

## Title Page

### Title:

**Published trials of TACE for HCC are often not registered and subject to bias**

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## **ABSTRACT:**

**Background & Aims:** In 2005, the registration of all randomized controlled trials (RCTs) before enrollment of participants became a condition for publication by the International Committee of Medical Journal Editors to increase transparency in trial reporting. This study assesses the proportion of registered RCTs among RCTs on transarterial chemoembolization (TACE) for the treatment of hepatocellular carcinoma (HCC) published after 2007, and compares registered primary outcomes (PO) with those reported in publications to determine whether primary outcome reporting bias favored significant outcomes.

**Methods:** We searched MEDLINE and EMBASE for reports of RCTs evaluating TACE for HCC treatment between September 1, 2007 and March 31, 2018. Registration and publication information for each included RCT was compared using a standardized data extraction form.

**Results:** Thirteen out of 53 (25%) included RCTs were correctly registered (i.e. before the starting date of the RCT), 14 (26%) were registered after the RCT starting date, and 26 (49%) were not registered. Six out of fourteen of the retrospectively registered RCTs (43%) were registered after their completion date. The PO was clearly reported in the published article of all registered RCTs, while the report was not clear in 8/26 (31%) of the non-registered RCTs ( $P = 0.01$ ). Among registered RCTs, 8/27 (30%) had major discrepancies between registered and published PO. The influence of these discrepancies could be assessed in six of them, and was shown to statistically favor significant results in two.

**Conclusions:** Registration and outcome reporting in RCTs on TACE for HCC are often inadequate. Registration should be reinforced because it is a key to transparency.

## **LAY SUMMARY:**

Trial registration is fundamental to our understanding and interpretation of results, as it provides information on all relevant clinical trials (to place the results in a broader context), and on the details of their associated protocols (to ensure that the scientific plan is followed). Once an RCT is completed, the trial results are usually publicly shared via scientific articles that are expected to thoroughly and objectively report them. This study shows that half of the randomized controlled trials evaluating transarterial chemoembolization for hepatocellular carcinoma were not registered, and identified major discrepancies between registered and published primary outcome favoring significant results.

## **Introduction**

Liver cancer, which is mainly hepatocellular carcinoma (HCC), is the third leading cause of cancer-related death worldwide, and its incidence is expected to increase in the future [1]. In 2002, in the studies by Llovet and Lo et al. [2, 3] transarterial chemoembolization (TACE) was shown to have a significant benefit to survival compared to the best supportive care for the treatment of HCC. Almost two decades later, TACE continues to be the first-line treatment for most HCC patients [4, 5]. At the same time, research on the efficacy and safety of TACE remains active, either with by innovating TACE treatment using emerging technologies, or by evaluating new treatment strategies and combinations of TACE with other treatments.

In 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a registration policy for Randomized Controlled Trials (RCT) to increase transparency in research. All RCTs that started recruiting on or after September 2005 were required to be registered prospectively on a publicly accessible web-based registry before participant enrollment as a prerequisite for publication in member journals [6]. Indeed, trial registration is fundamental to our understanding and interpretation of results, as it provides information on all relevant clinical trials (to place the results in a broader context), and on the details of their associated protocols (to ensure that the scientific plan is followed) [7, 8]. One of the main objectives of registration is to improve the transparency of study results [9].

Once an RCT is completed, the trial results are usually publicly shared via scientific articles that are expected to thoroughly and objectively report them. However, there may be significant differences between trial registration and published results. The term ‘outcome reporting bias’ refers to the selective reporting of results in trial publications, depending on the nature and direction of the results [10]. Although a study may be published in full, pre-specified outcomes may be omitted or misrepresented to report results more favorably.

The registration and selective reporting of studies on TACE for HCC have not been examined. Thus, our study had three objectives: to evaluate the proportion of registered RCTs on TACE treatment for HCC among trials published after 2007, to compare registered primary outcomes (POs) with those actually reported in publications, and finally to determine whether primary outcome reporting bias favored significant outcomes.

## **Methods**

We performed a methodological two-step review of RCTs evaluating the efficacy and/or safety of TACE for the treatment of HCC. First, we identified all RCTs published after September 2007 and systematically searched for registration on online registries. Then, for each registered RCT, we assessed possible selective outcome reporting.

