74065_Auto_Edited-check.docx

WORD COUNT	3590	TIME SUBMITTED	14-APR-2022 11:03PM
		PAPER ID	84824468

Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition

Zhang S *et al*. Is TACE failure reasonable

Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni

Abstract

Multi-session transarterial chemoembolization (TACE) usually needs for the treatment of intermediate-stage hepatocellular carcinoma (HCC), but it may not always have positive influence on prognosis due to high heterogeneities of HCC. To avoid ineffective repeated TACE, the concept of TACE failure/refractoriness has been proposed by several organizations and is being addressed with the complements of tyrosine kinase inhibitors. Whereas, the concept of TACE failure/refractoriness is controversial because of ambiguous definitions and low evidenced-based data. To date, only a few articles have explored the rationality concerning the definition of TACE failure/refractoriness, though the concept has been introduced and applied into many TACE-related clinical trials. This review will focus on some issues extracted from different versions of TACE failure/refractoriness, discussing the rationalities in related definitions, and elaborating the feasibility of continuing TACE after so-called failure/refractoriness based on published evidence. A suggestion to re-define TAEC failure/refractoriness is put forward as well.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Failure; Refractoriness

Zhang S, Zhong BY, Zhang L, Wang WS, Ni CF. Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition. *World J Gastrointest Surg* 2022; In press

Core Tip: The definitions in current concept of transarterial chemoembolization (TACE) failure/refractoriness are not capable of guiding clinical practice; persistent viable tumor lesion is a well-accepted item of TACE failure/refractoriness, but that is not the case when it comes to new lesions, portal vein tumor thrombosis or extrahepatic spread; patients with recurrent hepatocellular carcinoma after TACE constitute a heterogenous group and the treatment modalities need to be individualized.

INTRODUCTION

According to Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the standard approach for patients with intermediate stage (BCLC B) hepatocellular carcinoma (HCC)[1-3]. Nevertheless, the overall prognosis for patients undergoing TACE varies considerably because of the high heterogeneities of HCC in BCLC-B stage[4]. Besides, repeated TACE courses are associated with an increase in angiogenesis and embolization-related liver damage, all of which may negate benefits achieved in tumor or even adversely affect overall survival (OS)[4-6]. Thus, many explorations have been made in order to identify a turning point where the subsequent repeated TACE procedure could not be more beneficial than alternative treatments or best supportive care for patients[7,8]. With the clinical application of tyrosine kinase inhibitors (TKIs), some scholars put forward a new treatment paradigm where patients in intermediate stage HCC should switch to TKIs monotherapy once tumor progression occurs after TACE procedures[9,10], and as the consequence, the concept of TACE failure/refractoriness was introduced and proposed.

REVIEW ON DIFFERENT DEFINITIONS OF TACE FAILURE/REFRACTORINESS

The concept of TACE failure/refractoriness was initially proposed by Japan Society of Hepatology (JHS) in 2010[11] and revised by JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014 (Table 1) during a consensus meeting[6]. According to the definition, persistent viable of treated lesions, consecutive emergence of new intrahepatic tumors

and disease stage progression as well as continuous elevation of tumor markers were scenarios to terminate repeated TACE. Whereas, Korean scholars did not take the same views and they concluded 3 conditions, namely 3 times or more TACE procedures within 6 mo, advancing to portal vein tumor thrombosis (PVTT) and extrahepatic spread (EHS) as TACE failure/refractoriness[12]. These suggestions were supported by International Association for the Study of the Liver as well (Table 1)[13]. Notably, concept from Europeans seems to be more reliable in clinical practice (Table 1)[14]. They suggested that the determination of TACE failure/refractoriness should be in line with the indications of TACE. The result with stable disease (SD) meant to obtain therapeutic purpose if the goal of TACE was just for palliative therapy. Conversely, supposed TACE acted as a curative treatment, the result with SD or progression disease was identified as TACE failure/refractoriness. Currently, the concept of TACE failure/refractoriness has been widely introduced, especially in clinical trials for HCC[5,9,10,15,16]. Nevertheless, the contents in the concepts need further discussing owning to low evidenced-based data. This article attempts to give a comprehensive understanding concerning the omissions in the current definitions based on published evidence.

