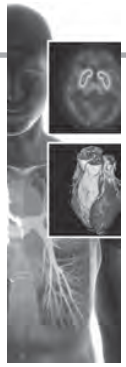

"TIPS and HCC: friends or foes?"

Portal hypertension and hepatocellular carcinoma [HCC] are major complications of liver cirrhosis and may coexist in the same patient. Transjugular intrahepatic portosystemic shunt [TIPS] is an effective treatment for recurrent variceal bleeding and refractory ascites although accumulating evidence has shown that its indication is gradually expanding. TIPS placement reduces portal flow by connecting splanchnic vessels to systemic circulation. As a consequence parenchymal portal venous flow is decreased so inducing an ischemic injury. In this condition, a possible activation of hepatic stellate cells, an induction of neoangiogenesis and an increase in secretion of HGF and VEGF may represent possible triggers for hepatocarcinogenesis. On these bases, several studies have explored a possible influence of TIPS on the onset of hepatocellular carcinoma [HCC] in cirrhotic patients. To date the results are controversial and the role of TIPS as risk factor for HCC is still unclear. Moreover, the diversion of portal flow and the onset of arterioportal shunts following TIPS insertion, may reduce the efficacy and the safety profile of transarterial treatments. Until now, very little evidence has been collected regarding this topic and the results are conflicting. Therefore, whether TIPS and hepatocellular carcinoma are either "Friends or Foes" is still an ongoing dilemma.

KEYWORDS: HCC; cirrhosis; portal hypertension; TIPS; hepatocarcinogenesis; TACE

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Introduction

Hepatocellular carcinoma [HCC] is the fifth most frequent malignancy in women and the seventh in men worldwide [1] and in about 80-85% of cases arises in a cirrhotic liver. Early diagnosis is mandatory to improve the prognosis of this tumour and the regular application of surveillance protocol is absolutely relevant in high- risk populations. Cirrhosis is considered the major risk factor for developing HCC [2]. Moreover, male sex, older age, advanced Child Pugh class, viral and alcoholic etiologies have been consistently associated with HCC in different studies [3,4]. Transjugular intrahepatic portosystemic shunt

[TIPS] is an established procedure for the treatment of portal hypertension complications. The largest body of evidence supports its application in recurrent or refractory variceal bleeding and refractory ascites. Its use has also been advocated for acute variceal bleeding, hepatic hydrothorax, and hepatorenal syndrome. With the replacement of bare metal stents with polytetrafluoroethylene-covered stents, shunt

patency has improved dramatically, thus, improving outcomes. However, to date, although TIPS significantly reduces the portal pressure and the recurrence of its complications, it doesn't improve survival of cirrhotic patients [5]. TIPS placement may induce hypoxic injury by either totally or partially diverting portal venous blood flow directly into systemic circulation. This reduction of parenchymal oxygenation may be involved in hepatocarcinogenesis through the activation of hepatic stellate cells [6]. Futhermore, TIPS could influence the outcome and safety of loco-regional treatment for HCC, as a result of the portal blood diversion following the stentinsertion. Until now very few papers have been written about a possible "interaction" between TIPS and HCC. Therefore, whether TIPS and HCC are "Friends or Foes" is still an ongoing dilemma.

Incidence of HCC in TIPS bearing patients: a relationship still hidden in the fog

A possible role of porto - systemic shunt in the development of hepatocellular carcinoma [HCC] was described for the first time in a post-mortem histological study published in the earliest 80's [7], which reported an increased prevalence of primary liver cancer after surgical porto-caval shunt. However, another cohort study didn't confirm this finding [8]. Currently, the most important porto-systemic shunt is represented by TIPS, whose application in the treatment of complication of portal hypertension has become a mainstay [9]. As a consequence, a possible impact on the development of HCC could lead to the application of more intensive surveillance protocol.

