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Role of Trans-Arterial Chemoembolization (TACE) in patients with hepatocellular carcinoma

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Abstract. – OBJECTIVE: One of the most frequent types of primary liver cancer is hepatocellular carcinoma (HCC). Due to the high incidence of hepatitis B infection, HCC accounts for about 5% of all cancers. HCC is indeed one of the largest leading causes of cancer deaths in the world and the third biggest cause of cancer-related death. The purpose of our research was to see how effective TACE (Trans-Arterial Chemoembolization) therapy was in those who had hepatocellular cancer.

MATERIALS AND METHODS: The Preferred Reporting Items for Systematic Reviews (PRISMA) statement was used to conduct the systemic review. From their inception through the first week of January 2022, the following electronic databases were thoroughly searched: PubMed, Embase, PsycINFO, and the Cochrane Library, with no language constraints. The search terms were "transarterial chemoembolization" or "chemoembolization" or "TACE" AND "hepatocellular carcinoma" or "hematoma" or "HCC" or "liver cancer" or "liver tumor" AND "sorafenib". The references of the discovered articles were also examined. The search included English papers with adult patients only.

RESULTS: A total of 1,234 studies were found for screening after searching the literature in multiple databases. 767 papers were removed based on titles and abstracts, but the complete text of the remaining 129 publications was full text and eligible. In total, 13 studies were included in this research. The study's screening flowchart was depicted using the PRISMA technique. The majority of the findings was of a small magnitude. Even with chronic liver disease and huge tumor groupings, they agreed on the safety and efficacy of such multiple closures prior to plan resection (50 mm). Even after curative resection, the prognosis for these patients remains poor because of portal vein thrombosis, high frequency of liver failure, and microscopic tumor thrombosis.

CONCLUSIONS: TACE is a low-cost palliative treatment for HCC. The initial tumor size is an independent predictor of survival.

Key Words:
Hepatocellular carcinoma, TACE, Transarterial chemoembolization, Hepatitis, Carcinoma.

Introduction

Hepatocellular carcinoma is a common primary liver malignancy (HCC). It is linked to cirrhosis, which is caused by alcohol and viruses. Due to the high frequency of hepatitis B, HCC accounts for 5% of all malignancies. Cancer-related mortality is the third main cause of death from HCC (after stomach and lung cancer). Hepatitis C infection is rising, and so is HCC. Chronic hepatitis B infection, which accounts for over 80% of cases globally, significantly influences demography. Asia has the greatest incidence. In Western nations, the rate is lower, and alcohol is more prevalent[1-4]. The 5-year cumulative risk of hepatitis B (HBV) infection is 10%, Hepatitis C (HCV) infection is 30%, alcoholism is 8%, and biliary cirrhosis is 5%. Other risk factors: food toxins, e.g., aflatoxins, Congenital biliary atresia, Metabolism inborn error, Diabetes mellitus, obesity, and Cholestatic syndrome[4].

Hepatocellular carcinoma is more frequent in men and is detected in late middle age or elderly people with an average age of 65 (75% cases). The tumor may also afflict children; in fact, behind hepatoblastomas, it is the second most frequent primary liver cancer in children. Hepatocellular carcinoma (HCC) is typically detected late in the course of the illness when symptoms and liver damage have already occurred. Virtually, no viable medication would increase survival at this late stage[5,6]. Furthermore, the treatment-related morbidity is too high. TACE is one of the most common first treatments for loco-regional HCC and tumors that do not meet the criteria. TACE can also be utilized as a neoadjuvant treatment before HR or RFA to decrease the tumor volume or micrometastasis. TACE was chosen because of HCC's neoangiogenic capabilities and mode of action on the tumor's hepatic arterial supplies. Throughout the tumor's early phases of development, the portal system supplies blood flow. Even the best HCC relies on hepatic artery supply

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since the tumor grows in size. This tumor feature represents the pathologic foundation for the radiologic HCC criteria. The hepatic artery branch is severed, causing hypoxia and necrosis. This is performed by using an image-guided catheter-based particle infusion to reduce arterial blood flow dramatically[7,8]. A chemotherapeutic drug is injected before vascular embolization. Doxorubicin, cisplatin, mitomycin, and epirubicin have all been utilized in the past as chemotherapy drugs.

