Title

Efficacy of TACE in TIPS patients: comparison of treatment response to chemoembolization for hepatocellular carcinoma in patients with and without a transjugular intrahepatic portosystemic shunt.

Journal

Cardiovascular radiology, 36(5)

Authors

Tong, Ricky
Kuo, Yuo-Chen
Fidelman, Nicholas
et al.

Publication Date

2013-10-01

DOI

10.1007/s00270-013-0698-8

Peer reviewed

Published in final edited form as:
Cardiovasc Intervent Radiol. 2013 October ; 36(5): . doi:10.1007/s00270-013-0698-8.

Efficacy of TACE in TIPS Patients: Comparison of Treatment Response to Chemoembolization for Hepatocellular Carcinoma in Patients With and Without a Transjugular Intrahepatic Portosystemic Shunt

Yuo-Chen Kuo, **Maureen P. Kohi**, **David M. Naeger**, **Ricky T. Tong**, **K. Pallav Kolli**, **Andrew G. Taylor**, **Jeanne M. Laberge**, **Robert K. Kerlan Jr.**, and **Nicholas Fidelman**
Department of Radiology and Biomedical Imaging, University of California San Francisco, 505 Parnassus Avenue, Room M-361, San Francisco, CA 94143, USA

Yuo-Chen Kuo: yuo-chen.kuo@ucsf.edu; Maureen P. Kohi: maureen.kohi@ucsf.edu; David M. Naeger: david.naeger@ucsf.edu; Ricky T. Tong: ricky.tong@ucsf.edu; K. Pallav Kolli: kanti.kolli@ucsf.edu; Andrew G. Taylor: andrew.taylor@ucsf.edu; Jeanne M. Laberge: jeanne.laberge@ucsf.edu; Robert K. Kerlan: robert.kerlan@ucsf.edu; Nicholas Fidelman: nicholas.fidelman@ucsf.edu

Abstract

Purpose—To compare treatment response after transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) in patients with and without a transjugular intrahepatic portosystemic shunt (TIPS).

Materials and Methods—A retrospective review of patients who underwent conventional TACE for HCC between January 2005 and December 2009 identified 10 patients with patent TIPS. From the same time period, 23 patients without TIPS were selected to control for comparable Model for End-Stage Liver Disease and Child–Pugh–Turcotte scores. The two groups showed similar distribution of Barcelona Clinic Liver Cancer and United Network of Organ Sharing stages. Target HCC lesions were evaluated according to the modified response evaluation criteria in solid tumors (mRECIST) guidelines. Transplantation rate, time to tumor progression, and overall survival (OS) were documented.

Results—After TACE, the rate of complete response was significantly greater in non-TIPS patients compared with TIPS patients (74 vs. 30 %, $p = 0.03$). Objective response rate (complete and partial response) trended greater in the non-TIPS group (83 vs. 50 %, $p = 0.09$). The liver transplantation rate was 80 and 74 % in the TIPS and non-TIPS groups, respectively ($p = 1.0$). Time to tumor progression was similar ($p = 0.47$) between the two groups. OS favored the non-TIPS group ($p = 0.01$) when censored for liver transplantation.

Conclusion—TACE is less effective in achieving complete or partial response using mRECIST criteria in TIPS patients compared with those without a TIPS. Nevertheless, similar clinical outcomes may be achieved, particularly in TIPS patients who are liver-transplantation candidates.

Keywords

Interventional oncology; Transjugular intrahepatic portosystemic shunt; Transarterial chemoembolization; Hepatocellular carcinoma

Correspondence to: Yuo-Chen Kuo, yuo-chen.kuo@ucsf.edu.

Conflict of interest The authors have no conflict of interest.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide [1]. Surgical resection and liver transplantation are potentially curative therapies for early stage HCC [2, 3]. However, only a minority of patients who present with early stage HCC are candidates for such surgical treatments [4]. Therefore, liver-directed therapies, such as transarterial chemoembolization (TACE), have emerged as a means to bridge or downstage patients to surgery [5–7] or offer palliation [8].

Transjugular intrahepatic portosystemic shunt (TIPS) placement is a common treatment for complications of portal hypertension, including variceal bleeding and refractory ascites [9]. Moreover, portal hypertension by itself may be associated with an increased risk for HCC independent of liver cirrhosis [10, 11]. Patients with a TIPS who subsequently develop HCC are not ideal candidates for TACE because portosystemic shunting alters the dual blood supply to the liver, which is advantageous for TACE therapy [12].

Little has been reported about TACE in HCC patients who have a functional TIPS [13–15]. The purpose of this study was to compare the imaging response after TACE in patients with and without TIPS. With decreased portal venous perfusion in TIPS patients, it may be hypothesized that TACE in TIPS patients may result in increased tissue ischemia and necrosis. Conversely, TIPS placement has been found to result in liver arterioportal shunting [16], which may decrease TACE's efficacy.

Materials and Methods

Patients

The study was approved by the Committee on Human Research of the Institutional Review Board at our institution. Informed consent waiver was obtained. A retrospective review of records from January 2005 to December 2009 at our institution identified 10 consecutive patients who received a TIPS at the time of undergoing TACE for HCC. Seven patients had undergone TIPS placement at a different institution. Three patients underwent a TIPS procedure at our institution in the previously described manner [17]. Stent patency was confirmed by abdominal Doppler sonogram performed within 6 months before TACE. In all TIPS patients, vascular flow was demonstrated throughout the stent with mid-stent Doppler velocities >60 cm/s [18, 19].

