DR. GIUSEPPE CABIBBO (Orcid ID : 0000-0002-0946-3859)

DR. GIACOMO EMANUELE MARIA RIZZO (Orcid ID : 0000-0001-9335-6740)

DR. CATERINA STORNELLO (Orcid ID : 0000-0002-7379-6834)

DR. ROBERTO CANNELLA (Orcid ID : 0000-0002-3808-0785)

PROF. SALVATORE GRUTTADAURIA (Orcid ID : 0000-0002-9684-8035)

PROF. CALOGERO CAMMA (Orcid ID : 0000-0002-9224-1914)

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TITLE: Are radiological endpoints surrogate outcomes of overall survival in hepatocellular carcinoma treated with transarterial chemoembolization?

Authors: Ciro Celsa[1-2*], Giuseppe Cabibbo[1*], Marco Enea[3], Salvatore Battaglia[4], Giacomo Emanuele Maria Rizzo[1], Anita Busacca,[1] Paolo Giuffrida,[1] Caterina Stornello,[1] Giuseppe Brancatelli[5], Roberto Cannella,[3,5] Salvatore Gruttadauria,[6,7] and Calogero Cammà[1]

[1] Section of Gastroenterology & Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy;

[2] Department of Surgical, Oncological and Oral Sciences (Di.Chir.On.S.), University of Palermo, Palermo, Italy;

[3] Department of Health Promotion Sciences Maternal and Infant Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy.
[4] Dipartimento di Scienze Economiche, Aziendali e Statistiche, University of Palermo, Palermo, Italy.
[5] Dipartimento di Biomedicina, Neuroscienze e Diagnostica avanzata (BIND), University of Palermo, Palermo, Italy.
[6] Department for the Treatment and the Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), UPMC (University of Pittsburgh Medical Center), Palermo, Italy.
[7] Department of Surgery, University of Catania, Catania, Italy.
*** These authors equally contributed to this work.**

Corresponding Author: Prof. Calogero Cammà; Section of Gastroenterology & Hepatology, PROMISE, University of Palermo, Piazza delle Cliniche, 2, 90127, Palermo, Italy. Phone number: +390916552145 Mail: calogero.camma@unipa.it

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ABSTRACT

Background& Aims Time to progression (TTP) and progression-free survival (PFS) are commonly used as surrogate endpoints in oncology trials. We aimed to assess the surrogacy relationship of TTP and PFS with overall survival (OS) in studies of transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (u-HCC) by innovative methods.

Methods A search of databases for studies of TACE for u-HCC reporting both OS and TTP or PFS was performed. Individual patient data were extracted from TTP/PFS and OS Kaplan-Meier curves of TACE arms. Pooled median TTP and OS were obtained from random-effect model. The surrogate relationships of hazard ratios(HRs) and median TTP for OS were evaluated by the coefficient of determination R^2.

Results We identified 13 studies comparing TACE versus systemic therapy or versus TACE plus systemic therapy and including 1932 TACE-treated patients. Pooled median OS was 11.2 months (95% Confidence Interval [95%CI] 7.9-17.8) and pooled median TTP was 5.4 months (95%CI 3.8-8.0). Heterogeneity among studies was highly significant for both outcomes. The correlation between HR TTP and HR OS was moderate (R2 = 0.65. 95%CI 0.08-0.81). R^2 value was 0.04 (95%CI 0.00-0.35) between median TTP and median OS.

Conclusion In studies of TACE for u-HCC, the surrogate relationship of radiology-based endpoints with OS is moderate. Multiple endpoints including hepatic decompensation, macrovascular invasion and extrahepatic spread are needed for future trials comparing systemic therapies or combination of TACE with systemic therapies versus TACE alone.

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Keywords: hepatocellular carcinoma; transarterial chemoembolization; surrogate endpoints; progression-free survival; time to progression; overall survival.

Lay summary

- Surrogate radiology-based endpoints such as time to progression (TTP) and progression-free survival (PFS) are commonly used in oncology. However, their surrogacy with overall survival (OS) in transarterial chemoembolization (TACE) trials for hepatocellular carcinoma (HCC) is not known.
- We analyzed individual survival patient data from 13 trials including 1932 TACE-treated patients and we found that the surrogacy of TTP with OS is moderate.
- The inclusion of multiple endpoints such as hepatic decompensation, macrovascular invasion and extrahepatic spread is needed to improve the interpretability of future trials comparing systemic therapies or combination of TACE with systemic therapies versus TACE alone.

Introduction

Hepatocellular carcinoma (HCC) represents the fourth cause of cancer-related death worldwide and the leading cause of death in patients with compensated cirrhosis.[1] The prognosis of HCC patients is highly heterogeneous as the majority of HCC cases occur in the setting of chronic liver disease and it depends on both tumor burden and the severity of liver function impairment.[2] Despite the application of surveillance programs in patients with cirrhosis, more than 60% of HCCs are diagnosed at unresectable stage (u-HCC), i.e. Barcelona Clinic Liver Cancer (BCLC) B (intermediate) and C (advanced) stages.[3] Transarterial chemoembolization (TACE) has shown a survival benefit in patients with intermediate stage HCC[4] and it is recommended as the standard of care for these patients by most clinical practice guidelines since 2003.[5,6] The innovations in TACE techniques occurred during the last decade, the heterogeneity in the schedule of TACE administration and the availability of new effective systemic treatments[7] increased the complexity in the design and interpretation of clinical trials, in the choice of the optimal endpoints and in the evaluation of the benefit of TACE in real-world practice.

