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Original Article

Transcatheter arterial chemoembolization for patients with hepatic metastasis of nonfunctional pancreatic neuroendocrine neoplasms

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Abstract: Background: Hepatic intra-artery embolization is always considered for pancreatic neuroendocrine neoplasms with liver metastases. Aims: To observe the outcome of transcatheter arterial chemoembolization (TACE) for unresectable hepatic metastatic nonfunctional tumors. Methods: The clinical data of 35 patients with pancreatic neuroendocrine neoplasms with liver metastases who underwent TACE were retrospectively analyzed. Results: This cohort study enrolled 20 males and 15 females. A total of 155-session of transcatheter arterial chemoembolization were operated and the mean value was 4.4-session. The effective rate of TACE was 71.6%. The median progression free survival time of cytoreduction with TACE was 17.5-month. The Overall survival rate (OS) of 1-year, 3-year and 5-year was 85.5%, 72.9% and 50.0%, respectively, the median OS was 48-month. Univariate survival analysis showed that younger age (< 60-year-old), originated from distal pancreas, lower grade, lower Ki-67 index (< 10%), well-differentiation, abundant feeding, primary lesion resection, and more than 4-session were the optimistic predictors ($P < 0.05$). The 5-year OS rate of patients with primary lesion resection versus without primary lesion resection was 75% versus 33.3%, which indicated that primary lesion resection was an independent prognostic factor ($P = 0.007$). Conclusion: As one of the local-regional therapies, TACE may be effective in patients with LM of pNENs. Primary lesion resection would influence their prognosis, as shows in this study.

Keywords: Pancreatic neuroendocrine neoplasm, liver metastasis, transcatheter arterial chemoembolization, primary lesion resection

Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are potentially malignant with indolent growth characteristic. Most patients with pNENs are asymptomatic because of the characteristics of non-function and specific anatomical site, which resulted that 30%-85% of patients were diagnosed as pNENs with liver metastasis (LM) at late stage [1-3]. The five-year survival rate of patients with advanced pNENs with LM ranged from 13% to 35% [4-6]. It is very necessary to take positive measures to treat patients with LM. A recent retrospective study enrolled 100 consecutive patients showed that patients with neuroendocrine tumor (NET) G1/G2 who accepted surgical resection had a good prognosis whereas most patients with neuroendocrine cancer (NEC) with distant metastasis had a poor prognosis [7]. The treatment strategy is selected according to the tumor staging classification and the WHO 2010 grading [8-10]. Up to now, tumor resection is the unique way to cure those patients with LM, but only a few patients meet the criteria. Debulking is considered especially for the patients with functional NENs. What's more, patients with hepatic diffuse metastases can't be cured by resection. Therefore, other therapies are taken for treating those patients with distant metastases, such as somatostatin analogues, targeted therapy, selective internal radiation therapy (SIRT), peptide receptor radionuclide therapy (PRRT) and etc. The therapeutic goal is to reduce the tumor burden as much as possible and offer symptomatic relief. But the efficacy of the drugs mentioned above such as octreotide, sunitinib, and everolimus are limited. Some reports showed that SIRT especially PRRT demonstrate

some effectiveness, but as the emerging measurement, the availability of these methods are poor. Hence, an alternative method should be developed to improve the poor outcome of the patients with LM. Generally, live metastases obtain nutrition mostly from the arteries, therefore occluding the vessels selectively which supply nutrition for the LM may achieve the aim to eliminate the tumors theoretically. Previous studies have indicated that transcatheter hepatic arterial embolization or chemoembolization (TAE/TACE), as the local-regional therapy, was effective for hepatic metastatic lesions from colorectal liver metastases [11-14]. Similar results were also acquired for patients with late stage gastroenteropancreatic NENs [15-17]. However, no Chinese evidence was reported for operating TACE on exclusive pancreatic NENs with LM. In this study, we reported a retrospective analysis about the patients with pNENs with LM who underwent TACE in our hospital and analyzed the factors that influence the outcome.

Patients and methods

Patients

Total 35 patients with nonfunctional pNENs with LM were enrolled in this study from Zhongshan Hospital Fudan University from September 2004 to December 2014. The study was authorized by the Hospital's Ethics Committee and all patients were informed consent. Their general, pathological and follow-up data were collected and analyzed retrospectively. The diagnosis was based on morphology and immunohistochemical assessment through the surgical specimen and hepatic biopsy by experienced pathologists.