### *a) Search strategy for published RCTs*

We systematically searched MEDLINE (PubMed interface) and EMBASE (Elsevier interface) on April 2019 to identify eligible published RCTs from September 1, 2007 to March 31, 2018 (see **Supplemental Material** for search terms and equations). We chose September 2007 to leave a reasonable delay after the prospective registration requirement date (i.e. September 2005) by the International Committee of Medical Journal Editors [6]. We also screened reference lists of included studies, and relevant systematic reviews and meta-analyses [11-16]. All the records from these searches were imported via EndNote into Rayyan (a free web application for screening abstracts) to proceed with the screening.

### *b) Identification of relevant published RCTs*

We identified all RCTs that assessed the efficacy and/or safety of TACE for HCC, regardless of the phase, from the retrieved records. To focus on trials in which TACE was the primary

treatment and was not an associated treatment, we excluded RCTs if the same TACE procedure was combined with another treatment and was therefore present in all groups or arms. We also excluded systematic reviews or meta-analyses, diagnostic studies, methodological publications, editorial style reviews, abstracts and posters, conference papers, case reports, studies not involving human participants or studies that were not in English. One reviewer (\_\_) examined each title, keywords and abstract and then selected full-text articles according to the pre-specified eligibility criteria.

c) *Data extraction of published RCTs*

One reviewer (\_\_) extracted all data from the original reports and supplementary files according to a standardized data collection form (**Supplemental Material**). For quality assurance a second reviewer (\_\_) collected data from a random sample of 10% of the RCTs. Disagreement was resolved by discussion.

The following characteristics were systematically recorded from the published article: study location (defined as Eastern-Asia, Western-Europe, North America and North Africa; location of international RCTs was determined according to the primary investigator); number of involved centers (either single or multicenter); presence of a university-affiliated center; phase of the RCT when stated; funding source (profit, nonprofit or mixed), sample size (defined as total number of randomized patients); date of journal publication; RCT start and completion dates; type of journal (i.e., radiological or clinical), median journal impact factor in the two years before publication; we additionally collected the interventions to which TACE was compared in each RCT.

We also assessed the methodological quality of the included RCTs using selected items from the Cochrane risk of bias tool [17], in particular, random sequence generation and allocation concealment. In addition, we investigated whether the delay between randomization and the

TACE procedure, the reasons for and percentages of withdrawal or patient dropouts, and a flow chart were reported in the published article. Finally, we evaluated whether the intention-to-treat analysis was correctly performed.

*d) RCT registration*

One reviewer (□) systematically looked to see if each published RCT was registered.

In particular we checked if the authors mentioned the registration of their trial in the published article and whether a registration number was provided.

When no registration number was reported in the published article, we searched for a corresponding registration using a combination of keywords, including a description of the interventions and population, location, responsible party and primary outcome name. We first searched meta-platforms including the Cochrane Central Register of Controlled Trials (CENTRAL), and the International Clinical Trials Registry Platform (ICTRP). We then searched the following primary registries: Clinicaltrials.gov, Clinicaltrialsregister.eu, the Chinese Clinical Trial Registry (ChiCTR) and the University Hospital Medical Information Network Clinical Trials registry (UMIN-CTR).

RCT registrations were classified according to the ICMJE statement: (1) prospectively registered if the initial registration date was before or within one month after the trial start date as stated in the registry (to allow for incomplete start dates and processing delays in the registry); (2) retrospectively registered; (3) not registered.

*e) Selective outcome reporting*

Finally, we evaluated the consistency between the primary outcomes as specified in the registered RCT (when possible in the version before patient inclusion began, including amendments, and if not in the most recent available version), and those defined in the

published articles. We also recorded whether the primary outcome (PO) was clearly identified in the article (defined and graded as primary and secondary upfront), and if multiple primary outcomes were investigated in the same RCT.

We defined major discrepancies according to the classification by Chan et al. [10], as those in which (1) a pre-specified primary outcome in the RCT registration protocol was later reported as a secondary outcome or was not labeled as either in the final published article; (2) a pre-specified primary outcome was omitted from the published articles; (3) the published primary outcome was described as a secondary outcome in the registry; and (4) a new primary outcome was introduced in the published articles.

f) *Results of the registered and published primary outcomes*

We extracted the P values from the full text article for all the registered primary outcomes and for all the outcomes reported in the article. We quoted results according to statistical significance: results significantly supporting or refuting the study intervention (i.e.,  $P < .05$ ), results that did not reach statistical significance (i.e.,  $P \geq .05$ ).