Additionally, doxorubicin-eluding beads have recently emerged as a promising TACE substitute. Drug-eluding beads are expected to enhance both treatment response rates and tumor necrosis as compared to conventional TACE. TACE had an 82% 1-year survival rate and a 63% 2-year survival rate for unresectable HCC, according to Lau et al[8]. TACE response is an independent predictor of survival. After two years, TACE-treated patients exhibited a 20-60% increase in survival. Post-embolization syndrome symptoms include stomach discomfort, nausea, ileus, and fever. TACE treatment has previously been deemed contraindicated in portal vein tumor thrombosis. Combined with a tumor thrombus-induced portal vein blockage, this hepatic arterial blood flow disruption may produce severe hepatic necrosis. Several prospective and retrospective studies[9,10] have indicated that TACE improves overall survival in cirrhotic HCC patients with portal vein tumor thrombosis. TACE and Sorafenib may also work synergistically.

Materials and Methods

The systematic review was carried out using the Preferred Reporting Items for Systematic Reviews (PRISMA) statement. In addition, a thorough search of the different electronic databases was done from their establishment through the first week of January 2022: PubMed, Embase, PsycINFO, and the Cochrane Library, without language restrictions.

The search terms were "transarterial chemoembolization" or "chemoembolization" or "TACE" AND "hepatocellular carcinoma" or "hematoma" or "HCC" or "liver cancer" or "liver tumor" AND "sorafenib". The references of the articles that were found were also checked. Only English papers with adult patients were included in the search.

Inclusion and Exclusion Criteria

Sorafenib plus TACE-focused studies as a combination therapy in unresectable HCC were considered. Adult patients and English publications were the only subjects of the studies. All of the following variables were required: overall survival (OS), adverse events (AEs), time to progression (TTP), disease control rate (DCR), and tumor response.

Studies that looked at the effectiveness of Sorafenib alone as a combo treatment were excluded. Editorials, letters, case reports, meta-analyses, and reviews in languages other than English were not examined. Studies that were irrelevant to our issue or did not provide useful information were omitted.

Following the initial discovery of papers from databases, two researchers examined abstracts and titles to screen studies for the above-mentioned criteria. The number of studies and the grounds for exclusion were documented at each screening step. Following that, an independent reviewer read the whole text of the work to be published and gathered pertinent information, such as treatment methods, baseline characteristics, TTP, OS, AEs, DCR, tumor responses, and HR. Finally, all data were gathered and analyzed. The two researchers' disagreements were discussed until a solution was found.

TTP was referred to as the period between the commencement of therapy and the final follow-up. The OS was computed from the first TACE through the date of death or the last follow-up. By integrating the partial response rate, stable sickness rate, and complete response rate, the DCR was created. Our meta-analysis focused on two forms of TACE: drug-eluting beads TACE (DEB-TACE) and traditional TACE (c-TACE). Combination therapy was classified as a treatment that included TACE before or after Sorafenib. During their treatment, patients should have at least one TACE session. Data was collected and evaluated separately using predesigned data extraction forms. The information was entered into the Cochrane review manager program.

Results

A total of 1,234 research articles were found for screening after searching the literature in different electronic databases. 767 papers were removed based on titles and abstracts, but the complete texts of the remaining 129 publications were full text and eligible. In total, 13 articles were considered in this research. The study's screening flowchart is depicted using the PRISMA technique (Figure 1).