In 2008, Banares *et al.,* suggested an association between the onset of HCC and the placement of TIPS in a case – control retrospective study [10]. However, the majority of patients enrolled in the TIPS cohort was Child-Pugh C and the possible impact of a more severe liver disease on the higher incidence of HCCcould be postulated. Two subsequent experiences didn't confirmed these data: the prospective study by Libbrecth *et al.* [11] and our case-control study [12] were concordant in showing a similar incidence of primary liver cancer in cirrhotics with and without TIPS. In particular, our study design was very similar to the one by Banares *et al.* but patients' selection was more careful and the proportion of patients with advanced liver disease and classifiable as Child-Pugh C was very low.

The development of liver cancer nodules was similar in cirrhotics with and without TIPS, although in stent bearing patients the onset time of HCC was briefer. Moreover, tumour diameter was slightly larger in TIPS patients and the localization was more frequent in the right lobe (TABLE 1). Although these data seem to suggest a possible relationship between TIPS and hepatocarcinogenesis, we concluded that in TIPS bearing patients without severe liver disease the application of more strict protocols of surveillance is not indicated; as such, the finding of a similar neoplastic disease stage at diagnosis of HCC in both groups seems to strongly support this idea and suggests that a similar chance of treatment could be offered in these patients without any change in surveillance intervals. Recently, another retrospective study [13] failed to confirm an association between TIPS insertion and HCC, but, interestingly, revealed an increased prevalence of liver dysplasia in patients with patent stent. Of note, the rate of small cell dysplasia, which is a precancerous lesion [14], was similar between patients with and without TIPS, while large cell dysplasia, whose role in HCC is still unclear, was more frequent in cirrhotic with inhabitant stent, maybe as a consequence of the histological locoregional modifications arising in liver parenchyma following TIPS placement. However, these results need to be interpreted cautiously because the short time of observation [12.1 months] could have influenced the negative outcome of the study. Overall, what few data exist are controversial and, currently, a clear role of TIPS in the development of hepatocellular carcinoma cannot be stated [15-22]. Therefore, there is no strict recommendation for shortening the surveillance interval in TIPS bearing patients.

Chronicle of a problematic relationship: TIPS and HCC from a clinical point of view

There are two different clinical settings in which a possible interaction between TIPS and HCC may be suggested. On one side, there are cirrhotic patients who underwent TIPS placement to treat complications of clinically significant portal hypertension [CSPH] and developed HCC during follow up [23,24].

On the other side, there are patients with an established diagnosis of HCC who developed refractory ascites or experienced recurrent bleeding episodes, thus becoming potential candidates for TIPS. These two scenarios put the physician in front of different clinical problems [25-29]. In the first case the question is: "How could TIPS interfere with the outcome of HCC treatment and the developing of metastasis? In the second case, we would ask: 1] How could HCC interfere with safety and technical feasibility of TIPS insertion? 2] Could TIPS make radical treatment [surgery], otherwise excluded for the presence of CSPH, feasible? 3] Could TIPS be an efficient bridge for liver transplant candidates? 4] Could TIPS be an efficient option in patients with advanced liver cancer [BCLC C and D]? Very few data have been described and to the best of our knowledge, all the papers about this topic are retrospective and included a small size population [30-36]. In following sessions we will discuss more carefully the key points mentioned above. In particular, with regard to the possible interference between TIPS and HCC treatment, no data exist about a possible role of TIPS insertion before surgical resection. Therefore, our attention will be focused on the outcome of locoregional treatment.