Overall survival (OS) is universally recognized as the gold standard endpoint to determine clinical benefit in oncology trials.[8] However, OS analyses require large-sample, long-duration trials, and its interpretation can be confounded by post-progression survival and treatment crossover.[9] Surrogate radiology-based endpoints, such as progression-free survival (PFS) and time-to-progression (TTP) have been proposed to address the limitations related to the use of OS. Specifically, PFS and TTP might provide an early assessment of antitumor treatment efficacy, independently from post-progression survival.[9] However, they are limited by the subjectivity inherent in radiological evaluation of progression and by the use of different response criteria.[10] Moreover, differently from PFS, TTP fails to capture death, that is a relevant indication of toxicity or lack of efficacy. To date, evidence on the surrogate relationship between radiology-based endpoints and OS in patients with u-HCC treated with TACE are lacking.

The aim of this study was to evaluate the surrogate relationship between radiology-based endpoints (TTP or PFS) and OS in studies of TACE for u-HCC.

Materials and Methods

Literature search and study selection

The MEDLINE database was searched systematically from January 1, 2008 to September 15, 2020 with the search terms “hepatocellular carcinoma” and “transarterial chemoembolization”. We decided to start literature search from 2008 (the year of Sorafenib approval) because before 2008

TACE was the only active treatment for u-HCC. We believe that this could reduce the heterogeneity related to the schedule of TACE administration. Moreover, we searched ClinicalTrials.gov for trials with results posted (Studies with results) using "hepatocellular carcinoma unresectable", and "transarterial chemoembolization" as keywords. Search criteria included interventional studies (for study type) and phase I to IV (for phase). We also searched abstracts presented in the ASCO (American Society of Clinical Oncology) Meeting Library and ESMO (European Society for Medical Oncology) Conference Platform during the last 5 years. Abstracts published subsequently as full-text studies already included in our analysis were excluded.

The inclusion criteria for retrieved studies were: being a comparative study for u-HCC with TACE as control arm; reporting Kaplan-Meier curves for OS and for at least one surrogate radiology-based endpoint (TTP or PFS); being a comparative study published after 2008. Non-comparative studies, review articles, letters, interim analyses, subgroup analyses of previously reported trials, duplicate reports, were excluded. Non-comparative studies on TACE were excluded because many of them lack data on TTP or PFS, therefore the surrogacy between OS and radiological-based surrogate endpoints could not be assessed. Each trial was evaluated by three independent investigators (Ci.C., G.R., and A.B.). Discrepancies among reviewers were not frequent (interobserver variation <10%) and resolved by discussion.

Data extraction

OS, TTP and PFS median times and hazard ratios (HRs) with corresponding 95% confidence intervals (95%CIs) were assessed as measures of treatment effect.

Study-level covariates included publication year; study design; number of patients in each arm; type of competitor arm; timing of first radiological assessment; follow-up duration; treatment-response radiological evaluation criteria.

Patient-level covariates included age, sex, etiology of cirrhosis, Child-Pugh class, alfafetoprotein (AFP) levels, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), number of nodules, presence of extrahepatic spread, BCLC stage, number of TACE procedures, previous HCC treatments.

Individual patient survival data extraction

We used Engauge Digitizer software[11] to extract individual patient data (IPD) from OS and TTP or PFS Kaplan-Meier curves and used Guyot algorithm[12] to reconstruct the data. This algorithm was applied to assembled patients with predicted survival times and a predicted event

of interest (i.e., alive or dead; progression or no progression) with digitized data on survival probabilities, time, and total numbers of patients and events. Each reconstructed survival curve was inspected for accuracy and compared with the originally published curves.

We used Combescure [13] nonparametric approach to obtain summary survival curves, which enabled assessments of pooled reconstructed survival probabilities. A random-effects model was used to detect between-study heterogeneity. The multivariate extension of DerSimonian and Laird's method was used to estimate a between-study covariance matrix.[14,15] Heterogeneity was assessed by the I^2 statistic.

Restricted mean survival time (RMST)

RMSTs, reflecting average survival from time 0 to a specified time-point t, were determined from Kaplan-Meier estimates of survival functions. An RMST can be interpreted readily as the area under the survival curve within a specific time window. For each trial, we reanalyzed the reconstructed IPD and then assessed RMSTs for OS and TTP or PFS at a pre-specified time horizon of 12 months.[16]

Statistical analysis

Linear meta-regression model, with sample size weighting of the trial arms from which the data were extracted, was employed to quantify the relationship between TTP or PFS and OS. Surrogacy was evaluated between HRs, median times, between different time-based endpoints [first quartile (Q1) and third quartile (Q3)] (milestone analysis), and between 12-month RMSTs. The strength of each association was assessed by calculating R^2 (the proportion of OS variance that is predictable from the surrogate endpoints), with values near 1 implying surrogacy and values close to zero suggesting no association.[17]

Sensitivity analyses

We performed the following sensitivity analyses: 1) including only patients with BCLC A-B stages. 2) including only RCTs; 3) including only studies in which TACE was compared versus TACE plus Sorafenib; 4) including only studies that used mRECIST as criteria for radiological response evaluation.

