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Transarterial Chemoembolization Failure/Refractoriness: JSH-LCSGJ Criteria 2014 Update

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Key Words

Transarterial chemoembolization ·
Hepatocellular carcinoma ·
Criteria of transarterial chemoembolization failure

Abstract

In the 2010 version of the Japan Society of Hepatology (JSH) consensus-based treatment algorithm for the management of hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE) failure/refractoriness was defined assuming the use of superselective lipiodol TACE, which has been widely used worldwide and particularly in Japan, and areas with lipiodol deposition were considered to be necrotic. However, this concept is not well accepted internationally. Furthermore, following the approval of microspheres, an embolic material that does not use lipiodol, in February 2014 in Japan, the phrase 'lipiodol deposition' needed to be changed to 'necrotic lesion or viable lesion'. Accordingly, the respective section in the JSH guidelines was revised to define TACE failure as an insufficient response after ≥2 consecutive TACE procedures that is evident on response evaluation computed tomography or magnetic resonance imaging after 1–3 months, even after chemotherapeutic agents have been changed and/or the feeding artery has been reanalyzed. In addition, the appearance of a higher number of lesions in the liver than that recorded at the previous TACE procedure (other than the nodule being treated) was added to the definition of TACE failure/refractoriness. Following the discussion of other issues concerning the continuous elevation of tumor markers, vascular invasion, and extrahepatic spread, descriptions similar to those in the previous version were approved. The revision of these TACE failure definitions was approved by over 85% of HCC experts.

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Introduction

Transarterial chemoembolization (TACE) [1, 2] is the standard treatment for intermediate-stage hepatocellular carcinoma (HCC) and benefits patients in two ways: providing a treatment response and minimizing liver function damage (fig. 1). However, when repeated, TACE loses its efficacy at some point and patients enter the so-called state of TACE failure/refractoriness [3]. When this is the case, multifocal nodules are commonly seen scattered in both lobes or as a huge HCC mass, and the noncancerous liver tissue will have deteriorated due to the damage caused by TACE, resulting in a reduced survival time (fig. 2). As a result, it has become apparent in recent years that the treatment modality should be switched before patients enter this state. The concept of TACE refractoriness was first proposed in the clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) [4] and then appeared in criteria published in Korea [5], criteria established by the European Association for the Study of the Liver (EASL) [3], and in the Assessment for Retreatment (ART) score system [6, 7], although the definition in the latter is slightly different from that for TACE refractoriness. In addition, other studies recommend the use of discontinuation rules or a scoring system, such as the Hepatoma Arterial-Embolisation Prognostic (HAP) score [8], to decide whether TACE should be continued. However, it should be noted that in Japan, HCC cases indicated for TACE generally involve only a limited number of small nodules because of a well-established nationwide surveillance program for HCC [9]. On the other hand, in the United States, Europe, and some Asian countries, patients already tend to have a huge tumor or multifocal bilobar intermediate-stage HCCs at the time of their first TACE treatment [10]. These patients should be further subclassified and treated as subgroups of individuals who would either respond or not respond favorably to TACE. To improve the prognosis of patients, the JSH criteria for TACE refractoriness recommend recognizing the time point of TACE refractoriness at the intermediate stage of the disease after having repeated TACE several times or even ≥10 times and having switched the treatment strategy to preserve residual liver function (fig. 2).

At the 50th Liver Cancer Study Group of Japan (LCSGJ) Congress (congress president: Prof. Masatoshi Kudo) held on June 5–6, 2014 in Kyoto, Japan, the definition of TACE refractoriness was updated by HCC experts, and a consensus meeting was convened to evaluate the proposed definition [11]. At this meeting, appropriate treatments for cases of TACE failure or refractoriness were also discussed. Moreover, during a session entitled 'The Definition of TACE Refractoriness' held at the 4th International Kyoto Liver Cancer Symposium (IKLS; congress president: Prof. Masatoshi Kudo) on June 7–8, 2014 in Kyoto, Japan, a voting system was used in a debate of the criteria. In this article, we report the updated JSH-LCSGJ criteria for TACE failure/refractoriness and the results of the meetings.

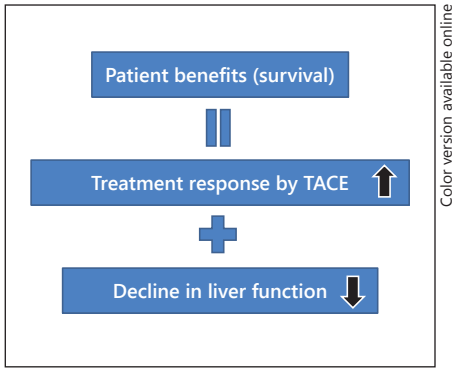

Fig. 1. Benefits of TACE for patients.

Consensus Meeting

Approximately 140 HCC experts, of which 51% were hepatologists, 6% surgeons, 6% oncologists, and 9% radiologists, used a voting system at the consensus meeting on TACE failure/refractoriness. The monthly number of cancer patients treated by the experts (proportion of experts) was as follows: <5 patients (16% of experts), 6–25 patients (46%), 26–50 patients (20%), 51–100 patients (9%), and ≥101 patients (9%). When asked which department performs TACE, 51% of experts answered internal medicine, 47% radiology, and 1% surgery. When asked about the number of patients they treated in a month, 30% of experts answered <5 patients, 11% 6–50 patients, and 4% answered ≥51 patients. Furthermore, when asked what primary embolic agent they used in TACE, 46% answered lipiodol, 35% porous gelatin sponge, 6% gelatin sponge, and 13% microspheres (beads). The primary anticancer agents used in TACE were, in descending order, epirubicin (44%), miriplatin (26%), cisplatin (24%), doxorubicin (4%), and mitomycin (3%). In addition, 56% of experts agreed and 17% disagreed with the question 'Do you think a scoring sys-