For the control population, 23 patients without TIPS who underwent TACE for HCC during the same 5-year time period were included in this study. Patients were selected based on similar Child–Pugh–Turcotte (CPT) and calculated Model for End-Stage Liver Disease (MELD) scores. Patient characteristics are listed in Table 1.

Every patient in the study had a diagnosis of HCC, which was based on European Association for the Study of the Liver guidelines [20]. All patients underwent a first TACE therapy for the target lesion at our institution and had a patent portal vein on pre-TACE cross-sectional imaging. One patient in the TIPS group had a previous TACE placed at an outside institution. Patients who underwent surgical resection, liver transplantation, or other liver-directed therapies to the target lesions before post-TACE follow-up imaging study were excluded. Patients without imaging before or after TACE were also excluded.

TACE

TACE was performed with a combination of doxorubicin hydrochloride (25 mg), mitomycin C (10 mg), and cisplatin (50 mg) administered in a 1:1 emulsion with ethiodized oil

(Ethiodol; Laboratoires Guerbet, Roissy, France). The aqueous component for the emulsion was Omnipaque-350 iodinated contrast agent (Amersham Pharmacia Biotech, Piscataway, NJ). The TACE regimen was similar for patients with and without TIPS. For patients with serum total bilirubin levels >3.0 mg/dL, the dose of doxorubicin was decreased by half (12.5 mg); this included 2 patients (20 %) in the TIPS group. Mitomycin C was withheld for patients with white blood cell count < 3,000/μL and/or platelet count < 60,000/μL (2 patients [20 %] in the TIPS group and 7 patients [30 %] in the non-TIPS group). Cisplatin was not administered to 2 patients (20 %) in the TIPS group and 6 patients (26 %) in the non-TIPS group who had a serum creatinine level >1.2 mg/dL.

Chemoembolization was performed in a selective fashion using a 3F microcatheter (Renegade HI-FLO; Boston Scientific, Natick, MA) coaxially placed into a second- or third-order branch off the right or left hepatic artery in close proximity to the target lesions. The end point of the embolization was defined as stasis of flow in the targeted second- or third-order branches of the selected hepatic artery. In case of residual arterial flow at the completion of drug delivery, flow stasis was achieved by injecting a slurry of gelatin sponge (Gelfoam; Pharmacia and Upjohn, Kalamazoo, MI).

Evaluation of Treatment Response

All patients underwent baseline multiphase, contrast-enhanced abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) a median of 34 days (range 1–151) before the TACE session. There were 12 target lesions in the TIPS group (2 of the 10 patients had 2 target lesions each) and there were 26 target lesions in the non-TIPS group (3 of the 23 patients had 2 target lesions each). All target lesions were hypervascular on the arterial phase of imaging and showed washout on the delayed phase. Tumor staging was based on the Barcelona Clinic Liver Cancer (BCLC) [21] and United Network of Organ Sharing (UNOS) TNM classifications.

All patients underwent multiphase, contrast-enhanced CT or MRI a median of 35 days (range 19–84) after TACE. Imaging treatment response was assessed in both groups after a single TACE session. Targeted HCC lesions were evaluated by the unidimensional modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines [22]. At baseline, the enhancing component of each target lesion had to be >1 cm in size by greatest single dimension to qualify as a measurable target lesion. Based on mRECIST, treatment response of the target lesion or lesions was defined by measurement of the single greatest dimension or sum of the greatest dimensions for multiple lesions and were classified as follows: complete response (CR) was disappearance of any intratumoral enhancement; partial response (PR) was at least 30 % decrease in the sum of enhancement dimension; progressive disease (PD) was at least 20 % increase in the sum of enhancement dimension; and stable disease (SD) was any response that does not qualify as PD or PR. Treatment responses were defined by a per-patient basis as opposed to per–target lesion basis. Based on mRECIST, tumor regions that retained ethiodized oil on post-TACE imaging were considered necrotic [22]. Objective response rate (ORR) was defined as the sum of CR and PR.

Post-TACE follow-up data were collected to determine the time to progression (TTP), which was defined as the time from TACE to objective tumor progression whether the lesion was hepatic or extrahepatic. Additional liver-directed therapies after initial TACE, as well as the liver transplantation rates, were noted. Overall survival (OS) was also determined, and mortality data were collected from the medical records or Social Security Death Index database. For patients who underwent liver transplantation, the pathology reports of the explanted livers were reviewed, and the pathologic TNM stage (pTNM) was determined [23]. Pathologic evaluation of liver explants involved serial 10-mm sections of the liver and microscopic evaluation of all macroscopically visible nodules for tumor size and percentage

necrosis [24]. The medical records after liver transplantation were evaluated for posttransplant HCC recurrence.

Statistical Analysis

Continuous variables, such as age, CPT score, MELD score, and tumor size, were compared between the two groups using Wilcoxon test. Categorical variables, such as HCC pattern and mRECIST outcomes, were compared using Fisher's exact test. TTP and OS were analyzed using Kaplan–Meier analysis with data censored at 1 and 3 years, respectively. For TTP, liver transplantation or surgical resection was noted as a censored event. For OS, all-cause survival analysis was performed both uncensored and censored for liver transplantation or surgical resection. Comparison of survival curves was made by log-rank test. A p value <0.05 was considered statistically significant.