COMPREHENSIVE ANALYSES OF THE ENDPOINTS FOR TACE IN TACE FAILURE/REFRACTORINESS

Persistent viable targeted lesion(s) after consecutive treatments

When insufficient response of intrahepatic tumor happens after multi-session TACE, it is sensible to define TACE failure/refractoriness and to stop TACE. The peripheral region as well as capsular of HCC nodules may be nourished by both hepatic artery and portal vein and, as a result, a substantial tumor necrosis by arterial embolization is not always guaranteed[17-19]. It has been reported that nourishing vessels of residual tumors may change from the hepatic artery to the portal vein after repeated TACE[20]. In addition, repeated chemoembolization increases the pressure to tumor micro-environment and may lead to phenotypic variation in surviving tumor cells, which tend

to be more malignant and chemoembolization-resistant[21-23]. It has been reported that locally recurrent HCC after TACE have a significantly shorter doubling time than primary HCC nodules[24].

How many sessions of TACE should be performed before abandoning TACE in case of insufficient tumor necrosis is a crucial issue. Georgiades *et al*[25] reported that 47% of non-responders to the first TACE ultimately achieved partial response (PR) or complete response (CR) after the second procedure, and median OS between patients who achieved response at the first or the second chemoembolization was comparable. Some experts had suggested, if target nodule(s) show no response after at least two consecutive sessions of TACE, it was reasonable to defined TACE-failure and trigger treatment stage migration[2,4,16,26]. Based on a large cohort study containing 4154 patients with HCC, Chen *et al*[27] found that HCC nodules became intensely unsensitive to chemoembolization after 3 sessions of TACE, with objective response rate (ORR) < 10%. Furthermore, patients whose tumors eventually attaining CR or PR within the first 3 TACE had a longer median OS than those who were not (43.4 mo *vs* 16.6 mo, $P < 0.001$). As a consequence, three sessions were recommended before abandoning TACE.

Nevertheless, residual tumors with persistent viability may not be an absolute indication for systemic monotherapy owning to the unsatisfied anti-tumor effect[28]. Other locoregional interventional methods, with a curative potential, are preferred options once tumor size meets indications. Chen *et al*[17] reported that subsequent microwave ablation (MWA) yielded a better survival time than sorafenib for patients with incomplete remission of targeted lesions after multiple sessions of TACE, with a longer progression-free survival (PFS) time (9.0 mo *vs* 2.8 mo, $P = 0.006$) and OS (Not reached *vs* 16.6 mo, $P = 0.001$). In addition, Yttrium-90 radioembolization and Iodine-125 (^{125}I) seed brachytherapy have been adopted to control target lesions[29-31]. TACE combined with systemic therapy or loco-regional therapy revealed favorable outcomes and well tolerance as well[15,31,32].

New intrahepatic lesion(s) appearing after consecutive treatments

Vascular endothelial growth factor (VEGF), which is regulated by hypoxia-inducible factor-1α, has been demonstrated as the most important element to neovascularization[33]. Whereas, substantial evidence was expected to elucidate the intrinsic connection between the transient upregulation of VEGF after TACE and intrahepatic metastasis. Tumor recurrences are frequently reported after TACE, whereas it is arbitrary to describe this scenario as absolute contraindication to repeated TACE[34,35]. First, TACE is traditionally recognized as a palliative, loco-regional therapy and it is unreasonable to define the occurrence of new lesions outside treated areas as disease progression[4,27,35]. Second, the frequent intrahepatic metastasis is the inherent nature of HCC and it happened in very early-stage. A clinicopathologic research found that nearly 19% small HCC patients (solitary nodule with the diameter no more than 3 cm) had satellite lesions, located in 2 cm or less from the main tumor and 1 mm to 5 mm in diameter[36]. Though these nondetectable and untypical micro-metastases are too small to be diagnosed as tumors according to European Association for the Study of the Liver (EASL)[3], they possess enormous potential to develop into typical tumor lesions and appeared as tumor local recurrence or intrahepatic metastases[37]. Besides, the malignance of HCC is positively associated with tumor size. It had been reported that approximately 51.3% of HCC nodules (with an average size of 5 cm) had microvascular invasion (MVI) and 42.4% of nucleus were of severe atypicality[38]. For patients with intermediate- or advanced-stage HCC, early tumor progression after locoregional therapy was almost inevitable because of heavy tumor burden and frequent MVI[15,32,39]. Combination therapy was expected to delay tumor recurrence[16]. As the matter of the fact, even the supporters of TACE failure/refractoriness are ambivalent on the issue whether the new lesion(s) after TACE is an condition of TACE failure/refractoriness[6,16,35]. In the TACTICS trial, the first randomized control trial (RCT) demonstrating the superiority of TACE plus sorafenib to TACE monotherapy in unresectable HCC, “TACE failure/refractoriness” was one of the major endpoints for TACE treatment. However, the study simultaneously emphasized multicentric occurrence and intrahepatic recurrence/metastases were the unique biological features

to HCC[35], and therefore it was reasonable to perform demand TACE to control new tumor lesions[40]. So far, there is still no convincing evidence to conclude that new intrahepatic tumor lesion attributes to biological features of HCC whereas consecutive intrahepatic metastasis should be defined as TACE failure/refractoriness.