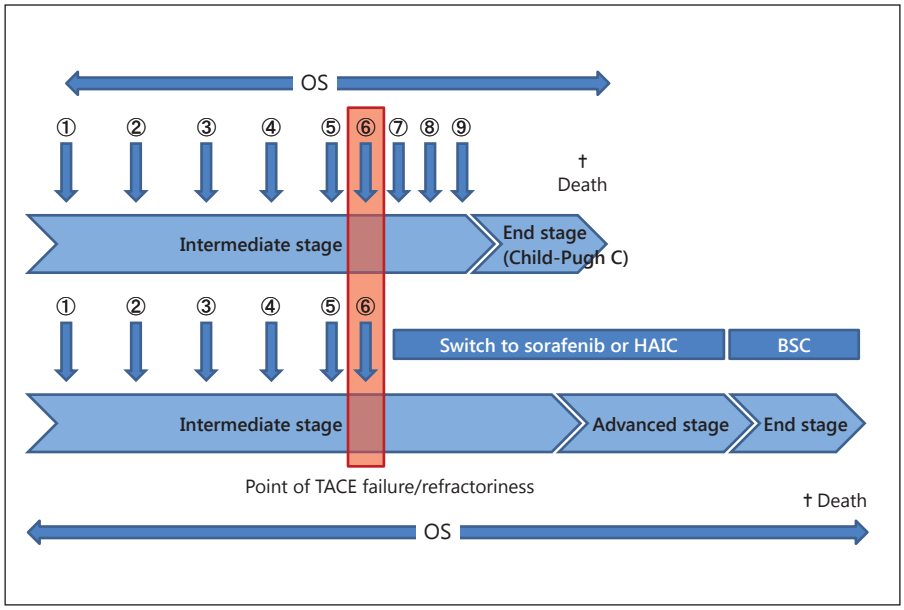

Fig. 2. Treatment strategy to prolong patient survival according to a TACE discontinuation and switching rule in patients with TACE failure/refractoriness. OS = Overall survival.

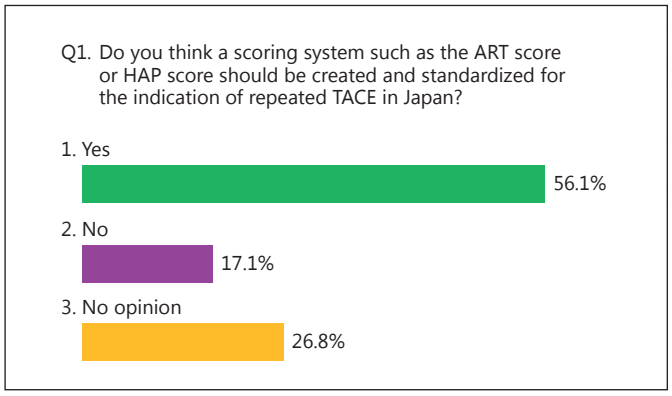

Fig. 3. Votes cast on the need for a scoring system for a TACE discontinuation rule.

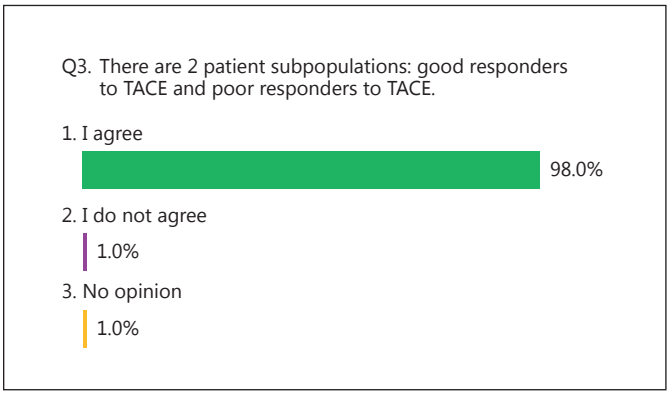

Fig. 5. Question and answers on whether there are two TACE responder subgroups.

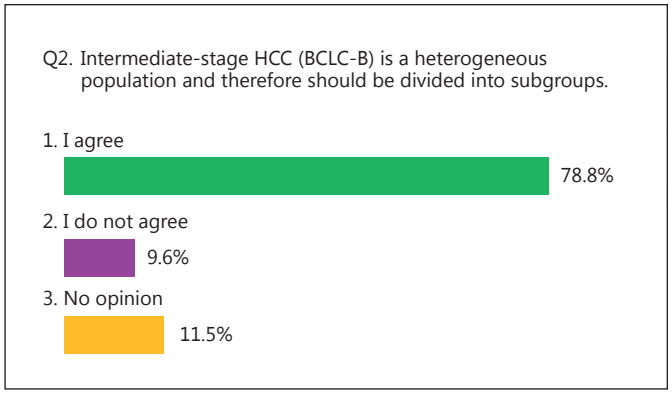

Fig. 4. Question and answers on intermediate-stage HCC.

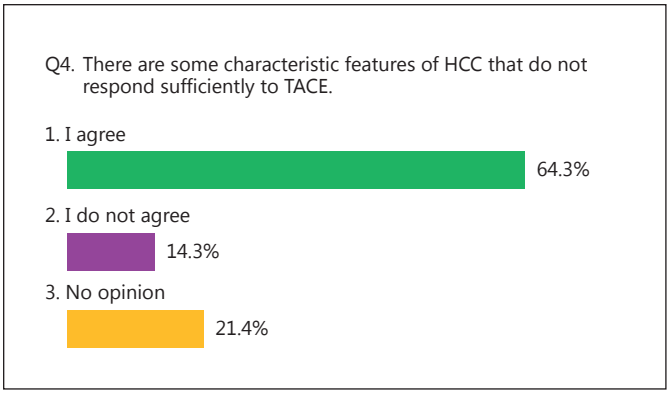

Fig. 6. Question and answers on whether there are some characteristic features in poor responders to TACE.