A discrepancy was said to favor statistically significant results if a new statistically significant primary outcome was introduced or if a non-significant primary outcome was defined as non-primary in the published article. We also judged the discrepancy as positive when a new statistically non-significant safety primary outcome was introduced in the published article. The influence of some discrepancies could not be assessed because the published text contained no results concerning the registered primary outcome. Thus, the positivity or negativity of the discrepancy was considered to be impossible to decide, and the study was considered impossible to assess.

g) *Statistical analysis*



Quantitative variables are described with medians (quartiles 1-3, Q1-Q3) and qualitative variables with numbers and percentages. Logistic regression was used to identify RCT characteristics associated with RCT registration status. Two-sided  $P < .05$  was considered to be statistically significant. All data were analyzed with R V.4.2 (<https://www.r-project.org>, the R Foundation for Statistical Computing, Vienna, Austria), (Supplementary CTAT Table).

#### h) Data sharing

Final data spreadsheet, including the list of eligible RCTs, is available in **Supplemental Material**.

## Results

The search retrieved 6104 references. A total of 349 reports were selected after screening titles, abstracts and keywords. A total of 75 published RCTs were eligible and 53 were included for analysis. The flow chart is reported in **Figure 1**.

#### a) *Registration of included RCTs*

The description of included articles is presented in **Table 1**. Twenty-six (49%) RCTs published after September 2007 (i.e., two years after the ICMJE statement for prospective registration of RCTs) were not registered. Registration of 14 of the 27 registered RCTs was retrospective (52%). Six of these retrospectively registered RCTs (43%) were registered after their completion date. RCTs that were retrospectively registered before their completion date were more recent (median [Q1-Q3], 2011 [2010-2013]) than those registered after their completion date (2007 [2004-2009],  $P = .02$ ).

Information on RCT registration was reported in the text of the article in 85% of the registered RCTs (13/13 of the prospectively registered and 10/14 of the retrospectively registered studies,  $P = .05$ ).

Prospectively registered RCTs were more recently published (median [Q1-Q3], 2016 [2013-2017]) than retrospectively registered (2014 [2012-2016]) and non-registered (2011 [2009-2013],  $P < 0.01$ ) studies. The median (Q1-Q3) journal impact factor was 15 (7.6-20.9) for prospectively registered RCTs, 5.6 for retrospectively registered RCTs and 2.3 for non-registered RCTs ( $P = .02$ ).

Registration rate by type of intervention TACE is compared to is presented in Figure 2.

*b) Methodological characteristics of RCTs according to registration status*

A flow chart was reported in 13/13 of the prospectively registered RCTs, 12/14 retrospectively registered RCTs (86%) and 8/26 of the non-registered RCTs (31%), ( $P < .01$ ). None of the prospectively registered RCTs reported a high-risk/unclear randomization sequence or allocation concealment compared to 2/14 (14%) and 2/14 (14%) of the retrospectively registered RCTs, and 14/26 (54%) and 17/26 (65%) of the non-registered RCTs ( $P < .01$ ). All prospectively registered RCTs (13/13) performed an intention-to-treat analysis, compared to 13/14 (93%) of the retrospectively registered RCTs, and 15/26 (58%) of the non-registered RCTs ( $P < .01$ ) (**Table 2**).

*c) Primary outcome of RCTs according to registration status*

The primary outcome was clearly defined in the published article of all registered RCTs (27/27), whereas this was not reported clearly in 8/26 non-registered RCTs (31%) ( $P < .01$ ). Multiple primary outcomes were reported in 1/27 registered RCT publications (4%), and in 8/26 non-registered RCTs (31%) ( $P = .01$ ). Among registered RCTs, multiple primary

outcomes were initially registered for 0/13 prospectively registered RCTs and 4/14 retrospectively registered RCTs (29%) ( $P = .01$ ).

