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Contents

Weekly Volume 24 Number 2 January 14, 2018

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Case Control Study

Contents

World Journal of Gastroenterology
Volume 24 Number 2 January 14, 2018

Contents

World Journal of Gastroenterology
Volume 24 Number 2 January 14, 2018

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MINIREVIEWS

Drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma: Current state of the art

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Abstract

Transarterial chemoembolization (TACE) represents the current gold standard for hepatocellular carcinoma (HCC) patients in intermediate stage. Conventional TACE (cTACE) is performed with the injection of an emulsion of a chemotherapeutic drug with lipiodol into the artery feeding the tumoral nodules, followed by embolization of the same vessel to obtain a synergistic effect of drug cytotoxic activity and ischemia. Aim of this review is to summarize the main characteristics of drug-eluting beads (DEB)-TACE and the clinical results reported so far in the literature. A literature search was conducted using PubMed until June 2017. In order to overcome the drawbacks of cTACE, namely lack of standardization and unpredictability of outcomes, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed. DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization, unlike cTACE in which applying the embolic agent is a second moment after drug injection. This way, risk of systemic drug release is minimal due to both high-affinity carrier activity of DEBs and absence of a time interval between injection and embolization. However, despite promising results of preliminary studies, clear evidence of superiority of DEB-TACE over cTACE is still lacking. A number of novel technical devices are actually in development in the field of loco-regional treatments for HCC, but only a few of them have entered the clinical arena. In absence of well-designed randomized-controlled trials, the decision on whether use DEB-TACE or cTACE is still controversial.

Key words: Embolization; Doxorubicin; Conventional; Hepatocarcinoma; Liver cancer; Survival

Core tip: Aim of this review is to summarize the main characteristics and the clinical results of drug-eluting beads (DEB)-transarterial chemoembolization (TACE). To obviate to the limitations of cTACE, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed. DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization. This way, risk of systemic drug release is minimal. However, despite promising results of preliminary studies, clear evidence of superiority of DEB-TACE over cTACE is still lacking. In absence of well-designed randomized-controlled trials, the decision on whether use DEB-TACE or cTACE is still controversial.

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INTRODUCTION

Transarterial chemoembolization (TACE) constitutes the gold standard for patients in intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system, specifically those presenting with large or multifocal hepatocellular carcinoma (HCC) with preserved liver function, deteriorated performance status, and neoplastic portal vein thrombosis (PVT) or extrahepatic metastases[1,2]. By the way, TACE may constitute a valuable therapy also in early stage patients unsuitable to curative treatments, such as hepatic resection, liver transplantation (LT) or ablative therapy[3]. TACE is performed through the injection of a chemotherapeutic drug (mainly doxorubicin or cisplatin) selectively into the artery feeding the target tumoral nodules, followed by embolization of the same vessel to obtain a synergistic effect of either cytotoxic activity and ischemia[4]. Injection should be continued until the contrast column clears within 2-5 heartbeats (so called "near stasis") and a number of different embolic agents may be used (see below) to avoid drug release into the systemic circulation[5].

The different post-treatment outcomes are probably due to the fact that TACE is a not well standardized procedure widely varying as for chemotherapeutic agents injected, treatment devices used and therapeutic schedule. In fact, overall survival (OS) of patients treated with TACE ranges from 3.4 up to beyond 40 mo (median 16.5 mo[6]). The best survival median reported is 48 mo in a series recently published by the Barcelona group[7].

INDICATIONS AND SAFETY

Current guidelines consider as optimal candidates to TACE patients with preserved liver function, namely under or equal to Child-Pugh (CP) B7 stage without ascites in accordance with European Association for the Study of the Liver (EASL) guidelines[2] or CP A stage according to American Association for the Study of Liver Diseases (AASLD) guidelines[1].

Table 1 reports main absolute and relative contraindications to TACE.

Despite decompensated cirrhosis is commonly considered an absolute contraindication to TACE, some authors still consider chemoembolization as an option in cases of impaired portal blood flow[3].