All patients were assigned to one of two Child-Pugh (CP) classes: A or B, with CP A being the most common (65-94%). BCLC B stage patients were recorded at about 20-100%, and the percentage of patients with BCLC C stage was between 1.9-80%. The performance level of the ECOG was reported to be 0 or 1 (94-100%). Hepatitis virus infection rates ranged between 24 and 100% in total. Table I lists all patients' baseline data, as well as the length of sorafenib treatment and the number of TACE sessions.

Prior to commencing Sorafenib, the patients were TACE-responsive. Some people in Ohki et al[14] study did not respond to TACE. Each trial's treatment techniques are also outlined in Table I. Table II displays the HR for TTP from nine studies. The overall HR for TTP was 0.66 (95% confidence interval (CI) 0.50-0.81, *p*-value = 0.002), showing that combination treatment substantially lengthened TTP, according to the forest plot. These findings could indicate that Asian countries have a significant positive TTP outcome. Disparities in survival outcomes between locations may be due to a variety of causes.

The most important conclusions of the research were of minimal importance. They concurred on the effectiveness and safety of such double occlusion prior to plan resection, even in the chronic liver disease and big tumor (50 mm) groups. The prognosis for these patients remains poor even after curative resection owing to the frequent occurrence of portal vein thrombosis, liver failure, or microscopic tumor thrombosis. We conclude that a lack of response after two consecutive TACE operations led to a poor OR, regardless of whether or not the TACE treatment was repeated. TACE