*d) Selective outcome reporting for registered RCTs*

Eight of the 27 registered RCTs (30%) had major discrepancies between the registered PO and those reported in the publication article (see **Table 3**). The frequency of discrepancies was higher in retrospectively registered RCTs (7/14, 50%) than in prospectively registered RCTs (1/13, 8%) ( $P = .01$ ). The list of major discrepancies is shown in **Box 1**. Only one of the four registries that initially reported multiple POs reported the same POs in the published article; the three others reported a single PO.

The influence of the discrepancy could be assessed in 6/8 (75%) of the RCTs with a PO discrepancy between the registry and the published article. The registered PO was omitted from the published article in the two remaining RCTs. Two of the six RCTs in which the discrepancy could be assessed, had a discrepancy that favored statistically significant results (one had discrepancy that favored statistically significant secondary outcomes and two non-significant primary outcomes; the other study had a new statistically non-significant safety primary outcome introduced in the published article).

## **Discussion**

In a previous study, we showed that despite the ethical commitments and public expectations for the disclosure of results, the availability of RCT results evaluating TACE for the treatment of HCC is very limited [18]. In this study we focused on RCTs on the same topic with results published after 2007, and showed that only half were registered. It is important to note that only 25% were prospectively registered as recommended by the ICJME guidelines. We also found that one third of registered RCTs had major discrepancies between the registered and

published primary outcomes, with 7% presenting with selective outcome reporting favoring the trial results.

Registration rates have already been studied in other specialties also highlighting the low proportion of correctly registered RCTs, although with some discrepancies. Rosenthal et al. focused on registered RCTs published in 2010 in three leading general surgical journals. This study identified 55 RCTs including four (8%) which were not registered, 46 (84%) which were retrospectively registered, and only five (9%) which were prospectively registered [19]. Bonnot et al. [20] investigated the registration of 183 RCTs published in 2013 in twelve high impact anesthesia journals. These authors showed that trial registration was lacking in 70 published reports (38%), and that 60 (53%) and 53 (29%) were retrospectively and prospectively registered, respectively. Finally, Mathieu et al. evaluated 323 RCTs published in 2008 in a panel of medical specialties in high-impact journals, and reported that trial registration was lacking in 89 (28%) published reports, while 45 (15%) had been retrospectively registered and 147 (46%) had been prospectively registered [21]. The fact that we did not focus on high-impact journals only probably explains the higher rate of unregistered trials in our study. Despite this difference, the proportion of prospectively registered RCTs observed in our study appears to be similar to that reported by Bonnot et al. and Mathieu et al., but higher than that of surgical RCTs published in high-impact journals. Although we covered a longer and later time period than Rosenthal et al. [19], the comparison seems valid because interventional oncology is often compared to surgery due to similarities between the two disciplines, with particular difficulty in designing RCTs, and complex interventions that are difficult to evaluate.

The 2005 ICJME initiative for trial registration is a significant step towards more transparent and accountable research. However, the timing of registration must still be improved. Indeed, only 25% of RCTs were registered prospectively. This is also in line with a previous report

[22]. One possible explanation is that researchers need time to adjust to new regulations and recommendations. We chose to analyze the results of RCTs published after 2007 to take this into consideration, but integrating new habits into research protocols may take more time. The fact that prospectively registered RCTs were published more recently than retrospectively registered or unregistered studies seems to support this hypothesis. Furthermore, the involvement of institutional boards and trial funders is likely to help enforce prospective trial registration [10, 23].

It is important to note that registration and especially prospective registration was associated with higher methodological standards (e.g. less allocation concealment, more intention-to-treat analysis, more frequent flow chart, etc). This is probably due to the higher standards of the journals publishing the results of registered RCTs, as confirmed by their higher impact factors. Indeed, clear journal submission guidelines are associated with better adherence to ICJME standards [21], which are mainly endorsed by journals with a high impact factor [24]. Altogether, trial registration and publication standards create a virtuous circle that is beneficial to the scientific community and, more importantly, to patients. Nevertheless, the positive affect of trial registration on the quality of research reporting cannot prevent possible selective reporting of outcomes.