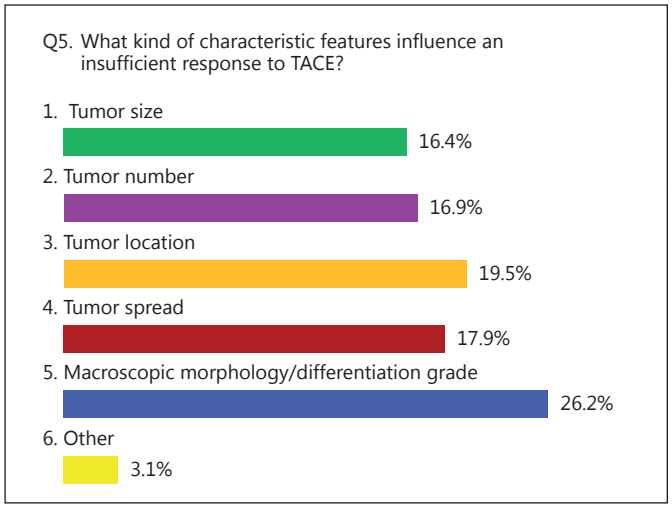

Fig. 7. Question and answers on the characteristic features of poor responders to TACE.

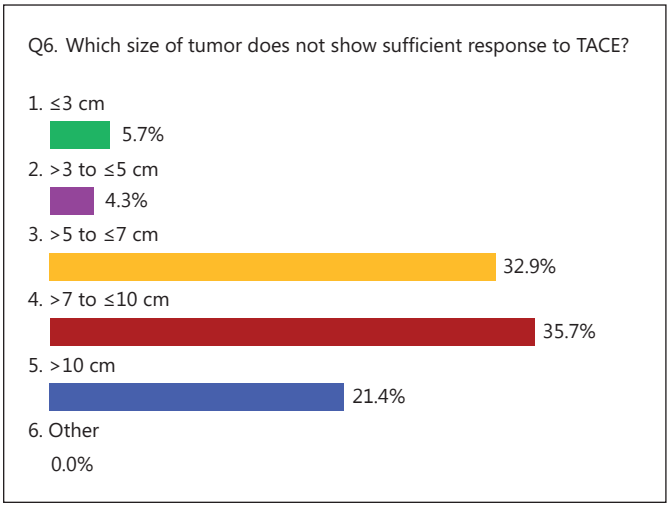

Fig. 8. Question and answers on the tumor size related to a poor response to TACE.

tem such as the ART score or HAP score should be created and standardized for the indication of repeated TACE in Japan?' (fig. 3).

Voting Results

Heterogeneity of Intermediate-Stage HCC

To the question asking if it is necessary on account of their heterogeneous nature to subgroup intermediate-stage HCCs (equivalent to stage B on the Barcelona Clinic Liver Cancer staging system), for which TACE is the standard treatment, 79% of experts agreed and 10% disagreed (fig. 4), suggesting that many experts are well aware of the extremely wide range of features of intermediate-stage HCCs, i.e. multifocal HCCs without vascular invasion or extrahepatic spread. In fact, 98% of experts agreed with the statement that some HCC cases respond well to TACE while others respond poorly to it (fig. 5). In addition, 64% of experts thought that HCCs which respond poorly to TACE exhibit specific features, indicating that many experts encounter such cases in clinical practice (fig. 6). When asked about the characteristic features of HCCs that respond poorly to TACE, experts mentioned equally the size, number, location, spread, and macroscopic morphology/pathological differentiation grade of HCCs (fig. 7). With regard to the size of HCC associated with a poor TACE efficacy, 5–7 cm was mentioned by 33% of experts, 7–10 cm by 36%, and ≥10 cm by 21%, suggesting that the efficacy of TACE decreases as the size of HCC increases (fig. 8). With regard to the number of HCC lesions associated with a poor TACE efficacy, 23, 42, and 32% of experts answered 4–6, 7–10, and ≥10, respectively (fig. 9). When asked about the extent of HCC that affects the TACE efficacy, 29 and 69% answered HCC spread over 'multiple segments' and 'both lobes', respectively (data not shown). As expected, 72% agreed that poorly differentiated HCCs respond poorly to TACE (fig. 10).

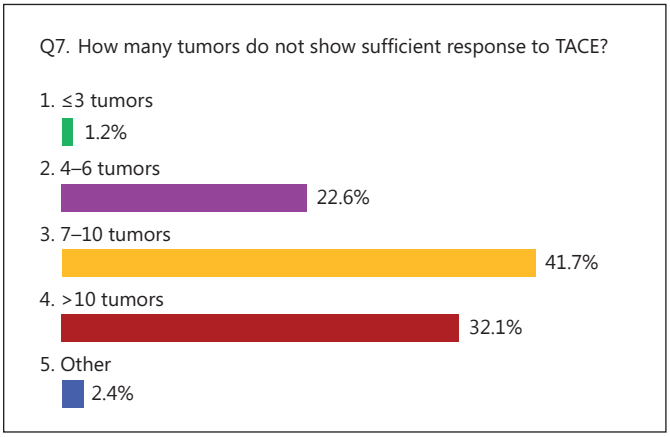

Fig. 9. Question and answers on the tumor number related to a poor response to TACE.

Contraindications of TACE

The following four contraindications for TACE are stated in the 2010 version of the JSH consensus-based

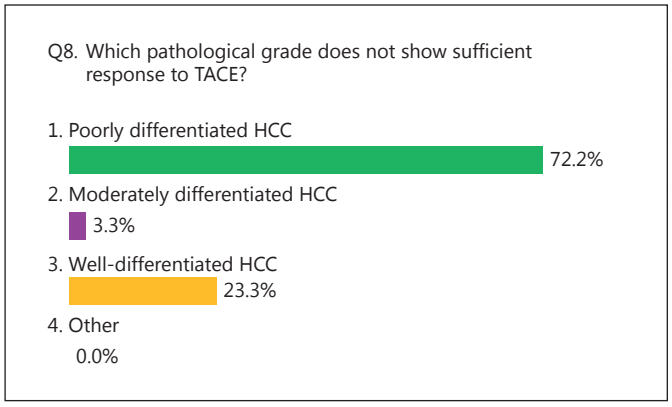

Fig. 10. Question and answers on the pathological grade related to a poor response to TACE.

