



Current trends in the treatment of hepatocellular carcinoma with transarterial embolization: a cross-sectional survey of techniques

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Abstract

Purpose Despite being accepted as a mainstay of treatment for hepatocellular carcinoma (HCC), technical aspects of transarterial chemoembolization (TACE) continue to vary by reporting author, leading to heterogeneity in the literature and making meaningful comparisons between treatments difficult. The goal of this survey was to report international chemoembolization practices for the treatment of HCC in an effort to understand current treatment strategies as a first step towards technique standardization.

Materials and methods An anonymous 18-question online survey, evaluating technical aspects of their TACE practice, was distributed via email to practicing members of the five largest interventional radiology societies in Chinese and English. A total of 1160 responses were obtained from 62 countries. Responses were categorized according to region of practice and analyzed using Fisher's exact test and chi-square test with Bonferroni correction as needed.

Results There were significant statistical differences between regions for nearly all questions. Doxorubicin was more commonly used among respondents from North America, Europe, and South Korea than Japan and China ($p = 0.0001$). For single and multiple HCCs, drug-eluting bead TACE was most popular in North America and Europe ($p = 0.0001$), while conventional TACE was most popular in Japan, Korea, and China ($p = 0.0001$). CT was the most commonly used modality for follow-up among all respondents, although MR was used more commonly in North America and in academic centers ($p = 0.0001$).

Conclusion This survey provides comprehensive information on and confirms the heterogeneous nature of current practice patterns in regard to TA(C)E for HCC.

Key Points

- *There is a lack of information regarding current practice patterns in the area of technical considerations when performing transarterial chemoembolization.*
- *Type of transarterial chemoembolization utilized to treat hepatocellular carcinoma varies widely across geographical area.*
- *Chemotherapeutic agents and embolic agents used to perform transarterial chemoembolization for the treatment of hepatocellular carcinoma vary widely across geographical areas.*

Keywords Chemoembolization · Hepatocellular carcinoma (HCC) · Survey

Abbreviations

AASLD American Association for the Study of Liver Disease
BCLC Barcelona Clinic Liver Cancer
CIRSE Cardiovascular and Interventional Radiology Society of Europe

CSIR Chinese Society of Interventional Radiology
cTACE Conventional transarterial chemoembolization
DEB-TACE Drug-eluting bead transarterial chemoembolization
EASL European Association for the Study of the Liver
HCC Hepatocellular carcinoma
JSIR Japanese Society of Interventional Radiology
KSIR Korean Society of Interventional Radiology
LRTs Locoregional therapies

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mRECIST	modified Response Evaluation Criteria in Solid Tumors
RECIST	Response Evaluation Criteria in Solid Tumors
SIR	Society of Interventional Radiology
TACE	Transarterial chemoembolization
TAE	Transarterial embolization

Introduction

Locoregional therapies (LRTs) are an accepted, and frequently applied, treatment for hepatocellular carcinoma (HCC) patients. While many LRTs have been created and found efficacious, transarterial chemoembolization (TACE) is perhaps the most studied and therefore most accepted. TACE is included in HCC treatment algorithms by virtually every major liver/HCC society including the Barcelona Clinic Liver Cancer (BCLC), American Association for the Study of Liver Disease (AASLD), and European Association for the Study of the Liver (EASL) [1–3]. While the body of literature is extensive in regard to TACE in the treatment of HCC, the technical aspects of the procedure itself frequently vary in even basic areas such as the choice of chemotherapy or if chemotherapy is used at all.

The two groundbreaking clinical trials, which firmly established the efficacy of TACE for the treatment of HCC by showing improved overall survival as compared to best clinical care, serve to demonstrate these technical differences [4, 5]. These two studies differed in chemotherapeutic agents used, use of antibiotics, embolization endpoint, and time between treatments. This heterogeneity has persisted in the TACE literature without clear evidence to guide practitioners in the most basic aspects of the procedure.