Results

The study groups were not significantly different in terms of age, sex distribution, CPT score, and MELD score (Table 1). The distribution of BCLC and UNOS TNM stages was also similar between the two groups ($p = 0.39$ and $p = 0.64$, respectively). The baseline sizes of the HCC lesions targeted by TACE were similar with a median single greatest dimension of 2.7 cm (range 1.2–4.8) for the TIPS and 2.6 cm (range 1.4–4.6) for the non-TIPS groups ($p = 0.91$). The right hepatic lobe was targeted in 8 patients (80 %) in the TIPS group and 15 patients (65 %) in the non-TIPS group.

Imaging treatment response, as evaluated by mRECIST criteria, is listed in Table 2. A statistically significant difference was seen in the response rates ($p = 0.05$). This is mainly reflected by a significantly greater rate of CR in the non-TIPS group compared with the TIPS group (74 vs. 30 %, $p = 0.03$). The ORR in the non-TIPS group was 83 % (19 patients) compared with 50 % (5 patients) in the TIPS group ($p = 0.09$). The disease control rate (CR, PR, or SD) was 100 % in the non-TIPS group and 90 % in the TIPS group ($p = 0.3$).

After TACE, 3 patients (30 %) in the TIPS group and 7 patients (30 %) in the non-TIPS group showed tumor progression at 1 year. TTP (Fig. 1) was not significantly different in the two groups ($p = 0.47$). Median TTP was 103 days (range 33–150) for the TIPS group and 232 days (range 26–330) in the non-TIPS group. In the TIPS group, 4 patients (40 %) underwent additional liver-directed therapies: 1 patient had two additional TACE sessions for local tumor progression of the target lesion; 1 patient had two additional TACE sessions for a stable but persistent target lesion and for two additional contralateral hepatic lobe lesions; and 2 patients each underwent percutaneous ethanol ablation for tumor progression of the target lesion and for a stable but persistent target lesion, respectively. In the non-TIPS group, 6 patients (26 %) underwent additional liver-directed therapies: 2 patients had additional TACE for new lesions; 1 patient had three additional TACE for multiple additional nontargeted lesions; 1 patient had one additional TACE for partial response of the target lesion after the initial session; 1 patient had TACE followed-up by radiofrequency ablation for a stable but persistent target lesion; and 1 patient had two additional TACE for a stable but persistent target lesion.

The liver transplantation rate was similar in both groups with 8 patients (80 %) receiving a transplant in the TIPS group and 17 patients (74 %) receiving a transplant in the non-TIPS group ($p = 1$). The time to transplantation trended shorter in the TIPS group with a median time of 128.5 days compared with 231 days in the non-TIPS group, however, this did not reach statistical significance ($p = 0.08$). Explanted liver pathology reports were available for 7 TIPS and all 17 non-TIPS patients. In the TIPS group, 3 patients (43 %) had no residual tumor, 1 patient (14 %) was pTNM stage I (solitary tumor ≤ 2 cm without vascular

invasion), 2 patients (29 %) were stage II (solitary tumor > 2 cm or multiple tumors in one lobe ≤2 cm without vascular invasion), and 1 patient (14 %) was stage IVa (multiple tumors in both lobes). In the non-TIPS group, 4 patients (23.5 %) had no residual tumor, 6 patients (35 %) were stage I, 4 patients (23.5 %) were stage II, 2 patients (12 %) were stage III (multiple tumors in one lobe > 2 cm), and 1 patient (6 %) was stage IVa. No explanted liver showed nodal or metastatic disease. Pathologic TNM stages of the explanted liver were similar between the two groups ($p = 0.65$). Two posttransplant recurrences were observed; both cases involved non-TIPS patients. One patient had a pTNM stage I liver explant with sacral bone metastatic recurrence 110 days after transplantation, and the other patient had no residual tumor on liver explant with lung recurrence 630 days after transplantation.

The 3-year OS (Fig. 2) uncensored for liver transplantation was not significantly different between the two groups ($p = 0.17$). In the TIPS group, the 3-year mortality rate was 40 % with a median time to death of 278 days (range 176–571). For the non-TIPS group, the 3-year mortality rate was 22 % with a median time to death of 629 days (range 383–903). When OS analysis was censored for liver transplantation, the non-TIPS group had significantly better survival ($p = 0.01$). Only 2 patients died within the first year after TACE; these patients were in the TIPS group and were not liver transplant candidates.

Discussion

For unresectable HCC, liver-directed therapies, such as TACE, have emerged as a way to bridge patients to surgery or transplantation [5–7] or to offer palliation [8]. TACE takes advantage of the hepatic dual blood supply, thus resulting in embolization of the hepatic arteries supplying the tumor [12] while preserving the portal venous nutrient flow to normal hepatocytes. As a corollary, patients with compromised portal venous flow may not be ideal candidates for TACE. Traditionally, TACE was absolutely contraindicated in this situation [25]. More contemporary experiences have supported the safety and efficacy of TACE in patients with impaired hepatopetal portal flow [26] or portal vein thrombosis [27].

A patent TIPS alters hepatic portal venous perfusion by decompressing portal venous flow into the systemic circulation. Therefore, in cases of patients with HCC who have a TIPS, TACE is considered a relative contraindication [28]. Published studies on the safety and efficacy of TACE in TIPS patients have been limited and have reported conflicting results [13–15]. Although TACE may be feasible and effective in select patients [13, 15], it may also be associated with increased hepatotoxicity compared with similar patients without TIPS [14].