Indeed, both EASL and AASLD guidelines strongly stand against use of TACE in PVT patients (defined as "advanced" according to BCLC staging system) because of the considerably increased risk of liver failure and consider sorafenib as the only validated option in attendance of definitive results of transarterial radioembolization (TARE) in such patients[8-10]. However, survival benefit of TACE over Best Supportive Care (BSC) has been observed in some small Asian RCTs and in a recent meta-analysis of 8 studies (of which 3 prospective) conducted in advanced HCC patients with PVT[11-13]. However, these results should be interpreted with caution since subjects with better liver function were preferably recruited in the TACE group while decompensated patients tended to be treated with BSC. The only published head-to-head comparison between TACE and sorafenib is a retrospective Austrian study which reported similar survival outcomes with a very competitive role of TACE in selected advanced patients (CP A and segmental PVT), as further confirmed in other observational studies[14,15]. By the way, the same selection bias can be detected in the Austrian study since thrombosis of the main trunk of portal vein (at more dismal prognosis) was more frequently observed in patients treated with sorafenib than in those who underwent TACE (25% *vs* 3%), thus claiming for great caution in interpreting this finding, and significantly higher severe adverse event (SAE) rate was experienced by TACE patients[14].

Hence, TACE may represent a valuable option for a specific subset of BCLC C patients (segmental PVT and CP A) who do not have access or are intolerant/unsuitable to sorafenib or TARE, however safety could represent an issue in these subjects and this therapeutic opportunity should be limited to highly-experienced centers[3].

Experts suggest also high tumor burden with massive replacing of both hepatic lobes as other absolute contraindication, whereas huge tumor nodule $\geqslant$ 10 cm, bile-duct occlusion, and untreated high-risk varices constitute relative contraindication rather than

Table 1 Absolute and relative contraindications to transarterial chemoembolization

Contraindications	
Absolute contraindications	Decompensated cirrhosis (Child-Pugh ⩾ B8)
	Extensive tumor with massive replacement of both entire lobes
	Severely reduced portal vein flow
	Technical impediments to hepatic intra-arterial treatment
Relative contraindications	Kidney failure
	Severe cardiopulmonary comorbidities
	Tumor size ⩾ 10 cm
	Untreated varices at high risk of bleeding
	Bile-duct occlusion

absolute ones[6].

A considerable number of patients treated with conventional TACE (cTACE) experience a transient episode of post-embolization syndrome (characterized by abdominal pain, fever and nausea), reported in 35% up to 100% of cases[16,17]. Treatment-related deaths are observed in ⩽ 2% of cases if proper selection of candidates is adopted[3,18].

Hence, according to current guidelines, TACE represents a safe treatment in selected subjects.

TREATMENT SCHEDULE

A single cycle of TACE is usually insufficient for effective treatment of intermediate-stage HCC and repeating TACE is widely recognized to prolong OS; however, guidelines do not specify the criteria for treatment repetition and current clinical practice relies only on expert opinions which suggest "on-demand" TACE (*i.e.*, number of sessions on the basis of tumor response after each TACE cycle) up to 3 to 4 times per year and switching to other therapeutic options in absence of response to at least 2 sessions[6,19].

As a consequence of the lack of sturdy and definitive data, there is great heterogeneity in applying TACE repetition in the common clinical practice, although a systematic review of observational and randomized trials reported a mean number of TACE sessions worldwide of 2.5 ± 1.5 per patient[20].

Many prognostic systems have been proposed to help the clinician in selecting appropriate candidates for starting or repeating TACE, but none of them achieved an universal validation mainly due to overfitting[21-23].

USEFULNESS OF DRUG INJECTION

Robust data in favor of a clear superiority of TACE (with chemotherapy injection) over TAE (bland embolization) is still lacking[24].

In fact, while the well-known hypervascularization of HCC nodules provides the rationale for the occlusion by embolic particles which results in tumour hypoxia and necrosis, on the other hand whether adding a local chemotherapeutic agent could determine a synergistic anti-tumor effect is still matter of debate[3,24].