TIPS and HCC: Influence on locoregional treatments

To the best of our knowledge there are no published series about the possible role of TIPS in the treatment of portal hypertension in potential surgery candidates, but we can speculate that patients with well-preserved liver function excluded from surgery for CSPH, according to the BCLC staging system [37], may benefit from stent insertion before surgical resection. Only one paper described the "interaction" between TIPS and ablative

treatment in comparison to TACE without any conclusion regarding the influence of stent insertion on treatment choice and outcome [38]. Not surprisingly a large part of the interest has been focused on transarterial locoregional treatments [TLR]. Due to decreased portal blood flow after TIPS placement, it may be suggested that TLR in patients with patent stent may result in increased tissue ischemia. Moreover, the onset of arterioportal shunt following TIPS insertion may decrease LTR efficacy. In spite of these considerations, literature about the application of transarterial treatment in TIPS patients is poor [several case series and only two case control studies]. In particular, of the published studies ([38-46]; TABLE 2) only two [38,39] described hepatotoxicity and the efficacy of SIRT while the rest are all focused on TACE. Overall, there is little data available; in fact, in all papers the populations enrolled are very small [from 5 to 20 pts]. Therefore the results need to be interpreted cautiously. Futhermore, although some case series reported a satisfactory safety profile for TACE in TIPS patients [39,40] two subsequent studies [40,41] didn't confirm this conclusion.

In particular, the series reported by Kohi *et al.* [42] represented the only case-control study regarding TACE hepatotoxicity in patients with [10 pts] and without stent [148 pts]. The majority of patients were BCLC A stage in both groups [TIPS group- 50 % vs. 52%- non TIPS group; p=0.97]. In this paper, 70 % of patients in the TIPS group experienced one or more hepatobiliary serious adverse events [SAE] versus 36 % in non-TIPS group [p=0.46]. Among the hepatobiliary SAEs documented, only the onset of grade 3 or 4 hyperbilirubinemia differs significantly between the two groups [60 % in TIPS group vs. 20 % in non-TIPS group; p = 0.009] although it was equally reversible in both. The rate of irreversible SAE was overlapping in the two cohorts. Of course this study has some limitations. In addition to its retrospective nature, the large difference in the number of patients enrolled in the groups [10 vs. 148] may have limited the power to detect small differences. Moreover, given that the rate of liver transplantation within on 1 year was significantly higher in the TIPS group with respect to the non-TIPS group, the possible impact of TACE related hepatotoxicity on overall survival [OS] in stent bearing patients is not evaluable. Taken together these data suggest that, although TACE hepatotoxicity seems to be increased in TIPS patients, this treatment may be convenient in patients who are candidates for OLT and require adequate control of neoplastic disease as a bridge to liver transplantation. But in patients who are not candidates for OLT, to establish whether or not TACE may be a convenient approach is difficult because data are lacking. Therefore, clinical good sense has a pivotal role and the careful selection of candidates is mandatory in these cases. From this point of view, in stent bearing patients with HCC, TACE should be reserved to those with a very well preserved liver function only if a superselective/selective approach is possible. These suggestions are more important if we consider that the number of TACE session required to achieve an objective response is higher than in patients without stent, as reported by Kuo *et al.* [43]. This experience represented the only case- control study about the efficacy of TACE in TIPS versus non TIPS patients and reports a greater number of patients requiring additional treatment after a first session of TACE in the TIPS group, although not significantly (40% vs. 26 %-non TIPS; p=0.4). Although this data doesn't seem encouraging, the time to progression was overlapping between the groups, but, also in this case, the higher rate of liver transplantation in TIPS group may have influenced this result.

Risk of spreading and lung dissemination after tips insertion

One reason for being particularly cautious when proposing TIPS in HCC patients is the fear related to the possibility of the tumour spreading as the stent may traverse malignant tissue, especially in centrally located nodules. To date, only two papers have investigated pulmonary spreading after TIPS insertion [44-47] in patients with HCC with controversial results as the lack of a control group and the short observation time makes the results difficult to interpret. In the paper of Bettinger *et al.,* only one patient developed lung metastasis 7 years after HCC diagnosis and 6 years after TIPS insertion. In this patient the tumour was not centrally located and TIPS was positioned away from the neoplastic lesion. Liu *et al* reported the onset of lung metastases in 7 pts; no differences were observed between patients with intratumoral stent and patients with stent far from the tumor. But this data is probably influenced by a very short median survival [77 days]. Moreover, about half of patients died within 30 days of TIPS placement. Therefore, whether or not TIPS is a real risk factor for the development of lung dissemination remains

uncertain.

