RESEARCH ARTICLE

Diagnosis and Therapy of Primary Hepatic Neuroendocrine Carcinoma: Clinical Analysis of 10 Cases

Li-Ming Wang, Song-Lin An, Jian-Xiong Wu*

Abstract

Background: Primary hepatic neuroendocrine carcinoma (PHNEC) is rarer than extrahepatic gastrointestinal neuroendocrine carcinoma (NEC). It is difficult to make a correct diagnosis and poses a challenge for management. Materials and Methods: Ten PHNEC patients were admitted to our hospital from June 2006 to June 2011. Laboratory tests and imaging scans were performed for diagnosis and exclusion of extrahepatic NEC. All patients were AFP - and CA199- . Seven patients had solid tumors with cystic changes on ultrasonography, CT and/or MRI. For the initial treatment, four patients received combined-therapy and six monotherapy. Considering overall treatment, six patients received combined-therapy and four patients monotherapy. Staging criteria of primary hepatocellular carcinoma (PHC, AJCC 7th edition) were used to differentiate the stage of all patients: 3 patients were stage I, 2 stageII, 4 patients stageIII and 1 stageIV. All patients were followed up and clinical data were gathered. Results: The median follow-up duration was 38.5 months. The 1-year, 2-year, 3-year and 6-year disease-free survival was 80.0%, 46.2% and 46.2% and 0% respectively. The overall survival rates were 100%, 67.1%, 67.1% and 33.6% respectively. Patients in early-stages (I/II) had similar disease-free and overall survival as those in advanced-stages (III/IV). Patients with monotherapy had significant shorter disease-free and overall survival than the patients with combination-therapy. Conclusions: PHNEC has a unique specificity during its occurrence and development. The staging criteria of PHC might not be suitable for the PHENT. More convenient and effective features need to be found in imaging and laboratory detection. Surgical resection, TACE, chemotherapy and radiofrequency ablation should be performed in combination and actively for patients with PHNEC or recurrence to get the best effectiveness; they might extend the disease-free and overall survival.

Keywords: Neuroendocrine carcinoma - carcinoid tumor - diagnosis - therapy

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Introduction

Neuroendocrine carcinoma (NEC) is commonly derived from the cells of neuroendocrine system and mostly seen in the gastrointestinal tract and pancreas. It usually secrets hormones like gastrin, chromogranin A, serotonin, ACTH, insulin, etc. (Gravante et al., 2008). Oberndorfer first defined it as karzinoid (carcinoid) in 1907; it is described as a tumor that resembles an adenocarcinoma, yet behaves in a more benign fashion. However, further clinical reports showed that some carcinoids still have the characteristics of invasion and metastasis. By now, they are usually supposed to be the low-grade malignant tumors that may cause the carcinoid syndrome by secretion of serotonin and other vasoactive hormones. The majority of NEC arises within the gastrointestinal tract, few within other organs like pancrease. Liver is a common site for metastasis of carcinoid origin and an unusual site for a primary carcinoid tumour to arise. Primary hepatic neuroendocrine carcinoma (PHNEC) is very rarer than extrahepatic gastrointestinal neuroendocrine tumors and is not included to a current WHO classification of neuroendocrine tumors (NET). There are few or none neuroendocrine cells in the liver compared to other organs, as the exact derivation of these tumors remains unclear. Therefore, it is difficult to reach a proper diagnosis and determine a therapeutic approach. Here, we present 10 cases in this paper to describe the clinical features, diagnosis, treatment and prognosis of these cases.