A landmark RCT conducted in early 2000s comparing cTACE, TAE and BSC was prematurely terminated because such was the superiority of cTACE over BSC that keeping enrolling patients resulted unethical[25]. Unfortunately, this prevented the possibility to verify the competitive efficacy of TAE and only a comparable trend in OS with respect to TACE could be observed[25]. Similarly, no difference in terms of survival rates and safety was reported in another important multicentric American RCT published this year[26]. However, positive results by adding doxorubicin to drug-eluting bead (DEB)-TACE over bland embolization has been recently found in a Greek trial[27] and in a retrospective Italian report assessing as primary endpoint the degree of necrosis in explanted livers during OLT[28].

To make even more complicated this matter, there is no univocal agreement on the optimal chemotherapy to use in TACE. Worldwide, the most commonly used agent is doxorubicin administered at a dose ranging from 30 to 75 mg/m^2 (to a maximum of 150 mg)[3,5]. However, robust data provided by properly conducted RCTs are needed in order to deliver definitive indications in this regard.

DEVELOPMENT OF DEB-TACE AND TECHNICAL ASPECTS

Despite its well-proved efficacy and superiority over BSC, cTACE presents several unsolved issues. In fact, although lipiodol acts as a carrier of doxorubicin to the target nodules, release of the injected drug into systemic circulation has been demonstrated maybe due to the non-concomitant embolization, thus allowing release of a certain amount of doxorubicin in the interval time between injection and embolization[29]. Other important limitation of cTACE is the lack of standardization as the injected particles are prepared extemporaneously, therefore is operator-dependent (not standardized) and unstable[3,29].

The optimal procedure should be able to selectively deliver the injected chemotherapeutic into the target tumor where the drug should be retained with no passage into blood stream to avoid systemic toxicity[3].

In order to obviate to the aforementioned limitations of conventional TACE, non-absorbable embolic microspheres charged with cytotoxic agents (DEBs) have been developed.

DEBs are composed of a hydrophilic, ionic polymer that can bind anthracyclines via an ion exchange mechanism. The drug is usually loaded into DEBs prior to the TACE procedure creating a solution at a pre-defined concentration and then merging it into a vial with a slurry of DC Bead from which the packing solution has been removed[30]. The drug takes from 30 min to 2 h (depending on bead size) to be loaded

with small beads loading faster because of surface area effects. The maximum drug loading capacity is determined by the quantity of drug-binding sites in the beads, thus being the maximum dose dependent on drug molecular mass[30,31]. This is why a group of experts in the field has suggested in a recent review a dosage of 75 mg doxorubicin loaded into one vial of DC Bead for disease within the Milan criteria and up to 150 mg doxorubicin loaded into two vials of DC Bead in the case of Milan-out patients[5].

DEBs are able to simultaneously exert both the therapeutic components of TACE, either drug-carrier function and embolization, unlike cTACE in which applying the embolic agent is a second moment after drug injection. This way, risk of systemic drug release is minimal due to both high-affinity carrier activity of DEBs and absence of a time interval between injection and embolization.

An *in vitro* analysis showed that DEB spheres could be easily loaded with doxorubicin way better than other commercial embolic microspheres[32]. Furthermore, drug loading led to a decrease in the average size of the beads in function of the bead size and drug dose [32]. Interestingly, the same study calculated half-lives of drug-elution of 150 h for the 100-300-mc range to a maximum of 1730 h for the 700-900-mc size range while there was a fast release of the chemotherapeutic agent from the unstable Lipiodol emulsion with a half-life of approximately 1 h[32]. Authors then concluded that DEBs lead to an accurate dosage of drug per unit volume of beads and drug release is predictable and sustained, unlike Lipiodol. In addition to all of these advantages, beads are easy to handle and to deliver thus making them a valuable option for superselective TACE[32].

Plasma concentration of doxorubicin resulted very low (0.009-0.05 mmol/L at different consecutive time-points) after DEB-TACE in an in-animal study conducted in a rabbit model, suggesting considerable doxorubicin retention into the tumor[33]. This was significantly lower (70%-85% decrease in plasma concentration) than control animals treated with doxorubicin intra-arterially[33]. Of note, doxorubicin concentration into the nodule had a peak at 3 d (413.5 nmol/g), remaining high to 7 d (116.7 nmol/g) and then declining at 14 d (41.76 nmol/g), indicating continuous release of the drug from the microparticles[33]. As a consequence of this slower release of doxorubicin, maximal tumor necrosis was observed at 7 d, with limited local complications[33].

