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ORIGINAL ARTICLE

The position of transarterial chemoembolization with drug-eluting beads and yttrium-90 transarterial radioembolization in patients with hepatocellular carcinoma: Consensus statements from a Delphi-method expert panel in Turkey

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PURPOSE

Clinical studies conducted in different geographic regions using different methods to compare transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) have demonstrated discordant results. Meta-analyses in this field indicate comparable overall survival (OS) with TACE and TARE, while reporting a longer time to progression and a higher downstaging effect with TARE treatment. In terms of isolated procedure costs, treatment with TARE is 2 to 3 times more, and in some countries even more, expensive than TACE. However, relevant literature indicates that TARE is more advantageous compared to TACE regarding the need for repeat procedures, costs of complication management, total hospital stay and quality of life. Heterogeneity of hepatocellular carcinoma (HCC) patients as well as the shortcomings of clinical classifications, randomized clinical trials and cost-effectiveness studies make it difficult to choose between treatment alternatives in this field. As in other countries, these challenges lead to differences in treatment choice across different centers in Turkey.

METHODS

The present expert panel used two round modified Delphi method to investigate the resources and clinical parameters referenced while selecting patients for drug-eluting beads (DEB)-TACE and TARE treatment modalities in Turkish clinical practice. The cost-effectiveness parameters and comparisons of these treatments have also been evaluated at a prediction level.

RESULTS

The panelists stated that they most commonly use the BCLC staging system for the management of HCC patients in Turkey. However, they did not find any of the staging systems or treatment guidelines sufficient enough for their clinical practice in terms of covering the down-staging intent of treatments. Since living donor transplant preference is higher in Turkey than the rest of the Western countries, down-staging treatments are thought to be more prioritized in Turkey than that in other Western countries. The panelists reached a consensus that TARE may provide improved OS and reduce the number of repeat procedures compared to DEB-TACE in intermediate-stage patients with a single tumor spanning a diameter above 5 cm who experience recurrence after previous treatment with TACE and most TACE-naïve patient groups in intermediate stage.

CONCLUSION

Based on the consensus on OS and the number of procedures, the panelists assumed that TARE would be more cost-effective than DEB-TACE in most groups of TACE-naïve patients in intermediate stage and in those with a single tumor spanning a diameter above 5 cm. It was also stated that the predicted cost-effectiveness advantage of TARE could be more pronounced in patients with a tumor diameter greater than 7 cm.

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death (1). Unlike other cancers, disease course and treatment vary based on the underlying liver disease and remaining liver reservoir in addition to tumor burden (2). Based on the treatment guidelines in this field, cases in the early stage are candidates for curative treatment options such as ablation, resection, and transplantation (2–4). Available clinical data show that only a limited number of cases are diagnosed at early stage and HCC cases encountered in daily clinical practice are often in more advanced stages of the disease (1, 5).

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According to the Barcelona Clinic Liver Cancer (BCLC) staging system, which is commonly referenced in this field, and treatment guidelines that adopt this system, transarterial chemoembolization (TACE) is the standard of care for patients with intermediate HCC (BCLC-B) (2, 6–11). Currently, the transarterial chemoembolization with drug-eluting beads (DEB-TACE) method is a novel TACE modality and a candidate to replace the lipiodol-TACE (conventional TACE) approach, which has been in use for a long time (12). Although transarterial radioembolization (TARE; selective internal yttrium-90 radiotherapy or SIRT) is not included in the BCLC staging system, it appears to be an alternative treatment method with increasing indications in parallel with the advances in angiography techniques and dosimetry at every stage included in BCLC guidelines (13).

Clinical studies conducted in different geographic regions using different methods to compare TACE and TARE have demonstrated discordant results. Meta-analyses in this field indicate comparable overall survival (OS) with TACE and TARE, while reporting a longer time to progression (TTP) and a higher downstaging effect with TARE treatment (14–21).

