Prediction Role of Baseline Digital Substraction Angiography in GEP Neuroendocrine Liver Metastases Treated with TAE/ TACE

Xiaofen Li（✉ lxf0827@163.com ）
  West China Hospital of Medicine, Sichuan University West China Hospital   https://orcid.org/0000-0002-1064-768X

Linjuan Li
  West China Hospital of Medicine: Sichuan University West China Hospital

Jin Pu
  West China Hospital of Medicine: Sichuan University West China Hospital

Jiaojiao Suo
  West China Hospital of Medicine: Sichuan University West China Hospital

Xuefeng Luo
  West China Hospital of Medicine: Sichuan University West China Hospital

Xin You
  West China Hospital of Medicine: Sichuan University West China Hospital

Zhengyin Liao
  West China Hospital of Medicine: Sichuan University West China Hospital

Dan Cao
  West China Hospital of Medicine: Sichuan University West China Hospital   https://orcid.org/0000-0003-2180-0464

Research Article

Abstract

Aim

Transarterial embolization (TAE) or transarterial chemoembolization (TACE) is an important treatment approach for unresectable liver metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The prediction tool for therapeutic evaluation is still unclear. This study was performed to assess the prediction role of baseline digital substraction angiography (DSA) in synchronous liver metastatic GEP-NETs treated with TAE/ TACE.

Methods

Twenty-two patients with synchronous unresectable liver metastatic GEP-NETs (G1/2) and treated with TAE/ TACE were retrospectively enrolled. Clinical characteristics, baseline DSA and computed tomography (CT) information were collected.

Results

Totally, the overall response rate of TAE/ TACE on liver metastasis was 45.5%. The average baseline CT ratio (the density of the target lesion / the density of abdominal aorta during arterial phase) between responsive group and nonresponsive group were not statistically different (0.30±0.06 versus 0.36±0.11, P=0.149). Whereas, the average baseline DSA ratio (the density of target lesion / the density of liver background on DSA imaging before TAE/ TACE) of responsive group was significantly lower compared with that of nonresponsive group (0.57±0.13 versus 0.70±0.15, P=0.037). Patients with a DSA ratio ≤0.64 were more responsive to TAE/ TACE than those with a DSA ratio ⏽0.64 (58.3% versus 30%). Univariate and multivariate analysis indicated that patients with lower hepatic tumor burden had longer PFS.

Conclusions

Baseline DSA ratio is a simple and potentially useful method to predict therapeutic effect of TAE/ TACE in liver metastases from GEP-NETs. And patients with lower hepatic tumor burden might indicate better prognosis. Prospective large-scale study is warranted.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare and heterogeneous neoplasms originating from the diffuse neuroendocrine system of the gastrointestinal tract and pancreas. It is reported that the incidence rate of GEP-NETs has been rising in the last decades[1]. According to statistics from the Surveillance, Epidemiology, and End Results (SEER) program, the current annual age-adjusted incidence of GEP-NETs is estimated to be 3.56 per 100,000 persons in the United States[2]. Despite the

indolent rate of tumor growth, over 20% NET patients present with distant metastasis at initial diagnosis, with liver the most common metastatic site[3].

According to current statistics, liver metastases occur in more than half of patients with GEP-NETs[4]. Current treatment approaches for management of liver metastatic GEP-NETs include surgery, somatostatin analogues, systemic chemotherapy, targeted drugs and intervention therapy. For patients with diffuse and bilobar liver metastases, transarterial embolization (TAE) or transarterial chemoembolization (TACE) is an important and appropriate treatment option to relieve symptoms and improve survival outcome, as suggested in several related guidelines[4, 5].

Previous studies have suggested that patients with severe symptoms, lower liver tumor burden on imaging examinations or lower level of serum pancreastatin may potentially benefit from TAE/ TACE[6–9]. However, the prediction tool for therapeutic evaluation of TAE/ TACE is still unclear and optimal candidates for this procedure remain undetermined. The aim of this study was to assess the prediction role of baseline digital substraction angiography (DSA) in synchronous liver metastatic GEP-NETs patients who underwent TAE/ TACE procedures.