In vivo demonstration of the aforementioned strengths of DEBs has been provided by a French study conducted in 6 HCC patients who had undergone DEB-TACE before OLT[34]. Doxorubicin was detected on the explanted livers in an area of at least 1.2 mm in diameter around the occluded vessel. The tissue concentration of drug ranged from 5 μmol/L at 8 h to 0.65 μmol/L at 1 mo[34]. Necrotic tissue was characterized by a more profound penetration and a higher concentration of the drug than non necrotized areas. Authors concluded that DEBs provide a sustained delivery of drug for a period of 1 mo and local tissue concentrations above cytotoxic into the target nodules[34].

The first clinical study reporting the efficacy of DEB-TACE was a phase II study by the Barcelona group[35]. In this pivotal paper conducted on 27 CP A HCC treated with DEB-TACE (500-700 μm particles), objective response rate (ORR) was 66.6% (of which 26% complete responses) after two consecutive sessions performed 2 mo apart[35]. Doxorubicin maximal concentration (Cmax) and area under the curve were considerable inferior in DEB-TACE patients in comparison with a previous cohort of cTACE patients (P = 0.00002 and P = 0.001, respectively)[35]. Moreover, SAE rate was very low with only two cases of liver abscesses experienced by treated patients[35]. These findings were reproduced by Poon *et al*[36] with the maximal dose of doxorubicin (150 mg). Noteworthy, no patients in both studies experienced doxorubicin-related systemic adverse events (alopecia, bone marrow toxicity, dyspnea or pulmonary embolism)[35,36].

In light of the aforementioned in-animal studies[32,37], 100-300 μm beads became the most frequently used particles and are still actually recommended[5].

In early 2010s, two retrospective European studies reported striking survival results in unresectable HCC patients treated with 100-300 μm DEB-TACE, particularly 43.8 mo in a Greek series[38] and 48 mo of median OS in the Barcelona group's article[7]. These findings, really of note considering that TACE represents only a palliative therapy, paved the way to a wide use of DEB-TACE in the clinical practice.

COMPARATIVE EFFECTIVENESS OF DEB-TACE AND cTACE

In spite of the interesting findings of the aforementioned studies[35,36], data on comparative efficacy between cTACE and DEB TACE is still matter of debate. In fact, the 4 comparative RCTs and several retrospective studies report conflicting results.

The PRECISION V trial, a broad multicentric RCT published in 2010, enrolled 212 patients (75% BCLC B, 25% A; 80% CP A, 20% B) treated at 2-monthly intervals according a pre-defined schedule up to a maximum of three sessions[39,40]. Higher complete response, objective response, and disease control rates were registered in the DEB-TACE group (300-500 and 500-700 μm) as compared to cTACE (27% *vs* 22%, 52% *vs* 44%, and 63% *vs* 52%, respectively) but the hypothesis of superiority was not supported (one-sided P = 0.11)[40]. Primary endpoint (tumor response) was reached only in the subgroup of more advanced patients, namely those CP B, Eastern Cooperative Oncology Group (ECOG), bilobar and recurrent disease,

Table 2 Clinical studies comparing drug-eluting beads and conventional transarterial chemombolization