TACE

Firstly, patients were hospitalized to have an overall check to assure they were physically suitable to avoid fatal complications intra- or post-operation. Contrast-enhanced CT/MRI scan was adopted to detect the tumor pre-treatment. The absolute contraindications of TACE include main portal vein occlusion and severe hepatic and renal dysfunction. Relative contraindications are detailed as follows: bilirubin > 2 mg/dl, coagulation disorders, serious bleeding tendency, severe infection, hepatic tumor burden > 75% and allergic to contrast medium, etc. TACE aims to block the arterial supplies of tumors. During the treatment, we used the classical Seldinger's technology to operate under the image guidance. Under radiological guidance, a catheter guided by a wire was put through the femoral artery into the abdominal aorta, then celiac trunk and finally the branch of the proper hepatic arteries supplying the tumors. In order to protect the major normal vessels, arterial angiography was performed through the common hepatic artery and the superior mesenteric artery (SMA). After that, appropriate chemotherapeutic agents 5-Fluorouracil (5-FU, 500-750 mg) and Oxaliplatin (100-150 mg) were injected into the vessels. Then, pharmorubicin/Epirubicin (20-30 mg) and super liquid iodized oil (5-20 ml) were mixed and injected through the micro-catheter to block the vessels which already contained the drugs. Gelfoam particles were used to obstruct the main arterial trunk subsequently. This procedure was repeated until the bloodstream was stopped and the deposition of the iodized oil was observed. In case that the hepatic function could deteriorate after the treatment, only one lobe was intervened in each session. Patients with bi-lobe or innumerable (< 75%) lesions were scheduled to take two or more therapeutic cycles.

After the treatment, hepatalgia was the immediate symptom in those patients, and the metastases were closer to the liver capsule, the pain was more intense. Analgesics were used to relieve the pain after operation. The hepatic function was monitored till recovery. Antibiotics were prophylactic used to prevent the liver abscesses. There was an internal period of 1-3 months for patients who needed to accept couple sessions for multiple lesions depending on the situation of patients. No other anti-tumor medicines were used before and during their sessions of TACE.

Tumor evaluation

The evaluation of efficacy was conducted within 2 months or at the time of their next session. Modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 was adopted to assess the therapeutic effect [18]. Symptomatic response, morphological response (reduction in tumor size on CT or MRI images) and biochemical response (reduction in serum markers) were included. According to the mRECIST criteria, we compared the overall diameters of

Table 1. General and pathological data of patients with pNENs with LM underwent TACE

Category	Cases	Proportion	Death* (%)	*P* value
Sex				
Male	20	57.1%	10 (50.0%)	
Female	15	42.9%	5 (66.7%)	0.071
Age				
< 60	24	68.6%	9 (62.5%)	
≥ 60	11	311.4%	6 (45.5%)	0.036
Primary Site (Pancreas)				
Head	15	42.9%	9 (40.0%)	
Body and tail	20	57.1%	6 (70.0%)	0.046
Primary lesion treatment				
Resection	20	57.1%	5 (75.0%)	
Without resection	15	42.9%	10 (33.3%)	0.005
LM area/liver area				
< 25%	29	82.9%	11 (62.1%)	
25%-50%	0	0%		0.250
50%-75%	6	17.1%	4 (33.3%)	
LM treatment				
Hepatectomy	8	22.9%	2 (75.0%)	
Without hepatectomy	27	77.1%	13 (51.9%)	0.240
Lymph node				
Metastatic	5	14.3%	2 (60.0%)	
Normal	30	85.7%	13 (56.7%)	0.609
Appearance of LM				
Synchronous	20	57.1%	10 (50.0%)	
Nonsynchronous	15	42.9%	5 (66.7%)	0.456
KI67 index				
< 10%	14	40.0%	2 (85.7%)	
≥ 10%	21	60.0%	13 (38.1%)	0.003
Tumor Grading				
G1	5	14.3%	0 (100%)	
G2	20	57.1%	9 (55.0%)	0.021
G3	10	28.6%	6 (40.0%)	
Differentiation				
Well	10	28.6%	1 (90.0%)	
Intermediate	13	37.1%	4 (69.2%)	0.004
Poor	12	34.3%	10 (16.7%)	
LM Blood Supply				
Abundant	22	62.9%	7 (68.2%)	
Poor	10	28.6%	8 (20.0%)	0.003
Default	3	8.5%	0	
TACE Session				
< 4	21	60.0%	11 (47.6%)	
≥ 4	14	40.0%	4 (71.4%)	0.023
Total	35		15 (57.1%)	