Materials And Methods

Patient Selection

The West China Hospital of Medicine, Sichuan University Ethic Committee for Clinical Investigation approved this study. And all methods were performed in compliance with the relevant guidelines and regulations. Medical information of patients diagnosed with synchronous liver metastatic GEP-NETs from January 1, 2016 to July 31, 2020 were reviewed retrospectively. Patients who met the following criteria were enrolled: 1) histologically confirmed GEP-NET; 2) clinically or pathologically diagnosed with synchronous liver metastasis between January 1, 2016 and July 31, 2020; 3) unresectable liver metastasis; 4) good performance status with an Eastern Cooperative Oncology Group (ECOG) score of < 2 (on a scale of 0 to 5, with a higher score indicating poorer performance status); 5) received TAE/ TACE procedure during disease process; 6) adequate clinical data.

Collected information included patient demographics, symptoms, hormonal functionality, tumor grade, TNM stage, baseline DSA ratio, baseline computed tomography (CT) ratio, liver specific tumor response, systemic therapy, and serum tumor marker (CEA and NSE) levels. In this study, liver specific tumor response was defined as radiographic response of liver metastases to treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[10]. Baseline DSA ratio was defined as the density of the largest target lesion on DSA imaging (hounsfield unit, HU)/ the density of liver background (HU) before TAE/ TACE, and CT ratio meant the baseline density of the largest target lesion on CT imaging （HU）/ the density of abdominal aorta (HU) during arterial phase. When the tumor grades between primary and metastatic tumors were different, the higher grade were taken and recorded.

Statistical Analysis

Quantitative data were compared by Student's t test and categorical data by Chi-square test. Statistical tests were two sided and P < 0.05 was considered statistically significant. All analyses were performed using SPSS Statistics 22.0 (IBM, Armonk, NY, USA).

Results

Patient characteristics

In total, 22 patients with unresectable liver metastatic GEP-NETs were enrolled. Table 1 listed patents' clinical and pathological characteristics. The mean age at diagnosis was 49.3±9.8 years (95% confidence interval (CI): 44.9-53.6 years). More than half of the patients (68.2%) were females. All of the patients were in good performance status with ECOG scores 0~1. The vast majority of primary tumors were located in pancreas (86.4%, 19/22) and non-functional (91.0%, 20/22). Most of patients (81.8%) presented with G2, while 13.6% with G3 and 4.5% with G1. The mean largest diameter of liver metastases before TAE/ TACE was 6.3±4.7 cm (95% CI: 3.8-7.5 cm). Most patients presented with elevated serum NSE (59.1%) and normal serum CEA (86.4%) before TACE.

Table 1
Baseline characteristics of patients with liver metastatic GEP-NETs

Variables	Patients		
		Number	%
Age (Year)		49.3±9.8[#]	-
Gender			
	Male	7	31.8
	Female	15	68.2
ECOG score			
	0	12	54.5
	1	10	45.5
Primary tumor location			
	Pancreas	19	86.4
	Duodenum	1	4.5
	Rectum	2	9.0
Tumor grade			
	G1	1	4.5
	G2	18	81.8
	G3	3	13.6
Hormonal functionality			
	Yes	2	9.0
	No	20	91.0
Hepatic tumor burden			
	<50%	11	50.0
	≥50%	11	50.0
Serum NSE			
	Normal	9	40.9

Note: [#]Data are mean ± standard deviation. Abbreviations: GEP-NETs, gastroenteropancreatic neuroendocrine tumors; ECOG, Eastern Cooperative Oncology Group; NSE, neuron specific enolase; CEA, carcinoma embryonic antigen

Variables		Patients	
	Elevated	13	59.1
Serum CEA			
	Normal	19	86.4
	Elevated	3	13.6
Extrahepatic metastases			
	Present	5	22.7
	Absent	17	77.3
Primary tumor resection			
	Yes	9	40.9
	No	13	59.1
Somatostatin analogues treatment			
	Yes	16	72.7
	No	6	27.3
Targeted agents treatment			
	Yes	5	22.7
	No	17	77.3
Systemic chemotherapy			
	No	16	72.7
	Yes	6	27.3
Total		22	100

Note: #Data are mean ± standard deviation. Abbreviations: GEP-NETs, gastroenteropancreatic neuroendocrine tumors; ECOG, Eastern Cooperative Oncology Group; NSE, neuron specific enolase; CEA, carcinoma embryonic antigen