In this study, the ORR was 50 % (5 patients) in the TIPS group after TACE. This rate is similar, but lower, than the ORR of 70 % reported by Kang et al. [13] in their cohort of 20 patients, which was likewise evaluated by mRECIST criteria. The comparatively lower response rate in this study may be attributed to differences in the number of TACE sessions. We assessed treatment response after a single, primary TACE session, whereas in the study by Kang et al. [13], most of their cohorts had multiple TACE sessions (median of 3 sessions), which presumably may account for the comparatively greater treatment response rate.

The primary aim of this study was to compare radiographic treatment response after TACE in comparable patients with and without TIPS. The effect of portal venous flow diversion by a patent TIPS on the efficacy of TACE is unclear. The diversion of portal venous flow by way of a TIPS might be expected to result in an increased risk of hepatic ischemia after TACE. Although HCC derives its blood supply primarily from hepatic arteries, portal venous contribution is observed in some HCCs [12, 29]. With this hypothetical framework,

it may be predicted that patients with TIPS might develop more extensive tumor necrosis. However, our findings suggest the opposite. The non-TIPS group had a statistically greater rate of CR compared with the TIPS group (74 vs. 30 %, $p = 0.03$). In addition, the ORR trended greater for the non-TIPS group (83 vs. 50 %); however, it did not reach statistical significance ($p = 0.09$).

This difference in treatment response may be explained by hepatic artery-to-portal vein (arterioportal) shunting (Fig. 3). In a study directly measuring flow in the portal vein and TIPS after TIPS creation, Itkin et al. [16] observed that ~30 % of flow through a TIPS was attributed to arterioportal shunting. Moreover, the investigators hypothesized that this may also partly account for the hepatofugal flow in the intrahepatic portal veins commonly observed after TIPS [18]. Arterioportal shunting likely has a negative effect on TACE efficacy. For one, it may divert a portion of the chemoembolic agents away from the tumor. In addition, arterioportal shunting alters the normal hemodynamics in the liver. In the setting of decreased portal perfusion, vascular autoregulation in the liver is known to upregulate hepatic arterial flow to compensate for decreased portal flow [30]. With increased reliance on the arterial circulation for perfusion to normal liver, the relative preferential arterial flow to an HCC lesion is impaired. Last, arterioportal shunts have been commonly observed in association with HCC, likely related to tumor vascular invasion [31, 32]. Vogl et al. [33] reported a significantly increased rate of progression after TACE by MRI volumetric measurements compared with patients without arterioportal shunting.

While imaging response after initial TACE was not as robust in TIPS patients, the clinical end point of TTP (Fig. 1) was not significantly different between the two groups. This may in part be due to the shorter time to liver transplantation (median time 128.5 vs. 231 days, $p = 0.08$) or the greater percentage of patients requiring additional liver-directed therapies (40 vs. 26 %, $p = 0.4$) in the TIPS group. As a result, a similar percentage of patients in both groups were bridged to liver transplantation (80 and 74 % of patients in the TIPS and non-TIPS groups, respectively). Moreover, because of the comparable liver transplantation rates, the OS (Fig. 2) between the two groups was also similar. When OS analysis was censored at liver transplantation, the TIPS group showed significantly inferior survival ($p = 0.01$). This was mainly due to the observation that the only mortality events within the first year corresponded to the 2 patients in the TIPS group who were not liver transplant candidates. Therefore, it is possible that TIPS patients may require more liver-directed therapies to achieve disease control, but clinical outcomes are similar, likely due to the availability of liver transplantation.

We previously reported the rate of hepatotoxicity in the TIPS group compared with non-TIPS patients [14]. In that analysis, the incidence of hepatobiliary severe adverse events was 70 % for TIPS patients, which was almost twice the rate (36 %) for the non-TIPS control group. These results suggest that TACE in TIPS patients may be inferior in terms of safety and efficacy compared with their non-TIPS counterparts. Particularly in patients with impaired hepatic function [15] who are not liver transplant candidates, TACE may present more risk than benefit. Nevertheless, for patients who are liver transplant candidates, TACE may be appropriate given the option of rescue transplantation should severe hepatotoxicity or liver decompensation occur.

This study is limited by the retrospective, case-control nature of the design. The sample size for the TIPS group was small, and the potential pool of non-TIPS patients was much larger. The planned sample size of the non-TIPS group was up to 3 times the number of TIPS patients. The validity of the study relied largely on the similarity between the two study groups. To decrease bias and maintain blinding to pre- and post-TACE imaging, inclusion of non-TIPS patients was based on biochemical markers of liver reserve, such as CPT and

MELD scores, rather than imaging characteristics. Nonetheless, tumor stages by BCLC criteria and UNOS TNM stages were similar between the two groups (Table 1). Inherently the application of mRECIST evaluation could not practically be blinded given the visualization of the TIPS on imaging. Imaging treatment response rates for the non-TIPS group (83 %) were similar to those reported (69–80 %) in previously published studies using mRECIST criteria [34–37]. Another limitation was the accurate assessment of TIPS patency at the time of TACE. Demonstrable TIPS patency within 6 months of TACE by Doppler sonogram allowed enough time for stent stenosis to develop before TACE. Lastly, the primary end point was to assess imaging response, and our sample size may not be powered to detect differences in TTP or OS. Furthermore, the additional liver-directed therapies undergone by a subgroup of patients may have also confounded survival outcomes.

