td>
<td>head</td>
<td>3×3×3</td>
<td>neuroendocrine</td>
</tr>
<tr>
<td>13</td>
<td>Hameed</td>
<td>28</td>
<td>2007</td>
<td>41</td>
<td>F</td>
<td>jaundice, abdominal pain</td>
<td>elevated</td>
<td>elevated</td>
<td>head</td>
<td>4.5×4×3</td>
<td>endocrine</td>
</tr>
<tr>
<td>14</td>
<td>Cardona</td>
<td>19</td>
<td>2007</td>
<td>58</td>
<td>F</td>
<td>back and flank pain</td>
<td>normal</td>
<td>N/A</td>
<td>body</td>
<td>3×2.5×2.5</td>
<td>no</td>
</tr>
<tr>
<td>15</td>
<td>Kubota</td>
<td>20</td>
<td>2007</td>
<td>56</td>
<td>M</td>
<td>diabetes</td>
<td>N/A</td>
<td>N/A</td>
<td>tail</td>
<td>6.3×6.2</td>
<td>no</td>
</tr>
<tr>
<td>16</td>
<td>Liu</td>
<td>44</td>
<td>2007</td>
<td>80</td>
<td>M</td>
<td>nausea, diarrhea, weight loss</td>
<td>normal</td>
<td>N/A</td>
<td>head</td>
<td>5×5×6</td>
<td>no</td>
</tr>
<tr>
<td>17</td>
<td>Jung</td>
<td>26</td>
<td>2010</td>
<td>46</td>
<td>M</td>
<td>dyspepsia</td>
<td>elevated</td>
<td>elevated</td>
<td>head</td>
<td>8×9</td>
<td>neuroendocrine</td>
</tr>
<tr>
<td>18</td>
<td>Petrelli</td>
<td>47</td>
<td>2011</td>
<td>37</td>
<td>M</td>
<td>incidental (abdominal mass)</td>
<td>N/A</td>
<td>normal</td>
<td>body</td>
<td>11</td>
<td>no</td>
</tr>
<tr>
<td>19</td>
<td>Kai</td>
<td>49</td>
<td>2012</td>
<td>79</td>
<td>F</td>
<td>incidental (asymptomatic)</td>
<td>elevated</td>
<td>elevated</td>
<td>tail</td>
<td>7</td>
<td>no</td>
</tr>
<tr>
<td>20</td>
<td>Kelly</td>
<td>48</td>
<td>2012</td>
<td>53</td>
<td>M</td>
<td>severe epigastric pain</td>
<td>elevated</td>
<td>N/A</td>
<td>body-tail</td>
<td>N/A</td>
<td>no</td>
</tr>
<tr>
<td>21</td>
<td>Huang</td>
<td>45</td>
<td>2012</td>
<td>52</td>
<td>M</td>
<td>incidental (asymptomatic)</td>
<td>N/A</td>
<td>elevated</td>
<td>head</td>
<td>0.5 nodule</td>
<td>neuroendocrine</td>
</tr>
</tbody>
</table>

CEA = Carcinoembryonic antigen; N/A = not available.

### Table 2. Outline of the main features characterizing presentation in 22 adult patients as reported in the literature

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidental</th>
<th>31.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (abdominal/back)</td>
<td>27.3%</td>
<td></td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>18.2%</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>18.2%</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>13.6%</td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>31.8%</td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>31.8%</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>18.2%</td>
<td></td>
</tr>
<tr>
<td>Diffuse or multifocal</td>
<td>13.6%</td>
<td></td>
</tr>
<tr>
<td>Size range, cm</td>
<td>0.5–11</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21–80</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female:male</td>
<td>8:14</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>45.4%</td>
<td></td>
</tr>
<tr>
<td>Elevated AFP</td>
<td>57.1%</td>
<td></td>
</tr>
<tr>
<td>Elevated CEA</td>
<td>47.6%</td>
<td></td>
</tr>
</tbody>
</table>
Histological Features

In the literature, there were 10 reported cases of ‘pure’ HC [11, 19, 20, 24, 26, 34, 43, 44, 47–49] and 11 of HC associated with another component. The admixed were as follows: 4 cases with neuroendocrine carcinoma [25, 26, 30, 45], 1 case associated with malignant glucagonoma [33], 1 with malignant insulinoma [28], 1 case with acinar [36] and 4 with ductal adenocarcinoma [33]. Cuilliere et al. [46] documented the only reported case of a benign hepatocellular neoplasm arising in the pancreas, which was an encapsulated solid adenoma in the pancreas that showed exclusively hepatocellular differentiation. The tumor was considered benign due to lack of mitoses, nuclear atypia, and vascular invasion. In cases where other components are associated with HC, the histological and immunohistochemical patterns of expression of these tumors would also be identified.