The heterogeneity of the literature is furthered by the fact that TACE is commonly used as an umbrella term used to describe several fundamentally different procedures, including conventional TACE (cTACE), drug-eluting bead TACE (DEB-TACE), and transarterial embolization (TAE). While all three procedures involve the selective catheterization of the artery(ies) feeding the tumor, conventional TACE then involves the delivery of chemotherapeutic agent(s) mixed with an ethiodol oil, which serves to prevent immediate wash-out of the chemotherapy. cTACE then follows the delivery of ethiodol oil/chemotherapeutic agent(s) with particle embolization to stop blood flow as well as increase chemotherapeutic dwell time [6]. DEB-TACE differs in that chemotherapy is loaded onto beads, which then slowly release it after arterial delivery, thus combining the embolization and chemotherapeutic steps [7]. Finally, TAE is very similar to TACE, and except in TAE, no ethiodol oil or chemotherapy is used; the lesion is treated with simple particle embolization [8].

The differences in fundamental technical aspects of the procedure make comparisons across clinical trials difficult. Furthermore, the variation is a symptom of lack of evidence as to the most efficacious ways to perform the procedure. This area is in dire need of well-done randomized controlled trials to answer these fundamental questions; however, before those can be designed, it is important to understand the current state of practice. Unfortunately, there is a paucity of this type of data in the literature, which is currently limited to a single country or interventional society [9–11].

Therefore, this paper aims to determine the current global practice patterns of TA(C)E through a survey which was distributed to the largest interventional radiology societies around the world.

Materials and methods

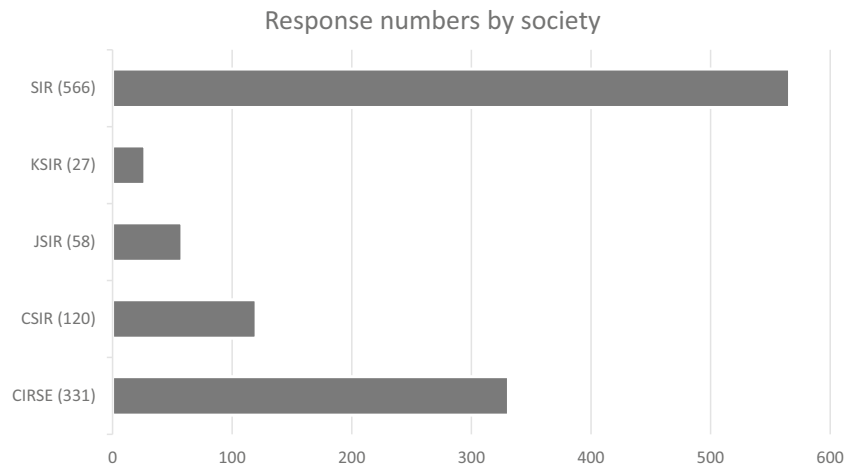
A questionnaire was developed by two interventional radiologists with expertise in oncology. It was then distributed to other interventional radiologists with expertise in oncology for review and comment. Finally, a consensus 18-question online survey, administered through Survey Monkey and Qualtrics, was distributed by email to members of the Cardiovascular and Interventional Radiology Society of Europe (CIRSE), the Chinese Society of Interventional Radiology (CSIR), the Japanese Society of Interventional Radiology (JSIR), the Korean Society of Interventional Radiology (KSIR), and the Society of Interventional Radiology (SIR). The survey is presented in the [Appendix](#) and was distributed in English and Chinese. Where appropriate, the responses were categorized and analyzed using Fisher's exact test and chi-square test with Bonferroni correction as needed. Responses were categorized according to region of practice. In total, nine regions were established, including China, Japan, Korea, North America, South America, Europe, Middle East/Africa, South Asia, and Oceania and analyzed. A *p* value of <0.05 was considered statistically significant.

Results

An estimated total of 15,704 surveys were distributed and 1160 responses were obtained from 62 countries, leading to a response rate of 7.4%. Fifty-eight responses were excluded because less than 90% of answers were completed. Responses by society can be found in [Fig. 1](#) and the responses by geographical location can be found in [Fig. 2](#). Of the completed responses, 566 (51.4%) were members of SIR, 331 (30.0%) of CIRSE, 120 (10.9%) of CSIR, 58 (5.3%) of JSIR, and 27 (2.4%) KSIR.