Conclusion

In summary, the results of our study shows that the radiographic response to TACE was inferior for patients with HCC and TIPS compared with patients without TIPS. Nevertheless, the clinical end points of TTP and liver transplantation were similar for both groups. As such, TACE in TIPS patients may be most appropriate in liver transplantation candidates, and additional studies will be necessary to confirm this. For non–transplant candidates, TACE may still be an option for TIPS patients; however, this must also be weighed with the decreased efficacy and increased hepatotoxicity [14] relative to their non-TIPS counterparts. The results of this study may aid in the multidisciplinary discussion regarding the treatment of HCC in patients with a TIPS.

Acknowledgments

Yuo-Chen Kuo received a grant from the National Institute of Biomedical Imaging and Bioengineering (T32 Training Grant No. EB001631-08) during the conduct of the study.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011; 61(2):69–90. [PubMed: 21296855]
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53(3): 1020–1022. [PubMed: 21374666]
3. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology. 2008; 134(6):1752–1763. [PubMed: 18471552]
4. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004; 10 Suppl 1(2):S115–S120. [PubMed: 14762851]
5. Bouchard-Fortier A, Lapointe R, Perreault P, Bouchard L, Pomier-Layrargues G. Transcatheter arterial chemoembolization of hepatocellular carcinoma as a bridge to liver transplantation: a retrospective study. Int J Hepatol. 2011; 2011:974514. [PubMed: 21994880]
6. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl. 2003; 9(6):557–563. [PubMed: 12783395]
7. Hayashi PH, Ludkowski M, Forman LM, et al. Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. Am J Transplant. 2004; 4(5):782–787. [PubMed: 15084175]
8. Brown DB, Nikolic B, Covey AM, et al. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol. 2012; 23(3):287–294. [PubMed: 22284821]
9. Haskal ZJ, Martin L, Cardella JF, et al. Quality improvement guidelines for transjugular intrahepatic portosystemic shunts. J Vasc Interv Radiol. 2003; 14(9 Pt 2):S265–S270. [PubMed: 14514831]

10. Kim MY, Baik SK, Yea CJ, et al. Hepatic venous pressure gradient can predict the development of hepatocellular carcinoma and hyponatremia in decompensated alcoholic cirrhosis. Eur J Gastroenterol Hepatol. 2009; 21(11):1241–1246. [PubMed: 19455045]
11. Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol. 2009; 50(5):923–928. [PubMed: 19303163]
12. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954; 30(5):969–977. [PubMed: 13197542]
13. Kang JW, Kim JH, Ko GY, Gwon DI, Yoon HK, Sung KB. Transarterial chemoembolization for hepatocellular carcinoma after transjugular intrahepatic portosystemic shunt. Acta Radiol. 2012; 53(5):545–550. [PubMed: 22547388]
14. Kohi MP, Fidelman N, Naeger DM, Laberge JM, Gordon RL, Kerlan RK Jr. Hepatotoxicity after transarterial chemoembolization and transjugular intrahepatic portosystemic shunt: do two rights make a wrong? J Vasc Interv Radiol. 2013; 24(1):68–73. [PubMed: 23176968]
15. Tesdal IK, Wikstrom M, Flechtenmacher C, Filser T, Dueber C. Percutaneous treatment of hepatocellular carcinoma in patients with transjugular intrahepatic portosystemic shunts. Cardiovasc Intervent Radiol. 2006; 29(5):778–784. [PubMed: 16779690]
16. Itkin M, Trerotola SO, Stavropoulos SW, et al. Portal flow and arterioportal shunting after transjugular intrahepatic portosystemic shunt creation. J Vasc Interv Radiol. 2006; 17(1):55–62. [PubMed: 16415133]
17. Clark TW. Stepwise placement of a transjugular intrahepatic portosystemic shunt endograft. Tech Vasc Interv Radiol. 2008; 11(4):208–211. [PubMed: 19527846]
18. Feldstein VA, Patel MD, LaBerge JM. Transjugular intrahepatic portosystemic shunts: accuracy of Doppler US in determination of patency and detection of stenoses. Radiology. 1996; 201(1):141–147. [PubMed: 8816535]
19. Haskal ZJ, Carroll JW, Jacobs JE, et al. Sonography of transjugular intrahepatic portosystemic shunts: detection of elevated portosystemic gradients and loss of shunt function. J Vasc Interv Radiol. 1997; 8(4):549–556. [PubMed: 9232569]
20. O'Neil BH, Venook AP. Hepatocellular carcinoma: the role of the North American GI Steering Committee Hepatobiliary Task Force and the advent of effective drug therapy. Oncologist. 2007; 12(12):1425–1432. [PubMed: 18165619]
21. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999; 19(3):329–338. [PubMed: 10518312]
22. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30(1):52–60. [PubMed: 20175033]
23. Nonami T, Harada A, Kurokawa T, Nakao A, Takagi H. Hepatic resection for hepatocellular carcinoma. Am J Surg. 1997; 173(4):288–291. [PubMed: 9136782]
24. Kwan SW, Fidelman N, Ma E, Kerlan RK Jr, Yao FY. Imaging predictors of the response to transarterial chemoembolization in patients with hepatocellular carcinoma: a radiologicalpathological correlation. Liver Transpl. 2012; 18(6):727–736. [PubMed: 22344899]
25. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002; 359(9319):1734–1739. [PubMed: 12049862]
26. Kothary N, Weintraub JL, Susman J, Rundback JH. Transarterial chemoembolization for primary hepatocellular carcinoma in patients at high risk. J Vasc Interv Radiol. 2007; 18(12):1517–1526. [PubMed: 18057286]
27. Georgiades CS, Hong K, D'Angelo M, Geschwind JF. Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol. 2005; 16(12):1653–1659. [PubMed: 16371532]
28. Liapi E, Geschwind JF. Transcatheter arterial chemoembolization for liver cancer: Is it time to distinguish conventional from drug-eluting chemoembolization? Cardiovasc Intervent Radiol. 2011; 34(1):37–49. [PubMed: 21069333]

