External Review of the Clinical Practice Guidelines for Liver Cancer 2017

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Introduction

The first edition of the scientific evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma was compiled in 2005 and was followed by revisions that incorporated the latest evidence every 3-4 years as planned, in 2009 (second edition), 2013 (third edition), and 2017 (fourth edition). Each edition was reviewed externally before publication. Immediately after the 2005 version was completed, an External Review Panel was established, and assessments of the validity, applicability, and usability were described at the end of the published Guidelines.

The 2009 version was published after a call for public comments online and extensive discussions at the JSH Annual Meeting. An External Review Panel was established after publication and its review was subsequently published in the official journal of the JSH[1]. Similarly, the 2013 version was completed after a call for public comments online and at a public hearing held during the JSH Annual Meeting, with a review by an External Review Panel published later. In the current edition of the Guidelines (2017 version), to address criticism that external review was not happening until after publication, the External Review Panel for the 2017 version was established after the draft was compiled and its review was completed prior to publication.

Purpose

In 2002, the Japan Council for Quality Health Care launched the Medical Information Network Distribution Service (MINDS) project to promote the development of EBM guidelines. The MINDS project provides a document[2] that assists the decision-making process of patients and healthcare professionals for highly important medical procedures, presenting systematic reviews of clinical evidence and grading recommendations to achieve the best treatment outcome and emphasizing the importance of the balance between benefit and harm for patients. With this intent in mind, the role of the External Review Panel is to objectively assess the validity and clinical applicability of the Guidelines and reflect the findings in the Guidelines. The 2017 version of the Guidelines was therefore externally reviewed immediately before publication and the results summarized to serve as references for the next review process.

Assessment methods

The External Review Panel consisted of 3 hepatologists (specialists in internal medicine, surgery, and radiology) who were not involved in the revision of the Guidelines and 3 non-hepatologists (specialists in internal medicine, surgery, and biostatistics) with expertise in developing clinical guidelines. The 6 appraisers independently rated the Guidelines and the scores were combined and analyzed.

Footnotes

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As for the 2013 version, the current Guidelines was externally reviewed using the modified version of the Appraisal of Guidelines for Research and Evaluation (AGREE II)[4] as the sole assessment tool (Table 1). Previously, the AGREE II, Shaneyfelt method[5], and Conference on Guideline Standardization[6] were used for external review of the 2005 and 2009 versions, but because the three tools are composed of similar questionnaire items, they generated similar results. The AGREE II questionnaire categorizes items by domain and uses a 7-point rating scale, whereas the other 2 tools use Yes-No questions. Accordingly, only the AGREE II was used to review the current version of the Guidelines.

In the AGREE II, 23 items are divided into 6 domains (Fig. 1): Scope and Purpose (3 items), Stakeholder Involvement (3 items), Rigour of Development (8 items), Clarity of Presentation (3 items), Applicability (4 items), and Editorial Independence (2 items). Two more questions are included at the end of the questionnaire for overall guideline assessment (Table 1). Except for the last 2 items, each item uses a 7-point rating scale, ranging from Strongly Disagree (1 point) to Strongly Agree (7 points). The second item for overall guideline assessment (i.e., “I would recommend this guideline for use”) is answered by selecting a response from the options “Yes”, “Yes, with modifications”, and “No”. There is also space provided for comments under each questionnaire item. The total score for each domain is calculated from the individual item scores, and the maximum and minimum possible scores in each domain are also calculated. Then, domain score (%) is calculated by dividing (Obtained score – Minimum possible score) by (Maximum possible score –

Minimum possible score) and multiplying by 100. Domain scores and comments from the appraisers are combined to reveal superior and inferior aspects of the Guidelines.

The external reviews of the 2017 version and previous versions were basically not compared because such comparison is beyond the scope of the external review and because the external reviews of different versions were not performed by the same appraisers. However, appreciable changes are mentioned in the Guidelines.

Results

Table 1 shows the scores for individual items and domains. The difference in domain scores was < 10% between hepatologists and non-hepatologists in all domains except for Stakeholder Involvement, suggesting that assessments were comparable between the two groups of appraisers (Table 1). Analysis of the domain scores by all appraisers revealed that Applicability was poorly rated (43%; factors contributing to the poor rating will be discussed later), whereas Clarity of Presentation, which evaluates whether the Guidelines recommend treatment modalities that produce optimum outcomes for patients, was rated high with a score of 80% (Fig. 1).