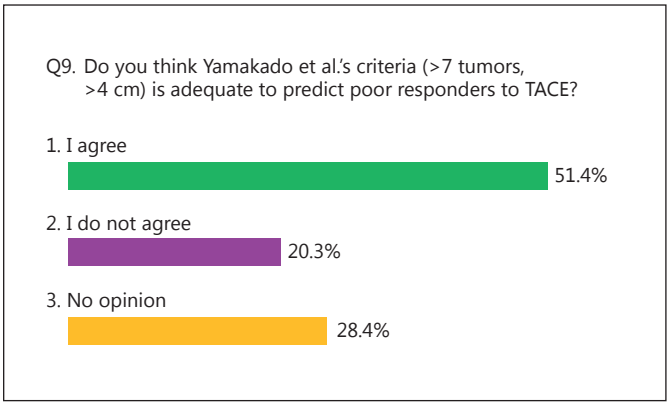

Fig. 11. Question and answers on Yamakado et al.'s [12] criteria.

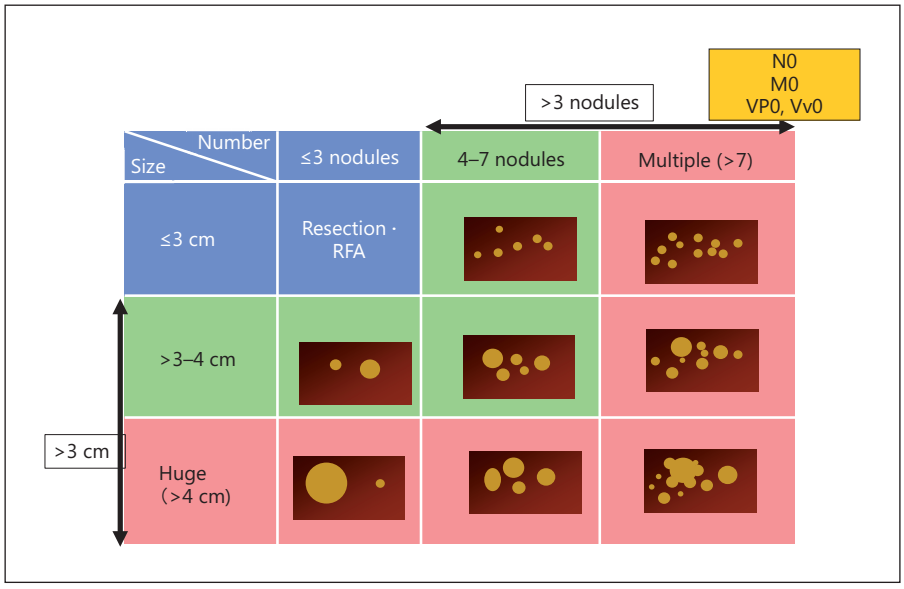

Fig. 12. Heterogeneity of intermediate-stage HCC. The green fields indicate good responders to TACE and the pink fields poor responders (colors refer to the online version only). RFA = Radiofrequency ablation.

practice guidelines [4], and no major amendments to these contraindications were made at the recent meeting.

- Blood vessels involved in treatment cannot be used and feeding vessels are unavailable for catheterization because of the damage caused by repeated TACE.
- Residual liver function graded as Child-Pugh C due to repeated treatment.
- HCC that has spread to the major branches of the portal vein (Vp3) or the portal trunk (Vp4).
- A large arterioportal shunt.

Poor Responders to TACE

In the question and answer session, experts agreed that >7 HCCs of >4 cm in size constitute an HCC subgroup that responds poorly to TACE. These criteria were adopted based on the findings of Yamakado et al. [12], stating that patients with tumors of >4 cm in size seldom benefit from TACE due to their poor response to the treatment and subsequent decline in residual liver function. Yamakado et al.'s criteria gained agreement from 51% of experts, indicating that >7 HCCs of >4 cm in size is essentially accepted as criterion defining a subgroup of patients responding poorly to TACE (fig. 11).

Good Responders to TACE

The meeting also revealed that a subgroup of patients with intermediate-stage HCCs who would benefit from TACE comprises individuals with 4–7 nodules of 3–4 cm

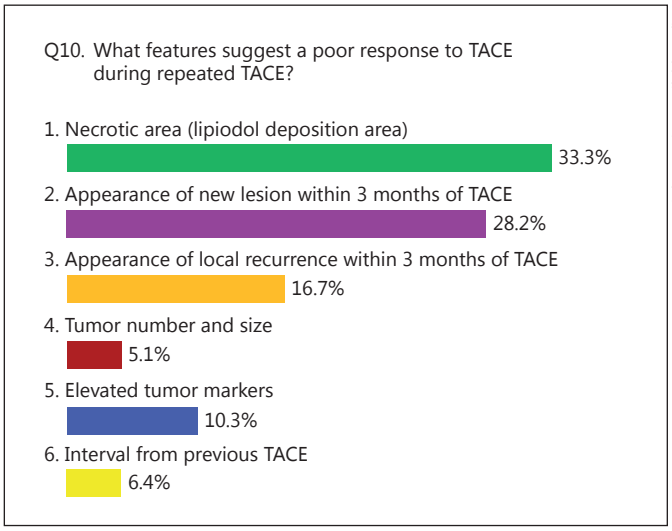

Fig. 13. Question and answers on factors related to a poor response to TACE.