In terms of isolated procedure costs, treatment with TARE is 2 to 3 times more, and in some countries even more, expensive than TACE (22, 23). However, relevant literature indicate that TARE is more advantageous compared to TACE with regard to need for repeat procedures, costs of complication management, total hospital stay, and quality of life (24). Globally, there is only a limited number of studies investigating the effects of TACE and TARE on national health budgets and comparing the cost-effectiveness of these methods (23, 25).

Heterogeneity of HCC patients as well as the shortcomings of clinical classifications, randomized clinical trials and cost-effectiveness studies make it difficult to choose between treatment alternatives in this field (2). As in other countries, these challenges lead to differences in treatment choice across different centers in Turkey.

The present expert panel used the modified Delphi method to investigate the resources and clinical parameters referenced while selecting patients for DEB-TACE and TARE treatment modalities in Turkish clinical practice. The cost-effectiveness parameters and comparisons of these treatments have also been evaluated at a prediction level.

Main points

- Living donor transplant preference is higher in Turkey than the rest of the Western countries; therefore down staging treatments are thought to be more prioritized in Turkey than in other Western countries.
- Based on the consensus on OS and the number of procedures, it was assumed that TARE would provide better cost-effectiveness advantage than DEB-TACE in most groups of TACE-naïve patients in intermediate stage and in those with a single tumor spanning a diameter above 5 cm.
- The predicted cost-effectiveness advantage of TARE could be more pronounced in patients with a tumor diameter greater than 7 cm.

Methods

Panelists

The panel consisted of six interventional radiologists, five nuclear medicine physicians, two hepatologists and one medical oncologist from ten different centers. All panelists have more than 20 years of experience in HCC management. Experts with different levels of TARE and TACE experience were selected equally in order to minimize the bias towards TARE or TACE dominated opinions. Each panelist is either a board member of an academic association, contributed to guideline developments on this subject or published articles on DEB-TACE and/or TARE. Even though all panelists are academicians, they fairly represent the state and private healthcare providers in Turkey.

Design

This expert panel was planned to be conducted in line with the intended target using the modified Delphi method. The Delphi method aims to achieve mutual decisions and consensus within the scope of a panel design upon individual opinions of experts in relevant fields when there is only limited data or scarce body of information to draw a conclusion or provide a takeaway message concerning a given subject matter (26, 27). A classical Delphi serves as a forum to seek a consensus among homogeneous groups of experts. The variant Modified Delphi includes a combination of Delphi with other methods, for example, scenario writing to develop relevant arguments and expose underlying reasons for different opinions on a specific issue. Modified Delphi is also described as a modification of the Classical Delphi technique, combining it with other methods such as employing a focus group, interviews, or results of a review to develop the first round. Our modified method was also a series of interviews, repeated surveys and feedbacks utilized to transform expert opinions into a consensus-based group decision (28).

In this modified context, the panel in question was implemented in 3 main steps (Fig.):

1. Half-structured interviews and systematic literature search

Before reviewing the relevant literature and preparing the first round questionnaire, an hour long one-to-one half-structured interviews were performed with each selected panelists by independent consultants, who then provided medical writing and moderation for this panel. The reason to perform these one-to-one external interviews was to understand panelists' perspectives and patient selection criteria for DEB-TACE and TARE treatments.

Based on the interview reports a bibliographic search was performed. An electronic search of the literature published from 2010 to 2020 was conducted in MEDLINE (via the PubMed interface), Web of Science, Google Scholar and EMBASE databases by using MESH (Medical Subject Heading, Medline) and EMBASE terms, as well as free text words. The search included the terms, transcatheter arterial chemoembolization, TACE, transcatheter arterial radioembolization, TARE, SIRT, liver cancer, hepatocellular carcinoma, HCC, and cost-effectiveness. Relevant reviews and meta-analyses of loco-regional treatments in unresectable HCC were examined for potential suitable studies. As further selection criteria, overall survival, progression-free survival, disease control rate, progression rate, rate of liver transplantation and cost-effectiveness comparisons between TACE and TARE were set to highlight. Relevant guidelines, BCLC, American Society of Clinical Oncology (ASCO and the ASCO gastrointestinal [ASCO GI]), European Society of Clinical Oncology (ESMO and ESMO GI), European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), and International Liver Cancer Association (ILCA), National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology in the years 2010 through 2020 were systematically reviewed.