Technical feasibility and safety profile

Primary hepatic malignancy is considered a relative contraindication for TIPS placement although relevant information doesn't exist to support this recommendation. Apart from the experience of few case reports, only five papers focused their attention on the technical feasibility and the safety profile of TIPS in patients previously diagnosed with HCC ([47-49]; TABLE 3). In the small case series [5 pts] of Sakaguchi *et al.* [39], the application of TIPS for the treatment of portal hypertension complication in the setting of HCC patients was described for the first time. The technical feasibility of TIPS insertion was 100 % and none of the patients developed severe adverse events. In all of them the stent was located far from the tumor. The rate of stent dysfunction was high [20%], although observation time was very short. This finding may probably be related to the application of bare stents rather than any influence of HCC. With regard to survival, the time of observation was too short for the assessment of this endpoint. In 2003, the experience of Wallace *et al.,* described the placement of TIPS through primary and secondary liver neoplasm in nine patients [cirrhotic and non-cirrhotic] with refractory ascites or recurrent bleeding. Similarly to what has been described by Sakaguchi *et al.,* technical success was achieved in 100 % of cases and nobody developed life-threatening events after stent implantation.

However, also in this case, only bare stents were used and the rate of TIPS dysfunction was high [33%] within 15 days from the procedure. Median overall survival [OS] was of only 229 days and, of note, two deaths occurred within 30 days of TIPS placement. Potential thoracic metastases were identified in two patients during follow up, but none of them had a preprocedural CT scan of chest. Therefore this data can't be correctly evaluated. Lowest rates of technical success of TIPS implantation [71%] were described in the series byJiang *et al.* [49], but this was the first experience which included patients with portal cavernoma. After ten years of "literary silence", the study by Liu *et al.* Published in 2014, represented one of the most important papers on this topic for the following reasons: 1] The observed population was the largest ever described in literature - 58 pts 2] all patients were affected by advanced HCC [35 with HCC stage C and 23 stage D accordingly to BCLC staging System] and portal vein thrombosis or cavernoma. Although the success rate of TIPS placement was 100 %, five patients in these studies experienced tumour rupture after stent insertion, contrary to previous reports. In two cases the intraabdominal hemorrhage was fatal. It's not clear whether or not, in these patients, the stent traversed the tumour, but we have to take into account that the extension of neoplastic disease was larger than in the previous reports. In particular, in patients who developed adverse events, the tumour burden was more than 10 cm. Moreover, the prognosis was very poor with a median survival of 77 days and restenting was necessary in twelve patients [21%] because of the onset of a TIPS dysfunction. Subsequently, Bettinger *et al.* Reports another series of 40 pts with successful implantation of TIPS. No severe complications were observed after stent placement and the overall survival was 180 days; also in this case patient's selection wasn't careful including BCLC D patients [20%]. Eight patients [20%] experienced TIPS dysfunction, only one case being related to tumoral invasion of the stent

Taken together, these data seem to suggest that, although TIPS is feasible in patients with HCC, its placement should be carefully evaluated case by case. In particular, in patients with advanced or end-stage HCC who are not candidate for liver transplantation, TIPS insertion may be not indicated for the following reasons: on one side, the poor cancer-related survival and, on the other side, the willingness to preserve the best quality of life [QoL] possible minimizing the morbidity related to invasive procedure. In fact, the onset of hepatic encephalopathy and also, the high rate of TIPS dysfunction, could lead to an important increase of the hospitalization rate, thus worsening the QoL. Therefore, in BCLC C and D patients, TIPS placement may only add management cost without improving prognosis. In addition, although a certain role of TIPS placement cannot be demonstrated, the safety profile of this procedure seems to be reduced in patients with large neoplastic disease and as a consequence, TIPS should be avoided in this setting.