Treatment

All patients underwent TAE/ TACE procedure after assessment of oncologists and interventional radiologists. During TACE procedure, with the help of DSA examination, hepatic artery was selected using a 5 French catheter through femoral arterial access. Next, tumor-feeding vessels were super-selected and infused with a mixture of iodized oil (10–20 mL) and cytotoxic agents (fluorouracil 1000 mg and doxorubicin 50 mg). Then embolization was performed using gelatin sponge particles to complete blood

flow stagnation. TAE procedure was similar to TACE, but without administration of iodized oil or cytotoxic agents, and completed by occlusion of the hepatic artery branch with polyvinyl alcohol particles.

As systemic therapy, 16 (72.7%) patients received somatostatin analogues, 5 patients were prescribed with targeted agents, and 6 patients received chemotherapy. Table 2 listed all the patients' systemic treatment agents.

Table 2
Systemic treatment of all the patients

Patients	Systemic treatment		
	Somatostatin analogues	Targeted agents	Systemic chemotherapy
No. 1	Octreotide LAR	Bevacizumab	Capecitabine+ temozolomide
No. 2	Octreotide LAR		
No. 3	Octreotide LAR		
No. 4	Octreotide LAR		
No. 5		Sunitinib	
No. 6	Lanreotide		
No. 7	Octreotide LAR		
No. 8	Octreotide LAR		
No. 9	Octreotide LAR		Capecitabine+ temozolomide
No. 10	Octreotide LAR		
No. 11	Octreotide LAR	Sunitinib	
No. 12	Octreotide LAR		
No. 13			Temozolomide
No. 14	Octreotide LAR		Capecitabine+ oxaliplatin
No. 15	Octreotide LAR		
No. 16	Octreotide LAR	Bevacizumab	Capecitabine+ temozolomide
No. 17			Capecitabine+ temozolomide
No. 18	Lanreotide		
No. 19	Lanreotide		
No. 20		Sunitinib	
No. 21	Octreotide LAR		
No. 22	Octreotide LAR		
Abbreviations: No., number; Octreotide LAR, octreotide long-acting repeatable			

Baseline Dsa Prediction Role In Therapeutic Evaluation

Therapeutic response was evaluated by abdominal computerized tomography (CT) or magnetic resonance imaging (MRI) at 2- to 3-month intervals according to RECIST 1.1 criteria. The largest target liver lesion of every patient was selected for therapeutic evaluation. The liver specific overall response rate (ORR) was 45.5% (10/22), with 10 patients evaluated as partial response (PR) and 0 complete response (CR). Figure 1 showed the best diameter change of target liver lesions from baseline. Among all the patients, the liver specific median progression free survival (PFS) was 17.5 months (95% CI 4.8-30.2 months), and overall survival (OS) were not reached (Figure 2). Kaplan-Meier analysis showed that patients with lower hepatic tumor burden (<50%) had significant longer PFS than higher hepatic tumor burden (≥50%) (62.2 vs 13.3months, P=0.030, Figure 2c). Other groups stratified by CT ratio, DSA ratio, age, sex, or NSE level showed no significant differences in PFS (Figure 2), which might be partly attributed to small sample size. Multivariate COX regression analysis revealed that hepatic tumor burden was an independent prognostic factor for PFS (Table 3).

Table 3
Univariate and multivariate analysis of all the patients

Variables	Univariate analysis		Multivariate analysis	
	mPFS (95%CI) [#]	P	HR (95%CI)	P
Hepatic tumor burden				
<50%	62.2(NA)	0.030	0.177(0.035-0.889)	0.035
≥50%	13.3(5.9-20.8)		1(Reference)	
CT ratio				
≤0.34	25.2(3.2-47.2)	0.096	0.220(0.036-1.325)	0.098
>0.34	11.0(3.9-18.1)		1(Reference)	
DSA ratio				
≤0.64	17.5(10.4-24.6)	0.825	0.296(0.040-2.192)	0.233
>0.64	13.3(0-31.7)		1(Reference)	
Age				
<49.3	17.5(1.8-33.2)	0.925	0.621(0.121-3.199)	0.569
≥49.3	13.3(9.8-16.8)		1(Reference)	
Sex				
Male	17.5(1.7-33.3)	0.179	2.513(0.459-13.749)	0.288
Female	29.9(10.3-49.5)		1(Reference)	
Note: [#]In months. Abbreviations: mPFS, median progression free survival time; HR, hazard ratio; CI, confidence interval				