Materials and Methods

Material

There are 10 PHNEC patients admitted to our hospital from June 2006 to June 2011, 5 were male and 5 were female. The average age was 43.70±14.13 years (25-62 years). Epigastric discomfort was complained in 6 cases diarrhea in 1 case, intermittent right upper quadrant

[1]*Department of Abdominal Surgery, Cancer Institute & Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China *For correspondence: dr.wujx@hotmail.com*

abdominal pain in 1case and 2 cases have no any symptom. 2 cases have the complication of hypertension. Of these, only 2 patients tested positive for hepatitis B infection and only 1 have liver cirrhosis. All patients were AFP(-) and CA199(-) except one with FER(+) and another one with CEA(++), which was 6 times more than normal. No one was tested with NSE preoperative. B-ultrasonography, computed tomography and/or magnetic resonance imaging scan were performed for diagnosis. According to CT and/or MRI detection, 5 patients had single lesion and 5 patients had multiple lesions in the liver, 3 of them had lesions more than 3. The average diameter of all lesions was 3.82±3.10cm (0.6-12.0cm).

Preoperative diagnosis was hepatocarcinoma in 5patients, metastatic tumor in 2 patients, angioleiomyolipoma in 2 patients and hamartoma in 1 patient. Of the 2 patients with the possibility of metastatic liver tumor, digestive endoscopy, endoscopic ultrasound, chest x-ray and thoracic cavity CT were performed, but had no any abnormal finding. Of the other 8 patients, after pathology diagnosis of NSE was reported, digestive endoscopy, endoscopic ultrasound and/or gastrointestinal contrast visualization were performed postoperatively to exclude the NEC in the stomach, duodenum, colon, or rectum. All patients were followed up at least 1 year after the initial treatment of PHNEC, any other extrahepatic lesion was not found radiologically during the follow-up, except for recurrence in the liver some years later after treatment.

Hepatectomy was taken in 8 patients who had been detected to have single lesion or multiple lesions but limited in one or two lobe. During operation, peritoneal cavity exploration was carried out to preclude tumors of the stomach, intestine, colon, and pancreas, no tumors were found outside the liver. 5 Patients with a single tumor received radical excisions; others 3 patients with multiple tumors underwent excision of all tumors or palliative cyto-reductive surgery of all visible lesion. After liver resection, 2 patients received transcatheter arterial chemoembolization (TACE), 1 patient received adjuvant systemic chemotherapy, the other 5 patients did not receive any treatment until recurrence was found. For the 2 patients who did not receive surgery resection, percutaneous ultrasound-guided biopsy was taken and pathology evidence showed the diagnosis of PHNEC. One of them received TACE combined with systemic chemotherapy; the other one only received multi-course systemic chemotherapy. For the 6 patients with recurrence, one received TACE combined with systemic chemotherapy and radiofrequency ablation; one received TACE combined with octreotide injection; one received reoperation; two received chemotherapy and one only received conservative treatment.

Postoperative diagnosis was confirmed by pathology and immunohistochemistry. Because there was no consensus for immunohistopathology stain, a total of 17 different immunohistochemistry markers were examined in all patients. The most commonly used markers were: AE1/AE3 to confirm the epithelial origin, hepato to exclude hepatocellular origin, syn and NSE to confirm neurosecretory character. Because of lacking of special staging criteria for PHNEC, staging criteria of primary hepatocellular carcinoma (PHC, AJCC 7th edition) was referred: 3 patients were stageI, 2 patients were stageII, 4 patients were stageIII and 1 patient was stageIV.

Statistic

For the convenience of statistic analysis, we defined the conceptions as follow: 1 early-stage: stage I/II; 2 advanced-stage: stage III/IV; 3 monotherapy: Receiving resection or chemotherapy alone as the initial or sequential therapy; 4 combined-therapy: receiving resection combined with TACE , chemotherapy or/and radiofrequency ablation as the initial or sequential therapy.

To compare the end of different stage, all the patients were divided into 2 groups: early vs. advanced. To compare the effect of different treatment, all the patients were divided into 2 groups: monotherapy vs. combination-therapy. Disease-free survival and overall survival were estimated by the Kaplan-Meier method. Disease-free survival was defined as the period from the initial date of treatment of PHNEC to the date of the tumor recurrence or death. Overall survival was defined as the period from the date of initial treatment for the PHNEC to the date of death related to any cause. Observations were right-censored at 2 July, 2012, based on the assumption that all deaths occurring up to this date would have been included in the database. Statistical analysis was performed using the SAS 9.2 statistic software program.