Conclusions

Although some speculations about a possible role of TIPS in the development of hepatocarcinogenesis may be suggested, the clinical experience doesn't confirm a higher incidence of HCC in stent bearing patients: to

date, only one paper confirms this association and three studies are contrary. Therefore, in these patients, there are not sufficient reasons for suggesting any change in surveillance for the detection of early HCC. In patients with an established diagnosis of HCC and CSPH, TIPS placement may hypothetically facilitate the access to surgery; however, data are still lacking. Prospective studies are required to verify whether or not surgery following the correction of portal hypertension by stent insertion is effective as in elective ideal candidates. On the contrary, in patients with advanced hepatocellular carcinoma, TIPS doesn't seem to have any role in the treatment of portal hypertension complications as it may worse the quality of life in a clinical setting characterized by poor survival. With regard to TACE, its efficacy seems to be reduced in patients with a patent stent, maybe as a consequence of the onset of arterioportal shunt following the TIPS placement; therefore more sessions of TACE are required in these patients to achieve an adequate neoplastic disease control. In addition, TACE seems to be less safe in patients with stent because it may worse liver function; as a consequence, it should be performed preferably in patients awaiting for liver transplantation. In conclusion, what is the answer to the initial question? Are TIPS and hepatocellular carcinoma friends or foes? It