The average baseline DSA ratio of the largest target lesion (the density of the target lesion on DSA imaging / the density of liver background before TAE/ TACE) was 0.64±0.15. And the average baseline DSA ratio in responsive group was significantly lower compared with that in nonresponsive group (0.57±0.13 versus 0.70±0.15, P=0.037, Figure 3a). Furthermore, patients with a DSA ratio ≤0.64 were more responsive to TAE/ TACE than those with a DSA ratio ≥0.64 (58.3% versus 30%), but the P value was greater than 0.05 probably due to small sample size. Figure 3b showed therapeutic evaluation in patients with a low DSA ratio (≤0.64) and a high DSA ratio (≥0.64). Figure 4a~c and 4d~f were representative images of patients with high and low DSA ratios. Meanwhile, we also assessed the role of baseline CT ratio of the largest target lesion (the density of the target lesion on CT imaging / the density of abdominal aorta during arterial phase) in therapeutic evaluation. The results showed that among all the patients, the average baseline CT ratio was 0.34±0.09. The CT ratios between responsive group and nonresponsive group were not statistically different (0.30±0.06 versus 0.36±0.11, P=0.149, Figure 3b).

Discussion

In this study, we summarized the characteristics and therapeutic response of patients with unresectable liver metastatic GEP-NETs treated with TAE/ TACE. We found that baseline DSA ratio of the target lesion could predict treatment response usefully. And patients with lower hepatic tumor burden might indicate better prognosis. To the best of our knowledge, this is the first study investigating the association between baseline DSA features and therapeutic response to TAE/ TACE.

Several studies investigated characteristics and survival outcome of patients with neuroendocrine liver metastases treated with TAE/ TACE[6–9, 11–13]. The hepatic ORR after TAE/ TACE procedure was reported to be 20-40%, which was in accordance in our study. In the study conducted by Dhir M. et al, age, grade, liver tumor burden, and serum chromogranin A level were independent prognostic factors for overall survival in neuroendocrine tumor liver metastases received TACE[11]. The study performed by Luo Y. et al showed that baseline MRI parameters (tumor volume and arterial enhancement) could act as independent prognostic factors for survival in patients with neuroendocrine liver metastases treated with TACE[8]. However, these studies only determined factors associated with survival outcome, not with response to TACE.

DSA is generously applied in TAE/ TACE procedure and a direct method to determine tumor vascularity. In hepatocellular carcinoma (HCC), the baseline characteristics of DSA imaging could potentially predict tumor response to TAE/ TACE[14–16]. The study conducted by Wang E. et al showed that hypervascular lesions on DSA imaging responded better than hypovascular ones (ORR: 68.2% vs. 25.6%, P < 0.001). Lesions with certain imaging features such as staining obviously, dilated and tortuous vessels, clear boundary, and et al. were defined as hypervascular lesions[15]. But this method greatly depended on the professional level of radiologists and consequently had low consistency. In our study, we used a quantitative data (DSA ratio) to measure tumor vascularity and evaluate response, which was simple and accurately measurable. Even doctors not majored in radiology could easily learn and master this new method.

Some limitations exist in our study. First, selection bias is inevitable due to the retrospective nature. Second, for the rarity of liver metastatic GEP-NETs, the sample size of our study is very small. We are making our effort to collecting more cases in the future.

Conclusions

In conclusion, baseline DSA ratio of the largest target lesion is a simple and potentially useful approach to predict therapeutic effect of TAE/ TACE in liver metastases from GEP-NETs. In addition, patients with lower hepatic tumor burden might indicate better prognosis. Large prospective study is warranted to confirm this.

Abbreviations

TAE, transarterial embolization; TACE, transarterial chemoembolization; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; DSA, digital substraction angiography; ORR, overall response rate; CI, confidence interval; NSE, neuron specific enolase; CEA, carcinoma embryonic antigen; PFS, progression free survival; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; SEER, Surveillance, Epidemiology, and End Results program; HU, hounsfield unit; CT, computerized tomography; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; PR, partial response; CR, complete response

Declarations

Conflicts of interest

The authors declare no conflict of interest.