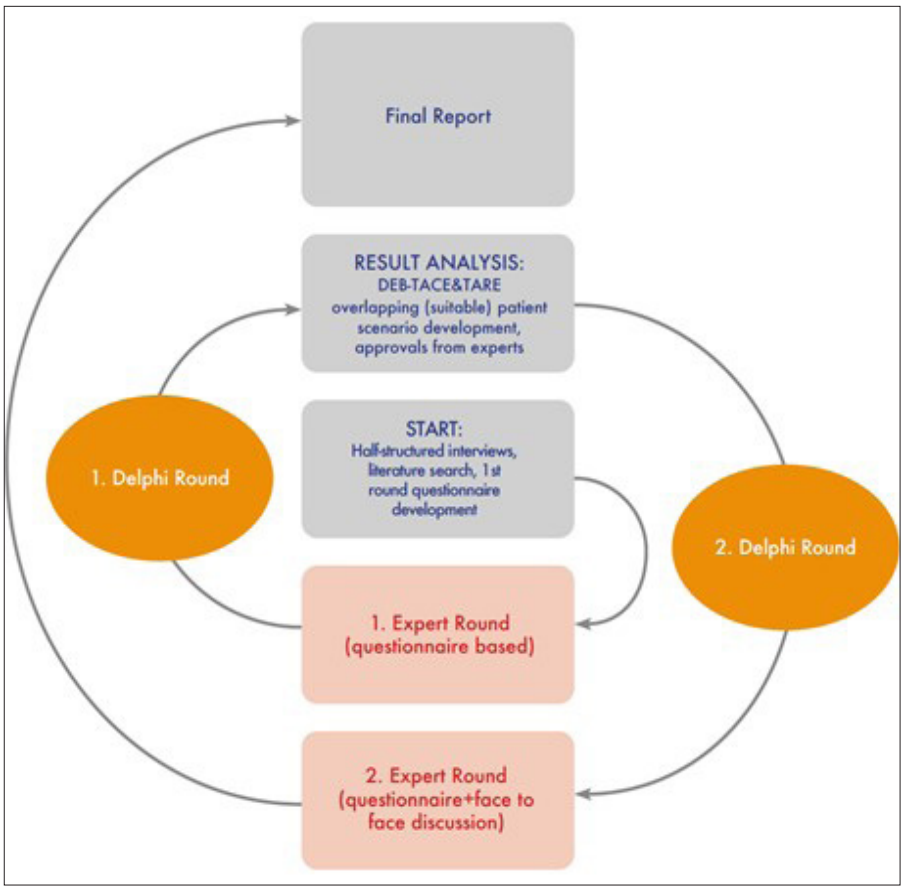

Figure. Modified Delphi process flow chart.

2. Preparation of first-round questions and evaluation of results

Questions in the first round were developed to explore the staging criteria, guidelines, clinical data and cost parameters the physicians in the panel relied on while choosing DEB-TACE or TARE methods in their treatment practice. A total of 37 questions were asked in the first round of this study to panelists (Appendix 1). First-round questions were designed using either a 5-point Likert response scale or with multiple-choice answers or ranking with an additional open-ended choice. An electronic questionnaire was used to collect the respondents' opinions. The consensus threshold was set at >60% for the answers to the first-round questions. Contradictions between different disciplines owing to the representation of various branches by different numbers of physicians were often negligible, which maintained the consistency of consensus opinions. Medical oncologist and hepatologists who are not actively involved in the application of the treatments but involved as decision-makers in the process were represented by a limited number of physicians in this panel and were consulted to check whether they disagreed with the first-round consensus points in order to confirm their agreement.

