Retrospective analysis of interventional treatment of hepatic metastasis from gastroenteropancreatic neuroendocrine tumors

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Abstract

Objective: To analyze the angiography appearance of liver metastases from gastroenteropancreatic neuroendocrine tumors (GEP-NETs), and evaluate the clinical efficacy and prognostic factors of interventional treatment for hepatic metastases.

Methods: Fifty GEP-NETs patients with hepatic metastases were treated from January 2012 to December 2016, and received transarterial embolization (TAE) in the hepatic tumor or hepatic arterial infusion chemotherapy (HAIC). All patients received 179 times of the intervention therapy in total.

Results: Blood supplies were identified in the 50 cases with angiography, which showed that 35 cases had abundant vessels, while 15 cases had poor blood supply. Twenty-two cases were found either collateral blood supply, or portal vein invasion or arterial-portal vein fistula. The best curative efficacy was complete remission (CR) in 4 cases, partial remission (PR) in 28 cases and stable disease (SD) in 18 cases during the process of treatment. The angiography (P=0.047) and the frequency of intervention (P=0.037) showed significantly statistical difference with Kaplan-Meier analysis. The Cox analysis showed that more than 3 times of interventional therapy was an independent prognostic factor.

Conclusions: Interventional treatment is safe and effective for GEP-NETs, and is beneficial to patients with main hepatic metastases after endocrine therapy.

Keywords: Gastroenteropancreatic neuroendocrine tumors; hepatic metastasis; angiography; interventional treatment; retrospective analysis

Introduction

Derived from peptidergic neuron and neuroendocrine cells, neuroendocrine tumors (NETs) are a group of heterogeneous tumors. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) account for 55%–70% of NETs (1,2). Originated from neuroendocrine system, GEP-NETs are found in non-specific organs.

Functional GEP-NETs secrete a variety of hormones that can trigger symptoms. Most GEP-NETs are nonfunctional, and its clinical manifestations only occurred lately in the process of disease. The incidence and prevalence of GEP-NETs have increased approximately 5-fold to 5.25/100 thousand in the past 30 years (3,4). Now, GEP-NETs rank the second common gastrointestinal tumor of the world, and many factors are related to the

survival of GEP-NETs (5).

Surgical resection is feasible to treat NETs and metastasis, which will increase survival in some patients for its effect and efficiency. Unfortunately, only 5%–10% of diagnosed patients are eligible for resection with a risk of extremely high recurrence rates. It was reported that 94% of patients will relapse within 5 years (6,7). Metastasis usually occurs in the prophase of NETs. The liver is the most common site of metastasis, accounting for 10%–65% (8,9). Liver metastasis has occurred in most patients at the time of diagnosis. Unresectable liver metastasis still should be treated actively to palliate symptoms and slow down or stabilize tumor growth. Theoretical studies have shown that hepatic metastases, especially larger metastases, are mainly supplied by the hepatic artery (10,11), which provided a theoretical basis for the interventional treatment of hepatic metastases derived from NETs.

Materials and methods

This study retrospectively reviewed the interventional treatment of patients with GEP-NETs in the Department of Interventional Therapy, Peking University Cancer Hospital, who mainly presented the symptom of hepatic metastasis. This retrospective analysis of the data was approved by the Institutional Review Board of Peking University Cancer Hospital.

Patients

All the patients were pathologically diagnosed based on hepatic aspiration biopsy. Patients received at least one complete cycle of interventional therapy for hepatic metastases. The first cycle of interventional therapy was completed between January 2012 and December 2016. The follow-up period ended in June 2017. All of the cases were followed-up for more than 6 months.

Interventional technique

Patients received transarterial embolization (TAE) in the hepatic tumor, and some patients (pathological grade G3 mostly) combined hepatic arterial infusion chemotherapy (HAIC).

Femoral arterial puncture was achieved with a modified Seldinger method. Angiographies of the celiac artery, hepatic artery and tumor blood vessels were used to determine the location and blood supply of the tumor via a catheter and the microvasculature, respectively.