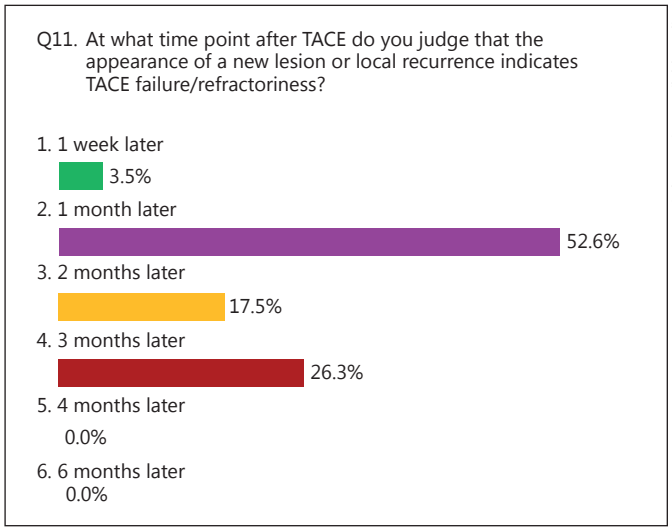

Fig. 14. Question and answers on the timing for evaluating TACE failure/refractoriness.

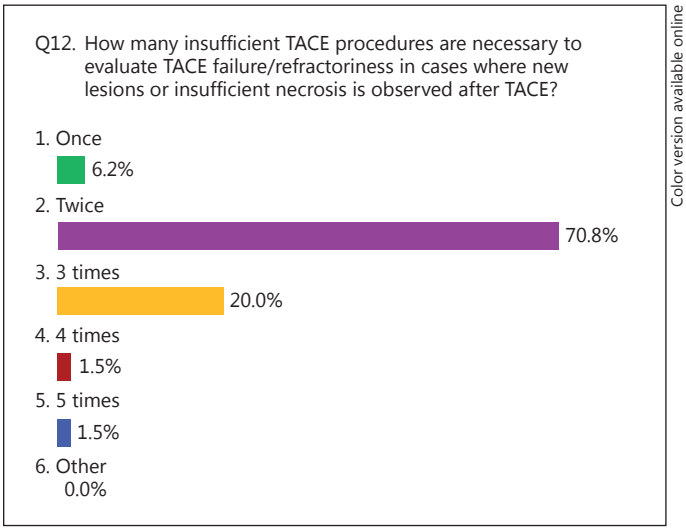

Fig. 15. Question and answers on the number of consecutive TACE procedures to evaluate TACE failure/refractoriness.

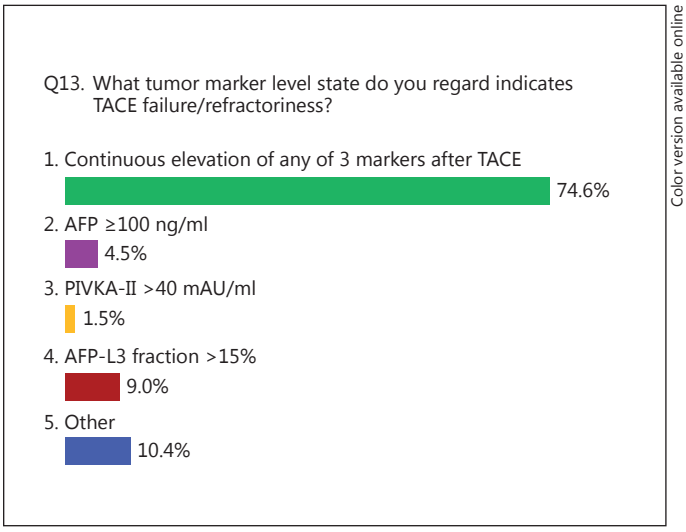

Fig. 16. Question and answers on the tumor marker levels related to TACE failure/refractoriness.

in size (fig. 12). When TACE has a high treatment efficacy and keeps the decline in residual liver function to a minimum, it is beneficial to HCC patients in this subgroup and makes long-term survival possible (fig. 1). Subsequently, even if HCC is still in the intermediate stage, it is extremely important to find out the time point of TACE failure as early as possible and switch the treatment strategy from that point on (fig. 2).

JSH TACE Failure/Refractoriness Criteria Updated by the LCSGJ in 2014

At the time of the consensus voting on TACE failure/refractoriness, when asked about the specific features of HCC cases that indicate a poor response to TACE even when repeated, 33% of experts answered insufficient necrosis (rate of lipiodol deposition), 28% answered the appearance of a new lesion within 3 months of TACE, and

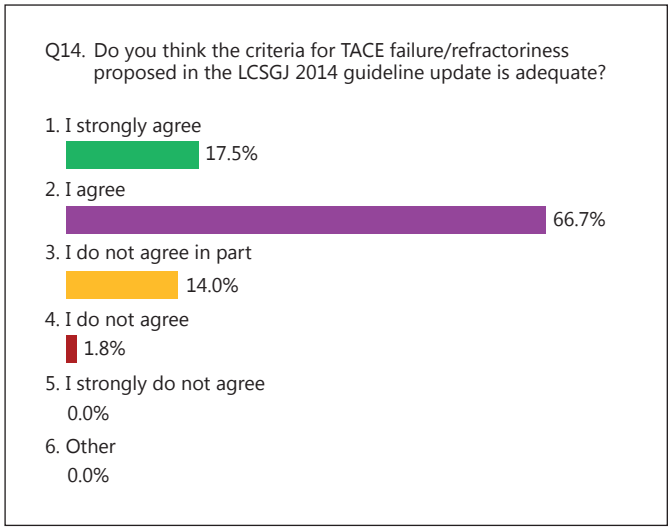

Fig. 17. The most important question asked, regarding whether the criteria for TACE failure/refractoriness updated in 2014 by the LCSGJ are adequate or not.