Respondents most commonly worked at an academic practice (397/1074, 37.0%), followed by a government hospital

Fig. 1 Response numbers by society. The number of responses is presented in parentheses following the society. *CIRSE* Cardiovascular and Interventional Radiology Society of Europe, *CSIR* Chinese Society of Interventional Radiology, *JSIR* Japanese Society of Interventional Radiology, *KSIR* Korean Society of Interventional Radiology, *SIR* Society of Interventional Radiology



(300/1074, 27.9%), community hospital (175/1074, 16.3%), and a secondary/tertiary referral center (202/1074, 18.8%).

There was a significant statistical difference among the cytotoxic agent(s) used, dosing of agent(s), type of procedure for single and multiple HCCs, the DEB type, amount of ethiodized oil, drug mixing method, procedural endpoint, type of embolic agent, use of additives and antibiotics, length of clinical follow-up, choice of imaging follow-up, and choice of tumor response between the regions (Table 1).

Evaluation of preferred materials and techniques

Respondents differed significantly, by region, in their preferred procedure (DEB-TACE, cTACE, etc.) for single and multiple HCCs ($p < 0.0001$). For single HCCs, compared with other groups, DEB-TACE was most popular in North America (318/527, 60.3%) and Europe (145/238, 60.9%) ($p < 0.01$), while cTACE was most popular in Japan (53/63, 84.1%), Korea (22/35, 62.8%), and China (61/131, 46.5%) ($p < 0.01$). For multiple HCCs, DEB-

TACE remained most common in North America (243/523, 46.4%) and Europe (108/236, 45.7%) ($p < 0.01$), and cTACE remained most common in Japan (37/61, 60.7%), Korea (21/34, 61.7%), and China (59/111, 53.4%) ($p < 0.01$). TAE was the procedure of choice for 2.9% (32/1094) of practitioners.

The responses for choice of cytotoxic agent can be found in Table 2; there was a statistically significant difference in chemotherapeutic agent preferred between regions ($p < 0.0001$). Doxorubicin was the most popular cytotoxic agent overall (779/1084, 71.7%) and more commonly used by respondents from North America, Europe, and Korea ($p < 0.01$). Pirarubicin was the most commonly used cytotoxic agent in China (27/128, 21.1%) and Epirubicin in Japan (43/59, 72.9%). Use of a combination of chemotherapeutic agents is infrequent with only 2.1% (23/1084) using triple-drug therapy and 2.8% (30/1084) using double-drug therapy.

The responses for choice of cytotoxic dose determination can be found in Table 3; there was a statistically significant difference in the dose determination method

Fig. 2 Responses by geographical area. The number of responses is written in parentheses following the region