*Death during the follow-up.

the lesions (main target lesions, diameter was greater than 10 mm) pre- and post-therapy and divided them into 4 groups: ① Complete Response (CR): Disappearance of all target lesions. ② Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of the target lesions taking as a reference the baseline sum longest diameter. ③ Progressive Disease (PD): At least a 20% increase in the sum of the longest diameters of the target lesions taking as a reference the smallest sum of the longest diameters of target lesions recorded since the treatment started; or the sum of longest diameters of target lesions demonstrated an absolute increase of at least 5 mm (the appearance of one or more new lesions was also considered as PD). ④ Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest diameters since the treatment started [18].

Statistic methods

The follow-up information of those patients was acquired from clinical records and the tumor registry at Zhongshan Hospital Fudan University. The statistic software SPSS for Windows (IBM SPSS version 19.0, 2010) was used to analyze data. The survival rate and survival time was calculated by Kaplan-Meier methods. Univariate and Multivariate survival analysis was performed by Cox proportional hazards method. Survival curves were compared by using the log-rank test. Data were reported as median or mean ± SD (standard difference). $P < 0.05$ was considered significant.

Results

General and pathological data

Total 35 patients were enrolled in this study with a diagnosis of pancre-

Table 2. Response evaluation of tumor morphology

Events	Frequencies	Reduction in sizes (mm)
CR	9	
PR	102	-15.21
PD	11	+8.96
SD	33	-5.08
Total	155	

atic neuroendocrine neoplasms with LM, aged from 26 to 79 years (mean, 54 ± 11 years), consisting 20 males and 15 females. They were treated with a total of 155 TACE sessions, which means 4.4 TACE sessions for each one (ranged from 1 to 16 for one's sessions). The tumors were located in the head of the pancreas in 15 patients (42.9%), and the rest were located in the distal pancreas in 20 patients (57.1%). A total of 20 patients were diagnosed as pNENs with synchronous liver metastases, while other 15 patients were diagnosed as pNENs with non-synchronous LM. The time of appearance of LM ranged from 3 to 144 months, with a median of 30-month. Tumor burden was involved in bi-lobe liver in 26 patients (74.3%) according to the images, 6 patients among these patients (6/26, 23.1%) had a tumor burden with exceeded 50% of the liver. The lesions of the other 9 cases (25.7%) were confined to one lobe and inferior to 25% (**Table 1**). TACE was chosen as the first-line therapy in 15 cases, whereas the other 20 patients were performed pancreatectomy and then treated with TACE. There were 8 (8/20) patients underwent partial hepatectomy (cytoreduction before TACE): if the primary lesions could be removed radically and safely, those patients were performed pancreatectomy firstly, and if the hepatic could receive the cytoreduction, hepatectomy was also considered anterior to TACE.

Pathological results demonstrated that Ki-67 index ranged from 1% to 95% with the mean value of 15.8% (± 22.39%) and nucleus mitotic counts were 0-80/10HPF with the mean value of 13/10HPF (± 17.43/10HPF). According to the 2010 World Health Organization gastroenteropancreatic neuroendocrine tumor classification criteria [19-21], the proportion of G1, G2 and G3 was 14.3%, 57.1% and 28.6%, respectively. The percentage of tumor differentiation of well-, intermediate- and poor- was 28.6%, 37.1% and 34.3%, respectively (**Table 1**).