3. Preparation of second-round questions and evaluation of results through face-to-face discussion

This round aimed to investigate the most impactful parameters on the cost-effectiveness of DEB-TACE and TARE in intermediate-stage HCC patients and challenged panelists to make cost-effectiveness assumptions by only using these parameters in order to set a speculative stage for future prospective multicenter investigations regarding the position and also for calculations on the cost-effectiveness of DEB-TACE and TARE in patients with HCC in Turkey. Patient scenarios to be utilized during the predictive comparison of these two treatment methods were created assuming that the hypothetical patients gained no significant advantage with any of the treatments, were in BCLC-B stage and had exceeded the possibility of invasive treatment. Owing to the limited duration of discussion in the second round, age, gender, underlying disease, ECOG performances, cirrhotic or noncirrhotic state of liver, Child-Pugh classification, vascular invasion, distance to vascular structures, bilirubin, albumin and alfa-fetoprotein values were assumed to affect both treatment methods in a comparable manner and scenario variations were based solely on tumor burden (Table 1). In this round, nuclear medicine specialists contributed to the discussion on TARE by only answering questions on the number of TARE procedures that would be necessary in each group of patient scenarios. The consensus threshold was >70% during the second round that took place in face-to-face setting. The consensus threshold was >60% in the first round survey and >70% in the second round as confidentiality could not be maintained during the face-to-face meeting and the likelihood of panelists being influenced from one another could not be ruled out. No demographic, clinical or laboratory data of any patient was used at any stage of this panel workflow, therefore there were no legal or ethical necessities in order to ask for a research ethics review committee, institutional review board approval, or informed consent statements from patients.

Results

Evaluation of systems that provide staging and prognosis predictions

When asked about the systems they prefer the most when staging and predicting prognosis in HCC patients, the panelists reached a consensus on the BCLC staging system. All physicians in the panel agreed that the BCLC system currently falls short in guiding intermediate- and late-stage HCC patients to appropriate treatment. The panelists agreed that the BCLC system falls short in covering the tumor burden, underlying liver disease, concomitant comorbidities, location of the tumor and its distance to vascular structures in patients with intermediate-stage HCC.

Panelists could not reach a full consensus with their answers on which guidelines they preferred for the diagnosis and treatment management of patients with HCC. It was expressed that medical oncologists in Turkey prefer the NCCN guidelines in this patient group (7). Hepatologists, on the other hand, stated that they most commonly refer to the AASLD and EASL guidelines for the same patient group (8, 9). Interven-

Table 1. "Overlapping" patient subgroups who are eligible for either DEB-TACE or TARE

	Tumor characteristics				
	Treatment status	Location	Number of lesions	Burden	Subgroup name
Patient group 1	Previously undergone TACE and developed recurrence	Single lobe	1	<5 cm diameter	1A
				5-7 cm diameter	1B
				>7 cm diameter	1C
	TACE-naïve*	Single lobe	1	<5 cm diameter	1D
				5-7 cm diameter	1E
				>7 cm diameter	1F
Patient group 2	Previously undergone TACE and developed recurrence	Single lobe	>1	Tumor volume in single lobe <30%, 2-3 nodules, max diameter 3 cm	2A
				Tumor volume in single lobe 50%-70%, 4-5 nodules, all ≤3 cm diameter	2B
				Tumor volume in single lobe 30%-50%, 2-3 nodules, max diameter 5 cm	2C
				Tumor lobe in single lobe >70%, at least 50% hepatic reserve in the opposite lobe	2D
	TACE-naïve*	Single lobe	>1	Tumor volume in single lobe <30%, 2-3 nodules, max diameter 3 cm	2E
				Tumor volume in single lobe 50%-70%, 4-5 nodules, all ≤3 cm diameter	2F
				Tumor volume in single lobe 30%-50%, 2-3 nodules, max diameter 5 cm	2G
				Tumor lobe in single lobe >70%, at least 50% hepatic reserve in the opposite lobe	2H
Patient group 3	Previously undergone TACE and developed recurrence	Both lobes	>1	Total tumor volume in both lobes <30%	3A
				Total tumor volume in both lobes 30%-50%	3B
				Total tumor volume in both lobes 50%-70%	3C
	TACE-naïve*	Both lobes	>1	Total tumor volume in both lobes <30%	3D
				Total tumor volume in both lobes 30%-50%	3E
				Total tumor volume in both lobes 50%-70%	3F