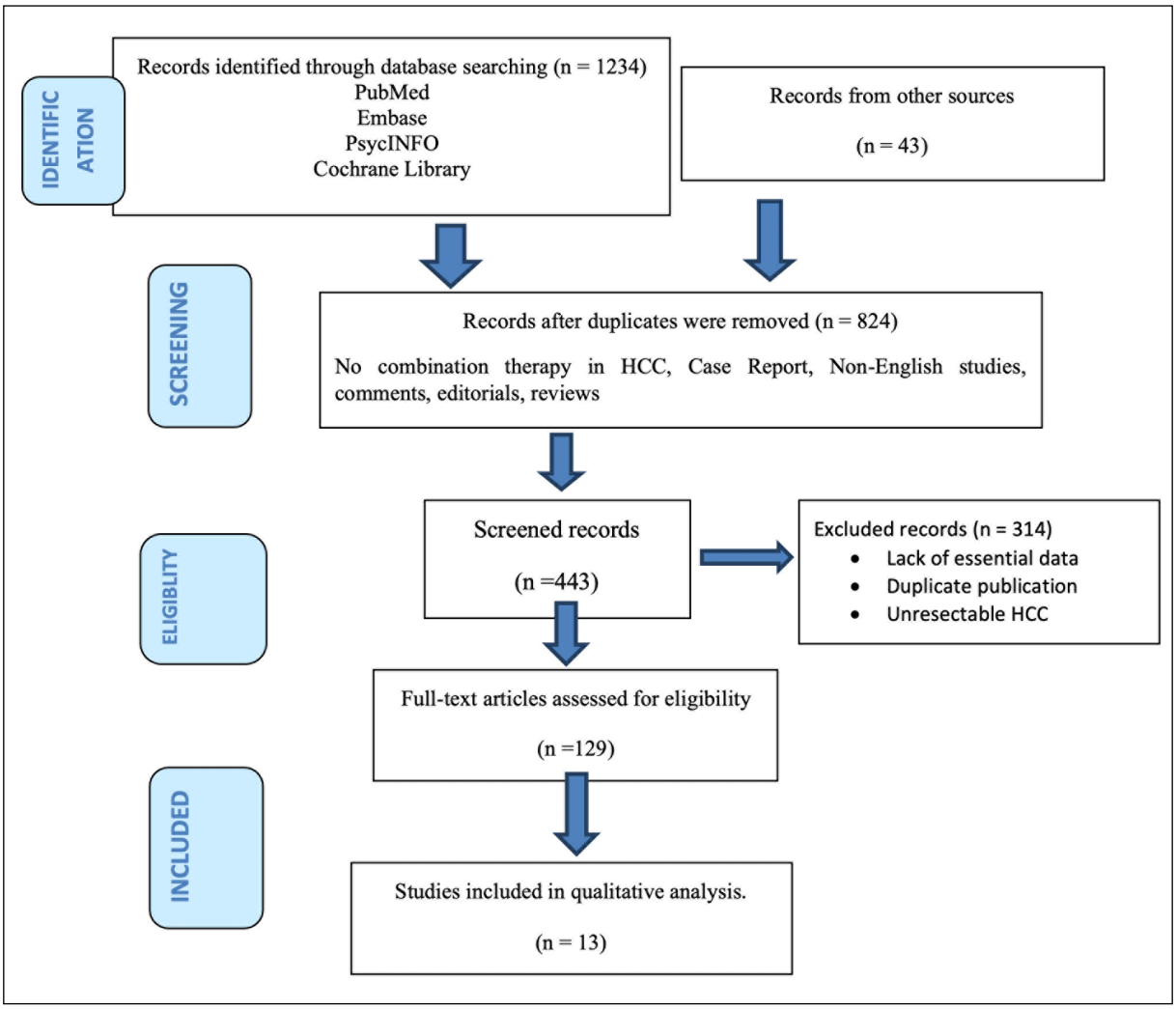

Figure 1. The PRISMA technique was used to create a schedule of records pertinent to the current study.

Table I. Baseline characteristics of study and patients.

SN.	Author references	No. of Participants	Study Design	Region	Etiology	No. of TACE	Treatment	Duration Time of orafenib
1	Erhardt et al[11]	38	Phase II	Germany	NA	2.0 (mean)	TACE is the only time when continuous Sorafenib is discontinued.	NA
2	Pan et al[12]	41	Retrospective	China	HBV 97.6%, HCV 2.4%	2.0 (median)	Sorafenib was administered three days following the initial TACE operation.	NA
3	Cosgrove et al[13]	50	Phase II	USA	HBV 8%, HCV 44%	2.0 (median)	Sorafenib was begun one week prior to the first cycle of DEB-TACE.	1.5 Month
4	Ohki et al[14]	95	Retrospective	Japan	ST:HCV 75.0%, T:HCV 67.6%	2.0 (median)	Sorafenib was initiated two weeks after TACE.	
5	Yao et al[15]	150	Prospective	China	ST:HBV 84%, T:HBV 83%	2.0 (median)	Sorafenib therapy was started one week before or after the first TACE treatment.	
6	Zhang et al (2016)[16]	20	Retrospective	China	HBV 80%	2.0 (median)	Sorafenib was administered 4-7 days before or after the TACE session.	NA
7	Varghese et al[17]	124	Retrospective	India	B:HBV 37.3% HCV 18.7% C:HBV 26.2% HCV 23%	2.0(median)	Sorafenib was started 5 days after TACE.	
8	Wan et al[18]	450	Retrospective	China	NA		Oral Sorafenib was given either before or after TACE.	
9	Sieghart et al[19]	15	Phase I	Austria	HBV 4%, HCV 20%	3.0 (median)	Sorafenib began two weeks before the first TACE	5.2 months
10	Chung et al[20]	151	Phase II Prospective	China and South Korea	NA	2.1(mean)	Sorafenib Begun 4-7 days after TACE	NA
11	Pawlik et al[21]	35	Phase II Prospective	USA	HCV 37%	2.0 (median)	One week before DEB-TACE, a week of continuous Sorafenib was started.	NA
12	Dai et al[22]	119	Retrospective	China	PVTT with HCC		Postoperative treatment	
13	Terasawa et al[23]	55	Prospective	France	Large HCC simultaneous		Preoperative treatment	

refractoriness, as defined by treatment criteria, seems to be supported by these data.