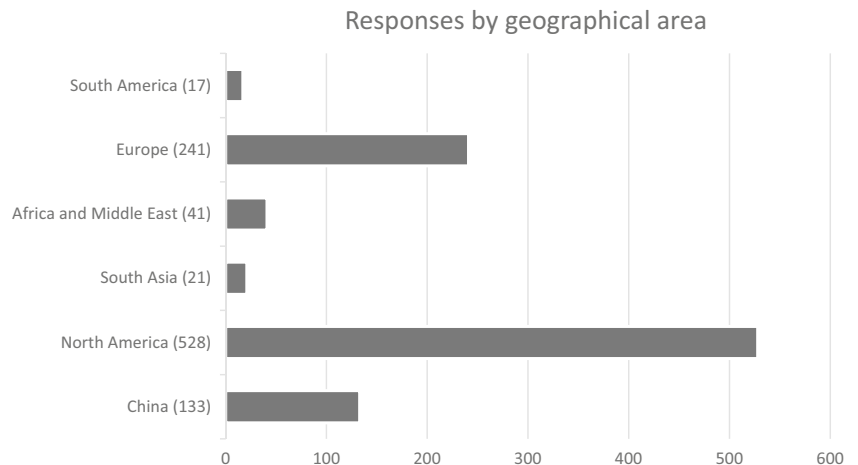


Table 1 Results of the differences in survey response by geographical region

Question	<i>p</i> value
Q3: Preferred cytotoxic agent	< 0.0001
Q4: How cytotoxic dose is determined	< 0.0001
Q5: Procedure preferred for single HCC	< 0.0001
Q6: Amount of ethiodized oil used	< 0.0001
Q7: Ratio of ethiodized oil used	< 0.0001
Q8: Ethiodized oil mixture technique	< 0.0001
Q9: Preferred type of DEB	= 0.01
Q10: Preferred size of DEB	> 0.05
Q11: Preferred procedural endpoint	< 0.0001
Q12: Preferred embolic agent	< 0.0001
Q13: Procedure preferred for multiple HCCs	< 0.0001
Q15: Use of antibiotics	< 0.0001
Q16: Typical clinical follow-up period	< 0.0001
Q17: Preferred imaging for follow-up	= 0.0001
Q18: Tumor response criteria	= 0.0001

p values were calculated using Fisher's exact test and chi-square test with Bonferroni correction as needed

Q question, HCC hepatocellular carcinoma, DEB drug-eluting bead

between regions ($p < 0.0001$). A fixed dose of cytotoxin per procedure was the most common response among all groups (588/1071, 54.9%). Most respondents in this group used between 50 and 100 mg of doxorubicin. Tumor size (256/1071, 23.9%), patient body surface area (56/1071, 5.2%), liver function (58/1071, 5.4%), and patient body weight (25/1071, 2.3%) were less commonly used to determine the dose. Asian countries favor basing dose on tumor size while North America and Europe

avored a fixed dose, resulting in statistically significant difference among regions ($p < 0.0001$).

The targeted embolic endpoint varied significantly among geographical regions ($p < 0.001$). The most common response was the use of a combination of flow reduction in the feeding vessel(s), complete stasis in the feeding vessel(s), and oil uptake by the tumor (311/907, 34.3%). This was followed closely by complete stasis of the feeding vessel(s) (301/907, 33.2%).

Pre- and post-procedural practices

There was a statistically significant difference in the use of antibiotics between regions ($p < 0.0001$). Peri-procedural antibiotics were statistically more commonly used by the members in North America (462/563, 82.1%), but not as commonly used in respondents from Europe (165/313, 52.7%), Japan (31/53, 58.5%), Korea (3/19, 15.8%), or China (16/112, 14.3%) ($p < 0.01$).

The typical clinical follow-up was between 2 weeks and 2 months in all groups (914/1088, 84.0%). Respondents were equally likely to follow up patients between 2 weeks and 1 month (412/1088, 37.9%) and between 1 and 2 months (502/1088, 46.1%). Very few respondents followed patients up at less than 2 weeks (84/1088, 7.7%) or at greater than 2 months (90/1088, 8.3%). CT was the most commonly used modality for follow-up among all respondents (698/1090, 64.0%), but MR was statistically used more by North American respondents compared with all other groups combined ($p = 0.0001$).

To determine the tumor response, modified Response Evaluation Criteria in Solid Tumors (mRECIST) (658/1038, 63.3%) and RECIST (239/1038, 23.0%) criteria were most commonly utilized. mRECIST was statistically used more

Table 2 Cytotoxin used

Cytotoxin	China	NA	Europe	Korea	Japan	SAS	SA	Oc	Africa/ME	Total (%)
Doxorubicin	16	461	187	33	4	15	15	12	36	779 (73.4%)
Pirarubicin	27	1	0	0	0	0	0	0	0	28 (2.6%)
Anthracycline and cisplatin	19	1	0	0	1	0	0	0	0	21 (2.0%)
Miriplatin	0	0	0	0	6	0	0	0	0	6 (0.6%)
Anthracycline and other	1	3	4	0	0	0	1	0	3	12 (1.1%)
Anthracycline, mitomycin C, and cisplatin	26	5	28	0	43	1	0	3	1	107 (10.1%)
Idarubicin	8	20	0	0	0	2	0	0	0	30 (2.8%)
TAE (no cytotoxin)	10	9	3	0	1	0	0	1	0	24 (2.3%)
Mitomycin C	16	1	3	0	0	1	0	2	0	23 (2.2%)
Mitoxantrone	0	4	0	0	0	0	0	0	0	4 (0.4%)
Cisplatin	1	17	8	0	0	0	1	0	0	27 (2.5%)
Total	124	522	233	33	55	19	17	18	40	