On-demand TACE for new intrahepatic lesions is safe and efficient in selected patients[12,41]. In a large cohort study, 264 patients with intermediate-stage HCC underwent TACE with "on demand" mode (range: 1-13 times; mean: 3 times)[12]. During the follow up, patients experiencing intrahepatic metastasis or total target tumor diameter increasing by 20% were defined as having progressive disease (PD), while those having PVTT invasion or EHS were defined as having stage progression (SP). The results showed that median OS was comparable between patients in PD (-) & SP (-) group (36.6 mo) and in PD (+) & SP (-) group (35.5 mo). However, evidence from above literatures only supports the feasibility of repeated TACE on new lesions, but by no means indicates that TACE can be implemented unrestrainedly. Liver function deterioration and hypoxia-induced pressure on residual HCCs have great influence on patients' survival. Additional systemic therapies including TKIs are hopeful to prolong the interval between two TACE sessions and to hamper intrahepatic micro-metastases[16,42]. Hence, the treatment decision has to be individualized according to expert evaluation. Several nomograms have been established to identify patients who may get benefit from repeated TACE, but rationalities of these nomograms are still under controversy[7,8,43].

Continuous elevation of tumor markers

On-scheduled tumor marker assessment is a crucial adjuvant method to evaluate tumor response as well as to surveil tumor recurrence. Sudden increasement in α-fetoprotein (AFP), AFP-L3 and/or des-gamma-carboxy prothrombin after treatments were thought to tumor progression or a change of tumor being more malignant[44,45]. However, that does not indicate definitive correlation with TACE failure/refractoriness. On the one hand, well-designed control study is expected to clarify the superiority of TKIs to TACE

in patients who experienced tumor marker flare after TACE. Though previous evidence stressed that rapid reductions in tumor markers were positive predictors to TACE and vice versa[46], subsequent treatments to deal with elevated tumor marker were not explored and recommended. Up to now, all TKIs targeting HCC, except ramucirumab which demonstrated apparent benefits in patients with AFP ≥ 400 ng/mL, are not designed for biomarker-selected population[47]. On the other hand, the significance of the tumor marker trends has not yet been fully elucidated in the management of HCC and the relationship between different tumor markers and morphological changes was unclear[21,46]. Just as EASL clinical practice guideline declared, the use of changes in serum biomarker levels for assessment of response (*i.e.* AFP levels) is under investigation[3]. Hence, when tumor markers are increased after TACE, subsequent treatment should be codetermined by tumor burden, liver function and tumor response to previous TACE, rather than abandoning TACE blindly[3,48]. Furthermore, "continuous elevation" is a vague definition and an immature quantification on "elevation" brings many subject factors into clinical decision. Ogasawara *et al*[10] suggested the level of AFP elevating by 20% from baseline as a cut-off value. Nevertheless, other researchers have different opinions[8, 45].

Appearance of vascular invasion* or *extrahepatic spread

Neither EASL nor the American Association for the Study of Liver Disease guidelines recommend TACE for treating HCC with PVTT or EHS[1,3]. However, according to the BRIDGE study that documented real-word clinical practice in HCC, TACE was still the most frequent first treatment in advanced-stage HCC[49]. A national questionnaire conducted in Korea also indicated that nearly half of clinicians would not abandon TACE in case of PVTT or EHS because of the vast heterogeneities of HCC[48]. Outcomes from SHARP and A-P clinical trials and the corresponding subgroup analyses just showed a marginal improvement of sorafenib over placebo in terms of PVTT with/without EHS[28,50-52]. Lenvatinib exhibited a promising short-term anti-tumor effect than sorafenib for patients suffering PVTT with/without EHS [Hazard ratio (HR):

0.64; 95% confidence interval (CI): 0.54-0.77], while the long-term prognosis was undefined (HR: 0.87; 95%CI: 0.73-1.04). It is worth stressing that though BCLC stage system recommends systemic therapy as the initial treatment for advanced-stage HCC, a special profile of an individual patients may induce a different option in clinical practice[48,49,53-55].