Results

Trial selection and characteristics

Our search identified 1,669 potentially relevant articles, of which 1,523 were excluded for not being consistent with our aim. After removing duplicate articles (n = 120), we identified 26 trials that were full-text reviewed to establish eligibility for quantitative analysis. Based on the full-text reviews, we determined that 13 studies fulfilled the inclusion criteria and they were selected for the main analysis (**Supplementary Figure S1**).[18-30]

The characteristics of the 13 studies in the main analysis, including 1,932 TACE-treated patients, are summarized in **Table 1.** The number of patients in each TACE arm ranged from 30[20] to 444[30]. Seven studies[18,19,23,27-30] were RCTs (6 were phase III), while the remaining were no RCTs (2 were prospective[21,26] and 4 were retrospective[20,22,24,25]). The control arm was represented mainly by combination of TACE plus systemic therapies (n=11, 9 in combination with Sorafenib[19.22,24-27,29], 1 with Brivanib[23] and 1 with Ginsenoside Rg3[28]), while in 2 studies it was represented by systemic therapy alone (Doxorubicin[18] or Orantinib[30]). mRECIST criteria were the most used (n=7 studies)[22-28]. The clinical characteristics of the patients included are reported in **Table 2.**

Kaplan-Meier curves for TTP and for PFS were available in 11[18,19,21-23, 25-30] and 3 studies[20,24,29], respectively. IPD for OS and TTP were extracted to obtain reconstructed survival curves. Extracted survival data are reported in **Supplementary Table S1**. Since Kaplan-Meier curves for TTP were not available in 2 studies,[20,24] PFS curves were considered for these studies. The OS pooled median was 11.2 months (95%CI 7.9-17.8. I^2=68.1%, p<0.001) (**Figure 1)** and the TTP pooled median was 5.4 months (95%CI 3.8-8.0. I^2=71.1%, p<0.001) (**Figure 2)**. Twelve-month OS and TTP RMSTs were 9.5 (95% CI 9.3-9.6) and 5.8 (95% CI 5.6-6.0) months, respectively. Twelve-month RMSTs for each trial are reported in **Supplementary Table S2.**

Surrogacy metrics

In the weighted linear regression between HR OS and HR TTP, the R^2 value was 0.65 (95% CI 0.08-0.81) (**Figure 3**). Surrogacy robustness was lower using different TTP time-points. We obtained a R^2 value of 0.04 (95% CI 0.00-0.35) and 0.02 (95%CI 0.00-0.29) between median TTP and median OS, by using linear regression (**Figure 4)** and logarithmic interpolation (**Supplementary Figure 2)**, respectively. We obtained a R^2 value of 0.06 (95% CI 0.00-0.37) between Q1-TTP and Q1-OS and a R^2 value of 0.08 (95% CI 0.00-0.40) between Q3-TTP and Q3-OS. Finally, in the weighted linear regression between 12-month TTP and OS RMSTs, the R^2 value was 0.02 (95% CI 0.00-0.30).

Sensitivity analyses

Sensitivity analysis conducted in patients with BCLC A-B stages showed OS pooled median of 23.5 months (95%CI 21.1 -25.6. I^2=60.8%, p<0.001) (**Supplementary Figure S3**) and TTP pooled median of 9.6 months (95%CI 7.8-11.0 I^2=52.1%, p<0.001) (**Supplementary Figure S4**). Twelve-month OS and TTP RMSTs were 9.7 (95% CI 9.5-10.0) and 7.4 (95% CI 7.1-7.8) months, respectively. R^2 values were 0.42 (95%CI 0.00-0.72) between Q1-TTP and Q1-OS, 0.31 (95%CI 0.00-0.66) between median TTP and median OS, 0.36 (95%CI 0.00-0.69) between Q3-TTP and Q3-OS and 0.33 (95% CI 0.00-0.61) between 12-month TTP and OS RMSTs.

A sensitivity analysis was conducted including only RCTs. The OS pooled median was 15.4 months (95%CI 9.8-24.8. I^2=69.0% p<0.001) (**Supplementary Figure S5**) and the TTP pooled median was 6.4 months (95%CI 3.7-10.7 I^2=74.0% p<0.001) (**Supplementary Figure S6**). Twelve-month OS and TTP RMSTs were 10.4 (95% CI 10.3-10.6) and 6.1 (95% CI 5.9-6.3) months, respectively. R^2 values were 0.08 (95% CI 0.00-0.52) between HR TTP and HR OS, 0.40 (95%CI 0.00-0.70) between Q1-TTP and Q1-OS, 0.48 (95%CI 0.00-0.74) between median TTP and median OS, 0.004 (95%CI 0.00-0.30) between Q3-TTP and Q3-OS and 0.54 (95% CI 0.00-0.77) between 12-month TTP and OS RMSTs.

Sensitivity analysis conducted in studies in which TACE was compared to TACE plus Sorafenib showed OS pooled median of 9.8 months (95%CI 6.1-19.4. I^2=69.0%, p<0.001) (**Supplementary Figure S7**) and TTP pooled median of 5.4 months (95%CI 3.4-9.5 I^2=62.3%, p<0.001) (**Supplementary Figure S8)**. Twelve-month OS and TTP RMSTs were 8.4 (95% CI 8.2-6.0) and 6.3 (95% CI 6.0-6.6) months, respectively. R^2 values were 0.96 (95% CI 0.64-0.98) between HR TTP and HR OS, 0.0003 (95%CI 0.00-0.07) between Q1-TTP and Q1-OS, 0.01 (95%CI 0.00-0.34) between median TTP and median OS, 0.52 (95%CI 0.00-0.75) between Q3-TTP and Q3-OS and 0.29 (95% CI 0.00-0.61) between 12-month TTP and OS RMSTs.