NA North America, SAS South Asia, SA South America, Oc Oceania, ME Middle East, TAE transarterial embolization

Table 3 Cytotoxin dose calculation

Cytotoxin dose calculation	China	NA	Europe	Korea	Japan	SAS	SA	Oc	Africa/ME	Total (%)
Fixed dose	32	357	137	2	11	11	10	11	17	588 (54.9%)
Body weight	1	1	15	2	0	0	0	0	6	25 (2.4%)
Body surface area	14	15	18	0	2	1	2	2	2	56 (5.2%)
Tumor size	47	77	37	29	43	7	2	5	9	256 (23.9%)
Liver function	31	14	7	0	3	0	1	1	1	58 (5.4%)
Other	5	47	23	2	3	1	1	4	2	88 (8.2%)
Total	130	511	237	35	62	20	16	23	37	

NA America, SAS South Asia, SA South America, Oc Oceania, ME Middle East

frequently in North America and Europe than those in the Asian Interventional Societies ($p = 0.0001$), and RECIST was statistically used more frequently by the Asian countries than in North America and Europe ($p = 0.0001$).

Effect of preference of DEB-TACE or cTACE on responses

To determine the effect of a respondents’ preference for DEB-TACE or cTACE on the other survey responses, a separate analysis was performed. The results for this analysis can be found in Table 4. The cytotoxic agent of choice for both those preferring cTACE (141/308, 45.8%) and DEB-TACE (478/506, 94.5%) was doxorubicin. However, there was a statistically significant difference between the two groups ($p < 0.0001$) with those preferring DEB-TACE being more likely to choose doxorubicin. There was a statistically significant difference in the dose calculation based on respondents’ preference for DEB-TACE or cTACE ($p < 0.0001$), with those who preferred DEB-TACE being more likely to utilize a fixed-dose calculation method. Similarly, while CT was the most common choice for follow-up imaging in both cTACE (221/304, 72.7%) and DEB-TACE (299/503, 59.4%)

respondents, those who preferred cTACE were more likely to follow up with CT than those who preferred DEB-TACE ($p = 0.0007$).

Discussion

HCC is the fifth most common cancer worldwide and the third most common cause of cancer mortality [12, 13]. While TA(C)E is considered a palliative treatment, it is frequently used and a part of virtually every societal treatment algorithm [1–3]. However, some of the basic technical aspects of the procedure change with provider. These technical differences make comparison of clinical trials difficult and speak to the lack of clear evidence to guide practitioners.

This study demonstrates that there are significant regional differences in the chemotherapeutic regimen, which is preferred by interventionalists. The preference of practitioners in China to use pirarubicin may be due to an in vitro study which demonstrated that pirarubicin ethiodol oil mixture was more stable and cytotoxic to HepG2 and Hu-H7 cells than doxorubicin ethiodol oil mixture [14]. However, several studies have failed to demonstrate clear superiority of one