29. Kudo M, Hatanaka K, Inoue T, Maekawa K. Depiction of portal supply in early hepatocellular carcinoma and dysplastic nodule: value of pure arterial ultrasound imaging in hepatocellular carcinoma. Oncology. 2010; 78(Suppl 1):60–67. [PubMed: 20616586]

30. Ezzat WR, Lautt WW. Hepatic arterial pressure flow autoregulation is adenosine mediated. Am J Physiol. 1987; 252(4 Pt 2):H836–HJ845. [PubMed: 3565595]

31. Okuda K, Musha H, Yamasaki T, et al. Angiographic demonstration of intrahepatic arterio-portal anastomoses in hepatocellular carcinoma. Radiology. 1977; 122(1):53–58. [PubMed: 186844]

32. Ngan H, Peh WC. Arteriovenous shunting in hepatocellular carcinoma: its prevalence and clinical significance. Clin Radiol. 1997; 52(1):36–40. [PubMed: 9022578]

33. Vogl TJ, Nour-Eldin NE, Emad-Eldin S, et al. Portal vein thrombosis and arterioportal shunts: effects on tumor response after chemoembolization of hepatocellular carcinoma. World J Gastroenterol. 2011; 17(10):1267–1275. [PubMed: 21455325]

34. Kim BK, Kim KA, Park JY, et al. Prospective comparison of prognostic values of modified Response Evaluation Criteria in Solid Tumours with European Association for the Study of the Liver criteria in hepatocellular carcinoma following chemoembolisation. Eur J Cancer. 2013; 49(4):826–834. [PubMed: 22995582]

35. Sato Y, Watanabe H, Sone M, et al. Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci. 2013; 118(1):16–22. [PubMed: 23167460]

36. Hu HT, Kim JH, Lee LS, et al. Chemoembolization for hepatocellular carcinoma: Multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. J Vasc Interv Radiol. 2011; 22(7):917–923. [PubMed: 21571545]

37. Bargellini I, Bozzi E, Campani D, et al. Modified RECIST to assess tumor response after transarterial chemoembolization of hepatocellular carcinoma: CT-pathologic correlation in 178 liver explants. Eur J Radiol. 2013; 82(5):e212–e218. [PubMed: 23332890]