Gross examination of the tumor could present a lobulated gray-greenish lesion, which is a typical aspect of HCC. Histological diagnosis of a pure form of HC may be straightforward. Figure 2 shows a sectioning of resected specimen showing a 5-cm pseudolobulated greenish mass of a pancreatic hepatoid adenocarcinoma in the head of the organ. Thickened cell plates with round nuclei and eosinophilic cytoplasm in a predominantly trabecular pattern (as well as aspect of lymphatic-vascular invasion) represented the typical microscopic appearance of the tumor. The more frequent immunohistochemical stains used for detection of HC are cytoplasmic positive reaction of cells that strongly express AFP, hepatocyte antigen, cytokeratin, and positive proteins include keratin/cytokeratin, cell adhesion molecule 5.2/AE, albumin, ACT, prealbumin, α1-antitrypsin protease inhibitor, and transferrin. This characteristic molecular marker expression pattern suggests HC [26].

The evidence of medium to large polygonal cells, eosinophilic to clear cytoplasm with vesicular nuclei and prominent nucleoli growing in a perisinusoidal pattern, along with the demonstration of the presence of bile and an immunohistochemical profile characteristic of HCC represent pathognomonic features [42]. Figure 3 shows the hematoxylin and eosin microscopic image of a cyto-
logic slide obtained by scraping of the fresh surgical specimen, showing the histologic appearance of the lesion. Figure 4 shows the immunohistochemistry with immunolabeling for anti-hepatocyte, for CD56, for CD10 and negative immunostaining for synaptophysin.

**Differential Diagnosis**

The histologic differential diagnosis of HC of the pancreas depends mostly on the degree of hepatoid differentiation, and the amount of the non-hepatoid component, if any. When diagnosing primary pancreatic HC, it is important to exclude metastatic HCC and ectopic HCC by clinical and pathological examination.

No standardized criteria for diagnosing HCs have been established, but morphological and immunohistochemical similarity to HCC is required. Morphological features may suggest hepatocellular differentiation, and bile production is confirmatory, but is usually only seen in well-differentiated tumors. The incidence of HCC spreading to the pancreas is only 2.7–5.6%, and the metastasis is usually a late finding [39, 42]; however, metastatic HCC must be considered. Long-term follow-up is needed to exclude the possibility that the pancreatic tumor represents a metastasis from the liver.

HC and HCC share numerous clinicopathological features, such as morphology, elevated serum AFP and AFP-positive staining on histology, canalicular-pattern CEA, and α1-antitrypsin. This makes differential diagnosis particularly challenging with an unknown primary tumor. Differentiating between the two can be made essentially by immunohistochemistry, with an expressed profile of CK [47].

Fig. 3. a Hematoxylin and eosin microscopic image of a cytologic slide obtained by scraping of the fresh surgical specimen, showing trabecular clusters of polygonal cells with round nucleus and small but evident central nucleolus and eosinophilic huge cytoplasm.

b Hematoxylin and eosin low-magnification microscopic image of the border of the lesion (right) in relationship to normal pancreas tissue (left).

c Hematoxylin and eosin high-magnification microscopic image showing pigmented deposits, brownish or greenish ones, at least in part made of bile.
If bile production cannot be identified histologically, then the differential diagnosis would also include other pancreatic tumors that have large eosinophilic tumor cells, such as intraductal oncocytic papillary neoplasms, pancreatoblastoma, and acinar cell carcinoma [24].

**Treatment Modalities and Long-Term Prognosis**

The treatment associated with the best disease-free survival remains to be radical surgical resection [11, 19, 20, 25, 26, 30, 33, 43, 45–49]. Of the 22 adult cases reported in the literature, 10 (46%) had distant metastases at presentation, 16 (87%) underwent surgery and 9 (41%) died of the disease [2, 23, 28, 33, 34, 47, 48]. The mean survival rate of patients that died of disease was 18 months.