Table 4 Differences by procedural preference

Question	Most common response for DEB-TACE	Most common response for cTACE	<i>p</i> value
Cytotoxic agent	Doxorubicin (141/308, 45.8%)	Doxorubicin (478/506, 94.5%)	< 0.0001
Dose calculation method	Fixed dose (152/306, 49.7%)	Fixed dose (319/504, 63.3%)	< 0.0001
Procedural endpoint	Complete stasis (129/330, 39.1%)	Combination of oil uptake and vessel flow reduction or stasis (138/292, 47.3%)	< 0.0001
Antibiotic usage	Prior to the procedure (179/505, 35.5%)	None (145/306, 47.4%)	< 0.0001
Follow-up	Between 1 and 2 months (226/501, 45.1%)	Between 1 and 2 months (146/305, 47.9%)	0.60
Follow-up imaging modality	CT (229/503, 59.4%)	CT (221/304, 72.7%)	0.007
Imaging criteria	mRECIST (313/499, 62.7%)	mRECIST (182/302, 60.3%)	0.21

p values were calculated using chi-square test

DEB-TACE drug-eluting bead transarterial chemoembolization, cTACE classic transarterial chemoembolization, CT computed tomography, mRECIST modified Response Evaluation Criteria in Solid Tumors

chemotherapeutic agent to another [15–17], while others have demonstrated better outcomes when using a three-drug regimen as compared to a single- or two-drug regimen [18, 19]. This study found the most commonly used chemotherapeutic regimen in North America and Europe was single-agent doxorubicin. This may relate to the fact that doxorubicin is loadable onto drug-eluting beads and therefore can be used for DEB-TACE [20, 21]. This theory seems to be supported by the fact that 94.5% of respondents who preferred DEB-TACE used doxorubicin as their cytotoxic agent of choice. This study found very few practitioners use triple- or double-drug therapy (2.1% and 2.8% respectively), despite the aforementioned studies suggesting triple-drug therapy may be superior [18, 19]. Again, this may be related to a preference of some regions for DEB-TACE, where only a single drug can be loaded, to cTACE.

This study found significant differences in preference of technique between regions with the majority of North American and European practitioners preferring DEB-TACE and the majority of Japanese and Korean interventionalists preferring cTACE, while TAE was the procedure of choice for very few clinicians across all regions. One possible explanation for the preference of DEB-TACE in North America is the fact that ethiodol oil and doxorubicin powder, both critical to cTACE, have been periodically unavailable in North America due to manufacturing concerns. Another explanation may be the lack of evidence to support one technique over the other. Further analyses also revealed that respondents' preference for DEB-TACE or cTACE significantly affected their responses to many of the other technical factors associated with TA(C)E (Table 4). This underlies that technical choices are not only significantly affected by geographical location, but also by preference of technique.

Early pathologic analysis of explanted livers, which had previously undergone either TAE or cTACE, seemed to suggest an improved complete pathologic response in the cTACE patients [22–24]. Further argument for the use of chemotherapy was seen when the Llovet et al trial was published. This trial was designed to compare not only cTACE and TAE to best supportive care, but each other [4]. While the trial demonstrated superior 1- and 2-year survival rates in the cTACE arm as compared to that in the TAE arm, statistical significance was not reached, possibly because trial enrollment was stopped early due to the superiority of both intervention arms to supportive care. However, in a recent trial by Brown et al comparing DEB-TACE to TAE, while OS was longer in the DEB-TACE cohort as compared to that in the TAE cohort (20.8 vs 19.6 months), this was not found to be statistically significant [8]. This study has its own limitation as the technique of embolization in both groups was heavily directed towards aggressive embolization to complete stasis. Nonetheless, the data is conflicting over the need to subject patients to chemotherapeutic agents at all. After the

introduction of drug-eluting beads and the subsequent development of DEB-TACE, comparisons between cTACE and DEB-TACE have also been made; while occasional studies have found the superiority of one treatment over the other, the majority of randomized controlled trials and meta-analyses have found equivalence of these techniques [7, 25–30]. A frequent argument for DEB-TACE over cTACE is the lower serum chemotherapeutic agent exposure; however, this has not consistently translated to fewer adverse events [7, 25–30]. One of the weaknesses of these studies is they most frequently compare single chemotherapeutic agent cTACE to DEB-TACE, given some studies have found that triple therapy is superior to single therapy; the cTACE response and survival levels may be suboptimal.