Results

All patients were confirmed pathologically to have PHNEC. They were followed up until July 2, 2012. Because serum 5-HT, chromogranin A (CgA), and urinary 5-hydroxyindoleacetic acid (5-HIAA) examinations cannot be conducted at our hospital, B-ultrasonography, CT or/and MRI were used for postoperative examination.

The median follow-up duration was 38.49 months (13.23-74.10 months). Until the end of our study, 60.0% of the patients (6/10) had recurrence, 40% of the patients had died. The 1-year, 2-year, 3-year and 6-year disease-free survival was 80%, 46.22%, 46.22% and 0% respectively. The longest disease-free survival time was 48.80 months and the median disease-free survival was 15.73 month. Until the final follow-up date, 6 patients survived. The 1-year, 2-year, 3-year and 6-year overall survival rate was 100%, 67.11%, 67.11% and 33.55% respectively. The longest postoperative overall survival time was 74.1 months and the median survival was 38.49 month.

For the 6 patients who received monotherapy as the initial therapy, 5 of them relapsed; for the 4 patients who received combined-therapy as the initial therapy, 1 of them relapsed. Overall, for the 6 patients who received combined-therapy as the initial or sequential treatment, 1 of them died; for the 4 patients who received monotherapy as the initial or sequential treatment, 3 of them died.

The disease-free and overall survival curves of different groups were analyzed according to the status of tumor stage or treatment. Patients with early-stage had similar disease-free survival and overall survival compared with the patients with advanced-stage (Figure

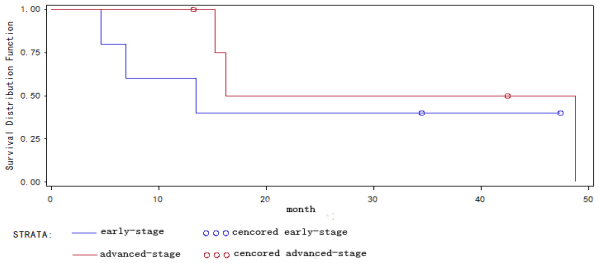

Figure 1. Disease-free Survival Analysis of PHNEC Patients by Stage of Early or Advanced

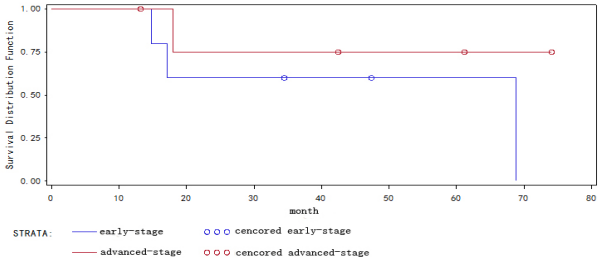

Figure 2. Overall Survival Analysis of PHNEC Patients by Treatment of Early or Advanced

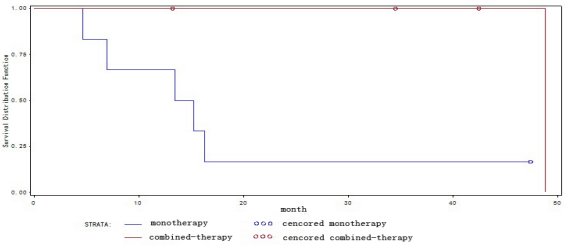

Figure 3. Disease-free Survival Analysis of PHNEC Patients by Treatment of Monotherapy or Combined-Therapy