In the studies that used mRECIST as criteria for radiological response evaluation, OS pooled median was 11.2 months (95%CI 8.0-17.9 I^2=71.3%, p<0.001) (**Supplementary Figure S9**) and TTP pooled median was 5.4 months (95%CI 3.8-7.9 I^2=71.1%, p<0.001) (**Supplementary Figure S10)**. Twelve-month OS and TTP RMSTs were 7.9 (95% CI 7.6-8.1) and 6.1 months (95% CI 5.8-6.4), respectively. R^2 values were 0.61 (95% CI 0.00-0.81) between HR TTP and HR OS, 0.75 (95%CI 0.07-0.87) between Q1-TTP and Q1-OS, 0.03 (95%CI 0.00-0.43) between median TTP and median OS, 0.35 (95%CI 0.00-0.67) between Q3-TTP and Q3-OS and 0.61 (95% CI 0.00-0.80) between 12-month TTP and OS RMSTs.

Discussion

In this study including individual data of about 2,000 patients with u-HCC underwent TACE, we found that HR TTP and HR OS were moderately correlated. Surrogacy relationships among outcomes were also low in milestone analyses, including median times, first and third quartiles, and 12-month RMSTs. To the best of our knowledge, this is the first study assessing the correlation between surrogate (TTP) and true (OS) endpoints in studies of TACE for u-HCC by using innovative methodological approach. Clinical heterogeneity of TTP and OS was a common feature of these studies. In this line, our pooled Kaplan-Meier curves of TTP and OS represent a useful benchmark for the design of future trials including TACE as comparator arm.

Next generation TACE trials, evaluating both the combination of TACE with immunotherapy[31-33] or comparing TACE with new systemic therapies, has highlighted the need to identify the most appropriate surrogate endpoints for early capture survival benefit. This is particularly relevant as major advances occurred over the last decade in systemic therapies and many patients now could benefit from early shift from TACE to first-line systemic therapy. To date, the optimal time of transition from TACE to systemic therapy remains elusive and validated consistent new methodological criteria for early defining progression or response to TACE are urgently needed. Although the surrogacy between radiology-based endpoints and OS has been assessed for systemic therapies,[34] similar analyses on TACE are lacking to date.

In the heterogeneous setting of u-HCC patients treated with TACE, the use of OS as primary endpoint may be confounded by post-progression sequential treatments. To overcome these limitations, radiology-based surrogate endpoints such as TTP and PFS have been proposed in TACE trials. Our analyses showed that TTP surrogacy of OS was moderate with the use of HRs. Although the HR is commonly used as comparative measure, its validity is limited by the requirement of assuming a proportional hazard over the entire follow-up period.[35] Therefore, in order to improve the surrogacy between TTP and OS, we also performed a milestone analysis. First quartile analysis is a cross-sectional assessment of treatment benefit at a meaningful time-point that overcomes the proportional hazards assumption. However, time-based outcomes do not reflect the entire survival history. To overcome this limitation, RMST represents an innovative methodology that has the advantage of being valid under any time-to-event distribution, regardless of the proportional hazards assumption.[36] Unlike HR, RMST is an absolute measure of survival time that enables a clinically meaningful interpretation of a treatment effect. Unfortunately, both milestone analysis and RMST analysis did not improve the surrogacy relationship between radiology-based endpoints and OS.

Why the surrogacy relationship between TTP and OS in this setting was not satisfactory? First, radiology-based endpoints fail to capture the events related to liver decompensation. In the setting of patients with successfully treated early HCC[37], we demonstrated that hepatic decompensation is the main driver of death. In the setting of u-HCC, TACE may impair liver function. Also in this setting, hepatic decompensation represents a competing risk with tumor progression, with a relevant impact on OS. Moreover, hepatic decompensation after TACE affects the eligibility of patients for subsequent systemic therapy.[38] The advent of highly effective first-, second- and even third-line systemic therapies changes the paradigm of the treatment of u-HCC, making systemic therapy not only a treatment following TACE but an effective alternative to TACE. Second, the current definition of radiological progression includes not only the dimensional increase of an existing lesion and/or the appearance of a new intrahepatic lesion, but also the occurrence of events with a relevant impact on OS, such as vascular invasion and extrahepatic spread. Novel endpoints such as time to occurrence of extrahepatic spread or vascular invasion should be further investigated in future trials.

Finally, differently from PFS, TTP is surrogate radiological outcome unable to capture death. PFS, a composite endpoint that includes HCC progression and death, represents the primary endpoint when sequential treatments are available, as demonstrated by a recently published decision model for systemic treatments.[39] In patients with u-HCC treated with systemic therapies, the surrogate relationship of PFS with OS is highly variable depending on treatment class and PFS early assessment is a robust surrogate endpoint of OS for immune-checkpoint inhibitors, but not for multikinase inhibitors.[34] However, the main limitation of PFS, as all the radiology-based outcomes, is that it does not take into account hepatic decompensation. In this line, the recently published TACTICS trial[40] comparing TACE plus Sorafenib with TACE, adopted as outcome unTACEable progression, defined not only by radiological progression but also as deterioration of liver function after TACE. Unfortunately, we were unable to include this trial in our analysis because OS was not analyzed.