Publications have shown that discrepancies between registries and publications are frequent [22, 25, 26]. A systematic review comparing registered and published outcomes in RCTs, including 27 studies from a panel of medical and surgical specialties, reported a median proportion of discrepancy of 31%, which is similar to our results [27]. However, we may have underestimated the selective reporting of outcomes associated with statistical significance because we could only access registered protocols [28]. Indeed, the extent of selective reporting in the results of unregistered RCTs remains unknown. Of course, the decision to omit outcomes from publications is not necessarily a sign of dishonest practices. It may be

related to a combination of space constraints, a lack of clinical importance, and statistical results [22, 29]. Nevertheless, selective reporting may result in a bias of favorably reporting efficacy which could cause physicians to perform interventions with no evidence of benefit. Similarly, underreporting toxicity could result in patients being exposed to treatments that may not be optimal, even with proven benefit.

Interventional radiologists, like other physicians, are generally not well-trained to identify outcome reporting bias. However, they should be aware that study reports may be biased, despite ICJME guidelines. One might argue that it is the role of publishers and peer reviewers to detect these types of bias to reduce their frequency in published results [30]. Unfortunately, our results suggest that they do not sufficiently take advantage of the benefits of the transparency provided by registration. Indeed, we found some evidence of selective outcome reporting in one third of published results. Therefore, since the consistency of outcomes between the registered protocol and published reports are available in online registries, readers should make a habit of consulting this information when a study can have a significant impact on clinical practices. Moreover, we believe that tracking registration status and selective outcome reporting are fundamental steps in the conduct of a meta-analysis as well as in the development of recommendations, as their omission could impact subsequent conclusions and statements.

Our study has limitations. First, it only focused on a specific treatment (TACE for treating HCC). Nevertheless, TACE remains the most frequent first line treatment in patients with HCC [31]. We did not include RCTs with combinations of TACE with other treatments because it would have been methodologically difficult to analyze the heterogenous data. Also, we did not contact the authors of unregistered RCTs to identify unreported POs and determine whether they did not reach statistical significance. Finally, we did not address the issue of selective reporting of non-primary outcomes, which may be more common. The strength of

this study is that it is the first to show that under-registration and selective outcome reporting are common in one of the most extensively studied and performed interventional oncology procedures.

## **Conclusion**

Trial registration improves the transparency of research and is a safeguard against reporting bias or other deviations from the planned study. The registration and timing of registration in RCTs on TACE for HCC must still be improved, and outcome reporting is too often inadequate in the results of registered trials. The registration of RCTs in interventional oncology of the liver should be reinforced.

**ABBREVIATIONS:**

*CENTRAL*: Cochrane Central Register of Controlled Trials

*ChiCTR*: Chinese Clinical Trial Registry

*HCC*: Hepatocellular Carcinoma

*ICMJE*: International Committee of Medical Journal Editors

*ICTRP*: International Clinical Trials Registry Platform

*PO*: Primary Outcome

*RCT*: Randomized Controlled Trials

*TACE*: Transarterial Chemoembolization

*UMIN-CTR*: University Hospital Medical Information Network Clinical Trials registry

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**Table 1.** General characteristics of included randomized controlled trials (RCTs) by registration status

Characteristics	Registered N = 27		Not registered N = 26	P
	Prospectively N = 13	Retrospectively N = 14		
<b>Study location</b>				0.63
Eastern-Asia (N = 39)	8 (21)	11 (28)	20 (51)	
Western-Europe (N = 9)	2 (22)	3 (33)	4 (45)	
Northern-America (N = 4)	3 (75)	0 (-)	1 (25)	
Northern-Africa (N = 1)	0 (-)	0 (-)	1 (100)	
<b>Number of centers</b>				0.20
Multicenter (N = 12)	4 (33)	4 (33)	4 (33)	
Single-center (N = 53)	9 (22)	10 (24)	22 (54)	
<b>Type of center</b>				0.21
University affiliated (N = 43)	11 (26)	12 (28)	20 (46)	
Non-university affiliated (N = 3)	0 (-)	0 (-)	3 (100)	
Both (N = 7)	2 (29)	2 (29)	3 (42)	
<b>Funding source</b>				0.08
Nonprofit (N = 50)	11 (22)	13 (26)	26 (52)	
Profit (N = 3)	2 (66)	1 (33)	0 (-)	
Mixed (N = 0)	0 (-)	0 (-)	0 (-)	
<b>Phase</b>				0.13
II (N = 8)	3 (37)	2 (25)	3 (37)	
III (N = 10)	6 (60)	2 (20)	2 (20)	
NA (N = 35)	4 (11)	10 (29)	21 (60)	
<b>Median sample size [min-max]</b>	189 [92-247]	131 [93-238]	97 [52-125]	<b>&lt;0.01</b>
<b>Type of journal</b>				0.27
Radiological (N = 14)	3 (21)	2 (14)	9 (65)	
Clinical (N = 39)	10 (25)	12 (31)	17 (44)	
<b>Median date of publication [Q1-Q3]</b>	2016 [2013-2017]	2014 [2012-2016]	2011 [2009-2013]	<b>&lt;0.01</b>
<b>Median date of first inclusion [Q1-Q3]</b>	2010 [2009-2013]	2010 [2008-2012]	2008 [2004-2011]	0.47
<b>Median journal impact factor [min-max]</b>	15 [7.6-20.9]	5.6 [3.4-7.2]	2.3 [1.5-2.9]	<b>0.02</b>