Efficacy and adverse reaction

The mean size of hepatic lesions before treatment was 39.79 ± 21.79 mm (ranged from 8 mm to 107 mm). The efficacy of the treatment was evaluated by comparing the sizes of remnant lesions before and after treatment within two months. On the basis of mRECIST 1.1 [18], CR, PR, PD and SD was recorded 9, 102, 11 and 33 times, respectively (**Table 2**). The overall effective rate of TACE (CR+PR) was 71.6%. Compared to the baseline, the mean reduction of lesions with PR or SD was 15.21 mm (38.2% shrinkage) and 5.08 mm (12.8% shrinkage) respectively. The median effective duration time of TACE (when progression or death was happened) was 17-month (range from 2 to 60 months).

No severe side effects were observed during the sessions. Most patients attained mildly hepatic function impairment within one month after treatment; they were soon recovered by nutritional support. Two patients developed liver abscesses after 4 or 8 sessions of TACE, and an episode of cholecystitis was observed in another patient suffered during his 10 sessions of TACE. Retroperitoneal lymphatic metastases were discovered in 4 patients during their treatment, so these patients had to change their treatment planning and they underwent radiotherapy.

Follow-up and survival analysis

Until 30 May 2015, the median time of follow-up was 39-month (40.4 ± 31.95 months). The median overall survival (OS) was 48-month (95% CI: 18.47-77.53) and the median progression-free survival (PFS) was 17.5-month. A total of 15 patients died and their time to death (TTD) ranged from 4 to 91 months, mean 29 ± 23.19 months. All the death is related with tumor and happened outside hospital. The survival rate of 1-year, 3-year and 5-year was 85.5%, 72.9% and 50.0%, respectively.

Univariate survival analysis demonstrated that patients with primary sites located in the head of the pancreas had poorer outcomes compared with those with primary sites in the body-tail. Among those 15 patients whose primary lesions were located in the proximal pancreas, 6 cases accepted pancreatectomy (2 patients died), and other 9 cases didn't accept pancre-

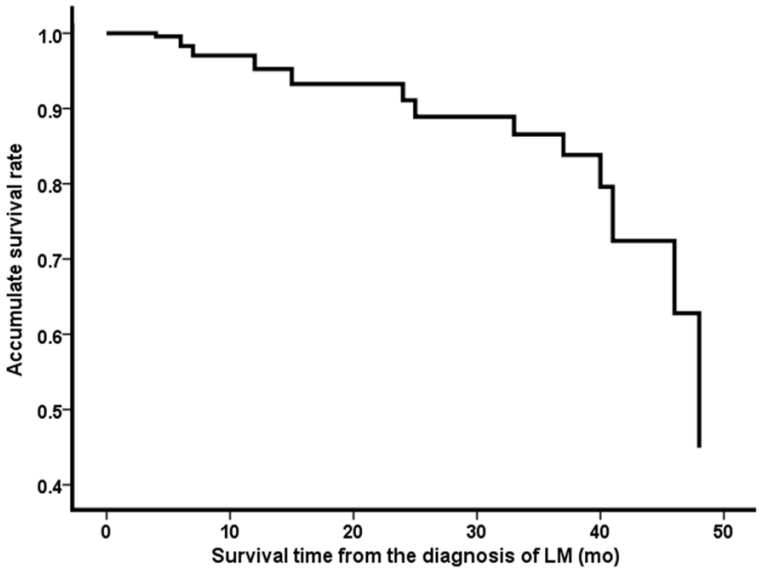

Figure 1. The survival curve of patients with pNENs with LM by multivariate survival analysis.

atectomy (7 patients died). Among those 20 patients whose tumors were located in the distal pancreas, 6 cases were treated without pancreatectomy (3 patients died). The results indicated that patients without pancreatectomy, or with older age (≥ 60 years), higher Ki-67 index (≥ 10%) and grading (G2, G3), their OS was shorter. What's more, the degree of differentiation was also a predictor for prognosis (**Table 1**).

It is well known that NENs have marked blood supplies. Theoretically, blood-blocking therapy should be appropriate for treating NENs. Thus, we performed digital subtraction angiography (DSA) and enhanced CT scan to evaluate the blood supply status of the LM and then observed the outcome. Lesions were defined as abundant blood supply with higher density and enhancement in contrast to the normal liver parenchyma. We discovered that those patients with LM with abundant blood supply had significantly better outcomes ($P < 0.05$) (**Figure 3**). Interestingly, compared with the control group, those patients with more than 4-session treatment had better outcomes (**Table 1**). The multivariate survival analysis revealed that primary lesions resection was an independent predictor for the prognosis ($P = 0.007$, RR = 13.897, 95% CI: 2.043-94.530) (**Table 3**; **Figure 1**).