Angiographies of the superior mesenteric artery, diaphragm artery, or middle adrenal artery were added when necessary. The catheters were super-selected into the liver and tumor blood vessels. Granular embolic agent and Lipiodol ultrafluid were chosen for embolization. Some patients were treated with HAIC after TAE. The HAIC procedure was performed as following: the catheter was placed in the blood supply artery of the metastasis lesion. Continuous infusion of chemotherapeutic drugs was performed by an external arterial infusion pump via the arterial catheter. Chemotherapy regimen 1 consisted of pumped oxaliplatin 75–100 mg/m² for 6 h followed by 5-fluorouracil 1.5 g/m² from 6 to 48 h. Chemotherapy regimen 2 consisted of paclitaxel 135 mg/m² (docetaxel 75 mg/m²) for 6 h via an arterial pump followed by cisplatin 75 mg/m² for next 6 h.

Evaluation of interventional treatment

Evaluation of interventional treatment was based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The main observed indexes were hepatic progression-free survival (HPFS) and overall survival (OS).

Statistical software SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Statistical descriptions of categorical data were reported as the frequency (%). HPFS were estimated with the Kaplan-Meier method. Kaplan-Meier curves were plotted by using the log-rank test to demonstrate the associations between survivals and factors. Angiography (hypovascularity/hypervascularity), collateral blood supply or portal vein invasion (yes/no), interventional therapy (TAE/TAE+ HAIC) and frequency of intervention (n≤3/n>3) were viewed as general factors in multivariable Cox regression models, which were used to estimate the hazard ratios (HRs) and identify the independent predictors of HPFS. P<0.05 (two-sided) was considered as the cut-off for significance.

Results

Origin of tumor

From January 2012 to December 2016, 50 GEP-NETs patients (22 male, 28 female) were treated in the Department of Interventional Therapy, Peking University Cancer Hospital. Age of patients ranged from 30 to 80 years, with a median age of 54 years. The origin of the tumor included pancreas (n=20), colorectum (n=11),

stomach (n=8), small intestine and duodenum (n=7), and liver and gallbladder (n=4).

Angiography appearance of liver metastasis

Tumor vascularity was observed in all cases after detailed angiography. The lesion staining should be judged by consensus of at least 2 experienced interventional physicians. If there is any difference, another chief physician should be judged as the final result.

Only 15 cases were found with poor blood supply, whereas 35 cases with abundant vasculature. Of the 50 patients, 22 had collateral blood supply, portal vein involvement or hepatic arterioportal fistulas. All the patients received a total of 179 times of intervention with a median of 3 times. Of them, 23 patients received embolization alone.

Therapeutic effect

Therapeutic effect was observed and evaluated after a complete cycle, and some patients got good results (*Figure 1*). Complete remission (CR) was found in 1 case, partial remission (PR) in 18 cases, stable disease (SD) in 27 cases and progressive disease (PD) in 4 cases. The best curative effect during treatment was 4 cases of CR, 28 cases of PR and 18 cases of SD. The valid control rate was 64%.

Survival data and response rate

After interventional treatment, the HPFS of all of the patients ranged from 1 to 37 months, with a median of 9 months and a mean of 11 months. In addition, 17 patients died during treatment. The OS ranged from 5 to 36 months, with a mean of 21 months and a median of 19 months.

Among the origin of tumor, the pathological grade,
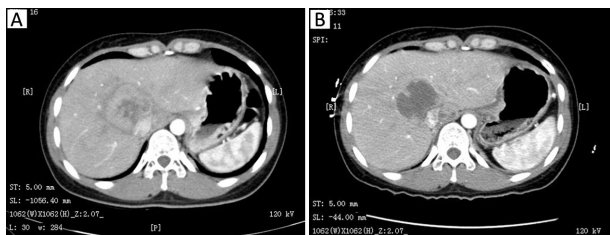
Figure 1 Comparisons between pre- (A) and post-treatment (B) on computed tomography (CT) images. Almost complete necrosis was achieved with no enhancement observed in the tumor site after interventional treatment.

angiography, vascular variation and frequency of interventional therapy, angiography (P=0.047) and frequency (P=0.037) showed significantly statistical differences (*Table 1*, *Figure 2A*, *B*). It means that the patients with rich angiography appearance or receiving more than 3 times of interventional treatment had longer HPFS.