Unless otherwise noted, data are numbers of RCTs, with the percentage in parentheses. Percentages are calculated per row

**Table 2.** Methodological characteristics of included randomized controlled trials (RCTs) by registration status

Characteristics	Registered N = 27		Not registered N = 26	P
	Prospectively N = 13	Retrospectively N = 14		
<b>Sequence generation*</b> (high/unclear)	0	2 (14)	4 (54)	<b>&lt;0.01</b>
<b>Allocation concealment*</b> (high/unclear)	0	2 (14)	17 (65)	<b>&lt;0.01</b>
<b>Reported delay between randomization and transarterial chemoembolization</b>	6 (46)	8 (57)	7 (27)	0.28
<b>Dropouts or withdrawal reported</b>	13 (100)	13 (93)	23 (88)	0.20
<b>Reason of dropouts reported</b>	13 (100)	13 (93)	20 (77)	0.13
<b>Intention to treat performed</b>	13 (100)	13 (93)	15 (58)	<b>&lt;0.01</b>
<b>Presence of a flow chart</b>	13 (100)	12 (86)	8 (31)	<b>&lt;0.01</b>

Dare numbers of RCTs, with the percentage in parentheses.

Percentages are calculated per column

\* According to the Cochrane risk of bias tool

**Table 3.** Proportion of randomized controlled trials (RCTs) with major discrepancies in the specification of primary outcomes when comparing registries and published articles

<b>Discrepancy between RCT report and registration (n = 27)</b>	<b>RCTs with discrepancies for primary outcome</b>
<i>Primary outcomes specified in protocols</i> <sup>a</sup>	8 (30)
Any change to registration-defined primary outcome	
Reported as secondary in published articles	6 (22)
Omitted from published articles	3 (11)
<i>Primary outcomes specified in published articles</i>	5 (19)
Any new primary outcome defined in published articles	
Changed from secondary in registration to primary in published articles	2 (7)
Not mentioned in protocol	2 (7)
Any discrepancy in primary outcome <sup>b</sup>	8 (30)