Limitations. First, although we extracted individual patient data for OS and TTP/PFS from Kaplan-Meier curves, the association between radiology-based endpoints and OS could not be evaluated at the individual level. Second, due to the lack of reporting of data on hepatic decompensation, we were unable to analyze the surrogacy between a composite endpoint including this relevant clinical event and OS. Third, we were unable to assess other potentially relevant patient-level covariates, such as the number of performed TACE in the individual patients, the pattern of progression, treatment-related toxicity, and the scores assessing liver function after TACE. [41] An individual patient data meta-analysis could better evaluate the

surrogacy between radiology-based endpoints and OS. Finally, the exclusion of non-comparative studies could reduce the transferability of our results to a real-world setting. However, we excluded non-comparative studies for the lack of data on TTP in many of them and because they did not perform a prospective systematic assessment of radiological progression, biasing the evaluation of surrogacy between OS and radiology-based endpoints.

In conclusion, in patients with u-HCC underwent TACE, the surrogacy relationship between TTP and OS resulted moderate also by using innovative approaches. Heterogeneity in TTP and OS were significantly high. Our pooled Kaplan-Meier curves of TTP and OS could represent a useful benchmark. Caution must be taken when interpreting TTP in the absence of OS data and novel surrogate endpoints, combining oncological progression with hepatic decompensation as competing risk, should be investigated to enhance the interpretability of future clinical trials of TACE.

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Figure legends

Figure 1. Pooled reconstructed survival curves for overall survival (OS) from studies of transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC).

Figure 2. Pooled reconstructed survival curves for time to progression (TTP) from studies of transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC).

Figure 3. Meta-regression analysis of the relationship between hazard ratio of TTP and hazard ratio of OS in studies of TACE for HCC.

Figure 4. Meta-regression analysis of the relationship between median TTP and median OS in studies of TACE for HCC.

Table 1. Characteristics and clinical outcomes of 13 studies of transarterial chemoembolization (TACE) for the treatment of unresectable hepatocellular carcinoma (HCC) included in the analysis.

Study, year	Type of study	Number of patients in TACE arm	Competitor arm	Overall Survival		Time to Progression		Progression-free Survival		Overall Disease Control (%)	Time to first radiological assessment	Radiological criteria for response evalutaion	Duration of follow-up (months or weeks)
				Median	HR (95% CI)	Median	HR (95% CI)	Median	HR (95% CI)				
Mabed et al. 2009 (18)	Phase III RCT	50	Systemic doxorubicin	38 weeks (range 22–72 weeks)	NA	32 weeks (range, 16–70 weeks)	NA	NA	NA	58	12 weeks	WHO (1981)	NA
Kudo et al. 2011 Korea-Japan post-TACE trial (19)	Phase III RCT	229	TACE + Sorafenib	26.1 months (95%CI 19.2-31)	1.06 (95% CI, 0.69–1.64)	3.7 months (95% CI, 3.5 - 4.0)	0.87 (95% CI 0.70–1.09)	NA	NA	NA	NA	LCSGJ (2004)	NA
Muhammad et al. 2013 (20)	Retrospective cohort study	30	TACE + Sorafenib	18.3 months (95%CI 11.8-32.9)	0.82 (95%CI: 0.38-1.77)	NA	NA	18.2 months	0.93 (95% CI, 0.45-1.89)	91.2	NA	NA	23 months (range 3-56)
Bai et al. 2013 (21)	Prospective non-randomized controlled trial	146	TACE + Sorafenib	5.1 months	0.61 (95% CI 0.423–0.884)	4.3 months	0.60 (95% CI 0.422 - 0.853)	NA	NA	44.5	NA	RECIST	21.4 weeks (range 0.5–103 weeks)
Hu et al. 2014 (22)	Retrospective cohort study	164	TACE + Sorafenib	4.9 months	0.63 (95% CI 0.48-0.84)	1.9 months	0.62 (95% CI 0.47 -0.82)	NA	NA	NA	6-8 weeks	mRECIST	6.9 months (range, 1.2 - 37.4)
Kudo et al. 2014 BRISK TA Trial (23)	Phase III RCT	253	TACE + Brivanib	26.1 months (95% CI 19.0-30.9)	0.90 (95% CI: 0.66-1.23)	4.9 months	0.61 (95% CI, 0.48-0.77)	NA	NA	78.65	NA	mRECIST	16 months
Okhi et al. 2015 (24)	Retrospective study	71	TACE + Sorafenib	467 days	0.43 (95% CI 0.24–0.76)	NA	NA	106 days	0.38 (95% CI 0.22–0.63)	NA	8-16 weeks	mRECIST	NA

Zhang et al. 2016 (25)	Retrospective study	60	TACE + Sorafenib	6.1 months (4.0 – 8.1)	NA	2.4 months (1.3–3.4 months)	NA	NA	NA	43.3	NA	mRECIST	12.5 months (range, 1.03–44.23)
Yao et al. 2016 (26)	Prospective, nonrandomized, comparative study	100	TACE + Sorafenib	11.5 months (95% CI 7.8, 15.2)	0.481 (95% CI 0.297, 0.778)	6.7 months (95%CI 6.1 - 7.2)	0.453 (95% CI 0.302, 0.680)	NA	NA	24	4-6 weeks	mRECIST	13.9 months (range: 2.8–28.7months)
Lencioni et al. 2016 SPACE trial (27)	Phase II RCT	153	TACE + Sorafenib	NR	0.898 (95% CI, 0.606–1.330)	166 days (95% CI: 113, 168 days)	0.797 (95% CI, 0.588–1.080)	NA	NA	64.7	8 weeks	mRECIST	272 days
Zhou et al. 2016 (28)	Phase III RCT	76	TACE + Rg3	10.1 months (95% CI: 9.14, 11.06)	0.63 (95% CI, 0.46-0.85)	3.2 months (95% CI, 2.51 - 3.89)	0.82 [95% CI, 0.62 - 1.08]	NA	NA	51.3	4-6 weeks	mRECIST	NA
Meyer et al. 2017 TACE 2 trial (29)	Phase III RCT	156	TACE + Sorafenib	598.0 days (500.0–697.0 days)	HR 0.91 (95% CI 0.67–1.24)	320.0 days (234.0 -400.0 days)	0.88 (95% CI 0.67–1.17)	235 days (209–322 days)	0.99 [95% CI 0.77–1.27]	78	10 weeks	RECIST 1.1	162 days (70.0–323.5 days)
Kudo et. Al 2018 ORIENTAL trial (30)	Phase III RCT	444	Orantinib	32.3 months (28·4–not reached)	1.090 (95% CI, 0.878–1.352)	2.5 months (95% CI, 1.4 - 2.9)	0.858 (95% CI 0.744–0.990)	NA	NA	NA	6 weeks	NA	17.3 months (IQR 11.3–26.4)