Study	Arm	Sample size	Study design	Region	CP (A/B/C)	BCLC (A/B/C)	1-yr survival
Lammer *et al*[40] 2010	DEB-TACE	93	RCT	Europe	77/16/0	24/69/0	NA
	cTACE	108			89/19/0	29/79/0	
Song *et al*[43] 2012	DEB-TACE	60	R	South Korea	56/4/0	27/33/0	88%
	cTACE	69			62/6/0	28/41/0	67%
Sacco *et al*[41] 2011	DEB-TACE	33	RCT	Italy	29/4/0	22/11/0	94.10%
	cTACE	34			25/9/0	22/12/0	90%
Van Malenstein *et al*[44] 2011	DEB-TACE	16	RCT	Belgium	14/2/0	9/5/2002	NA
	cTACE	14			14/0/0	10/3/2001	
Golfieri *et al*[42] 2014	DEB-TACE	89	RCT	Italy	75/14/0	41/26/22	86.20%
	cTACE	88			77/11/0	41/23/24	83.50%
Ferrer *et al*[45] 2011	DEB-TACE	47	P	Spain	NA	NA	88%
	cTACE	25			NA	NA	90%
Dhanasekaran *et al*[46] 2010	DEB-TACE	45	R	United States	11/12/2022	NA	58%
	cTACE	26			11/4/2011	NA	31%
Wiggermann *et al*[47] 2011	DEB-TACE	22	R	Germany	22/0/0	1/17/3	70%
	cTACE	22			22/0/0	4/15/2	55%
Recchia *et al*[48] 2012	DEB-TACE	35	P	Italy	NA	NA	63.40%
	cTACE	70			NA	NA	49.30%
Facciorusso *et al*[49] 2015	DEB-TACE	145	R	Italy	129/16/0	58/81/6	85%
	cTACE	104			93/11/0	41/63/0	92%
Arabi *et al*[50] 2015	DEB-TACE	35	R	Saudi Arabia	24/11/0	NA	72.70%
	cTACE	19			17/2/0	NA	74.50%
Kloeckner *et al*[51] 2015	DEB-TACE	76	R	Germany	51/22/3	8/34/34	45%
	cTACE	174			103/64/7	30/59/85	52%
Megias *et al*[52] 2015	DEB-TACE	30	R	Spain	46.7%[a]	NA	68%
	cTACE	30			63.3%[a]		58%
Liu *et al*[53] 2015	DEB-TACE	53	R	Taiwan	53/0/0	0/53/0	NA
	cTACE	64			64/0/0	6/58/0	
Scartozzi *et al*[54] 2010	DEB-TACE	64	R	Italy	57.1%[a]	NA	74%
	cTACE	87			58.6%[a]		93%

Percentage of CP A patients. CP: Child-Pugh; BCLC: Barcelona clinic liver cancer; DEB-TACE: Drug-eluting beads transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; RCT: Randomized controlled trial; P: Prospective non-randomized study; R: Retrospective study, [a]$P < 0.05$.

where DEB-TACE outperformed cTACE[40]. The sole result clearly in favor of DEB-TACE was a better safety profile with significant decrease in serious liver-related adverse events ($P < 0.001$) and systemic side effects (particularly alopecia) ($P = 0.0001$), while the incidence of post embolization syndrome was comparable in the treatment groups[40]. Unfortunately, the short follow-up time prevented assessment of OS and Time-to-Progression (TTP).

Two Italian RCTs failed to find any significant difference in tumor response and survival between the two TACE regimens[41,42]. In particular, the broad PRECISION ITALIA trial, a multicentre, RCT comparing "on demand" cTACE (with epirubicin injection) and DEB-TACE (100-300 μm loaded with 50 mg of doxorubicin), was stopped for futility at the second interim analysis when only 83% of the original planned sample size had been enrolled[42]. Of note, 46 (26%) patients were classified as BCLC C due to ECOG-1 status. Tumor response was similar between the two groups with the only difference registered as for complete response at 1 mo which resulted significantly higher after cTACE likely due to the lipiodol "staining" effect on CT-scan. In fact, at successive response assessments in concomitance with lipiodol discharge from the target nodule, this difference disappeared[42]. No difference neither in median TTP (9 mo in both treatment groups, $P = 0.766$) nor in 2-year survival rate (primary endpoint: 55.4% after cTACE and 56.8% after DEB-TACE, $P = 0.949$) was observed, hence the decision to prematurely stop the trial because the primary endpoint would have not been met[42]. Unlike the PRECISION trial, there was no significant difference in the incidence of AEs[42].

Retrospective studies reported discordant results, with only a single outlier Korean series clearly in favor of DEB-TACE[43].

Table 2 reports clinical studies comparing DEB-TACE and cTACE published so far[40-54].