Discussion

It is ticklish to treat patients with pNENs with LM. Until now, studies focused on this topic are still not enough. The 5-year survival rate of those patients without any treatment is 20%-40% according to the existing researches [22, 23]. Lesions resection was the optimal choice for patients with pNENs with LM. It can remove the neoplasm, as well as offer symptomatic relief. However, most of these patients cannot be treated with a radical resection, and common therapeutic measures combined with liver direct and/or in-direct therapies were taken for those cases. But the best therapy strategy of combination is still unclear, which should be emphatically discussed. TACE is the common local-regional therapy for patients with hepatic lesions and chemo-drugs mixed with lipodol, which has been used for more than 20 years [24-26]. In our study, we aim to observe the efficacy of TACE with different conditions.

In this study, the response rate of those non-symptoms patients was 71.6% and the median OS was 48-month. Grading is one of the most important prognostic factors for NENs. Most studies concentrated on G1 or G2 patients, just a few studies focused on G3 patients who had a poor outcome with systemic chemotherapy [27, 28]. Totally, in our study, there were 5 cases of G1, 20 cases of G2 and 10 cases of G3 patients with LM with TACE. For G1/G2 patients, the response rate was 74.5% and the specific median OS cannot be calculated but was more than 50-month. The response rate was similar to the reported studies, however, the median OS of G1/G2 in this study was better than the reported data [29-31]. This would be attributed to the appropriate therapy strategy and the improvement of the technology of TACE. For G3 patients, the response rate was 50.0%, the median OS was 40-month and 5-year survival rate was 40.0%. Although the results of G3 group were inferior to the others ($P < 0.05$,