Ethics approval

This study was approved by the West China Hospital, Sichuan University Ethic Committee for Clinical Investigation.

Consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from all patients at the time of admission as a routine practice at West China Hospital, Sichuan University.

Availability of data and material

The data used to support the findings of this study are available from the corresponding author upon request.

Code availability

Not applicable.

Authors' contributions

Li X and Cao D conceived of and designed the study. Li X, Luo X, You X and Liao Z performed the analyses. Li X, Li L, Pu J and Suo J prepared tables and figures. Li X and Li L wrote the main manuscript. All authors approved to the submission.

References

1. M. Cives, J.R. Strosberg, Gastroenteropancreatic Neuroendocrine Tumors. CA Cancer J. Clin. **68**(6), 471–487 (2018)

2. A. Dasari et al., Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol **3**(10), 1335–1342 (2017)

3. M. Riihimaki et al., The epidemiology of metastases in neuroendocrine tumors. Int J Cancer **139**(12), 2679–2686 (2016)

4. M. Pavel et al., ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology **95**(2), 157–176 (2012)

5. A. Frilling et al., Recommendations for management of patients with neuroendocrine liver metastases. The Lancet Oncology **15**(1), e8–e21 (2014)

6. S. Gupta et al., Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer **104**(8), 1590–1602 (2005)

7. D. Strosberg et al., Prognostic Impact of Serum Pancreastatin Following Chemoembolization for Neuroendocrine Tumors. Ann Surg Oncol **25**(12), 3613–3620 (2018)

8. Y. Luo et al., Prognostic value of baseline volumetric multiparametric MR imaging in neuroendocrine liver metastases treated with transarterial chemoembolization. Eur Radiol **29**(10), 5160–5171 (2019)

9. Y. Luo et al., Semi-quantitative visual assessment of hepatic tumor burden can reliably predict survival in neuroendocrine liver metastases treated with transarterial chemoembolization. Eur Radiol **29**(11), 5804–5812 (2019)

10. E.A. Eisenhauer et al., New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer **45**(2), 228–247 (2009)

11. M. Dhir et al., Initial Treatment of Unresectable Neuroendocrine Tumor Liver Metastases with Transarterial Chemoembolization using Streptozotocin: A 20-Year Experience. Ann. Surg. Oncol.

24(2), 450–459 (2016)

12. S. Grozinsky-Glasberg et al., Hepatic intra-arterial therapies in metastatic neuroendocrine tumors: lessons from clinical practice. Endocrine **60**(3), 499–509 (2018)

13. M. Pericleous et al., Hepatic artery embolization in advanced neuroendocrine tumors: Efficacy and long-term outcomes. Asia Pac J Clin Oncol **12**(1), 61–69 (2016)

14. J.P. Miller, R. Ramaswamy, O. Akinwande, Using principal component analysis for the prediction of tumor response to transarterial chemoembolization. Abdominal Radiology **44**(7), 2594–2601 (2019)

15. E. Wang et al., *Tumor Hypervascularity and hand-foot-skin reaction predict better outcomes in combination treatment of TACE and Sorafenib for intermediate hepatocellular carcinoma.* BMC Cancer, 2019. 19(1)