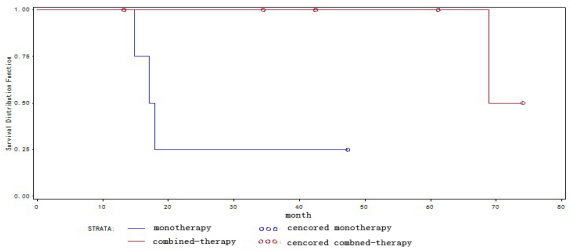

Figure 4. Overall Survival Analysis of PHNEC Patients by Treatment of Monotherapy or Combined-Therapy

1, p=0.4154 and Figure 2, p=0.3077). Patients with monotherapy had significant shorter disease-free and overall survival than the patients with combined-therapy (Figure 3, p=0.0318 and Figure 4, p=0.0221).

Discussion

Origin and symptom

Carcinoid tumors are also defined as neuroendocrine carcinoma. To solve the confusion around the terms carcinoid and NEC, the World Health Organization named these species of tumors as NEC in 2000, and classified them into 3 categories: 1) well-differentiated NEC, i.e., typical carcinoid or carcinoid; 2) moderately-differentiated NEC, i.e., atypical carcinoid; 3) poorly-differentiated NEC, i.e., small cell carcinoma. Carcinoid tumours have their origin in neuroendocrine stem cells (known as enterochromaffin cells or Amine Precursor Uptake Decarboxilase cells) derived from the embryonic neuronal crest. Gastrointestinal tract NEC is often metastized to the liver, but PHNEC is very rare because liver has few or none enterochromaffin cells, unlike other organs (pancreas, for example). The origin of primary hepatic carcinoid tumors is not well known and Several theories have been proposed so far. They may arise from scatter neuroendocrine cells in the intrahepatic biliary epithelium. These cells are also observed in hepatobiliary cystadenomas. It is also hypothesized that chronic inflammation in biliary system may initiate intestinal metaplasia, which predisposes to the development of neuroendocrine tumors. Another possibility is that they originate from ectopic pancreatic or adrenal tissues found within the liver (Gravante et al., 2008). However, the majority of these tumors showed no pancreas specific endocrine function (Balta et al., 2008). It is even speculate that the PHNEC originated from a poorly differentiated tumor clone of an HCC that underwent neuroendocrine differentiation, and that this tumor was the end stage of the transitional period from HCC to NEC (Yang et al., 2009).

Based on the combination of typical clinical symptoms, NEC can be determined as functioning or non-functioning. The clinical symptoms of PHNEC are more atypical, such as upper abdominal pain or discomfort like fullness, as well as diarrhea or weight loss (Gravante et al., 2008). In some cases, it appeared as nonbacterial thrombotic endocarditic (Lee et al., 2011). or Zollinger Ellison syndrome (Rascarachi et al., 2009). More than 10% cases are asymptomatic. Only a small percent of patients accuses symptoms of a typical carcinoid syndrome such as skin flushing, abdominal pain and diarrhea (Lin et al., 2009). Most patients are discovered by health examination with a solid liver mass. Within our series, only 2 patients had abdominal pain and diarrhea. Generally, PHNEC occurs at various ages and is slightly more frequent in females (58.5%) the single lesion is more frequent and there is no significant difference between the two lobes of the liver (Gao et al., 2011). But in our report, mainly in young and middle-age, there is no gender specific (5 *vs* 5), the amount of patients with single lesion was same as that with multiple lesion (5 vs. 5).

Diagnosis

The radiology diagnosis of PHNEC is often detected as hypervascular solid masses with or without cystic areas. It has poor specificity as the appearance on ultrasound, CT or MRI due to the similarity of PHNEC to hemangioma and HCC. Solid masses with cystic areas and hyperechoic or mixed pattern with central or peripheral calcifications and fibrous scars are common findings of PHNEC detected by ultrasonic. Contrast-enhanced US showed a rapid and dense enhancement without parenchymal stain (Komatsuda et al., 2005). Concerning CT findings in PHNEC, in most cases noncontrast images show