DEB-TACE, drug-eluting bead transarterial chemoembolization; TARE, transarterial radioembolization.
*TACE-naïve: no previous TACE treatment.

tional radiologists and nuclear medicine physicians indicated that they refer to the ASCO and AASLD guidelines for diagnosis, and the NCCN guidelines for therapeutic approaches (10, 11). The panelists stated that TARE being included only as an alternative treatment in BCLC guideline does not affect their treatment preferences in these patients, and that they may choose to use TARE as the main treatment if they find the patient eligible for this method. Panelists also agreed that their own clinical experience provides a guide for their practices as well as guidelines. The reason behind their common thoughts were identified as they find the BCLC recommendations lacking updates on the downstaging treatment modalities, which increase the possibility of transplantation, and the individualized treatments based on molecular diagnosis (the use of biomarkers in the clinic for HCC) are not adequately covered in these guidelines.

General assessment of treatments

The panelists reached a consensus that the most important clinical effectiveness parameters are OS and progression-free survival (PFS) rates of treatments in early-stage HCC patients, and OS and downstaging in intermediate-stage patients. There was a consensus that TARE and DEB-TACE are similar in terms of OS in HCC patients with overlapping indications for these two methods while TARE may provide superior outcomes compared to DEB-TACE in terms of PFS, TTP, local tumor response, and downstaging effects. In addition to this consensus, panelists also agreed that TARE may provide superior outcomes compared to DEB-TACE in all effectiveness and safety parameters, including OS, in patients previously untreated with TACE (i.e., TACE-naïve patients). The physicians in the panel reached a consensus that their treatment preference would be mostly influenced by other effectiveness parameters such as TTP and downstaging in patients for whom they would expect similar OS outcomes with TARE and DEB-TACE. There was a consensus among the panelists on downstaging and TTP being the most important parameters with direct effect on OS in intermediate-stage HCC patients. Panelists agreed

that isolated procedure costs would be the least effective parameter in their choice of treatment. A consensus was reached that TARE is likely to provide superior outcomes compared to DEB-TACE in terms of side-effect rates following the procedure, severity of side effects, the need to repeat the procedure and total length of stay. Agreeing that TARE may be more advantageous than DEB-TACE in terms of post-treatment quality of life and the overall risk-benefit profile, the panelists also reached a consensus that these parameters are as important as effectiveness in intermediate-stage patients. There was a consensus that TARE may be more advantageous than DEB-TACE in terms of costs arising from post-treatment side-effect management, total length of stay and repeat procedures.

Additionally, panelists agreed that the therapeutic success of TARE is directly proportional to the optimization of personalized dosimetry and that TARE may provide better effectiveness and safety outputs compared to DEB-TACE in units that have a similarly high level of experience with TARE and DEB-TACE. A consensus was also reached that the overall predictions concerning clinical effectiveness and safety parameters would vary across different patient subgroups.

Effectiveness, cost difference predictions and cost-effectiveness assumptions between DEB-TACE and TARE in intermediate-stage patient scenarios created based on tumor burden

Consensus opinions in the first group of patient scenarios

Physicians who participated in the panel reached a consensus that TARE may provide more favorable outcomes compared to DEB-TACE in terms of OS, TTP, downstaging, bridging to transplantation and post-transplantation success in patients with a single tumor larger than 5 cm in a single lobe in the group with recurrence after previous TACE.

They agreed on the prediction that the average number of sessions required in patients with a tumor diameter of 5-7 cm who recur after previous treatment with TACE would be 1 for TARE and 2 for DEB-TACE. Panelists stated they would not expect an increased number of sessions in the event that TARE is preferred in TACE-naïve patients and that DEB-TACE may require up to 3 subsequent procedures on average.

A consensus was reached that the average number of sessions required in patients with a single tumor larger than 7 cm who recur after previous treatment with TACE would be 1 for TARE and 3 for DEB-TACE. Physicians predicted that the number of sessions would remain at 1 for TARE in patients previously untreated with TACE (i.e., TACE-naïve) who have a tumor larger than 7 cm and agreed that the number of subsequent procedures may exceed 3 on average when DEB-TACE is preferred in this patient group.