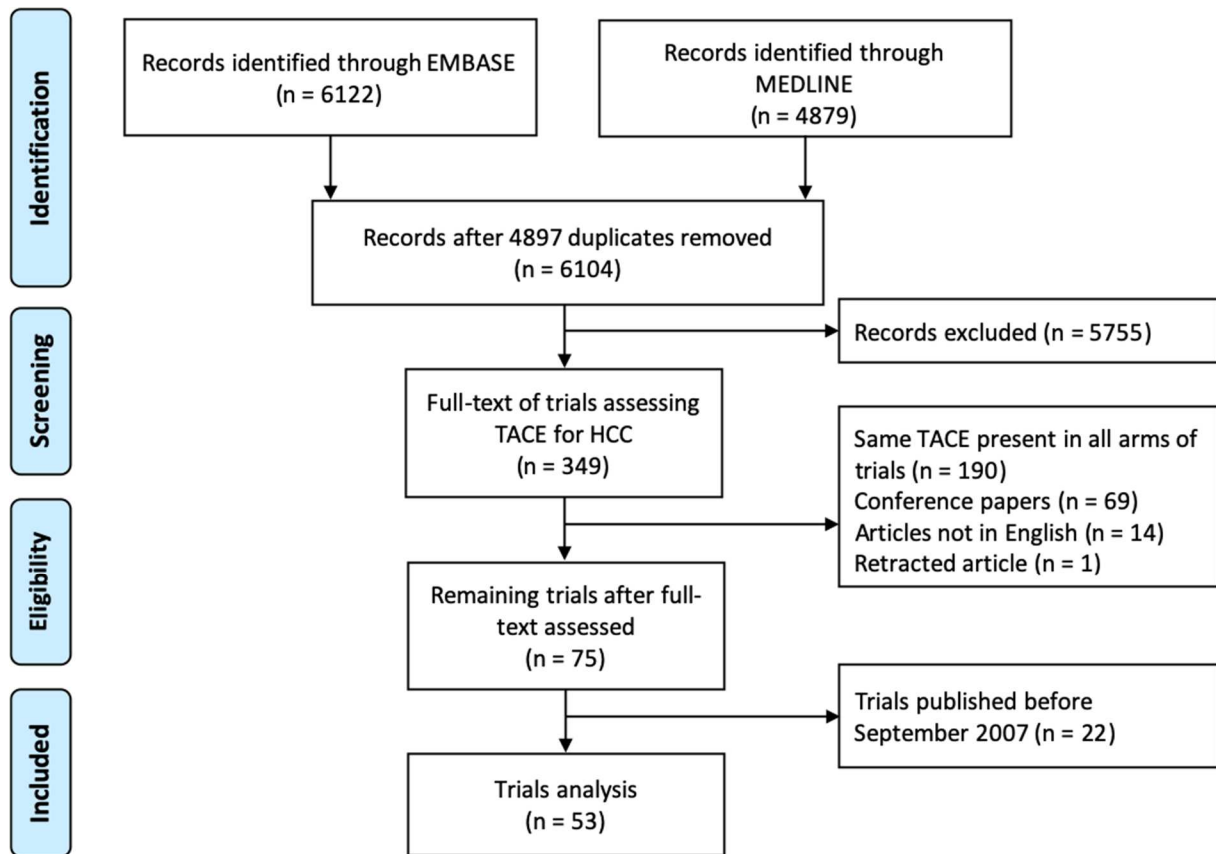
Data are numbers of RCTs, with the percentage in parentheses.

<sup>a</sup> Categories are not mutually exclusive: one RCT could have more than one type of discrepancy for different primary outcomes.

<sup>b</sup> Primary outcomes defined in either registration or published articles.

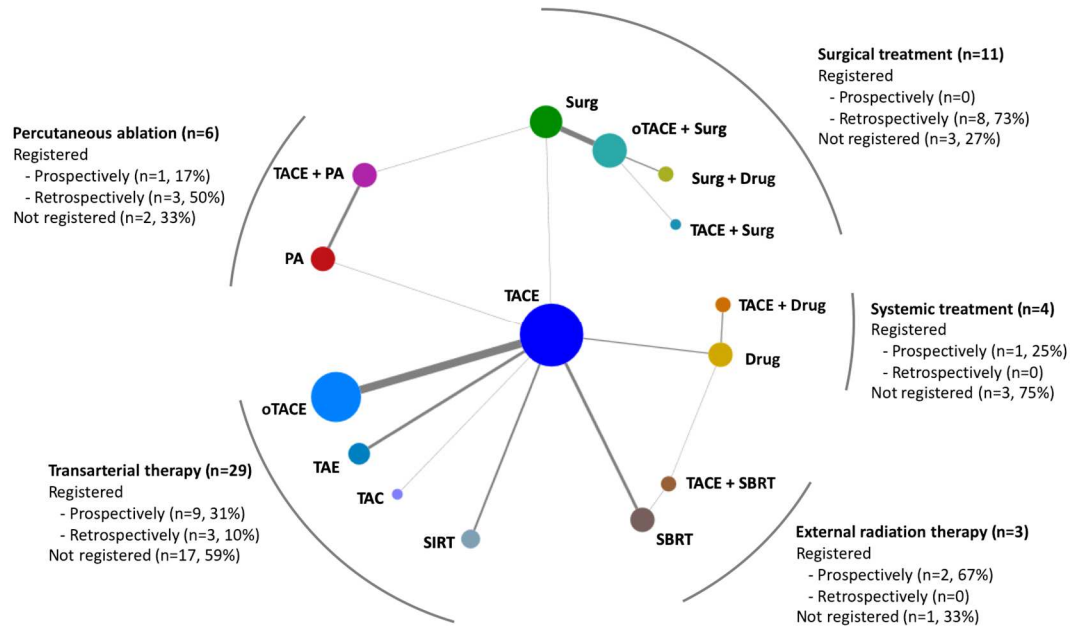
**Box 1. List of major discrepancies between randomized controlled trials (RCT) registry and published article in the specification of primary outcomes (PO)**