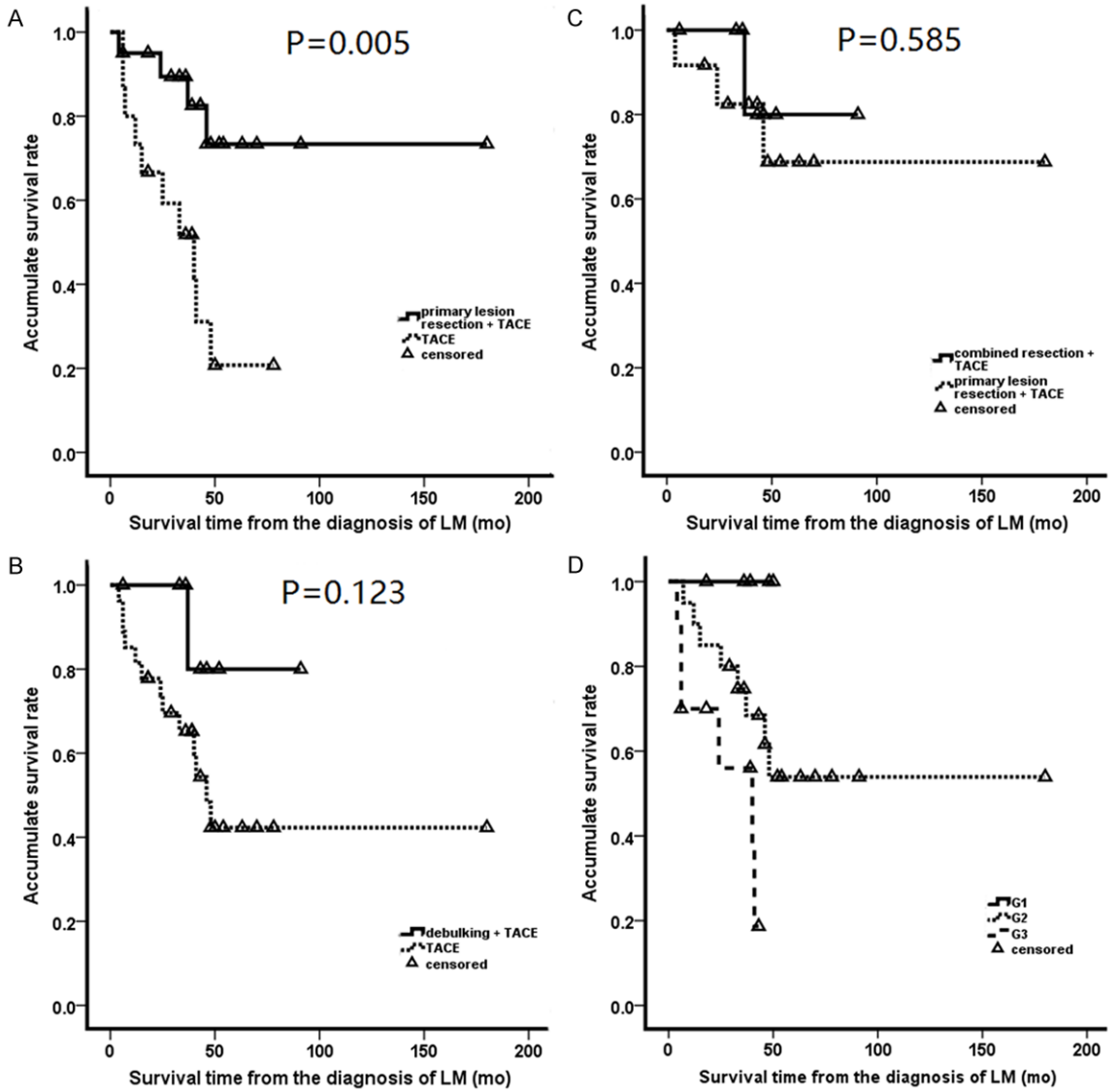

Figure 2. The accumulate survival rate of patients with pNENs with LM. A: The 5-year survival rate of patients with primary lesion resection was higher compared with those patients without primary lesion resection. (P = 0.005). B: The 5-year survival rate of patients with hepatic debulking was higher compared with patients without hepatic debulking. (P = 0.123). C: The 5-year survival rate of patients with combined resection (pancreatectomy + hepatectomy) was higher compared with patients with primary lesion resection. (P = 0.585). D: The overall survival rates of patients with pNENS with LM grading G1, G2, G3.

Table 1; **Figure 2**), it demonstrated that TACE still had a role in their survival. The heterogeneity exists in G3 pNENs. Those G3 patients could survive longer if other therapies combined with TACE were taken for them, but unfortunately, there were hardly new advances in this field. The 1-year and 5-year survival rates of those 35 patients were 85.5% and 50.0%, respectively. However, the 5-year survival rate of those who underwent TACE merely was significantly lower than those who were treated with TACE combined with pancreatic lesion resection (20.7% vs 73.4%, P = 0.005). Besides, univariate survival analysis demonstrated that patients with tumor located in the head of the pancreas had poorer outcomes compared with those with tumors located in the body-tail. Among those 15 patients whose primary lesions were in the proximal pancreas, 9 (60.0%) cases were dead, and 7 of those 9 cases did not underwent pancreatectomy. For the patients whose tumors located in the distal pan-