REFERENCES

1. Ferlay J, Shin HR, Bray F *et al.* Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer.* 127, 2893-2917 (2010).
2. Schafer DF, Sorrell MF. Hepatocellular carcinoma. *Lancet.* 353, 1253-1257 (1999).
3. Bruix J, Sherman M, Llovet JM *et al.* Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the *Liver. J. Hepatol.* 35, 421-430 (2001).
4. Velázquez RF, Rodríguez M, Navascués CA *et al.* Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology.* 37, 520-527 (2003).
5. Qi XS, Bai M, Yang ZP *et al.* Selection of a TIPS stent for management of portal hypertension in liver cirrhosis: an evidence-based review. *World J. Gastroenterol.* 20, 6470-6480 (2014).
6. Ankoma-Sey V, Wuang Y, Dai Z. Hypoxic stimulation of vascular endothelial growth factor expression in activated rat hepatic stellate cells. *Hepatology.* 31, 141 – 148 (2000).
7. Bjørneboe M, Andersen JR, Christensen U. Does a portal-systemic shunt increase the risk of primary hepatic carcinoma in cirrhosis of the liver? *Scand J. gastroenterol.* 20, 59–64 (1985).
8. Elizalde JI, Castells A, Planas R. Prevalence of hepatocellular carcinoma in cirrhotic patients with portosystemic shunt. Cohort analysis. *Gastroenterol. Hepatol.* 19, 189–193 (1996).
9. Boyer TD, Haskal ZJ. American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009 *Hepatology.* 51, 306 (2010).
10. Bañares R, Núñez O, Escudero M *et al.* Patients with cirrhosis and bare-stent TIPS may have increased risk of hepatocellular carcinoma. *Hepatology.* 41, 566-571 (2005).
11. Libbrecht L, Maleux G, Verslype C Influence of TIPS on development of hepatocellular carcinoma in cirrhosis. *Hepatology.* 42, 236 (2005).
12. De Santis A, Iegri C, Kondili L. Hepatocellular carcinoma in cirrhotic patient with trans-jugular intrahepatic portosystemic shunt: a retrospective case–control study. *Dig. Liver. Dis.* 46, 726-730 (2014).
13. Borentain P, Garcia S, Gregoire E. Transjugular intrahepatic porto-systemic shunt is a risk factor for liver dysplasia but not for hepatocellular carcinoma: arestrospective study of explanted livers. *Dig. Liver. Dis.* 47, 57-61 (2015).
14. Libbrecht L, Desmet V, Roskams T. Preneoplastic lesions in human hepatocarcinogenesis. *Liver. Int.* 25, 16-27 (2005).
15. Faouzi S, le Bail B, Neaud V (1999) Myofibroblast are responsible of collagen synthesis in the stroma of human hepatocellular carcinoma: an in vivo and in vitro study. *J. Hepatol.* 30, 275-284.
16. Dubuisson L, Lepreux S, Bioulac-Sage P *et al.* Expression and cellular localization of fibrillin-1 in normal and pathological human liver. *J. Hepatol.* 34, 514-522 (2001).
17. Thompson AI, Conroy KP, Henderson NC. Hepatic stellate cells: central modulators of hepatic carcinogenesis. *BMC Gastroenterol.* 15, 63 (2015).
18. Guirouilh J, Castroviejo M, Balabaud C *et al.* Hepatocarcinoma cells stimulate hepatocyte growth factor secretion in human liver myofibroblasts. *Int. J. Oncol.* 17, 777-781 (2000).
19. Guirouilh J, Le Bail B, Boussarie L *et al.* Expression of hepatocyte growth factor in human hepatocellular carcinoma. *J. Hepatol.* 34, 78-83 (2001).
20. Efimova EA, Glanemann M, Liu L *et al.* Effects of human hepatocyte growth factor on the proliferation of human hepatocytes and hepatocellular carcinoma cell lines. *Eur. Surg. Res.* 36, 300-307 (2004).
21. Monvoisin A, Neaud V, De Lédinghen V. Direct evidence that hepatocyte growth factor-induced invasion of hepatocellular carcinoma cells is mediated by urokinase. *J. Hepatol.* 30, 511-518 (1999).
22. Suzuki A, Hayashida M, Kawano H. Hepatocyte growth factor promotes cell survival from fas-mediated cell death in hepatocellular carcinoma cells via Akt activation and Fas-death-inducing signaling complex suppression. *Hepatology.* 32, 796-802 (2000).
23. Schmidt C, Bladt F, Goedecke S *et al.* Scatter factor/hepatocyte growth factor is essential for liver development. *Nature.* 373, 699-702 (1995).
24. Park YN, Kim YB, Yang KM. Increased expression of vascular, endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis. *Arch. Pathol. Lab. Med.* 124, 1061-1065 (2000).
25. Yamaguchi R, Yano H, Iemura A *et al.* Expression of vascular endothelial growth factor in human hepatocellular carcinoma. *Hepatology.* 28, 68-77 (1998).
26. Li XM, Tang ZY, Zhou G *et al.* Significance of vascular endothelial growth factor mRNA expression in invasion and metastasis of hepatocellular carcinoma. *J. Exp. Clin. Cancer. Res.* 17, 13-17 (1998).
27. Yao D-F, Wu X-H, Zhu Y. Quantitative analysis of vascular endothelial growth factor, microvascular density and their clinicopathologic features in human hepatocellular carcinoma. *HBPD. INT.* 4, 220-226 (2005).
28. Zhou J, Tang ZY, Fan J *et al.* Expression of platelet-derived endothelial cell growth factor and vascular endothelial growth factor in hepatocellular carcinoma and portal vein tumor thrombus. *J. Cancer. Res. Clin. Oncol.* 126, 57-61 (2000).
29. Zhu AX, Duda DG, Sahani DV et al. HCC

depends?

and angiogenesis: possible targets and future directions. *Nat. Rev. Clin. Oncol.* 8, 292-301(2011).