Another area with significant differences across regions was the dose of chemotherapeutic drug used. North Americans and Europeans favored a fixed dose, while interventionalists in Asia tended towards dosing based on tumor size. These differences may in part be due to the preference of North Americans and Europeans to use DEB-TACE where 50 mg of doxorubicin is loaded on each vial of beads, and typically, 1–2 vials are used, whereas those in Asia tended to prefer cTACE, where dose can be more easily adjusted. This theory seems to be supported by the fact that respondents who preferred DEB-TACE were statistically more likely to use a fixed-dose calculation than those who preferred cTACE. While studies clearly identifying a clinical benefit for higher dose of chemotherapeutic agent are missing, there is some evidence that dose can play an effect on adverse events. The PERCISION V study, which compared DEB-TACE to cTACE, used a body surface area dosing for the cTACE arm resulting in most patients receiving between 100 and 150 mg of doxorubicin, a higher dose than many other studies [7]. The study found a difference in adverse events between the two arms, which was primarily driven by nearly 20% of patients developing alopecia in the cTACE arm. Alopecia is a rarely reported side effect of cTACE in other studies, and this may explain why other studies have not shown a difference in adverse events between the two techniques [28, 29].

Three prior surveys have probed the practice patterns for TA(C)E therapy or follow-up [9–11]. All have been relatively small and limited to a single interventional society. Gaba surveyed 268 SIR members regarding TACE [9]. Bergellini et al presented responses from 78 Italian treatment centers regarding their use of LRTs for HCC [10]. Finally, Gaba et al queried 361 SIR members about their follow-up practices following LRTs for primary and secondary malignancies of the liver [11]. While all three surveys presented interesting data on practice trends from their collective populations, they were unable to compare these trends across regions and had much smaller sample sizes than this study.

This study has several limitations. While a relatively large number of responses were obtained, the majority were from two societies (CIRSE and SIR). Questionnaires are also known to be prone to response bias, which may affect their accuracy. While the questionnaire did probe the techniques of responding practitioners, its multiple-choice format may have missed some nuances. Furthermore, it did not probe the reasons behind interventionalists' choices. Finally, this paper does not include information about practitioners' practice regarding other LRTs such as radioembolization or thermal ablation nor does it investigate outcomes. Due to the desire to keep the survey short and to increase response rate and the desire to probe technical choices made during the TA(C)E procedure, these topics were not breached. Despite these flaws, this provides the most comprehensive to date analysis of TA(C)E treatment practices over diverse demographic areas. The survey demonstrates that there is significant heterogeneity across even basic technical aspects of the TA(C)E procedure.

In conclusion, practitioners across diverse demographic areas differ in the way they perform TA(C)E for patients with HCC. Furthermore, the practitioners' preference for cTACE or DEB-TACE significantly effects other procedural choices. These differences lead to difficulty in comparing studies in this field and are driven by the lack of high-level data to guide treatment teams. Further, well-done randomized controlled trials are needed to help determine the most effective technical methods to perform TA(C)E.

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Compliance with ethical standards

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Informed consent Informed consent was not required because this was a survey of practicing Interventional Radiologists.

Ethical approval Institutional Review Board approval was not required because this was a survey of practicing Interventional Radiologists.

Methodology

- Cross-sectional survey study
- Multicenter study

Appendix 1

Survey Text:

Transcatheter Arterial (Chemo)embolization (TA(C)E) Survey

This *short* (one-page) survey should not take more than two minutes of your time. This survey was designed to obtain a general idea of the type of TA(C)E procedures that you typically perform. It is important to answer at least one answer per question, as follow up questions may drop down. Thank you very much for your participation.

1. What country do you practice in?
 - a. (Answer field blank)
2. What type of practice are you in?
 - a. Academic
 - b. Private practice – community hospital
 - c. Private practice – secondary or tertiary referral center
 - d. Government hospital
 - e. Other (please specify)
 - i. (Answer field blank)
3. For TA(C)E procedures at your institution, what is the common cytotoxic agent used for the treatment of hepatocellular carcinoma (HCC)?
 - a. Doxorubicin
 - b. Epirubicin
 - c. Cisplatin
 - d. Mitoxantrone
 - e. Mitomycin C
 - f. SMANCS
 - g. Pirarubicin
 - h. Nemorubicin
 - i. Miriplatin
 - j. Idarubicin
 - k. Irinotecan
 - l. Anthracycline (e.g. Doxorubicin, Epirubicin) and Mitomycin C
 - m. Anthracycline and Cisplatin
 - n. Anthracycline, Mitomycin C, and Cisplatin
 - None of the above (bland transarterial embolization (TAE))

Other (please specify)
4. For TA(C)E procedures at your institution, how is the dose of cytotoxin agent determined?