Vascular invasion

With the development of embolization techniques, TACE has been safely and effectively performed in some patients with adequate collateral pathways around the occluded portal vein[15,48,55-58]. These advanced stage populations were defined as "Quasi-C" patients (segmental PVTT, Child-Pugh A, and acceptable performance status). A meta-analysis showed that TACE conferred a longer OS in patients with branch PVTT than those with main trunk PVTT (11 mo *vs* 5 mo, $P < 0.001$)[59]. Significantly, for PVTT invading main trunk, initial portal vein re-canalization using irradiation stent with subsequent selective TACE was effective to hamper disease progression, with median stent patency of 8 mo and median OS of 12.5 mo[60]. Wang *et al*[61] introduced a modified ^{125}I seed brachytherapy to treat main trunk PVTT and exhibited a favorable outcomes when combined with TACE (median OS: 9.8 mo). Besides, combination therapy of TACE and TKIs stated better results for selected patients with PVTT[62]. According to a large cohort study, compared with sorafenib monotherapy, TACE combined with sorafenib showed a trend towards significant risk reduction in patients (n = 1136) with vascular invasion (HR: 0.78; 95% CI: 0.59-1.02)[63]. Recently, a RCT conducted by Ding *et al*[62] reported that TACE plus lenvatinib had a more favorable efficacy *vs* TACE plus sorafenib in patients with PVTT, especially for those with Vp1-3 type (HR: 0.12; 95% CI: 0.03-0.42, $P < 0.01$) or heavy tumor burden (HR: 0.30; 95% CI: 0.15-0.61, $P < 0.01$). It is deserved to emphasize that PVTT is a complex system and optimal treatment strategy is individual rather than univocal. For patients whose tumor thrombus involving segmental of the portal vein or above, surgery is a potential option once tumor burden downstages to Milan criteria in the

liver; for patients who miss curative treatment, TACE, TKIs and other modalities may play a complementary role in control disease progression[57]. So far, many novel treatment strategies have been investigated for PVTT and yielded exciting results, providing patients with more treatment options [30,57,60,64,65].

Extrahepatic spread

Subgroup analysis from SHARP clinical trial reveal that sorafenib only conferred an additional survival time of 0.6 mo compared with placebo[52]. Due to the fact that more than two-thirds of patients with EHS died of intrahepatic tumor progression rather than extrahepatic disease, aggressive treatment targeting intrahepatic disease might be still available and beneficial to selected patients with EHS[15,53,63]. Results fromKirstein *et al*[53] suggested that TACE was not inferior to sorafenib in patients with limited EHS of HCC, with median OS of 88 mo *vs* 7 mo forfor sorafenib *vs* TACE (P = 0.31212) before propensity score matching (PSM) analysis and 4.0 mo *vs.* 8.0 mo after PSM (P = 0.613). In another large cohort study containing 186 patients with EHS, TACE appeared to be more beneficial in patients aged below 60 years (HR: 0.58, 95% CI: 0.37-0.91, P = 0.017) or complicated with PVTT (HR: 0.44, 95% CI: 0.25-0.79, P < 0.001)[66]. Choi *et al*[55] compared combination treatment (TACE plus sorafenib) with sorafenib alone in advanced stage patients. The combination group demonstrated a more significant survival benefit than monotherapy both in time to progression (2.7 mo *vs* 2.1 mo, P = 0.011) and median OS (8.9 mo *vs* 5.9 mo; P = 0.009). Subgroup analysis revealed that combination therapy was more efficacious in patients who had good liver function and EHS. Hence, though systemic therapy is recommended as first choice for patients with EHS, TACE may still be a potential alternative for selected patients.

SUGGESTIONS TO DEFINE TACE FAILURE/REFRACTORINESS

For patients with intermediate-stage HCC, multidisciplinary treatment is compulsory to overcome the vast heterogeneities in HCC and different treatment modalities are cooperator rather than competitors. The term “failure” or “refractoriness” is initially