16. G. Vesselle et al., Predictive factors for complete response of chemoembolization with drug-eluting beads (DEB-TACE) for hepatocellular carcinoma. Eur Radiol **26**(6), 1640–1648 (2016)
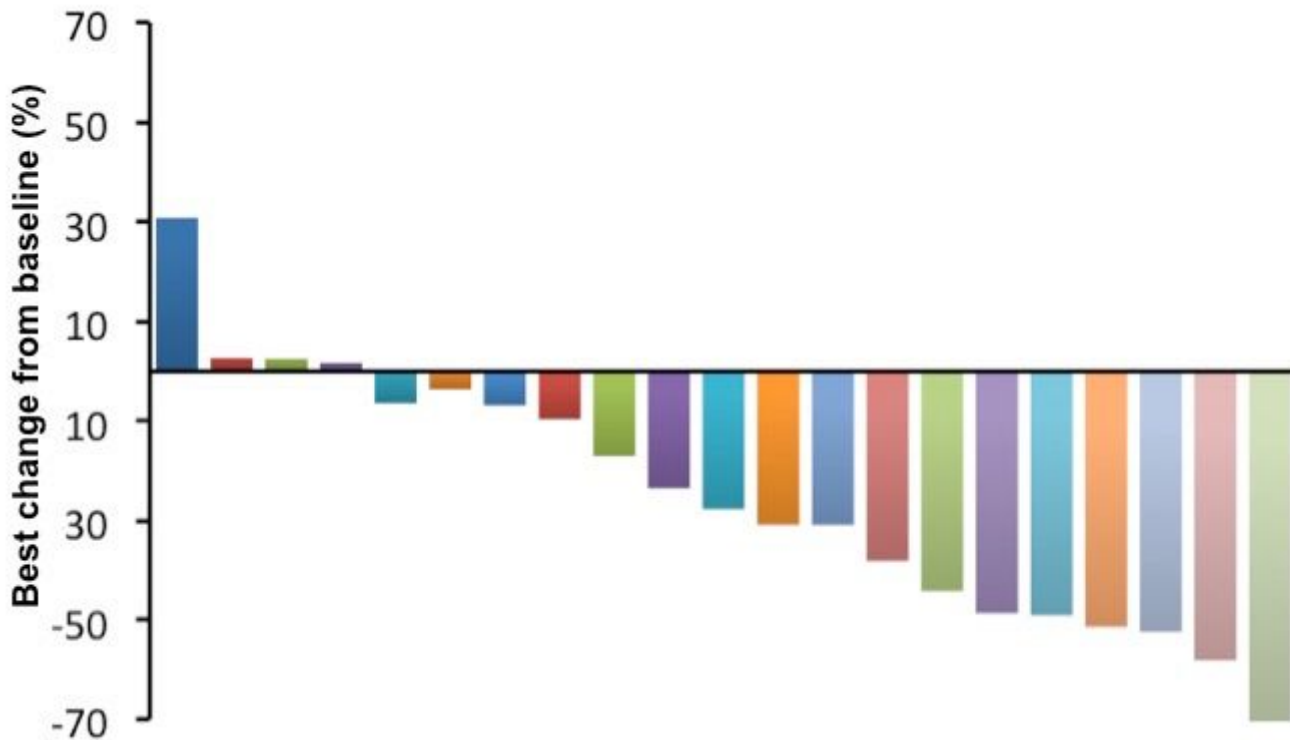
Figures

Figure 1

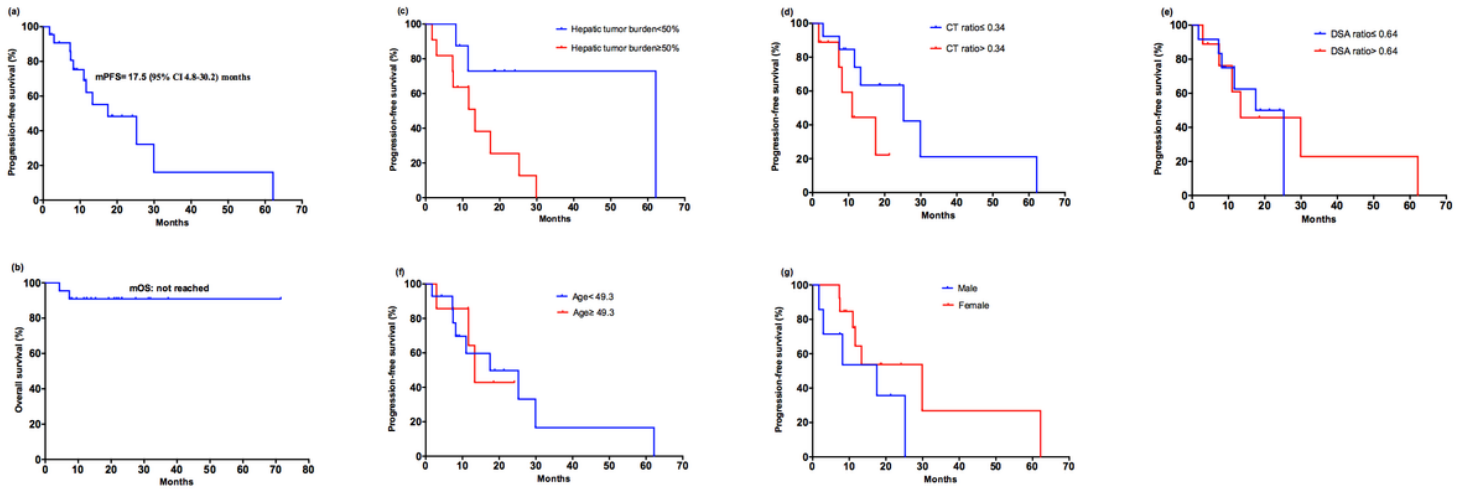The best diameter change of target liver lesions from baseline (overall response rate=45.5%).