- a. Fixed dose (e.g. 50mg Doxorubicin for every person). Please list dose below.
 - b. Body weight (e.g. 1mg Doxorubicin for every kg). Please list amount per kg below.
 - c. Body surface area (e.g. 50mg/meter²). Please list amount per meter² below.
 - d. Tumor size
 - e. Liver function (AFP, etc.)
 - f. Other (please specify)
5. What is your typical procedure for a single HCC?
- a. Ethiodized oil TACE (cTACE)
 - b. Drug-Eluting Beads TACE
 - c. Bland Transarterial Embolization (TAE)
 - d. Technique depends on the extension and location of the tumor
 - e. Other (please specify)
6. What amount of ethiodized oil is typically used?
- a. Not applicable
 - b. 0-5ml
 - c. 5-7.5ml
 - d. 7.5-10ml
 - e. >10ml
 - f. Other
7. What is the ratio (volume:volume) of ethiodized oil to cytotoxic agent used in your procedure?
8. How is the ethiodized oil mixed with the cytotoxic agent?
- a. Not applicable
 - b. Pump between stop cock (to and fro) – ethiodized oil tube injected into cytotoxin tube
 - c. Pump between stop cock (to and fro) – cytotoxin tube injected into ethiodized oil
 - d. Pump between stop cock (to and fro) – no preference in order mixed
 - e. Mixed with a machine
 - f. No specific method
 - g. Other (please specify)
9. What type of drug-eluting beads do you use?
- a. Not applicable
 - b. Tandem
 - c. Pearl
 - d. QuadraSpheres
 - e. LC/DC
 - f. Other (please specify)
10. What size of drug-eluting beads do you use (please specify)?
- a. (Answer field blank)
11. What is your procedural endpoint?
- a. Administration of fixed dose
 - b. Flow reduction in the feeding vessel(s)
 - c. Complete stasis in the feeding vessel(s)
 - d. Oil uptake by tumor
 - e. A combination of B and D or C and D
 - f. Other (please specify)
12. Are embolic agents used in your procedure?
- a. No
 - b. Yes – Gelatin (specify product below)
 - c. Yes – Non-spherical polyvinyl alcohol (specify product below)
 - d. Yes – Spherical (specify product below)
13. What is your typical procedure for multiple HCCs?
- a. Ethiodized oil TACE (cTACE)
 - b. Drug-Eluting Beads TACE
 - c. Bland Transarterial Embolization (TAE)
 - d. Technique depends on the extension and location of the tumor
 - e. Other (please specify)
14. Are additives used with the primary cytotoxic agent (water-soluble contrast, solubility agents, etc.)?
- a. No
 - b. Yes (please specify)
15. Do you routinely use antibiotics with TA(C)E procedures?
- a. No
 - b. Yes, before
 - c. Yes, during
 - d. Yes, after
 - e. A combination of the factors listed above
16. When is your typical clinical follow up for TA(C)E procedures?
- a. Less than 2 weeks
 - b. 2 weeks – 1 month
 - c. >1 month - <2 months
 - d. >2 months

17. What type of imaging follow up do you perform?
- CT (specify interval below)
 - MR (specify interval below)
 - Other (please specify below)
18. What criteria do you use to determine tumor response?
- European Association of the Study of Liver (EASL)
 - World Health Organization (WHO)
 - Response Evaluation Criteria in Solid Tumors (RECIST)
 - Modified Response Evaluation Criteria in Solid Tumors (mRECIST)
 - Other (please specify)

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