derived from systemic chemotherapy in oncology where current chemotherapeutic strategy fails to hamper overall tumor progression including tumor recurrences and new lesions. TACE is only a locoregional therapy but disease progression of HCC involves intrahepatic areas and extrahepatic tissues. In the absence of prospective well-designed studies, a persuasive definition of TACE failure/refractoriness should be largely rely on the nature of the treatment, that is, a locoregional therapy. In 2020, a nationwide online survey comprising 257 clinicians in 184 hospitals was conducted to recognize TACE failure/refractoriness among clinicians treating HCC in China[67]. The survey showed that 89.1% (n = 229) of participants deemed TACE as a palliative therapy though sometimes could be a curative modality. While the outcome of TACE was full of variation (n = 244), almost all the participants (n = 252) would still choose TACE as the first choice for intermediate-stage HCC. When came to TACE failure/refractoriness, nearly three-quarters (n = 199) acknowledged the rationality of the concept, whereas 91.4% (n = 235) of the respondents did not agree with the current definitions. A clear majority of clinicians would perform TACE combined therapy to patients with segmental PVTT (n = 242) or EHS (n = 253) supposed the liver function was well preserved. Besides, only 42 (16.3%) respondents unequivocally stated that new intrahepatic tumor lesions were indication for TACE failure/refractoriness; and 36.6% (n = 94) gave an equivocal answer. Among the remaining 121 respondents who answered "No" to the question, most of patents preferred combination therapy, including TACE (n = 80) and ablation (n = 80), to control new lesions. Additionally, one hundred and sixty-six (64.6%) participants agreed that repeated TACE can be performed if tumor necrosis was insufficient and feeding arteries were available. Whereas, one hundred and fifty participants (58.4%) believed the time of repeated TACE on pre-treated lesions should be limited in 3 times. Notably, 98.1% (n = 252) of the respondents expressed a strong desire for the improvement of TACE, including the preferable embolization agents, chemotherapeutic drugs followed by embolization technique and more advanced microcatheter. Based on the above discussion and evidence, if intrahepatic targeted lesions are well controlled by proper TACE regimens,

TACE should not be indiscriminately abandoned in the context of disease progression including new lesions, PVTT and EHS. But, if three consecutive insufficient tumor response happened in targeted lesions, TACE should not be repeated and TACE failure/refractoriness is proposed.

FUTURE OF TACE FAILURE/REFRACTORINESS

Treatment modalities for unresectable HCC has gone through profound changes and TACE faces unprecedented challenges, where novel treatment strategies may substitute for TACE as the first treatment option for selected patients in intermediate-stage HCC (ABC-HCC, NCT04803994; RENOTACE, NCT04777851). As a consequently, the concept of TACE failure/refractoriness may be expanded or re-defined as other proposals, for example, TACE unsuitability and TACE impossible. However, such concepts should not be overemphasized before substantial evidence is published, because managements for unresectable HCC are no longer conversions between various monotherapies in the era of comprehensive therapy. The evolution of TACE will not stop and many pathways are under construction, including new embolic or chemotherapeutic agents in order to necrose tumor completely, combination treatments with newly-developed immune checkpoint inhibitors (LEAP-012, NCT04246177; EMERALD-1, NCT03778957; CheckMate74W, NCT04340193; IMMUTACE, NCT03572582). In the near future, outcomes from these RCTs may re-position the role of TACE in the management of HCC.

CONCLUSION

TACE failure/refractoriness is a scientific proposal for HCC but certain definitions in current concepts are debatable. Tumor progression after TACE is of high heterogeneity and therefore subsequent treatment is an individual profile rather than a univocal recommendation. We put forward new opinions concerning TACE failure/refractoriness which might be more reasonable in clinical practice.

Table 1 Different concepts of transarterial chemoembolization failure/refractoriness

Guidelines/articles	Contents
JSH-LCSGJ criteria 2014[6]	(1) Intrahepatic lesion: Two or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE ; (2) Continuous elevation of tumor makers immediately after TACE even though slight transient decrease is observed; (3) Appearance of vascular invasion; and (4) Appearance of extrahepatic spread
International Association for the Study of the Liver[13] Europe[14]	No response after 3 or more TACE procedures within a 6 mo period, to the same area Depending on the purpose of TACE, if TACE is used as palliative therapy, stable lesions can be regarded as effective. Conversely, if TACE is used as a curative therapy, stable lesions are considered as TACE-failure

JSH-LCSGJ: JSH-Liver Cancer Study Group of Japan; TACE: Transarterial chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging.