In light of the prediction that OS and the number of repeat procedures appear to be in favor of TARE, the panelists assumed that TARE may offer a better cost-effectiveness potential than DEB-TACE in patients with a single tumor spanning a diameter above 5 cm who experience recurrence after previous treatment with TACE. They stated that this probability may be more apparent in patients with a tumor diameter greater than 7 cm owing to the improved OS and the higher difference in repeat procedures.

Consensus opinions in the second patient group

A unanimous consensus was reached that TARE may provide more favorable outcomes compared to DEB-TACE in terms of TTP, downstaging, and the chance to bridging to transplantation in patients with multiple tumors located in a single lobe who experience recurrence after previous treatment with TACE, including all the subgroups stratified based on total tumor volume in a single lobe and tumor size. There was a consensus on expecting comparable OS outcomes with TARE and DEB-TACE. The panelists agreed that TARE would require one less unit procedure than DEB-TACE in all these patient groups stratified into four subgroups. The panelists reached a consensus that the difference in the number of procedures between these two treatments may be maintained in the TACE-naïve group. Cost-effectiveness assumptions could not be made since a marked difference was not expected in terms of OS and the number of procedures in this patient group.

Consensus opinions in the third patient group

A unanimous consensus was reached among the physicians who participated in the panel that TARE may provide more favorable outcomes compared to DEB-TACE in terms of TTP and downstaging in patients with multiple tumors located in both lobes who experience recurrence after previous treatment with TACE, including all the groups stratified based on total tumor volume in both lobes. The panelists reached a consensus that the average number of procedures may be 1 with TARE and 3 with DEB-TACE in those with a tumor volume equal to or less than 30% who have previously undergone TACE among these patient subgroups, and that the average number of repeat procedures may be 2 with TARE and 3 with DEB-TACE in those with a tumor volume above 30%. The physicians stated that the number of these treatment procedures may be maintained with TARE and numerically increase with DEB-TACE in TACE-naïve patients. The panelists assumed that TARE and DEB-TACE may offer comparable cost-effectiveness for patients with a tumor volume equal to or less than 30%, since a marked difference was not expected in terms of OS and the number of procedure expectation in each treatment may provide a similar treatment cost.

A unanimous consensus was reached that TARE may provide more favorable outcomes compared to DEB-TACE in terms of all parameters including OS in those without previous TACE treatment among the 3 main patient groups and the specified subgroups described as those within BCLC-B margins. Therefore, a consensus was reached that TARE may offer better cost-effectiveness potential than DEB-TACE based on the expectation of superior OS outcomes with the former method in TACE-naïve patient groups. This probability was more apparent in patients with a single tumor spanning a diameter above 7 cm in the TACE-naïve group owing to the higher difference in repeat procedures in favor of TARE (Table 2).

Discussion

This expert panel used the Delphi method to investigate the treatment guidelines or parameters based on which DEB-TACE and TARE treatments are positioned in practice for HCC patients in Turkey. Predictive cost-effectiveness comparisons of these treatments were performed in patient scenarios with intermediate-stage HCC stratified according to tumor load.

The panelists stated that they most commonly use the BCLC staging system for the management of HCC patients in Turkey. However, they did not find any of the staging systems or treatment guidelines suffi-

Table 2. Consensus status regarding efficacy parameters and required number of sessions