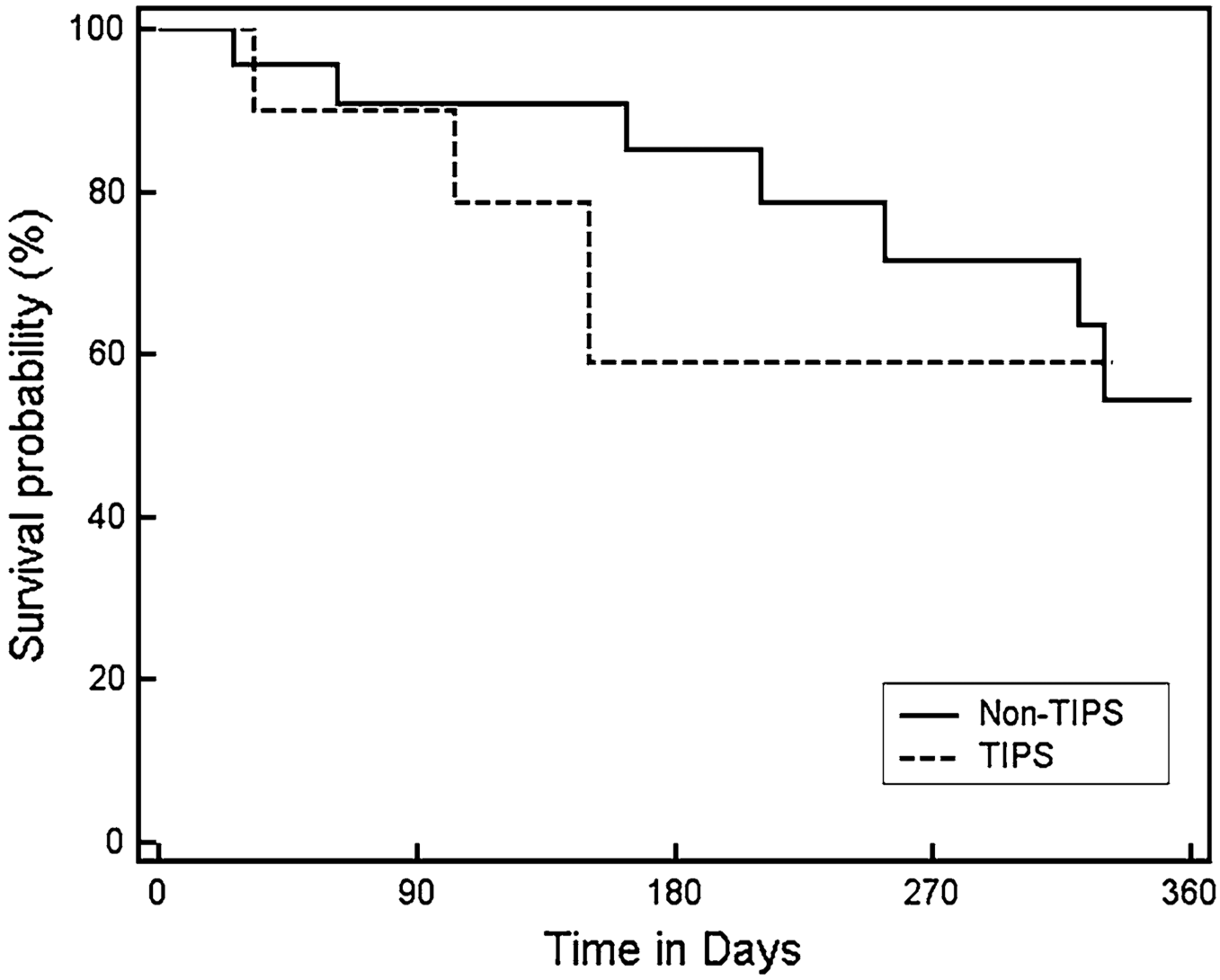

Fig. 1.
Time-to-progression curve of TACE in patients with and without TIPS (p = 0.47)

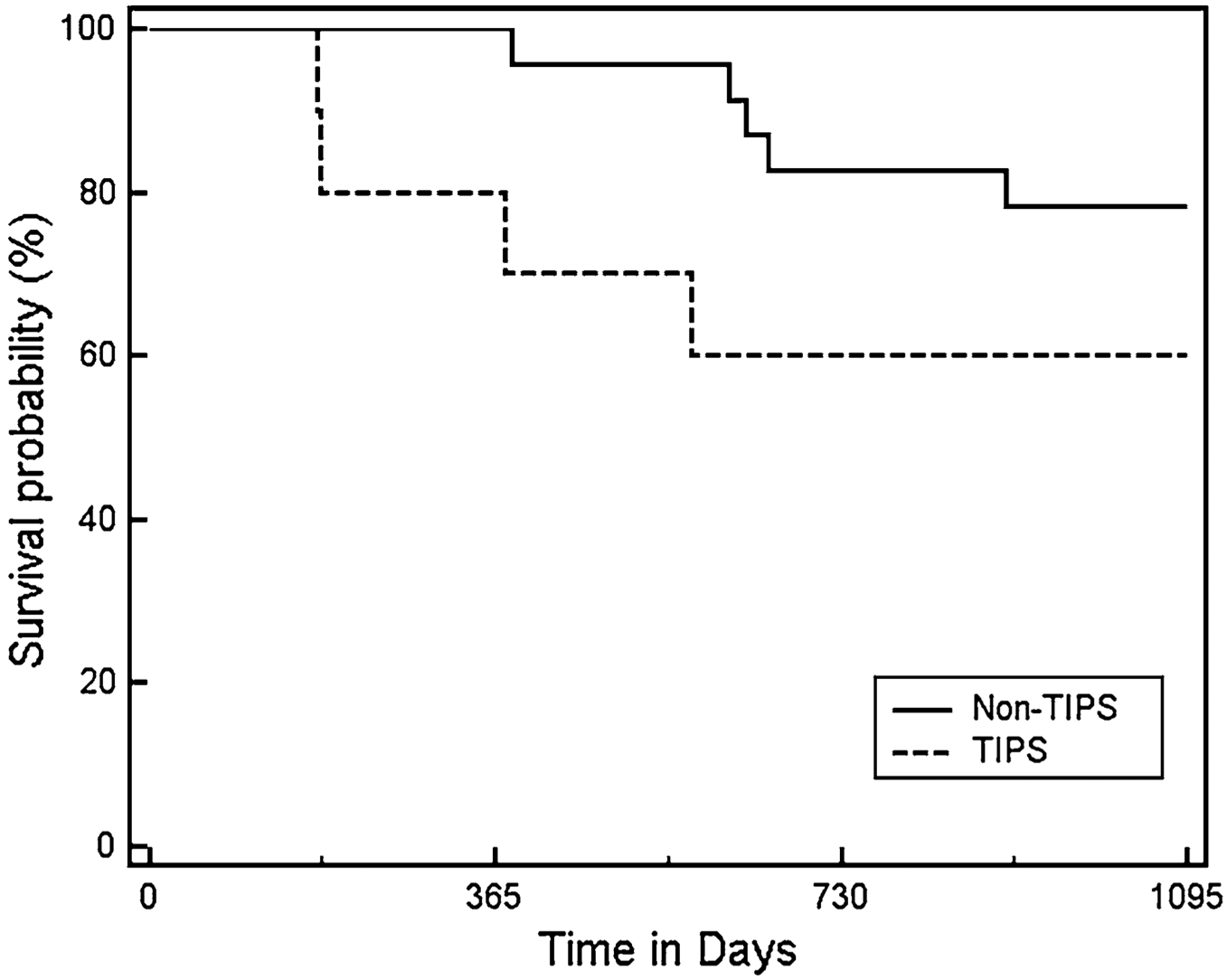

Fig. 2.
Three-year overall survival curve of TACE in patients with and without TIPS ($p = 0.17$)