HR, Hazard Ratio. 95% CI, 95% Confidence intervals. IQR, interquartile range. NA, not available. NR, not reached. LCSGJ, Liver Cancer Study Group of Japan. WHO, World Health Organization. RECIST, Response evaluation criteria in solid tumors. mRECIST, modified Response evaluation criteria in solid tumors.

Table 2. Clinical characteristics of HCC patients treated with TACE included in the study.

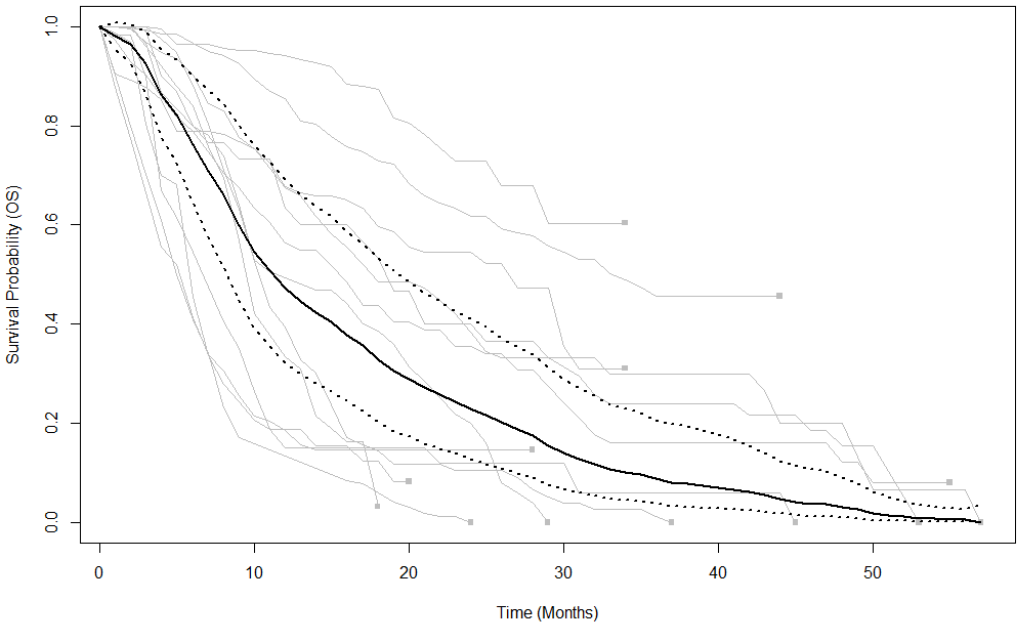
Study, year	Male Gender, n (%)	Median Age, years	Etiology of liver disease, n (%)	Alfafetoprotein (ng/mL), median (range) or n(%)	Child-Pugh class, n (%)	ECOG-PS status n (%)	Number and type of HCC lesions, n (%)	Vascular Invasion or Extrahepatic Spread, n (%)	BCLC stage n (%)	Number of TACE procedures, n (%)	Type of TACE, n (%)
Mabed et al. 2009 (18)	32 (64)	52	**HCV** 37 (74) **HBV** 6 (12) **No viral hepatitis** 4 (8) **HBV and HCV** 3 (6)	-	**A** 34 (68) **B** 16 (32)	**0** 13 (26) **1-2** 37 (74)	-	-	**Okuda stage** **I** 26 (52) **II** 24 (48)	-	**cTACE**
Kudo et al. 2011 Korea-Japan post-TACE trial (19)	168 (73.4)	70	**HCV 148 (**64.6) **HBV 52 (**22.7) **Alcohol 12 (**5.2) **Other 11 (**4.8)	-	-	**0** 202 (88.2) **1** 27 (11.8)	**≤ 3 nodules:** 169 **(**73.8) **>3 nodules:** 60 (26.2)	0 (0)	**B** 229 (100)	**1** 148 (64.6) **2** 81 (35.4)	**cTACE**
Muhammad et al. 2013 (20)	**-**	59.2	**HCV** 17 (56.6) **HCV and alcohol** 11 (36.6) **Non alcohol/ non HCV** 1 (3.4) **Alcohol** 1 (3.4)	8.1 (1.9-6000)	-	-	-	-	**A** 22 (73.3) **B** 8 (26.7)	-	**cTACE**