low-density masses, and some have cystic component. Dynamic contrast CT shows enhanced masses in the early phase and low density masses in the late phase (Ulusan et al., 2005). On MRI PHNEC usually present with low intensity in T1-weighted images and high intensity on T2-weighted images, typically appear as a large dominant hypervascular mass accompanied by satellite nodules, with rapid washout and capsular enhancement on dynamic MR imaging and restricted diffusion on DWI(Li et al., 2013). Generally, the majority of PHNEC are intense, hypervascularised tumours, which explains the contrast enhancement in ultrasound and CT images, in a similar fashion as the hepatocarcinoma. In our series, we found 70% of our patients with solid tumor with cystic changes on ultrasonography, CT, and MRI. It differs from the colliquation necrosis in HCC and maybe helpful for differential diagnosis. When diagnosing a PHNEC, an extrahepatic primary tumor must be excluded. Octreoscan is always recommended since it may detect small metastasic deposits. With a specificity near 83%, Octreoscan can be an ideal imaging procedure to discover concealed foci (Oberg et al., 2005) PET scan may visualize somatostatin receptor type 2 lacking neuroendocrine tumours which are impossible to detect on somatostatin receptor scintigraphy. It was reported that PET-CT specificity and sensitivity are increased with some specific metabolic substrates, even discovering a tumor as small as 2 mm in diameter (Orlefors et al., 2005).

Pathologic diagnosis is the most accurate diagnostic method to differentiate this uncommon type of tumors from other NEC or other liver solid tumors, especially hepatocellular carcinoma (HCC). The liver biopsy is the gold standard for preoperative diagnosis and is strongly recommended by some research (Jia et al., 2012), but arguments still occur on the value and risk of it (Skagias et al., 2010); therefore, postoperative pathologic examination is the main method for a final diagnosis. From the histologic point of view the hepatic carcinoma appears as a hemorrhagic, not capsulated mass, with central, irregular fibrosis and hyaline degeneration. Routine HE satining is not specific for diagnosis, but it is helpful in classifying the tumor grade. The tumoural cells display an eosinophilic cytoplasm and irregular, hyperchromic nucleus Some special stains, such as Massons and Grimelius, can raise the diagnosis rate to 80% or above (Bastaki et al., 2005). In inmunohistochemistry these cells present a strong positivity for neurosecretory markers as chromogranin, synaptophysin, neuron specific enolase(NSE) meanwhile markers as serotonin, pancreatic polypeptide or gastrin are inconsistently positive (Soga et al., 2002). Immunohistochemical analysis also raises the positive rate and accuracy through detecting PHNEC correlative markers, such as CgA and neurilemma cell S-100 protein. Among these, our result was NSE 100% (5/5) and synaptophysin 90% (9/10).

Therefore, the diagnosis of NEC is mainly based on histological and immunohistochemistry examination. But differentiation between primary and secondary hepatic NEC is impossible identified by histology alone. It requires meticulous radiological inspection to rule out an occult extrahepatic malignancy with hepatic metastasis.