The role of adjuvant therapy after surgery resection is still unclear and is based on few experiences as shown in table 3. Although some authors have advocated adjuvant chemotherapy because of the metastatic potential of the tumor [28], others have indicated no discernible events [24, 28, 33]. A certain degree of response to chemotherapy with long-term survival was reported in locally unresectable, metastatic or recurrent disease [30, 33]. Therefore, aggressive treatment seems warranted even in the case of locally advanced diseases, and resection of metastases may be considered as well [24]. Due to its rarity, the natural history and prognosis of the disease cannot be accurately predicted. The longest period achieved without any adjuvant therapy was 48 months [43]. The longest

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**Fig. 4.** a Immunolabeling for anti-hepatocytes. b Immunolabeling for CD56. c Immunolabeling for CD10. d Negative immunostaining for synaptophysin.
disease-free interval after resection reported in the literature is 102 months with adjuvant chemotherapy [33]. This suggests chemotherapy may have a role in recurrent, residual unresectable and metastatic disease, but data are limited.

So far, the limited data suggest that around 50% of adult patients will die of this disease within 3 years from initial diagnosis. Owing to its rarity, the treatment approach is far from being standardized. It is suggested therefore that surgical resection is the treatment of choice whenever possible, and complete resection of the tumor appears to be the best option; however, long-term follow-up is warranted since recurrence seems common.

**Survival and Outcome**

Pancreatic forms of HC are extremely uncommon, with 22 cases [2, 11, 19, 20, 23–26, 28, 30, 33, 34, 43, 44–49] being reported at the time of writing this review. Literature review shows divergent results in terms of survival. Thirteen reports have long-term follow-up (over 1
year) [19, 20, 24, 28, 30, 33, 43, 46], with 1 patient disease free at 3-year postoperative follow-up [20]. Among the 22 reported cases of HC of the pancreas, 2 patients that underwent surgical resection had a good outcome; 1 patient survived for 18 months [24] and another patient died 8.5 years later. Results are shown in table 3.

Table 3 summarizes therapy and related outcome of adult pancreatic hepatoid adenocarcinoma. Patients presenting with metastatic HCs at the time of diagnosis showed the typical pattern of liver involvement from upper gastrointestinal tract malignancies, with a 10.5 months median of overall survival (range 1–102). Petrelli et al. [47] reported a case of a 37-year-old patient having a pancreatic mass and multiple liver nodules and treated with multi-target tyrosine kinase inhibitor sorafenib. Off-label chemotherapy resulted in 7 months of progression-free survival. The patient eventually died of disease 1 year after the diagnosis. Although evidence is limited, one may speculate that pancreatic HC shows the typical features of an aggressive malignant upper gastrointestinal tumor [47].

With regard to pure forms, the one reported by Yano et al. [34] had the worst outcome after radical surgery (5 months). Such outcome may be correlated with the extension of the neoplasm at the time of diagnosis and, in particular, with the reported massive vascular invasion. On the opposite side of the spectrum, Cuilliere et al. [46] report a good outcome after excision of a small, incidentally discovered and exempted from vascular invasion tumor (at 12 months after surgical resection, the patient is alive and disease free). Long-term outcome of HC appears unclear due to its rarity and possible heterogeneity. In the case of a double component, a concomitant ductal adenocarcinoma or a poorly differentiated endocrine tumor will reasonably affect the prognosis, more than the hepatoid component. Pure forms represent on the other hand tricky entities that should be considered on a case-by-case basis.

With regard to chemotherapeutic agents, fluorouracil can be used to provide some symptom control, and gemcitabine has proved useful as a palliative agent in patients with advanced pancreatic cancer. Doxorubicin-based regimens have the greatest efficacy but little impact on overall survival in HCC, indicating its minimal responsiveness to systemic chemotherapy. Likewise, chemotherapeutic agents have limited effectiveness against tumors of the pancreas or liver, no standard therapy exists for treating hepatoid tumors [47].

**Conclusion**

Pancreatic HC is an extremely uncommon neoplasm. Preoperative diagnosis is challenging since diagnosis depends mainly on specific pathological findings, even with appropriate imaging and cytological examination. This neoplasm can share microscopic features with other more common pancreatic tumors, such as neuroendocrine tumors. Both the surgeon and pathologist should consider this entity in differential diagnosis of ‘unusual’ mass forming pancreatic tumors. Biological behavior of pure forms seems to be more indolent in comparison with heterogeneous tumors. Owing to its rarity, the treatment approach is far from being standardized; however, surgical resection is the treatment of choice whenever possible. Surgical excision may be associated with good long-term results, but further studies and longer follow-up are needed to correctly assess prognostic features. While complete resection of the tumor appears to be the best option, chemotherapy and radiotherapy may have a role in recurrent, residual unresectable and metastatic disease, but data are limited.

**Disclosure Statements**

The authors declare that they have no conflicts of interest.

**References**