Figure 2

Progression free survival and overall survival curves. (a) Progression free survival of all the patients: 17.5months (95% CI 4.8-30.2 months); (b) Overall survival of all the patients: not reached; (c) Progression free survival stratified by hepatic tumor burden (hepatic tumor burden< 50% vs. ≥50%: 62.2 vs 13.3months, P=0.030); (d) Progression free survival stratified by CT ratio (CT ratio≤0.34 vs. >0.34: 25.2 vs 11.0months, P=0.096); (e) Progression free survival stratified by DSA ratio (DSA ratio≤0.64 vs. >0.64: 17.5 vs 13.3months, P=0.825); (f) Progression free survival stratified by age (age < 49.3 vs. ≥49.3: 17.5 vs 13.3months, P=0.925); (g) Progression free survival stratified by sex (male vs. female: 17.5 vs 29.9months, P=0.179); (h) Progression free survival stratified by serum NSE level (normal vs. elevated: 11.1 vs 25.2months, P=0.289).
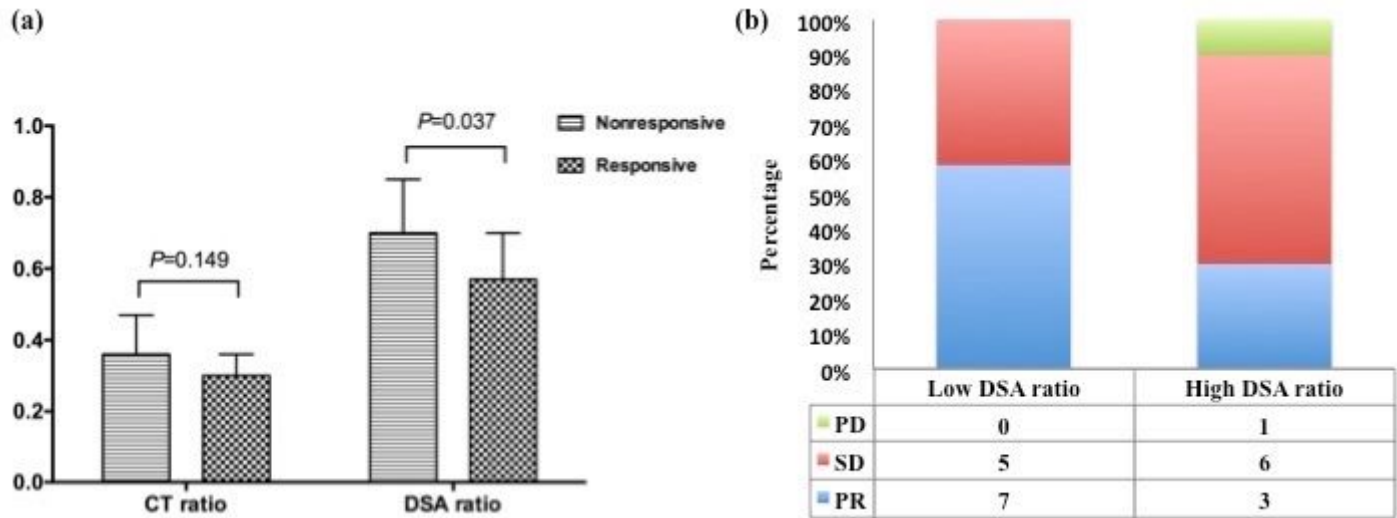