Bai et al. 2013 (21)	146 (89)	-	**HBV** 147 (89.6) **No viral hepatitis** 10(6.1)	-	**A** 115 (70.1) **B** 49 (29.9)	**0** 30 (36.6) **1** 38 (46.4) **2** 12 (14.6) **3** 1 (1.2) **4** 1 (1.2)	-	**Macroscopic vascular invasion** 18 (11.0) **Extrahepatic spread** 47 (28.6) **Both** 20 (12.2)	**B** 45 (27.4) **C** 119 (72.6)	-	**cTACE**
Hu et al. 2014[§] (22)	140 (85.4)	60	**HBV** 139 (84.8) **HCV** 7 (4.3) **No viral hepatitis** 10(6.1)	≥400**:** 119 (72.6)	**A** 103 (62.8) **B** 61 (37.2)	-	-	**Main portal vein thrombosis** 35 (21.3) **Portal vein branch thrombosis** 45 (27.4) **Extrahepatic spread** 49 (29.9) **Portal vein thrombosis and extrahepatic spread** 35 (21.4)	**C** 164 (100)	-	**cTACE**
Kudo et al. 2014 BRISK TA Trial (23)	216 (85)	59	**HBV** 168 (66) **HCV** 42 (17) **Alcohol** 38 (15) **Others** 8 (3)	< 100: 119 (47)	**A** 231 (91) **B** 20 (8) **C** 2 (1)	**0** 203 (80) **1** 50 (20)	**Single nodule** 83 (33) **Multinodular** 170 (68) **Tumor size** **≤ 10 cm** 195 (77) **>10 cm** 58 (23)	-	**A** 57 (23) **B** 150 (59) **C** 44 (17) **D** 2 (1)	**-**	**cTACE**
Okhi et al. 2015 (24)	**Male** 54 (71.1)	72.9	**HCV** 48 (67.6)	-	**A** 40 (56.3)	-	-	0 (0)	**B** 71 (100)	-	**cTACE**

Zhang et al. 2016 (25)	58 (97)	- 48.6	**HBV** 53(88) **Others** 7 (12)	<400: 18 (30) >400: 42 (70)	-	**0** 52 (87) **1** 8 (13)	**Mean Tumor size (cm)** 10.3 ± 3.4 **≤ 1 nodule:** 22 (37) **>1 nodules:** 38 (63)	**Extrahepatic spread** 12 (20) **Combined PVTT** 29 (48) **Location of HVTT (Vv2/Vv3),** 21/39 (35/65)	**C** 60 (100)	-	**cTACE**
Yao et al. 2016 (26)	87 (87)	55.9	**HBV** 83 (83) **HCV** 4 (4) **HBV and HCV** 3 (3) **No viral hepatitis** 10 (10)	299.6 (8.1,8899.7)	**A** 86 (86) **B** 14 (14)	**0** 21 (42) **1** 58 (29)	**Single nodule** 15 (15) **Large mass type** 31 (31) **Multiple nodules** 51 (51) **Diffuse lesion** 3 (3)	**Extrahepatic spread** 49 (51)	**B** 40 (40) **C** 60 (60)	**-**	**DEB-TACE**
Lencioni et al. 2016 SPACE trial (27)	126 (82.4)	63	**HBV** 50 (32.7) **HCV** 41 (26.8) **Alcohol use** 30 (19.6) **Non-alcoholic** 7 (4.7)	<400 : 112 (73.2) ≥400: 41 (26.8)	**A** 152 (99.3) **B** 0 (0) **Not known** 1 (0.7)	-	-	0 (0)	**B** 153 (100)	-	**DEB-TACE**
Zhou et al. 2016 (28)	63 (82.9)	52.4	**HBV** 70 (92.1)	Normal 12(15.8) <400: 11 (14.5) 400-100: 28 (36.8) 1000-10 000: 19 (25) >10 000: 6 (7.9)	-	**0** 58 (76.3) **1** 18 (23.7)	**Multinodular** 51 (67.1) **Bulky tumor** 16 (21.0) **Diffuse** 9 (11.8)	**Extrahepatic spread** 32 (42)	**C** 76 (100)	-	**cTACE**

Meyer et al. 2017 TACE 2 trial (29)	138(88)	68 (63-74)	**Alcohol** 40 (33) **HCV** 9 (7) **HCV and alcohol** 12 (10) **HBV** 7 (6) **HBV, HCV** 3 (2) **HBV, HCV, and alcohol** 2 (2) **HBV and alcohol** 2 (2) **Other** 47 (39)	25 (5–280)	**A** 148 (95) **B** 3 (2**)** **Not Know 5** (3)	**0** 97 (62) **1** 58 (37) **Not known** 1 (1)	-	0 (0)	**B** 156 (100)	**0** 11 (7) **1** 65 (41) **2** 40 (26) **3** 21 (13) **4** 10 (6) **>5** 4 (3) **Not known** 6 (4)	**DEB-TACE**
Kudo et. Al 2018 ORIENTAL trial (30)	176 (82.6)	71	**HCV** 122 (57.3) **HBV** 30 (14.1)	22.5 (0.0–32200.0)	**A** 213 (100)	**0** 195 (91.5) **1** 18 (8.5)	-	**Portal invasion** 37 (8)	**0** 9 (4.2) **A** 54 (25.4) **B** 119 (55.9) **C** 30 (14.1)	-	**cTACE**

PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus. cTACE, conventional transarterial chemoembolization. DEB-TACE, drug-eluting beads TACE.