Considering that there was no substantial difference in survival between the initial CR group and the delayed CR group, we believe that repeated TACE is necessary to achieve CR, resulting in a survival advantage even in later TACE sessions. Individuals who initially exhibited an OR had a substantially greater survival rate than others who did not display an OR after repeated TACE, trailed by patients who demonstrated an OR in consecutive TACE sessions. This indicates that if an OR to TACE occurs, it is suggested to repeat TACE for survival purposes; however, if an OR does not exist twice in a row, additional TACEs may be superfluous.

Discussion

TACE is the most often utilized therapeutic option in those who have hepatocellular carcinoma (HCC) and are not candidates for therapeutic options. The rest of the world has a unique epidemiological heterogeneity when it comes to the etiology and stage of HCC at diagnosis; Asia and Africa contribute to over 80% of HCC cases[11].

Despite the fact that cirrhosis is the most prevalent cause of HCC, the etiology of cirrhosis has been found to affect HCC patients' prognosis. This was not taken into account in every suggestion or prognostic assessment. HBV is to blame for 54.4% of all HCC cases found globally, while HCV is to blame for 31.1%. A small percentage of HCV-infected patients, however, are drinkers[30,31]. Zhou et al[32] reported on the impact of viral hepatitis on survival in a meta-analysis of 4,744 patients, 2,008 of whom were HBV positive and 2,222 of whom were HCV positive, whereas 514 were HBV and HCV negative. When compared to patients with negative serology, those with viral hepatitis had a dismal prognosis. They also advocated for the use of adjuvant antiviral therapy after HCC treatment to prevent tumor recurrence.

HCV-related HCC, on the other hand, is more common in countries such as Japan, Spain, and others. Most of our patients (66/73; 90.41%) were symptomatic at presentation and had a somewhat large tumor size at the outset, indicating advanced illness. The treatment of these folks was incredibly tough. People with smaller tumors were included in Japan's largest documented TACE experience, with a research sample of 8510 patients (24% with 2 cm and 75% with 5 cm). TACE's utility in treating bigger liver tumors has received little attention (mean diameter approximately 7 cm)[33].

SPACE was the first large-scale multinational randomized controlled study of Sorafenib or placebo in conjunction with TACE for intermediate-stage HCC. It revealed no significant difference in TTP between the combination treatment and TACE alone groups[28]. Following that, a flood of clinical trials conducted around the world assessed the efficacy of combination medicine, with the vast majority concluding that it was more effective in terms of TTP than monotherapy. The majority of the comparative studies we reviewed discovered that, as compared to TACE alone, combining TIPS with Sorafenib increased TTP in patients who were not responding to TACE[15,22,26].

Table II. Median Time to progression, the hazard ratio and 95% confidence intervals for the combined therapy group against the TACE alone group.

SN.	Authors years	Combination group (95% CI)/months	HR (95% CI)	TACE alone group (95% CI)/months
1	Sansonno et al[24]	9.2	2.5 (1.66-7.56)	4.9
2	Zhang et al[16]	4.9 (3.7-6.0)	NA	2.4 (1.3-3.4)
3	Bai et al[25]	6.3	0.6 (0.422-0.853)	4.3
4	Hu et al[26]	2.6	0.62 (0.47-0.82)	1.9
5	Huang et al[27]	5.4	0.99 (0.67-1.47)	3.7
6	Lencioni et al[28]	5.6	0.797 (0.588-1.08)	5.5
7	Muhammad et al[29]	NA	0.93 (0.45-1.89)	NA
8	Ohki et al[14]	6.3	0.38 (0.22-0.63)	3.5
9	Yao et al[15]	10.2	0.403 (0.251-0.646)	6.7

In a small prospective case-control study, Zhao et al[34] treated 48 patients with inoperable HCC using PVTT. TACE was used in combination with PVCE in 23 of them, while TACE was used alone in the remaining patients. The TACE+PVCE group had a significantly greater rate of PVTT decrease, and the combination treatment also alleviated gastrointestinal symptoms more effectively (p-value = 0.05). During the 1-year follow-up, the survival rate also improved (48% *vs.* 25%, p-value = 0.05). Further research comprised 116 PVTT HCC patients who were administered with TACE alone (64 patients) or TACE with PVE (52 patients) and monitored for a longer period of time[34]. The combination therapy group had a significant prognostic benefit, according to the findings. The advantages were underlined even more in patients with Type-I PVTT, where tumor thrombi were restricted to partial branches of the portal vein or above it, according to the subgroup analysis[34-36].