Patient group	Consensus Status						
	TTP	Downstaging	Proceeding with transplantation	Post-transplantation success	OS	Number of sessions	Assumption of cost-effectiveness
1A	No consensus	No consensus	No consensus	No consensus	No consensus	TARE: 1 DEB-TACE: 2	No consensus
1B	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Consensus (TTP, OS, downstaging)	TARE: 1 DEB-TACE: 2	TARE may have similar or superior cost-effectiveness to DEB-TACE
1C	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Consensus (TTP, OS, downstaging)	TARE: 1 DEB-TACE: 3	TARE may have superior cost-effectiveness to DEB-TACE
1D	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 1 DEB-TACE: 3	TARE may have similar or superior cost-effectiveness to DEB-TACE
1E	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 1 DEB-TACE: 3	TARE may have similar or superior cost-effectiveness to DEB-TACE
1F	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 1 DEB-TACE: >3	TARE may have superior cost-effectiveness to DEB-TACE
2A	TARE Full consensus	TARE Full consensus	TARE Full consensus	Similar for TARE and DEB-TACE Full consensus	TARE Consensus (TTP, downstaging) Comparable OS	TARE: 1 (or 2) DEB-TACE: 2-3	No consensus
2B	TARE Full consensus	TARE Full consensus	TARE Full consensus	Similar for TARE and DEB-TACE Full consensus	TARE Consensus (TTP, downstaging) Comparable OS	TARE: 1 (or 2) DEB-TACE: 2-3	No consensus
2C	TARE Full consensus	TARE Full consensus	TARE Full consensus	Similar for TARE and DEB-TACE Full consensus	TARE Consensus (TTP, downstaging)	TARE: 1 (or 2) DEB-TACE: 2-3	No consensus
2D	TARE Full consensus	TARE Full consensus	TARE Full consensus	Similar for TARE and DEB-TACE Full consensus	TARE Consensus (TTP, downstaging) Comparable OS	TARE: 1 (or 2) DEB-TACE: 2-3	No consensus
2E	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: >1 DEB-TACE: >2-3	TARE may have similar or superior cost-effectiveness to DEB-TACE
2F	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	No consensus	TARE may have similar or superior cost-effectiveness to DEB-TACE
2G	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	No consensus	TARE may have similar or superior cost-effectiveness to DEB-TACE
2H	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	No consensus	TARE may have similar or superior cost-effectiveness to DEB-TACE
3A	Full consensus	TARE Full consensus	No consensus	No consensus	TARE Consensus (TTP, downstaging) Comparable OS	TARE: 1 DEB-TACE: 3	TARE may have similar cost-effectiveness to DEB-TACE
3B	Full consensus	TARE Full consensus	No consensus	No consensus	TARE Consensus (TTP, downstaging)	TARE: 2 DEB-TACE: 3	No consensus
3C	TARE Full consensus	TARE Full consensus	No consensus	No consensus	TARE Consensus (TTP, downstaging)	TARE: 2 DEB-TACE: 3	No consensus
3D	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 2 DEB-TACE: >3	TARE may have similar or superior cost-effectiveness to DEB-TACE
3E	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 2 DEB-TACE: >3	TARE may have similar or superior cost-effectiveness to DEB-TACE
3F	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE Full consensus	TARE: 2 DEB-TACE: >3	TARE may have similar or superior cost-effectiveness to DEB-TACE

TTP, time to progression; OS, overall survival; TARE, transarterial radioembolization; DEB-TACE, transarterial chemoembolization with drug-eluting beads.

cient enough for their clinical practice in terms of covering the downstaging intent of treatments. Downstaging treatment approaches are known to increase potential eligibility for curative treatments, mainly transplantation, which significantly contribute to OS (29–31). In a 2017 study, Mehta et al. (30) observed OS in patients referred to transplantation after downstaging treatments and reported a 5-year survival of 80% (30). Approximately 3% to 5% of liver transplants are living-donor transplants in the United States and Europe while this rate is about 70% in Turkey (32–34). Transplant from a living donor allows improved and faster planning compared to a transplant from cadaver, increasing the probability to receive a transplant without progression in patients who previously undergo downstaging treatment (33). Therefore, downstaging treatments are thought to be more prioritized in Turkey than in other Western countries.