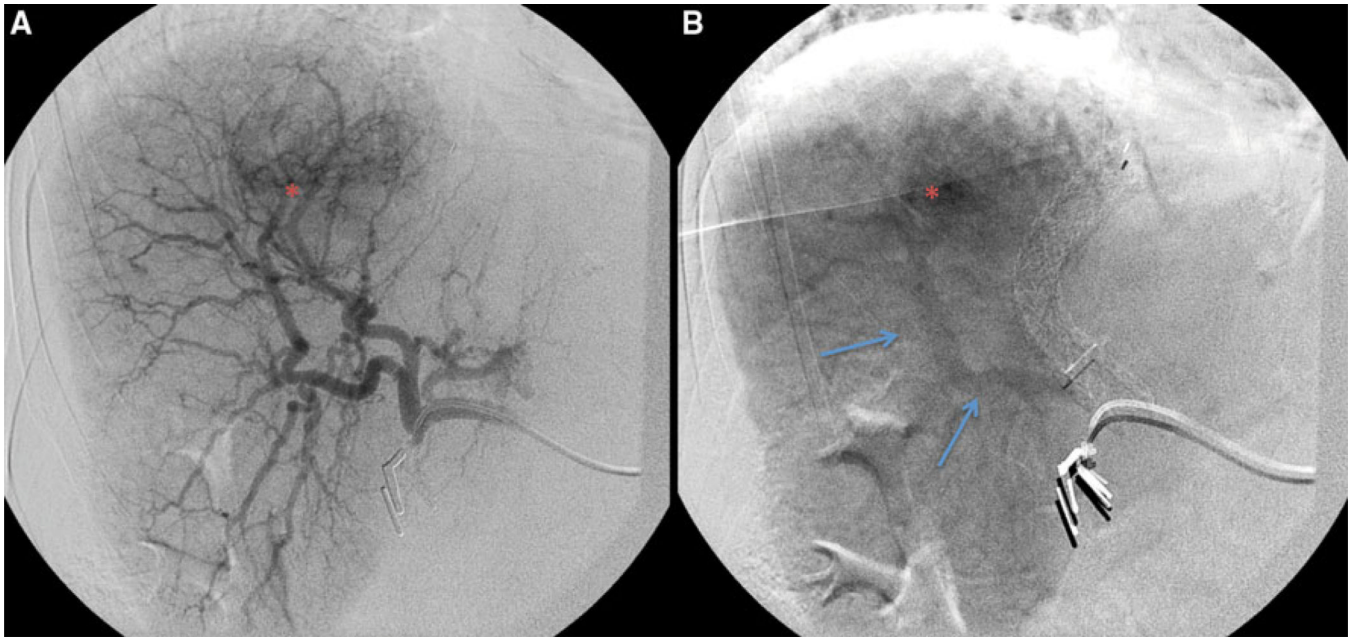

Fig. 3.

A 62-year-old woman with liver cirrhosis secondary to nonalcoholic steatohepatitis with a transjugular intrahepatic portosystemic shunt and a 4.5-cm segment 8 HCC. *Right* hepatic arteriogram in the arterial phase **A** showing tumor blush (*red colored star*). A couple of seconds later during the same injection **B** shows contrast opacification of *right* portal vein branches (*blue arrows*), which is compatible with arterioportal shunting

Table 1

Patient Characteristics

Variables	TIPS group (*n* = 10)	Non-TIPS group (*n* = 23)	*p*
Age (y)[a]	59 (51–72)	58 (51–70)	0.60
Male sex	9 (90 %)	19 (83 %)	1.0
CPT Class			0.13
A	5 (50 %)	8 (35 %)	
B	3 (30 %)	14 (61 %)	
C	2 (20 %)	1 (4 %)	
CPT Score[a]	7 (5–11)	7 (5–11)	0.75
MELD Score[a]	14 (10–18)	12 (10–16)	0.13
BCLC Stage			0.39
0	1 (10 %)	1 (4 %)	
A	5 (50 %)	16 (70 %)	
B	2 (20 %)	5 (22 %)	
C	0	0	
D	2 (20 %)	1 (4 %)	
TNM Stage			0.64
I	1 (10 %)	3 (13 %)	
II	7 (70 %)	16 (70 %)	
III	1 (10 %)	4 (17 %)	
IVa	1 (10 %)	0	
Target tumor size (cm)[a,b]	2.7 (1.2–4.8)	2.6 (1.4–4.6)	0.91

TIPS transjugular intrahepatic portosystemic shunt, *CPT* Child–Pugh–Turcotte, *MELD* Model for End-Stage Liver Disease, *BCLC* Barcelona Clinic Liver Cancer, *TNM* United Network of Organ Sharing classification

[a] Data are presented as median with range in parentheses

[b] Measurements represents single greatest dimension of the targeted lesions

Table 2

Treatment Response by mRECIST

	TIPS group (*n* = 10)	**Non-TIPS group (*n* = 23)**	***p***
Complete Response	3 (30 %)	17 (74 %)	0.03
Partial Response	2 (20 %)	2 (9 %)	
Stable Disease	4 (40 %)	4 (17 %)	
Progressive Disease	1 (10 %)	0 (0 %)	
Objective Response[a]	5 (50 %)	19 (83 %)	0.09
Disease Control[b]	9 (90 %)	23 (100 %)	0.3

TIPS transjugular intrahepatic portosystemic shunt, *mRECIST* modified response evaluation criteria for solid tumors

[a] Defined as the sum of Complete Response and Partial Response

[b] Defined as the sum of Complete Response, Partial Response, and Stable Disease