In clinical trials involving HCC patients with portal venous invasion, combination treatment was shown to be more effective than TACE alone in terms of TTP and OS. The combination treatment was shown to be harmful in HCC patients with portal vein invasion. The degree of portal vein invasion may have an impact on survival. Additionally, the favorable OS of combination therapy in patients with a poorer baseline status might be attributed to the convergence of systemic and loco-regional therapies[37,38]. Some other research[26] found that age was not a determinant of therapeutic response in advanced HCC patients when comparing the combined effectiveness of elderly and non-elderly people.

TACE is well known low-risk technique with a low fatality rate that has been steadily decreasing throughout the last twenty years (reportedly 10% in 1991, 1.1% in 1999, and 0.5% in 2006). Hepatic failure (40.1%), cancer mortality (18.2%), and HCC rupture were the major cause of mortality in the TACE research with the greatest sample size. There appears to be no agreement on whether or not patients should have TACE sessions repeated. TACE is repeated at defined intervals in some centers, ranging between 2-3 months. We repeated TACE sessions four weeks following treatment based on the findings of a follow-up CT. This policy was comparable to that used in Takayasu et al[33] state wide's multicentric Japanese investigation. TACE is said to be more effective when repeated based on follow-up imaging data rather than at predefined intervals[39,40].

Conclusions

To conclude, TACE is a pain-relieving method that is both safe and effective. At the time of diagnosis, the patients usually had aggressive cancers. TACE has provided advantageous results, with survival rates comparable to those described by other investigators. In hepatocellular carcinoma individuals, the initial tumor size was the most influential independent predictive factor.

Conflicts of Interest

The author declares that he has no conflicts of interest.

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Ethical Approval

Not applicable.

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References

1) Kumar V, Abbas AK, Fausto N, Robbins SL, Cotran, Ramzi S. Pathologic basis of disease. W B Saunders Co 2005; 1915-2003.
2) Dähnert W. Radiology review manual. Lippincott Williams & Wilkins 2003.
3) Smith MT, Blatt ER, Jedlicka P, Strain JD, Fenton LZ. Best cases from the AFIP: fibrolamellar hepatocellular carcinoma. Radiographics 2008; 28: 609-613.
4) Antila KM, Mäkisalo H, Arola J Kristel N. Best cases from the AFIP: biliary papillomatosis. Radiographics 28: 2059-2063.
5) Willatt JM, Hussain HK, Adusumilli S, Marrero JA. MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies. Radiology 2008; 247: 311-330.
6) Kim KW, Kim MJ, Lee SS, Kim HJ, Shin YM, Kim PN, Lee MG. Sparing of fatty infiltration around focal hepatic lesions in patients with hepatic steatosis: sonographic appearance with CT and MRI correlation. AJR Am J Roentgenol 2008; 190: 1018-1027.