The panelists reached a consensus that TARE may provide improved OS and reduce the number of repeat procedures compared to DEB-TACE in intermediate-stage patients with a single tumor spanning a diameter above 5 cm who experience recurrence after previous treatment with TACE and in most TACE-naïve patient groups in the intermediate stage. While relevant literature indicates that the effectiveness of TACE may decrease with increasing tumor diameter, different opinions have been reported concerning tumor size. A study from Italy showed that TACE provided less response to treatment in patients with a nodule greater than 5 cm compared to those with smaller tumors, and another study reflecting expert opinions from Japan revealed that the diminished response was more pronounced in tumors greater than 7 cm (35, 36). Some of the literature based on clinical studies in this field have suggested that TARE may be a better treatment alternative than TACE in patients with a small number of large tumors or those with unilobed location (13, 37). While the data on DEB-TACE is insufficient in this regard, it is stated that this method may be more effective than conventional TACE in large tumors since it allows a higher drug density in the target mass compared to that achieved with conventional TACE (38, 39).

Based on the consensus on OS and the number of procedures, the panelists assumed that TARE would provide better cost-effectiveness advantage than DEB-TACE in most groups of TACE-naïve patients in the intermediate stage and in those with a single tumor spanning a diameter above 5 cm. It was also stated that this predicted cost-effectiveness advantage could be more pronounced in patients with a tumor diameter greater than 7 cm. The cost-effectiveness studies conducted in this field showed significance for OS and isolated procedure costs (including repeat procedures) as comparison parameters (23). Hospital-based costs, including the management of complications, had been reported to have insufficient value to create a difference in such analyses (23). However, a recent study investigated the estimated cost-effectiveness of one specific TARE modality; glass microspheres with Y-90 (TheraSphere) against other embolic treatments in UK population with early-to-intermediate stage HCC who are unresectable at presentation and are eligible for transarterial embolization (TAE), cTACE or DEB-TACE. The primary output in this study was the incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life years (QALY) gained. An ICER of under £20,000/QALY gained for an intervention was defined as cost-effective and represented an efficient use of healthcare resources. TARE patients were predicted to gain 0.7 additional QALYs compared to all other treatments. The base case ICERs for TARE were £17,300, £17,279 and £23,020 per QALY gained compared to TAE, cTACE and DEB-TACE, respectively. In the TARE cohort, 87% more patients were predicted to achieve downstaging compared to all other treatment options (25). To date, no other studies have specifically compared DEB-TACE and TARE in terms of cost-effectiveness beside the mentioned UK study with glass microsphere Y-90 TARE method. In the international literature, there is only one cost-effectiveness study comparing TACE versus TARE. In this study, which was conducted using patient data from all BCLC stages, a clear prediction could not be made for patients with intermediate BCLC stage (23).

It has been reported that structural damage may occur in the hepatic artery in HCC patients treated with TACE, thus the success of TARE treatment may decrease in these patients (40). On the other hand, the increased benefit observed with TARE in recent years has been associated with the widespread application of individualized dosimetry. Garin et al. (41) reported that OS was prolonged without an increase in liver toxicity in patients undergoing TARE treatment with the intensification concept and individualized dosimetry application (41). In a recent study, Garin et al. (42) found that compared with standard dosimetry, personalized dosimetry significantly improved the objective response rate in patients with locally advanced HCC. The results of this study suggest that personalized dosimetry is likely to improve outcomes in clinical practice and should be used in future trials of selective internal radiation therapy (42).

Better understanding of the effectiveness and safety of TARE warrants data from TACE-naïve patients, who are well-selected in light of scientific data and in whom individualized dosimetry methods are applied. Furthermore, OS data of DEB-TACE and TARE (including post-transplantation) and geographical factors that affect OS need to be investigated in Turkey, which is one of the leading countries that prefer using these treatments. This expert panel is hoped to be a starting point for future studies to be designed in this field.

The consensus opinions reached in this panel are undoubtedly no further than estimations and interpretations. The present study has all the limitations arising from the nature of the Delphi method (18, 19). The fact that actual patient data was not used, the patient scenario groups being created solely based on tumor burden, lack of consideration of remaining liver reservoir and performance status (both of which important for the prognosis), the different representation rates of specialties, and the limited number of expert opinions result in a limitation in reflecting the treatment approaches in Turkey at an ideal level.

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Conflict of interest disclosure

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