74065_Auto_Edited-check.docx

ORIGINALITY REPORT

18%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.xiahepublishing.com Internet	149 words — 4%
2	www.e-cmh.org Internet	120 words — 3%
3	Young Chang, Soung Won Jeong, Jae Young Jang, Yong Jae Kim. "Recent Updates of Transarterial Chemoembolilzation in Hepatocellular Carcinoma", International Journal of Molecular Sciences, 2020 Crossref	32 words — 1%
4	Jian Lu, Ming Zhao, Yasuaki Arai, Bin-Yan Zhong et al. "Clinical practice of transarterial chemoembolization for hepatocellular carcinoma: consensus statement from an international expert panel of International Society of Multidisciplinary Interventional Oncology (ISMIO)", Hepatobiliary Surgery and Nutrition, 2021 Crossref	28 words — 1%
5	office.wjgnet.com Internet	26 words — 1%
6	doaj.org Internet	23 words — 1%
7	mafiadoc.com Internet	22 words — 1%

8	www.dovepress.com Internet	22 words — 1%
9	www.thieme-connect.com Internet	21 words — 1%
10	www.easl.eu Internet	19 words — < 1%
11	Atsushi Hiraoka, Yoshihiro Ishimaru, Hideki Kawasaki, Toshihiko Aibiki et al. "Tumor Markers AFP, AFP-L3, and DCP in Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization", Oncology, 2015 Crossref	17 words — < 1%
12	"Radiotherapy of Liver Cancer", Springer Science and Business Media LLC, 2021 Crossref	16 words — < 1%
13	"The 7th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2016). Advancing HCC Management through Multi-Disciplinary Approach. Hong Kong, SAR (China), July 8-10, 2016: Abstracts", Liver Cancer, 2016 Crossref	16 words — < 1%
14	www.tandfonline.com Internet	16 words — < 1%
15	Sadahisa Ogasawara, Yoshihiko Ooka, Keisuke Koroki, Susumu Maruta et al. "Switching to systemic therapy after locoregional treatment failure: Definition and best timing", Clinical and Molecular Hepatology, 2020 Crossref	14 words — < 1%
16	livrepository.liverpool.ac.uk Internet	14 words — < 1%

17	www.e-roj.org Internet	14 words — < 1%
18	Takuji Torimura, Hideki Iwamoto. "Optimizing the management of intermediate-stage HCC: current trends and prospects", Clinical and Molecular Hepatology, 2020 Crossref	13 words — < 1%
19	att.ebm-library.jp Internet	12 words — < 1%
20	clinicalsup.jp Internet	11 words — < 1%
21	Altwegg, Romain. "Second-line therapy for gemcitabine-pretreated advanced or metastatic pancreatic cancer", World Journal of Gastroenterology, 2012. Crossref	10 words — < 1%
22	www.med.kindai.ac.jp Internet	10 words — < 1%
23	www.reportworld.co.kr Internet	10 words — < 1%
24	www.science.gov Internet	10 words — < 1%
25	Jieun Byun, So Yeon Kim, Jin Hyoung Kim, Min Ju Kim, Changhoon Yoo, Ju Hyun Shim, Seung Soo Lee. "Prediction of transarterial chemoembolization refractoriness in patients with hepatocellular carcinoma using imaging features of gadoxetic acid-enhanced magnetic resonance imaging", Acta Radiologica, 2020 Crossref	9 words — < 1%

26	Jordi Bruix, Morris Sherman. "Management of hepatocellular carcinoma", Hepatology, 2005 Crossref	9 words — < 1%
27	Carlos Aguado. "Should capecitabine replace 5-fluorouracil in the first-line treatment of metastatic colorectal cancer?", World Journal of Gastroenterology, 2014 Crossref	8 words — < 1%
28	Jin-Woo Lee, Ji Hye Jang, Young-Joo Jin, Ji Taek Hong. "Transarterial chemoembolization for hepatocellular carcinoma: an evidence-based review of its place in therapy", Journal of Hepatocellular Carcinoma, 2015 Crossref	8 words — < 1%
29	www.transform.ar.gov Internet	8 words — < 1%
30	Gan-Lu Deng. "Chemotherapy and target therapy for hepatocellular carcinoma: New advances and challenges", World Journal of Hepatology, 2015 Crossref	7 words — < 1%
31	Temraz, Sally. "Sequencing of treatment in metastatic colorectal cancer: Where to fit the target", World Journal of Gastroenterology, 2014. Crossref	7 words — < 1%
32	Woong Sub Koom, Hwa Kyung Byun. "Chapter 13 Transarterial Chemoembolization Plus External Beam Radiotherapy", Springer Science and Business Media LLC, 2021 Crossref	6 words — < 1%

EXCLUDE BIBLIOGRAPHY OFF