7) Choi BI, Lee KH, Han JK, Lee JM. Hepatic arterioportal shunts: dynamic CT and MR features. Korean J Radiol 2002; 3: 1-15.
8) Lau WY. Hepatocellulararcarcinoma. World Scientific Pub Co Inc 2008.
9) Grendell JH, Friedman SL, McQuaid KR. Current diagnosis & treatment in gastroenterology. McGraw-Hill Medical 2003.
10) Stubbs RS, Wickremesekera SK. Selective internal radiation therapy (SIRT): a new modality for treating patients with colorectal liver metastases. HPB (Oxford) 2004; 6: 133-139.
11) Erhardt A, Kolligs F, Dollinger M, Schott E, Wege H, Bitzer M, Gog C, Lammert F, Schuchmann M, Walter C, Blondin D, Ohmann C, Häussinger D. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. Cancer Chemother Pharmacol 2014; 74: 947-954.
12) Pan T, Li XS, Xie QK, Wang JP, Li W, Wu PH, Zhao M. Safety and efficacy of transarterial chemoembolization plus Sorafenib for hepatocellular carcinoma with portal vein tumor thrombus. Clin Radiol 2014; 69: e553-561.
13) Bai W, Wang YJ, Zhao Y, Qi XS, Yin ZX, He CY, Li RJ, Wu KC, Xia JL, Fan DM, Han GH. Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: A propensity score matching study. J Dig Dis 2013; 14: 181-190.
14) Ohki T, Sato K, Yamagami M, Ito D, Yamada T, Kawanishi K, Kojima K, Seki M, Toda N, Tagawa K. Efficacy of Transcatheter Arterial Chemoembolization Followed by Sorafenib for Intermediate/Advanced Hepatocellular Carcinoma in Patients in Japan: A Retrospective Analysis. Clin Drug Investig 2015; 35: 751-759.
15) Yao X, Yan D, Zeng H, Liu D, Li H. Concurrent sorafenib therapy extends the interval to subsequent TACE for patients with unresectable hepatocellular carcinoma. J Surg Oncol 2016; 113: 672-677.
16) Zhang YF, Wei W, Wang JH, Xu L, Jian PE, Xiao CZ, Zhong XP, Shi M, Guo RP. Transarterial chemoembolization combined with Sorafenib for the treatment of hepatocellular carcinoma with hepatic vein tumor thrombus. Once Targets Ther 2016; 9: 4239-4246.
17) Varghese J, Kedarisetty C, Venkataraman J, Srinivasan V, Deepashree T, Uthappa M, Ilankumaran K, Govil S, Reddy M, Rela M. Combination of TACE and Sorafenib Improves Outcomes in BCLC Stages B/C of Hepatocellular Carcinoma: A Single Centre Experience. Ann Hepatol 2017; 16: 247-254.
18) Wan X, Zhai X, Yan Z, Yang P, Li J, Wu D, Wang K, Xia Y, Shen F. Retrospective analysis of transarterial chemoembolization and Sorafenib in Chinese patients with unresectable and recurrent hepatocellular carcinoma. Oncotarget 2016; 7: 83806-83816.
19) Sieghart W, Pinter M, Reisegger M, Müller C, Ba-Ssalamah A, Lammer J, Peck-Radosavljevic M. Conventional transarterial chemoembolization in combination with Sorafenib for patients with hepatocellular carcinoma: a pilot study. Eur Radiol 2012; 22: 1214-1223.
20) Chung YH, Han G, Yoon JH, Yang J, Wang J, Shao GL, Kim BI, Lee TY, Chao Y. Interim analysis of START: Study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with Sorafenib in patients with hepatocellular carcinoma trial. Int J Cancer 2013; 132: 2448-5248.
21) Reyes D, Azad N, Koteish A, Kamel I, Hamilton J, Pawlik T, Choti M, Bhagat N, Geschwind JF. Abstract No. 4: Phase II trial of Sorafenib combined with doxorubicin eluting bead-transarterial chemoembolization for patients with unresectable hepatocellular carcinoma: Interim efficacy analysis. J Vasc Interv Radiol 2011; 22: S4-5.
22) Dai B, Lei S, Yang Z, Du X. Efficacy and safety of postoperative adjuvant transcatheter arterial chemoembolization plus portal vein chemotherapy for hepatocellular carcinoma patients associated with portal vein tumor thrombus. Chin J Gen Surg 2019; 28: 188-194.
23) Terasawa M, Allard MA, Golse N, Sa Cunha A, Cherqui D, Adam R, Saiura A, Vibert E. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization alone before major hepatectomy for patients with large hepatocellular carcinoma: an intent-to-treat analysis. Surgery (United States) 2020; 167: 425-431.
24) Sansonno D, Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F. Transarterial Chemoembolization Plus Sorafenib: A Sequential Therapeutic Scheme for HCV-Related Intermediate-Stage Hepatocellular Carcinoma: A Randomized Clinical Trial. Oncologist 2012; 17: 359-366.
25) Bai W, Wang YJ, Zhao Y, Qi XS, Yin ZX, He CY, Li RJ, Wu KC, Xia JL, Fan DM, Han GH. Sorafenib in combination with transarterial chemoembolization improves the survival of patients with unresectable hepatocellular carcinoma: A propensity score matching study. J Dig Dis 2013; 14: 181-190.
26) Hu H, Duan Z, Long X, Hertzanu Y, Shi H, Liu S, Yang Z, Woloschak GE. Sorafenib Combined with Transarterial Chemoembolization versus Transarterial Chemoembolization Alone for Advanced-Stage Hepatocellular Carcinoma: A Propensity Score Matching Study. PLoS One 2014; 9: e96620.
27) Huang YH, Chen W, Li JP, Chen B, Yang JY. Clinical value of continuous administration of Sorafenib in combination with modified transarterial chemoembolization in patients with unresectable hepatocellular carcinoma. Chin Med J 2013; 126: 385-386.
28) Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, Paik SW, Reig M, Do YK, Chau G-Y, Luca A, del Arbol LR, Leberre M-A, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo