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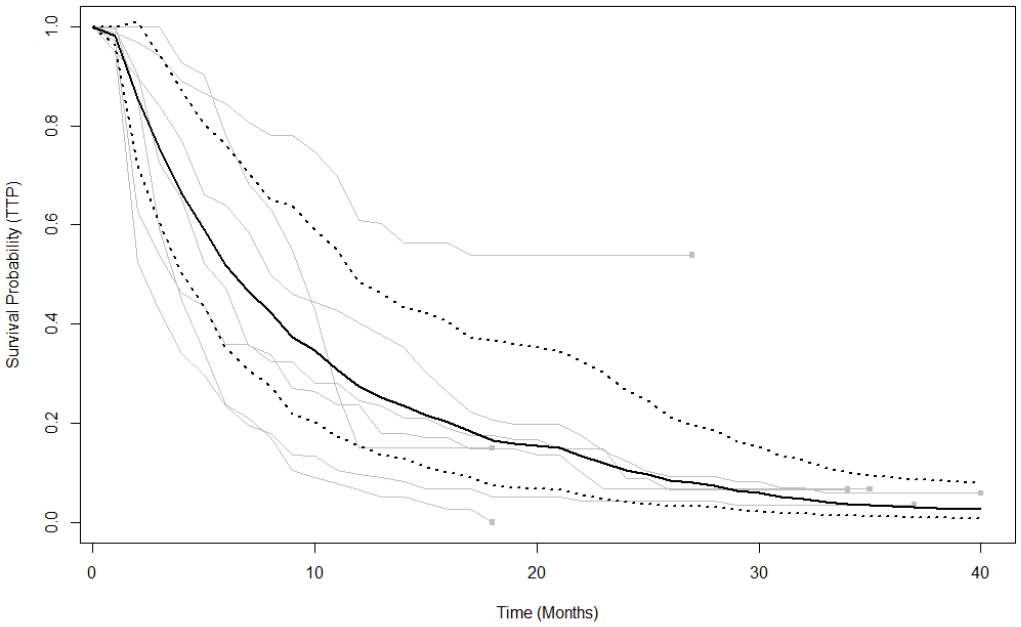

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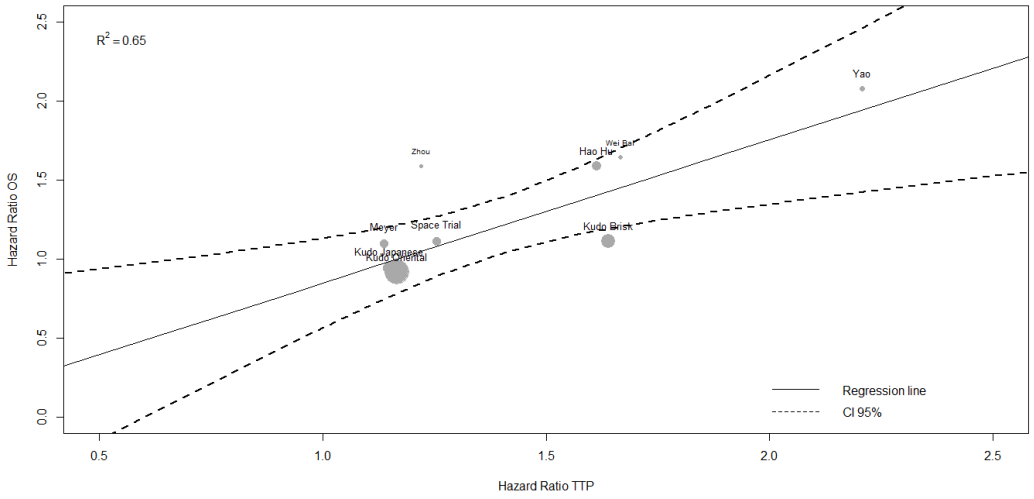

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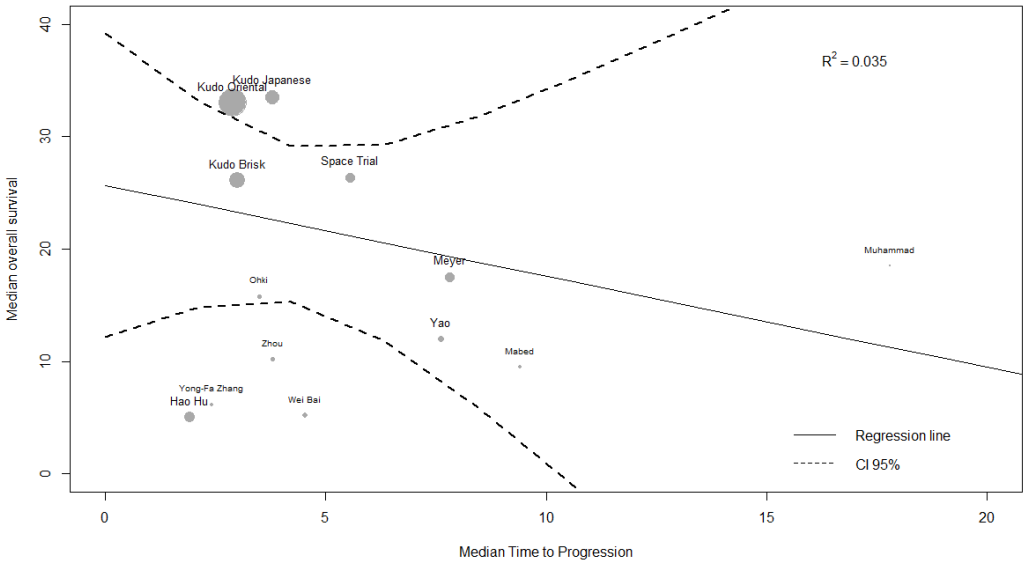

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