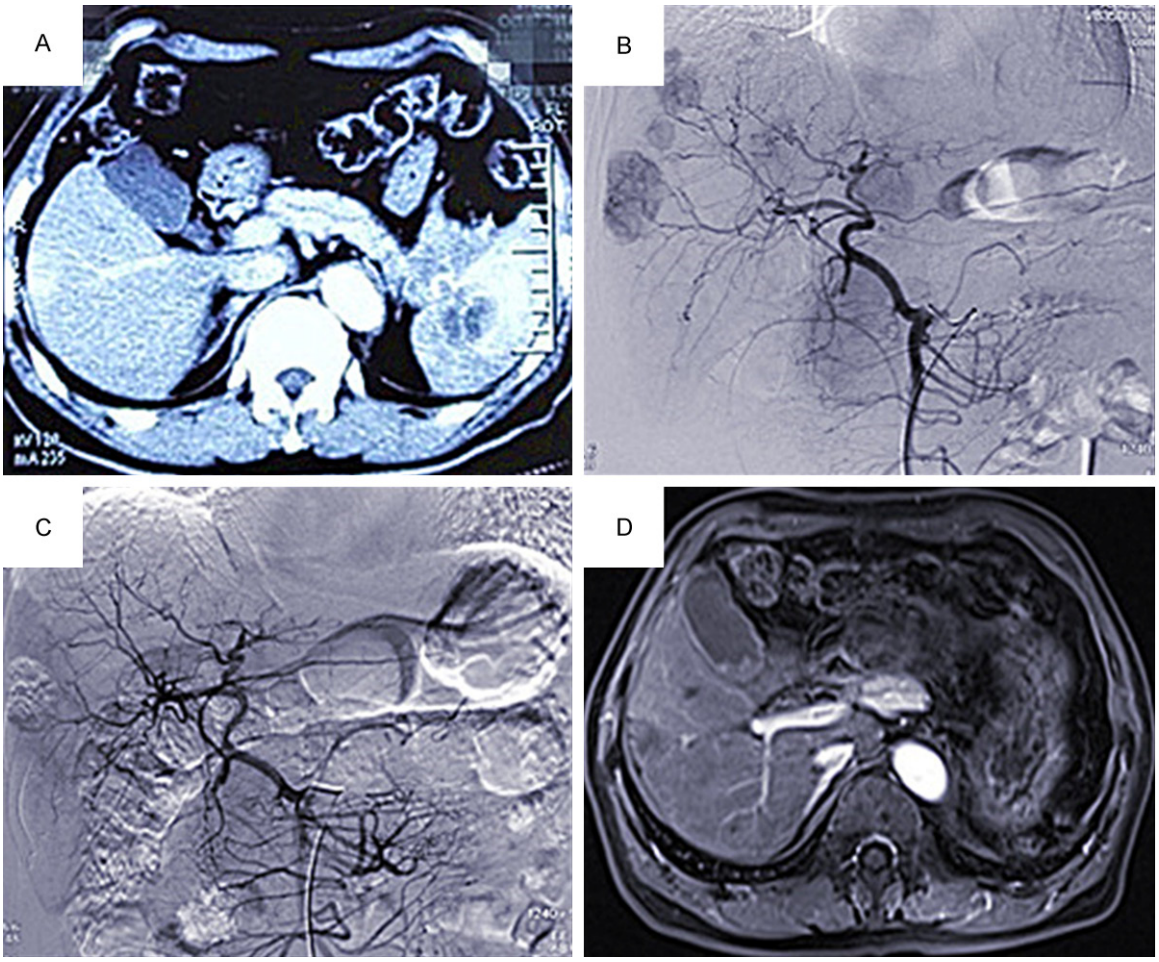

Figure 3. This was a male patient who had epigastric pain, 60-year-old, diagnosed as pNENs with multiple liver metastases grading G2 by abdominal enhanced CT and pathology analysis of the biopsy. sCgA = 453 ng/ml. Distal splenopancreatectomy, left hemicolectomy and hepatic debulking were operated two weeks later. A total of two-session TACE were performed in the next two months. A: Pre-surgery, CT showed the abundantly feeding neoplasms in the liver and distal pancreas. B: During the first session, the radiography showed hepatic abundantly vascular lesions. C: In the second session, DSA showed good lipiodol deposition and no staining on the lesions. D: After the two-session, enhanced MRI showed the shrinkage of target lesions. No enhanced signals existed in the remnants, sCgA = 53 ng/ml.

creas (20 patients), 6 cases were treated without pancreatectomy (among these 6 patients, 3 died). It was obvious that patients with LM can acquire more benefits when the primary lesions were removed. These results indicated that the resection of the primary lesions may decrease the relapse chance of the hepatic metastases.

Debulking was another way to treat those patients with pNENs with LM. In this study, 8 patients accepted debulking and pancreatectomy. The 5-year survival rate of those 8 patients was greater than the others (80.0% vs 42.3%) (P = 0.123). Besides, for patients treated with combined resection (pancreatectomy + hepatectomy), the 5-year survival rate was higher than those treated with primary lesion resection (80.0% vs 68.8%) (P = 0.585). There was no significant difference between these two groups in this study, but the analyzed data indicated that hepatectomy or hepatic debulking was still worth of performing. A further study enrolled more subjects is needed to support this view. Thus, we suggested that for patients with pNENs with LM, primary lesion resection was preferential considered, and if feasible, hepatectomy or debulking was also considered due to they could benefit from them.