plus TACE with doxorubicin eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016; 64: 1090-1098.

29) Muhammad A, Dhamija M, Vidyarthi G, Amodeo D, Boyd W, Miladinovic B, Kumar A. Comparative effectiveness of traditional chemoembolization with or without sorafenib for hepatocellular carcinoma. World J Hepatol 2013; 5: 364-371.

30) Budny A, Kozłowski P, Kamińska M, Jankiewicz M, Kolak A, Budny B, Budny W, Niemunis-Sawicka J, Szczypiór G, Kurniawka B, Burdan F. Epidemiologia i czynniki ryzyka rozwoju raka wątrobowokomórkowego [Epidemiology and risk factors of hepatocellular carcinoma]. Pol Merkur Lekarski 2017; 43: 133-139.

31) Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: epidemiology, etiology, and carcinogenesis. J Carcinog 2017; 16: 1.

32) Zhou Y, Si X, Wu L, Su X, Li B, Zhang Z. Influence of viral hepatitis status on prognosis in patients undergoing hepatic resection for hepatocellular carcinoma: a meta-analysis of observational studies. World J Surg Oncol 2011; 9: 108.

33) Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-469.

34) Zhao Y, Zhang Q, Yuan W. The clinical study of pvce with tace for primary hepatocellular carcinoma portal vein tumor thrombus. J Guangxi Med Univ 2009; 86: 840-842.

35) Tan X, Xie P, Liu J, Wu H, Xie Y. Therapeutic value of transcatheter arterial chemoembolization combined with portal vein embolization for primary hepatocellular carcinoma with portal vein tumor thrombus: a pilot study. Asia Pac J Clin Oncol 2015; 11: e6-12.

36) Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011; 18: 74-80.

37) Li X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. World J Gastroenterol 2004; 10: 2878.

38) Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of Sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008; 7: 3129-3140.

39) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.

40) Paul SB, Chalamalasetty SB, Vishnubhatla S, Madan K, Gamanagatti SR, Batra Y, Gupta SD, Panda SK, Acharya SK. Clinical Profile, Etiology and Therapeutic Outcome in 324 Hepatocellular Carcinoma Patients at a Tertiary Care Center in India. Oncology 2009; 77: 162-171.