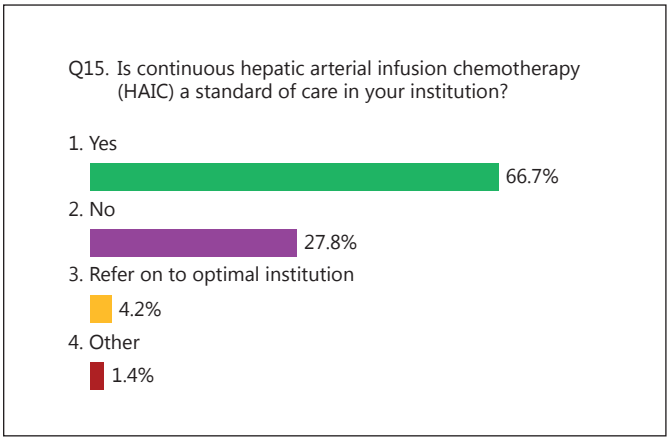

Fig. 18. Question and answers on continuous HAIC.

Table 1. Definition of TACE failure/refractoriness (LCSGJ)

(1)	Intrahepatic lesion	
	i	Two or more consecutive insufficient responses of the treated tumor (viable lesion >50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE
	ii	Two or more consecutive progressions in the liver (tumor number increases as compared to tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE
(2)	Continuous elevation of tumor markers immediately after TACE even though slight transient decrease is observed	
(3)	Appearance of vascular invasion	
(4)	Appearance of extrahepatic spread	

17% answered local recurrence within 3 months of TACE (fig. 13). Furthermore, the largest proportion of experts (53%) answered '1 month' to the question on the interval between the previous TACE procedure and the appearance of a new lesion or local recurrence that indicates TACE failure/refractoriness (fig. 14). To the question asking at what point they consider TACE to be ineffective for HCC when observing the appearance of new lesions or no necrosis after TACE, 71% answered they would think it is ineffective when a similar treatment outcome occurs twice (fig. 15). About 75% of experts consider TACE failure/refractoriness to be the case when the level of any of 3 tumor markers continues to increase after TACE, even if they show a slight short-term decrease (fig. 16). Based on the answers to these questions, the definition of TACE failure/refractoriness after treatment was revised.

Table 1 shows the JSH criteria for TACE failure/refractoriness updated at the 50th LCSGJ Congress in 2014. Since 84% of experts agreed that the updated criteria are appropriate, they are now recommended for the assessment of TACE failure/refractoriness (fig. 17).

Treatment Options after TACE Failure/Refractoriness

Before the session on treatment options after TACE failure/refractoriness, 67% of experts reported that continuous hepatic arterial infusion chemotherapy (HAIC)

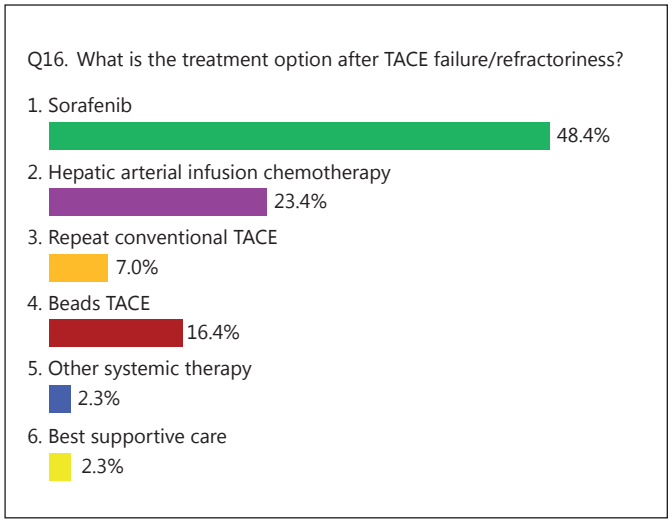

Fig. 19. Question and answers on the general treatment strategy after TACE failure/refractoriness.

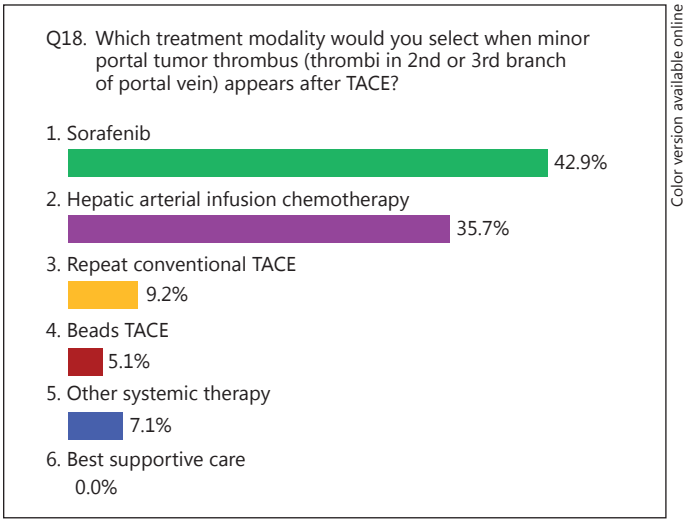

Fig. 21. Question and answers on the treatment strategy after TACE failure/refractoriness in patients with minor portal tumor thrombus.

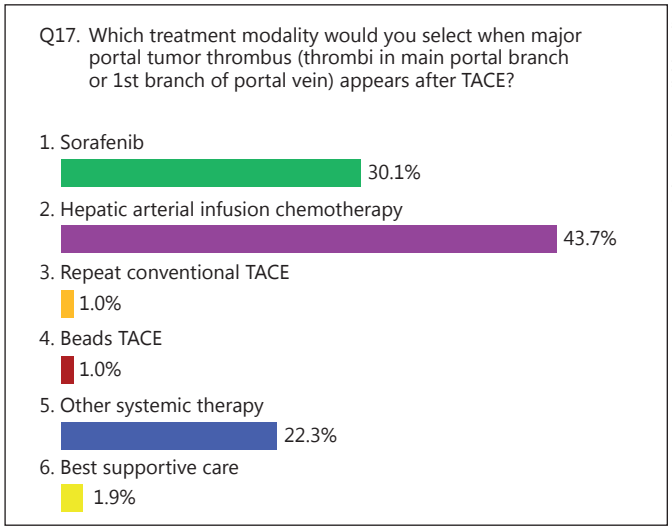

Fig. 20. Question and answers on the treatment strategy after TACE failure/refractoriness in patients with major portal tumor thrombus.