Table 3. Multivariate survival analysis in COX proportional hazards model (5-year overall survival)

	Survival rate	*P* value	Relative risk (RR)	95% CI
Age				
< 60	62.5%	0.083	0.168	0.022-1.267
≥ 60	45.5%			
Primary Site (Pancreas)				
Head	40.0%	0.120	0.362	0.101-1.304
Body and tail	70.0%			
Primary lesion treatment				
Resection	75.0%	0.007	13.897	2.043-94.530
Without resection	33.3%			
KI67 index				
< 10%	85.7%	0.305	5.326	0.218-130.138
≥ 10%	38.1%			
Tumor Grading				
G1	100%			
G2	55.0%	0.787	1.313	0.181-9.515
G3	40.0%			
Differentiation				
Well	90.0%			
Intermediate	69.2%	0.569	1.724	0.264-11.246
Poor	16.7%			
LM Blood Supply				
Abundant	68.2%	0.609	1.402	0.383-5.1228
Poor	20.0%			
TACE Session				
< 4	47.6%	0.862	0.770	0.040-14.658
≥ 4	71.4%			

According to the univariate survival analysis, patients that had younger age (< 60 years), lower Ki-67 index (< 10%), grading G1/G2, well-differentiation neoplasms got better outcomes compared to others, which suggested that these factors could be the indexes for prognosis. Interestingly, we found that patients had better prognosis when they got more than 4-session of TACE. There are many confounding factors existed and it was difficult to be clarified. Besides, we divided those patients into two groups according to the images from DSA or contrast-enhanced CT/MRI and found that patients with abundantly feeding lesions had a long survival time than the control group without abundantly feeding lesions. Targeted drugs like sunitinib malate contribute to antiangiogenesis, but its role was limited [32]. Sunitinib malate could initiate many toxic reactions like hand-foot syndrome, thrombocytopenia, neutrocytopenia. These reactions have accumulative effects and are difficult to interfere unless cutting or withdrawing drugs. The median PFS was 17.5-month and the adverse reactions or complications were rare in this study. A multivariate survival analysis showed that there was no significant difference in clinical outcomes between patients with good pathological evidences (low Ki 67 index, low grading G1/G2) and poor pathological evidences. However, based on these data and our experience, TACE is more appropriate for treating patients with good pathological evidences and comprehensive therapies combined with direct or indirect therapies for treating liver should be advised and explored for patients with poor pathological evidence. Remarkably, there are some extremely probable optimistic factors for patients with non-synchronous LM or ≤ 20% of LM area/liver area. This needs to be proven by sponsoring a further study with more subjects.

Hepatic metastatic lesions of pNENs are easy to relapse [33-35]. Therefore, post-operative follow-up was performed. Imageology is often used but limited because of its restricted predictability and operability. Detecting Serum marker like carbohydrate antigen 199 (CA199) is convenient and helpful for pancreatic carcinoma patients but has no big value for pNENs. Chromogranin exists broadly in the chromaffin granules of neuroendocrine cells with well-differentiation and it could be a potential diagnostic and prognostic factor. A lot of studies indicated that serum Chromogranin A (sCgA) was a very useful predictor [36-38]. In our study, a total of 19 patients accepted sCgA detection (CIS Bio, normal range: 27-94 ng/ml). 4 cases had abnormal rising sCgA lever during their treatments. The progression or extensive metastases occured when the sCgA level was over

400 ng/ml (2 patients died). However, it is still controversial. Some researchers discovered that pNENs with low sCgA level may be progressive so that it could contribute to false diagnosis [39-41]. These disputes emphasized that using single marker for diagnosing pNENs would be inappropriate. Therefore, it is suggested that sCgA could be a routine monitor marker for patients with pNENs, especially for G1 or G2 patients. Meanwhile, other markers like CgB and NSE should be used to improve the veracity of diagnosis of pNENs [42].

Conclusion

Our results indicate that TACE is an effective treatment in patients with liver metastases of nonfunctional pNENs and primary lesion resection is an independent predictor for prognosis. For appropriate patients, active primary lesion resection was suggested, so the patients could acquire longer survival from TACE even without other measures. On account of this, it is a retrospective study with small sample, so some bias is inevitable.

Disclosure of conflict of interest

None.

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