Forty-three patients were examined with somatostatin receptor scintigraphy (SRS). The patients with positive results could get longer HPFS (P=0.018) (*Table 1*, *Figure 2C*).

In the Cox regression models, only frequency of intervention (n≤3/n>3) was an independent predictor of HPFS [χ^2=4.095; P=0.043; HR=0.533, 95% confidence interval (95% CI): 0.287–0.989] (*Figure 2B*). The other variables were not statistically significant in these models. This analysis showed that more than 3 times of interventional therapy made sense for patients.

Side effects

The postoperative side effects included such tolerable reaction as nausea, vomiting, pain and myelosuppression. All side effects were 1–2 degrees, which could be relieved with symptomatic treatment. Two months after interventional treatment, there was one case of pulmonary embolism, two cases of diaphragmatic abscess and one case of pancreatitis. The above symptoms were alleviated after symptomatic treatment.

Discussion

For patients with GEP-NETs, it is critical to optimize palliative care for effective and efficient treatment of hepatic metastases. According to the current National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) consensus, interventional therapy is an important method for the palliative, multidisciplinary cooperative treatment of advanced hepatic metastasis from NETs based on systemic therapy. However, additional data are required concerning the methods, treatment protocols, chemotherapy and complications for interventional therapy.

Most of the hepatic metastases from NETs are found with abundant blood supply, approximately 90% of which are supplied by the hepatic artery. The theory provided a theoretical basis for the interventional treatment of blood vessels (12). We observed that the blood supply of most

**Table 1** Complete statistics of eligible patients (N=50)

Cases	n	HPFS (month)	95% CI		P
			Upper	Lower	
Origin of tumor					0.979
Pancreas	20	9	13.383	4.617	
Rectum and colon	11	8	11.987	6.013	
Stomach	8	8	12.158	3.842	
Small intestine and duodenum	7	13	21.199	4.801	
Liver and gallbladder	4	7	23.333	0.000	
Pathological grade					0.074
G1+G2	31	11	14.510	7.490	
G3	19	7	8.972	5.028	
Angiography					0.047
Hypovascularity	15	7	8.525	4.475	
Hypervascularity	35	12	15.718	9.282	
Collateral blood supply or portal vein invasion					0.987
No	28	8	11.889	4.111	
Yes	22	10	14.399	5.601	
Interventional therapy					0.396
TAE	23	12	19.766	4.234	
TAE+HAIC	27	9	11.449	6.551	
Frequency of intervention					0.037
n≤3	30	7	8.530	5.470	
n>3	20	13	15.818	10.182	
SRS	43				0.018
Positive	31	12	15.004	8.996	
Negative	12	5	9.244	0.756	

TAE, transarterial embolization; HAIC, hepatic arterial infusion chemotherapy; SRS, somatostatin receptor scintigraphy; HPFS, hepatic progression-free survival; 95% CI, 95% confidence interval.

hepatic metastases was abundant (35/50) and primarily from the hepatic artery (13). Our analysis shows that patients with rich tumor staining had longer HPFS. We found 22 of the cases with collateral blood supply or portal vein invasion. Compared with 2.8%–8.1% of hepatic metastases from a common gastrointestinal tumor which had collateral blood supply, our findings were more serious in terms as progression (14,15). A poor treatment outcome will be caused by any lateral slip of the collateral blood supply, portal vein invasion, hepatic artery portal vein or hepatic venous fistula. The poor treatment outcome would lead to pulmonary embolism or other severe complications from an ectopic embolism. Admittedly, there were few studies on this topic. It may be related to the compensation of tumor blood vessels and tumor progression after repeated interventional therapies, and further exploration is

required. The patients receiving more than 3 times of interventional treatment got longer HPFS, which means that multiple interventional therapies are required to achieve a satisfactory embolization effect.