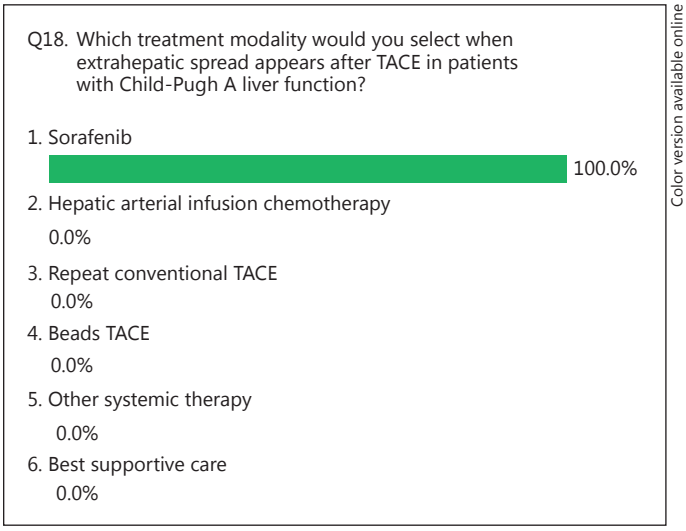

Fig. 22. Question and answers on the treatment strategy after TACE failure/refractoriness in patients with extrahepatic spread.

[13] is the routinely performed treatment modality at their institution, indicating its widespread use in Japan (fig. 18). When asked what their treatment of choice is in TACE failure/refractoriness cases (Q16), 48% of experts answered sorafenib and 23% answered HAIC (fig. 19). However, when asked what their treatment of choice is in cases of major portal vein thrombus after TACE (Q17), 30% answered sorafenib and 44% answered HAIC (fig. 20). On the contrary, for TACE failure/refractoriness cases with minor portal vein thrombus and Child-Pugh A liver function, 43 and 36% of experts stated that sorafenib and HAIC, respectively, was their treatment of choice (fig. 21). The difference in the answers to Q16 and Q17 reflects the potential risk that sorafenib administration can lead to liver failure in HCC cases with major portal vein thrombus. In contrast, HAIC is indicated even in cases of major portal tumor thrombus. Lastly, 100% of experts answered that sorafenib is their treat-

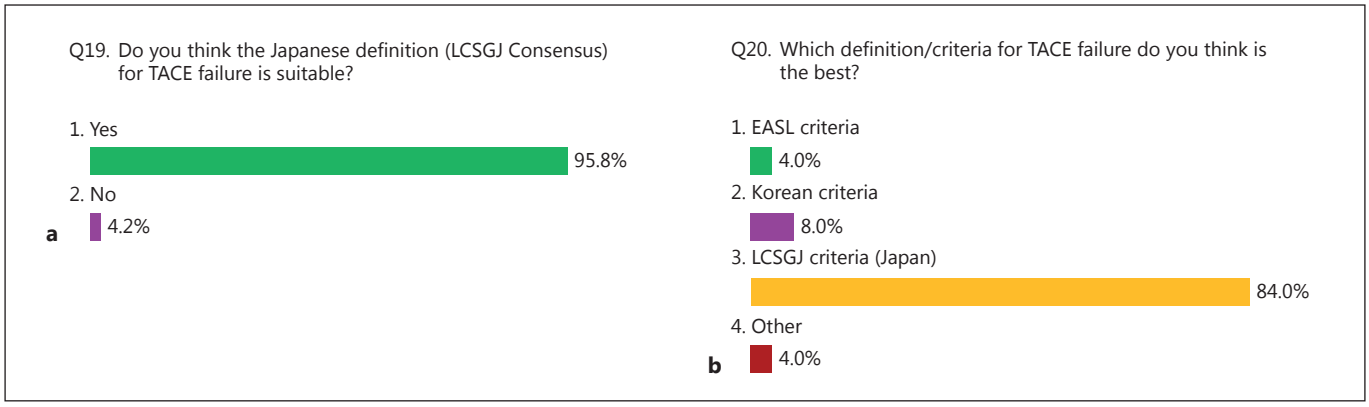

Fig. 23. Question and answers at the 4th IKLS on the suitability of the updated TACE failure/refractoriness criteria agreed upon at the LCSGJ consensus meeting (**a**) and on which definitions/criteria for TACE failure/refractoriness are the best (**b**). Of the experts present, 60% were from Japan, 20% from other Asian countries, and 20% from Europe and the USA.