Treatment

There are no certain standards for the therapy of PHNEC, Surgery could be the only curative option (Modlin et al., 2010) and provides the most favorable outcomes including long-term survival (Huang et al. ,2010) Massive research reported that the survival rate is satisfactory in spite of recurrence (Bastaki et al., 2005). The 5-year recurrence rate is 26% (Zhang et al., 2008) and the 5-year survival rate is 78-80% (Knox et al., 2003; Zhang et al., 2008). The administration of preoperative chemotherapy, radiation therapy, or chemoembolization did not impact survival (Knox et al., 2003) When possible, the preferred treatment for PHNEC is the surgical resection for the cases without distant metastasis nor lymph node metastasis (Shinkawa et al., 2013). Even for the giant case, curative resection could induce long-time survival (Sotiropoulos et al., 2013). Efficient pre-operative resectability assessment using computer-assisted volumetric analysis could improve the total resection rate (Tang et al., 2013). There is still no report of effective systemic chemotherapy for PHNEC. transcatheter arterial chemoembo-lization (TACE), as the common treatment protocol for liver cancer, has an ideal effect for metastatic hepatic NEC according to a report, (Bloomston et al., 2007) For PHNEC, TACE has been reported to achieve good palliation in some unresectable patients (Touloumis et al., 2008), but there is no certain result with a large sample set. In some report, TACE is recommended for cases with unresectable and/or recurrence tumors, but the long-term survival is not usually good enough. Primary surgery integrated with chemotherapy, TACE or even radiotherapy is considered to be an effective modality (Jia et al., 2012). Until the end of our study, 60% of the patients (6/10) had recurrence and 40% patients (4/10) died, including patients with well-differentiated tumors. Survival-analysis of our study showed some results that different from results above-mentioned. Compared with combined-therapy group, monotherapy group had a significantly shorter disease-free survival and overall survival. In our series, one patient with single lesion only received hepatectomy, he had survived for less than 18 months; on the other hand, one patient with single lesion and portal vein tumor embolus received hepatectomy combined with TACE, he had a 49 months disease-free survival and has survived for more than 61 months during the follow-up; one patient who received TACE combined with systemic chemotherapy because of multiple liver lesion has survived for more than 42 months without any sign of recurrence or new lesion; another patient with multiple lesion only received systemic chemotherapy and only obtain 4 months disease-free survival and 15 months overall survival. These results suggest that resection of all tumors could lead to a higher survival rate but maybe not enough, combined therapy including variety of current treatment (resection, TACE, chemotherapy, radiofrequency ablation and octreotide injection et al), might lead to more better clinical outcomes.

There is still no report of typical treatment for recurrence. TACE was effective for the recurring tumor (Huang et al., 2010). The effectiveness of other local treatments such as radiofrequency therapy and PEIT has

not been reported yet. These methods may be considered for small tumors with diameters ≤3 cm because of direct damaging effect on the tumors (Huang et al., 2010). When a not well defined lesion is observed, a palliative cyto-reductive surgery in combination with transcatheter arterial embolization (TACE) and subsequent administration of lanreotide (long acting somatostatin analogue) might be effective, as Touloumis et al. showed recently (Touloumis et al., 2008). In our series, four patients with recurrence received monotherapy (chemotherapy or resection even conservative treatment) and all died; two patients with recurrence received combined-therapy and survived till now. One of them had multiple recuring tumors 16 months after hepatectomy. He received TACE in combination with radiofrequency therapy and chemotherapy alternatly within 2 years and the tumors decreased significantly without any new recurrence during a 58-month follow-up. These suggest combined-therapy would result better outcomes than monotherapy even in recurrence patient.

Pathology stage is the most important indication for predicting prognosis and instructing treatment. Yet the current NET staging criteria only designed for gastrointestinal tract NET. We attempt to differentiate the stage of PHNEC by the staging criteria of PHC, but the results were disappointing. The early-stage patients had a similar disease-free and overall survival compare with advanced-stage patients, no matter how the treatment was taken. These suggested that the nature of PHNEC might be different from PHC, the staging criteria of PHC might not be suitable for the PHENC.

Summary

As a rare liver primary tumor, PHNEC has a unique specificity during its occurrence and development. It is necessary to develop more convenient and effective features in imaging and laboratory detection to differentiate PHNEC from other solid liver masses. The postoperative diagnoses of PHNEC mainly bases on pathological and immunohistochemical examinations and the exclusion of metastasis disease. The nature of PHNEC is different from PHC; the staging criteria of PHC might not be suitable for the PHENC. At present, surgical resection is the preferred treatment; TACE is effective to offer excellent palliation. Combined therapy including variety of current treatment might significantly extend the disease-free and overall survival for patients with PHNEC no matter single or multiple lesions. To patients with recurrence, combined therapies were also recommended.

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