At present, drug-loaded microspheres (Drug-Eluting, Beads, CalliSpheres) and Yttrium 90 radioactive microspheres were not comprehensively applied to check up blood vessels. Interventional treatment of blood vessels is mostly with vascular embolization. When the effect of multidisciplinary treatment was poor, or when the angiography showed a poorly stained tumor, HAIC should be added as a treatment (16). For general cases, no significant difference was found between TAE alone and TAE with HAIC. However, in cases of hypovascularity angiography, only those cases treated with HAIC had obtained the effect of PR.
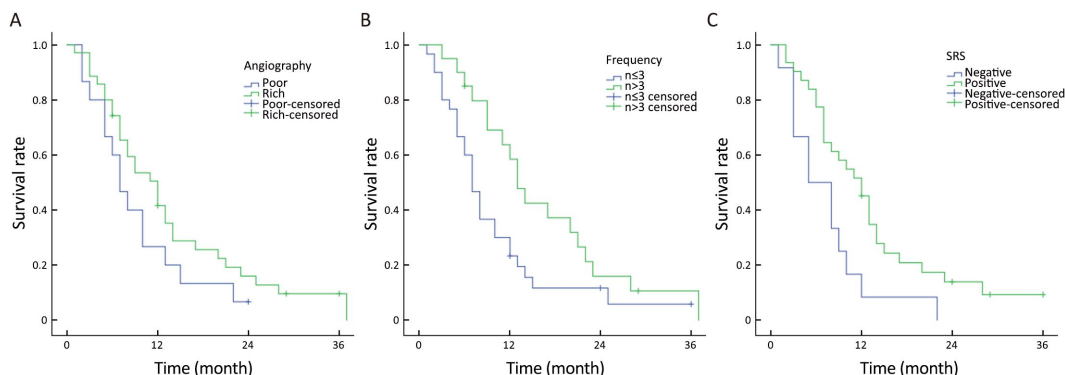
Figure 2 Hepatic progression-free survival (HPFS) curves according to (A) angiography (poor *vs.* rich blood supply); (B) frequency of interventional treatment (n≤3 *vs.* n>3); (C) somatostatin receptor scintigraphy (SRS) results (negative *vs.* positive).

We performed SRS examinations for some of the patients, and patients with the positive results were able to get a longer HPFS. Theoretically, the results of positive SRS correlated with hypervascular tumors (17).

For patients with hepatic metastases from NETs, it is commonly accepted that there is no difference between TAE and HAIC albeit clearly demonstrated (18,19). A consistent trend was observed in our cases even complications was widely found in HAIC (20,21). Patients who received HAIC suffered from pancreatitis and subphrenic abscess. As long as the discovery and treatment were timely, there would be no serious consequences.

As to patients received intervention as first- and second-line therapy, it was reported (12) that the valid control rates were 74% and 75%, respectively. When the intervention was performed as third-line and follow-up therapy, the valid control rates were 59% and 40%, respectively. In mostly relapsed cases of this study, interventional therapy was often used as a second- or third-line therapy. The overall response rate (64%) was similar to that of the third-line treatment. During the multidisciplinary treatment of GEP-NETs, especially in the cases with hepatic metastases as the main symptoms, we suggest that the blood supply of liver lesion should be examined by imaging, especially for those with positive SRS. The interventional therapy can be considered earlier. The number of treatment should be more than 3 times.

Conclusions

Vascular intervention therapy is safe and effective for patients with hepatic metastasis from GEP-NETs. In recent years, interventional therapy is widely selected to treat hypo- and hypervascularized hepatic tumors, and the

therapeutic effect has been confirmed. It is sure that along with the gradual improvement of interventional therapy and achievements in clinical prospective trials, more treatment options will be offered based on interventional multidisciplinary collaborative therapy for NETs to achieve a more definitive treatment effect.

Acknowledgements

Footnote

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