- *RCT 14* - Registered PO (disease free survival) omitted from published report
- *RCT 111* - Registered POs (overall survival and quality of life) omitted from published report.
- *RCT 27* - Registered PO (overall survival) replaced by a registered secondary outcome (disease free survival)
- *RCT 29* - Registered PO (overall survival) changed to secondary
- *RCT 155* - Registered PO (progression free survival) changed to secondary
- *RCT 15* - Registered PO (disease free survival) omitted from published report and replaced by a new PO (recurrence free survival)
- *RCT 23* - Registered PO (overall survival) changed to secondary. Registered POs (time to progression, quality of life, response rate) omitted from published report. New primary outcome (recurrence free survival)
- *RCT 89* - Registered PO (overall survival) replaced by a registered secondary outcome (progression free survival)



**Figure 1. Selection of randomized controlled trials (RCTs)**

*TACE*, Transarterial chemoembolization; *HCC*, Hepatocellular carcinoma



**Figure 2. Network graph of included randomized controlled trials showing the registration rate by type of intervention compared to TACE.**

Each node represents a treatment and each edge a randomized comparison of two treatments. Thickness of each edge increases with the number of randomized comparisons.

Interventions are pooled according to main treatment category. For each group of intervention, number and percentage of registered trials is presented.

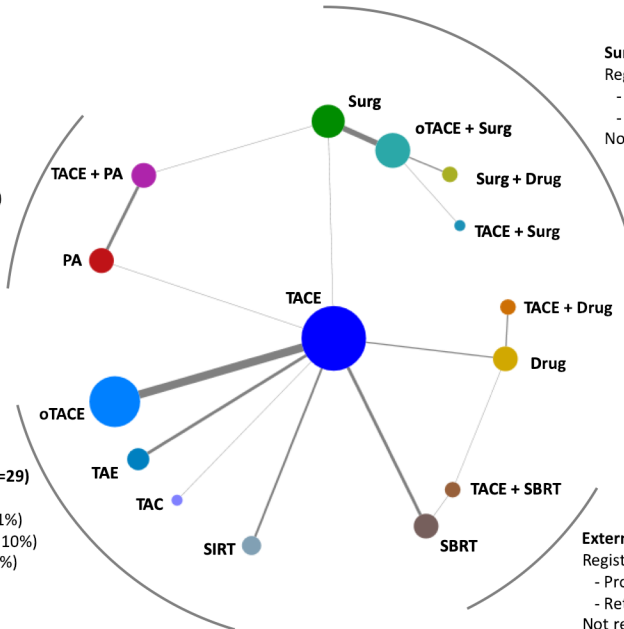
*TACE*, Transarterial chemoembolization; *oTACE*, Other type of TACE; *TAE*, Transarterial Embolization; *TAC*, Transarterial chemotherapy; *SIRT*, Selective Internal RadioTherapy; *SBRT*, Stereotactic body radiation therapy; *Surg*, Surgery; *PA*, Percutaneous Ablation.



**Percutaneous ablation (n=6)**

Registered

- Prospectively (n=1, 17%)
  - Retrospectively (n=3, 50%)
- Not registered (n=2, 33%)



**Surgical treatment (n=11)**

Registered

- Prospectively (n=0)
  - Retrospectively (n=8, 73%)
- Not registered (n=3, 27%)

**Systemic treatment (n=4)**

Registered

- Prospectively (n=1, 25%)
  - Retrospectively (n=0)
- Not registered (n=3, 75%)

**Transarterial therapy (n=29)**

Registered

- Prospectively (n=9, 31%)
  - Retrospectively (n=3, 10%)
- Not registered (n=17, 59%)

**External radiation therapy (n=3)**

Registered

- Prospectively (n=2, 67%)
  - Retrospectively (n=0)
- Not registered (n=1, 33%)