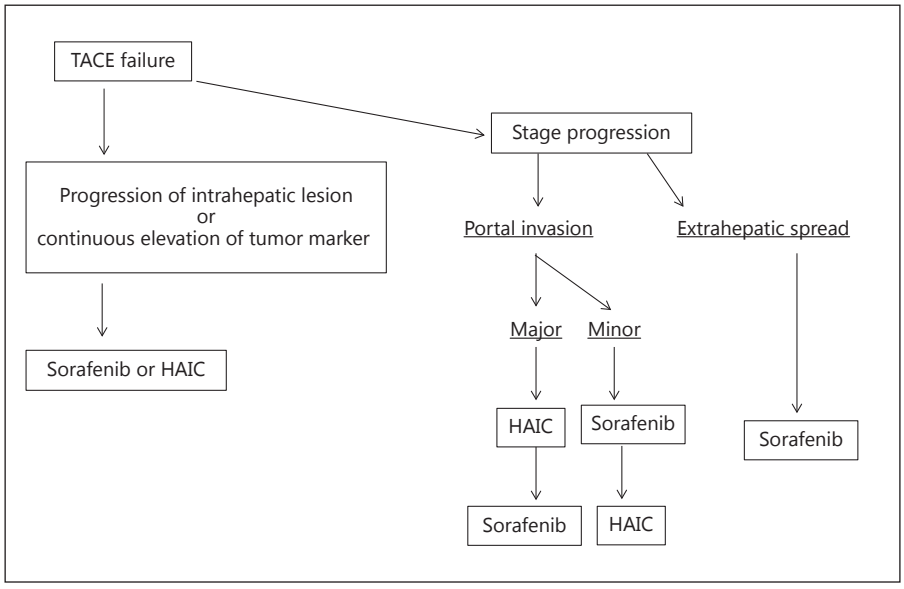

Fig. 24. Treatment strategy after TACE failure/refractoriness.

ment of choice for extrahepatic spread developed after TACE in HCC patients with Child-Pugh A liver function (fig. 22).

Also, at the 4th IKLS, 96% of HCC experts (60% from Japan, 20% from other Asian countries, and 20% from Europe or the USA) agreed that the criteria for TACE failure/refractoriness proposed at the 50th LCSGJ Congress were appropriate (table 1; fig. 23a). To the question on which definition/criteria for TACE failure/refractoriness the experts thought was the best, 84% answered the revised JSH criteria proposed by the LCSGJ (fig. 23b).

Conclusion

The definition of TACE failure in the JSH clinical practice guidelines has been updated based on agreement from 84% of HCC experts attending a consensus meeting held at the 50th LCSGJ Congress in 2014. The updated criteria also obtained 96% approval at the 4th IKLS.

To prolong the survival of HCC patients, it is important to switch treatment from TACE to, for example, sorafenib or HAIC as soon as the criteria for TACE failure/refractoriness are fulfilled, even if HCC is still in the intermediate stage. HAIC is the first treatment choice in

TACE failure/refractoriness cases with stage progression or major portal vein infiltration, whereas sorafenib is recommended in TACE failure/refractoriness cases with minor portal vein infiltration (fig. 24). Further studies are needed to determine the efficacy of microsphere TACE, such as drug-eluting beads TACE, in cases of TACE failure/refractoriness.

Consensus Statement (≥67% Agreement)

(1) Intermediate-stage HCC is a heterogeneous disease and therefore should be subgrouped (79%).

(2) There are 2 subgroups in the intermediate stage of HCC: good responders to TACE and poor responders to TACE (98%).

(3) Intrahepatic lesions not responding to TACE show insufficient necrosis (33%), the appearance of new lesions within 3 months (28%), or local recurrence within 3 months after TACE (17%) (total: 78%).

(4) Incomplete control of intrahepatic lesions within 1–3 months of TACE initiation should be included in the TACE failure criteria (96%).

(5) Timing of the judgment of TACE failure is after 1–3 months (96%).

(6) Two consecutive poor responses to TACE is an adequate criterion for TACE failure (71%).

(7) Continuous increase in any tumor marker should be included in the TACE failure criteria (75%).

(8) Continuous HAIC is widely performed in Japan (67%).

(9) When extrahepatic spread emerges during repeated TACE sessions, the treatment strategy should be changed to sorafenib (100%).

(10) The 2014 updated JSH criteria for TACE failure/refractoriness are adequate (84% at the 50th LCSGJ Congress and 96% at the 4th IKLS).

Informative Statement (≥50% Agreement)

(1) There are characteristic features of HCC that do not respond to TACE (64%).

(2) Yamakado et al.'s [12] criteria (HCC >4 cm and >7 nodules) are accepted as criteria for poor responders to TACE (51%).

Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

References

1 Lencioni R: Chemoembolization in patients with hepatocellular carcinoma. Liver Cancer 2012;1:41–50.
2 Minami Y, Yagyu Y, Murakami T, et al: Tracking navigation imaging of transcatheter arterial chemoembolization for hepatocellular carcinoma using three-dimensional cone-beam CT angiography. Liver Cancer 2014;3:53–61.
3 Raoul JL, Gilabert M, Piana G: How to define transarterial chemoembolization failure or refractoriness: a European perspective. Liver Cancer 2014;3:119–124.
4 Kudo M, Izumi N, Kokudo N, et al: Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–364.
5 Park JW, Amarapurkar D, Chao Y, et al: Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). Liver Int 2013;33:327–337.
6 Sieghart W, Hucke F, Pinter M, et al: The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261–2273.
7 Kudo M, Arizumi T, Ueshima K: Assessment for retreatment (ART) score for repeated transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2014;59:2424–2425.
8 Kadalayil L, Benini R, Pallan L, et al: A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol 2013;24:2565–2570.
9 Kudo M: Japan's successful model of nationwide hepatocellular carcinoma surveillance highlighting the urgent need for global surveillance. Liver Cancer 2012;1:141–143.
10 Kim DY, Han KH: Epidemiology and surveillance of hepatocellular carcinoma. Liver Cancer 2012;1:2–14.
11 Kudo M, Matsui O, Izumi N, et al: JSH consensus-based clinical practice guideline for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver Cancer 2014;3:458–468.
12 Yamakado K, Miyayama S, Hirota S, et al: Subgrouping of intermediate-stage (BCLC stage B) hepatocellular carcinoma based on tumor number and size and Child-Pugh grade correlated with prognosis after transarterial chemoembolization. Jpn J Radiol 2014;32:260–265.
13 Kudo M: Treatment of advanced hepatocellular carcinoma with emphasis on hepatic arterial infusion chemotherapy and molecular targeted therapy. Liver Cancer 2012;1:62–70.