A recent meta-analysis of 12 studies (4 RCTs and 8 observational) performed by my group reported similar pooled odds ratios of survival rate at 1, 2 and 3 years with a decreasing trend in favor of DEB-TACE (0.76, 0.68 and 0.57, respectively)[55]. This result was mainly determined by the difference in follow-up length between the two treatment groups in the retrospective reports since DEB-TACE patients, being DEBs recently introduced in the clinical practice, reported more frequent censored data and more limited absolute number of deaths[55]. In order to partially obviate to this bias, we plotted relative hazard ratios which are less sensitive to follow-up time bias and final result was a ratio close to 1 with no difference between the

two groups and low evidence of heterogeneity[55]. In particular, when restricting the analysis to only RCTs, the efficacy between the two techniques was absolutely comparable[55].

Our findings updated those of previous meta-analyses which had concluded that DEB-TACE is superior to cTACE as for objective response; by the way, these systematic reviews included a limited number of studies and were underpowered to properly explore the sources of the high heterogeneity found in their results[56,57]. Instead, no difference concerning neither tumor response nor safety profile was found in our meta-analysis which is in keeping with another recent systematic review[58].

In conclusion, as clearly stated in the editorial to this paper, no evidence enough to support the current extensive use of DEB-TACE exists[59]. The same editorial, commenting a cost-effective analysis published by the Bologna group[60], stated that the suggested cost-effectiveness advantage of DEB-TACE requires further trials conducted in countries other than Italy and with standardized procedures and clinical settings[59].

LATEST ADVANCEMENTS IN THE FIELD OF TRANSARTERIAL CHEMOEMBOLIZATION

Although a clear evidence of the superiority of DEB-TACE is still lacking, novel beads have been recently developed and clinically tested. As previously described, small microparticles have been found to determine necrosis of the target lesion as they lead to a more distal embolization, thus also obstructing collateral vessels[32,36,37]. Some concerns have been initially raised on the potential extrahepatic toxicity of these micro-particles due to the theoretical risk of their extrahepatic passage via collateral small vessels[61,62], but successive clinical reports have debunked this issue since smaller particles have been proved as safe if not more than conventional 100-300 μm and 300-500 μm[63-65]. In fact, Larger particles results in more proximal embolization and consequently in broader area of ischemia, thus increasing the risk of liver damage.

An Italian prospective series from Milan showed interesting results with DEBs 70-150 μm (M1®, BTG, United Kingdom)[66]. In this study conducted on 45 HCC early/intermediate patients, complete response was achieved in one third of them (33.3%) whereas other 20 (44.4%) reached partial response, accounting for a 77.7% ORR[66]. The histological analysis of 28 nodules in 13 explanted livers showed 100% necrosis (complete pathologic necrosis) in 7 cases and 90%-99% necrosis in 3 cases[66]. Noteworthy, only one SAE (grade 3) was reported, namely a case of bleeding from esophageal varices caused by the worsening of the portal hypertension[66]. These findings have been later confirmed in other retrospective studies[64,65].

HepaSphere microspheres 30-60 μm (Biosphere®, Merit, United States) constitute another promising device. HepaSphere 30-60 μmol/L is a new size of a loadable microsphere that has a dry caliber of 30-60 μmol/L that expands to 166-242 (197 ± 31) μmol/L in saline and 145-213 (148 ± 45) μmol/L after loading with doxorubicin[67]. In addition, doxorubicin was found to be released by the beads over 1 mo after TACE. Moreover, the concentration of doxorubicin in the treated tissue was high with very low plasma levels of the drug[67,68]. A recent Greek study enrolling 45 patients treated with HepaSphere microspheres 30-60 μmol/L found a complete response rate of 22.2% for the target lesions and ORR of 68.9%[69]. No patient died in the first year after TACE and no SAE was registered[69].

By the way, in absence of RCTs comparing these novel microspheres, no definitive indication can be released on which DEB should be used in the common clinical practice, and the decision still relies on local expertise or availability of device.

CONCLUSION

A number of novel technical devices are actually in development in the field of loco-regional treatments for HCC[70,71], but only a few of them have entered the clinical arena. Beside the lack of RCTs, many other issues remain unsolved, such as understanding the real balance between the two components of the therapy (*i.e.*, ischemia and cytotoxicity), further defining the several steps of hepatocarcinogenesis which could be targeted by combined pharmacological and interventional therapy[72-75], and identifying reliable prognostic markers in order to deliver a more precise oncology in patients really amenable of loco-regional treatments[76,77].

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