Figure 3

(a) Average CT and DSA ratios in responsive and nonresponsive groups (CT ratio: 0.30±0.06 vs. 0.36±0.11, P=0.149; DSA ratio: 0.57±0.13 vs. 0.70±0.15, P=0.037). (b) Hepatic response in low and high DSA ratio groups.
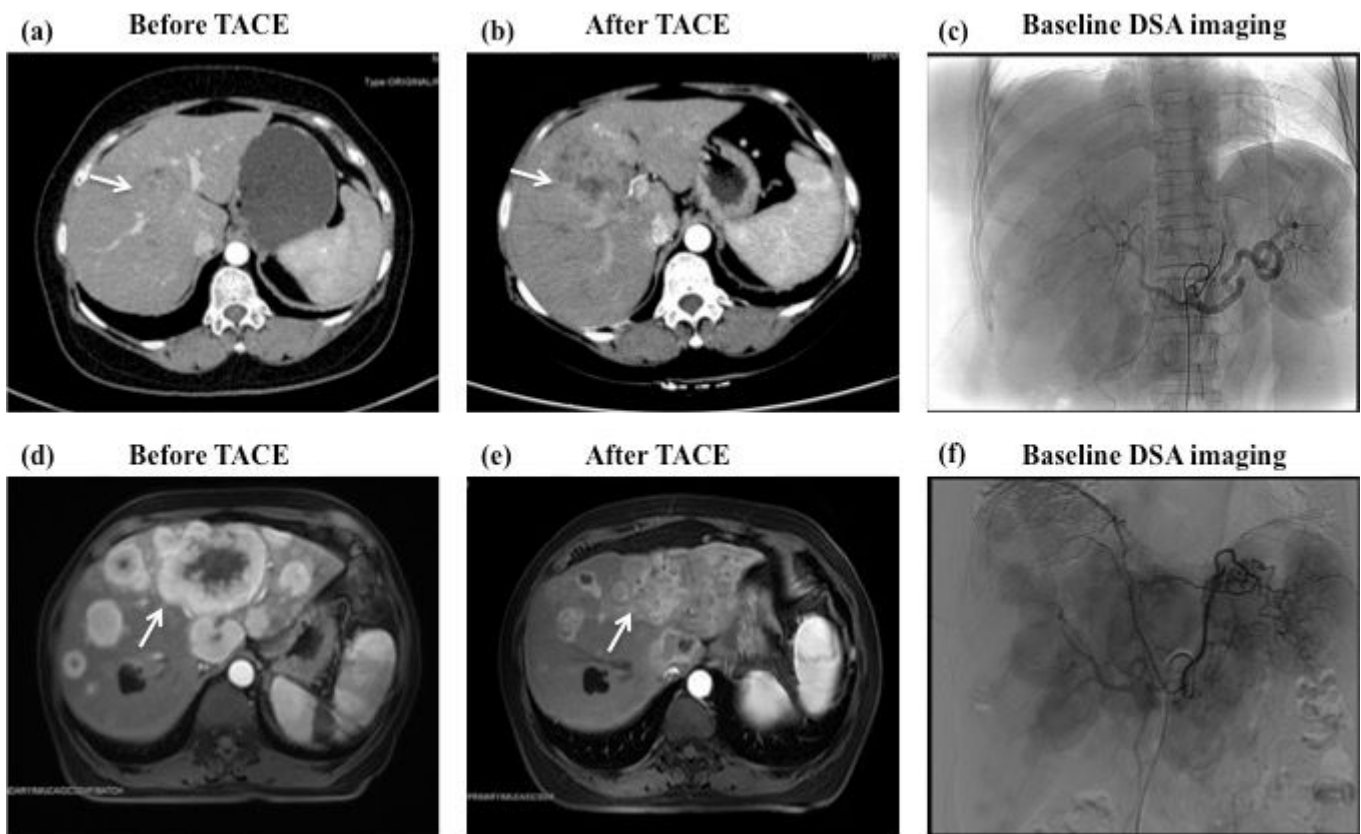
Figure 4

Representative images of patients with high and low DSA ratios. (a) Representative images of a patient evaluated as progressive disease (DSA ratio=0.92); (b) Representative images of a patient evaluated as partial response (DSA ratio=0.33).