30. Llovet JM, Peña CEA, Lathia CD. SHARP Investigators Study Group: Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin. Cancer. Res*. 18, 2290-2300 (2012).
31. Lin N, Chen Z, Lu Y *et al.* Role of activated hepatic stellate cells in proliferation and metastasis of hepatocellular carcinoma. *Hepatol. Res.* 45, 326-336 (2015).
32. Corpechot C, Barbu V, Wendum D *et al.* Hypoxia-induced VEGF and collagen I expressions are associated with angiogenesis and fibrogenesis in experimental cirrhosis. *Hepatology.* 35, 1010-1021 (2002).
33. Aleffi S, Petrai I, Bertolani C S, et al. Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. *Hepatology.* 42, 1339-1348 (2005).
34. Taura K, De Minicis S, Seki E (2008) Hepatic stellate cells secrete angiopoietin 1 that induces angiogenesis in liver fibrosis. Gastroenterology 135: 1729-38.
35. Borkham-Kamphorst E, van Roeyen CR, Ostendorf T *et al.* Pro-fibrogenic potential of PDGF-D in liver fibrosis. *J. Hepatol.* 46, 1064-1074 (2007).
36. Novo E, Cannito S, Zamara E. Proangiogenic cytokines as hypoxia-dependent factors stimulating migration of human hepatic stellate cells. *Am. J. Pathol.* 170: 1942-1953 (2007).
37. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin. Liver. Dis.* 19, 329-338 (1999).
38. Padia SA, Chewning RH, Kogut MJ *et al.* Outcomes of Locoregional Tumor Therapy for Patients with Hepatocellular Carcinoma and Transjugular Intrahepatic Portosystemic Shunts. *Cardiovasc. Intervent. Radiol.* 38, 913-921 (2015).
39. Sakagughi H, Uchida H, Maeda M. Combined transjugular Intrahepatic portosystemic shunt and segmental lipiodol hepatic artery embolization for the treatment of esophagogastric varices and hepatocellular carcinoma in patients with cirrhosis: preliminary report. *Cardiovasc. Intervent. Radiol.* 18, 9-15 (1995).
40. Bettinger D, Knuppel E, Euringer W. Efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPSS) in 40 patients with hepatocellular carcinoma. *Aliment. Pharmacol. Ther.* 41, 126-136 (2015).
41. Tesdal K, Wilkstrom M, Flechtenmacher C. Percutaneous treatment of hepatocellular carcinoma in patients with transjugular intrahepatic portosystemic shunts. *Cardiovasc. Intervent. Radiol*. 29, 778-784 (2006).
42. Kohi MP, Fidelman N, Naeger DM *et al.* Hepatotoxicity after transarterial chemoembolization and transjugular intrahepatic portosystemic shunt: do two rights make a wrong? *J. Vasc. Interv. Radiol.* 24, 68-73 (2013).
43. Kuo YC, Kohi M, Tong R. 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. *Cardiovasc. Intervent. Radiol.* 36, 1-14 (2013).
44. Kang J, Kim J, Ko G. Transarterial chemoembolization for hepatocellular carcinoma after transjugular intrahepatic portosystemic shunt. *Acta. Radiologica.* 53, 545-550 (2012).
45. Wang Z, Zhang H, Zhao H. Repeated transcatheter arterial chemoembolization is safe for hepatocellular carcinoma in cirrhotic patients with transjugular intrahepatic portosystemic shunt. *Diagn. Interv. Radiol.* 20: 487-491 (2014).
46. Laurence AD, Kulik L, Baker T. Yttrium-90 Radioembolization for the treatment of unresectable hepatocellular carcinoma in patients with transjugular intrahepatic portosystemic shunts. *J. of Vasc. Interv. Radiol.* 24, 74-80 (2013).
47. Liu L, Zhao Y, Qi X. Transjugular intrahepatic portosystemic shunt for symptomatic portal hypertension in hepatocellular carcinoma with portal vein tumor thrombosis. *Hepatolo. Res.* 44, 621-630 (2014).
48. Wallace M, Swaim M. Transjugular intrahepatic portosystemic shunts through hepatic neoplasms. *J. Vasc. Interv. Radiol*. 14, 501-507 (2003).
49. Jiang Z, Shan H, Shen X. Transjugular intrahepatic portosystemic shunt for palliative treatment of portal hypertension secondary to portal vein tumor thrombosis. *World J. Gastroenterol.* 10, 1881-1884 (2004).