Item scores differed ≥ 20% between hepatologists and non-hepatologists for Items 4, 5, 15, and 18 (non-hepatologists rated low) and Item 20 (hepatologists scored low) (Fig. 2, red lines). For Item 4. “The guideline development group includes individuals from all relevant professional groups” (scores, 94% vs. 67%), non-hepatologists commented that the role of each member was not described and they requested more detailed information than that provided by a list of committee members. Also, there was a comment that the Revision Committee did not include palliative care specialists, nurses, or patients. Item 15. “The recommendations are specific and unambiguous” was rated relatively poorly by non-hepatologists (scores, 89% vs. 61%) for the reason that recommendations in the Guidelines sometimes do not lead to concrete actions: for example, “Abdominal drainage is not always necessary after elective hepatectomy” for CQ27, and “Because each drug used in molecular-targeted therapy is associated with common or severe side effects, it is important to follow-up patients carefully and respond to adverse events properly, including reducing drug dosage and prescribing drug holidays” for CQ47. Items 5, 18, and 20, all of which were poorly rated by both hepatologists and non-hepatologists, will be discussed in the next section.

As many as 6 items were poorly rated (score percentage, ≤ 60%) by all appraisers, as follows. In the Scope and Purpose domain, only Item 3. “The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described” (47%) was poorly rated by both hepatologists and non-hepatologists. This is because the term “liver cancer”, as in the title of the Guidelines, did not clearly explain whether this includes all types of primary liver cancer or only HCC. This problem has been addressed by revising the Guidelines based on the scores and comments received during the external review.

In the Stakeholder Involvement domain, Item 5. “The views and preferences of the target population (patients, public, etc.) have been sought” (47%) was rated especially poorly by non-hepatologists. This is because the Revision Committee did not include patient representatives and because it seems to have been extremely difficult to hear patients’ opinions and comments while preparing the guidelines, that is, during the public hearing organized by the Liver Cancer Study Group of Japan and through the call for public comments and external reviews on the JSH webpage.

In the Rigour of Development domain, only Item 7. “Systematic methods were used to search for evidence” (56%) was rated poorly. This was because even though the previous 2013 version summarized the literature search queries at the end of the Guidelines, the current edition did not, presumably because the same search queries were used. This required the appraisers to look these up in the previous version.

All items in the Clarity of Presentation domain were rated highly, whereas 3 of the 4 items in the Applicability domain were rated poorly. Item 18. “The guideline describes facilitators and barriers to its application” (56%) was rated poorly because the Guidelines did not provide sufficient information about National Health Insurance coverage status and cost-benefit of costly medical care such as liver transplantation, molecular-targeted therapy, and particle therapy. For Item 20, “The potential resource implications of applying the recommendations have been considered” (31%), it was pointed out that in addition to the above treatment modalities, the cost-benefit of sorafenib therapy, which was stated at the end of the previous version, was not commented on in the current edition by committee members who are experts in health economics. Item 21, “The guideline presents monitoring and/or auditing criteria” (8%) had the lowest score among the 23 items. All members pointed out the lack of description of audit criteria, which has been pointed out since the 2005 version. In the Editorial Independence domain, none of the items were rated poorly.

Noteworthy comments for items with a score ≥ 60% are as follows. In relation to Item 9. “The strengths and limitations of the body of evidence are clearly described” (78%) and Item 10. “The methods for formulating the recommendations are clearly described” (89%), the comments were that the GRADE system used in the current edition has no clear explanation, and the grading of recommendations in a meeting or by a show of hands should not be not advocated because the process often involves bias. Also, although COIs are first mentioned in Item 23. “Competing interests of guideline development group members have been recorded and addressed” (64%), all External Review Panel members pointed out that more detailed descriptions and explanations are needed for some COIs, such as an individual member’s COIs relation to each CQ and academic COIs (in addition to funding-related COIs).

In the Overall Guideline Assessment domain, Item 1. “Rate the overall quality of this guideline” had a high score of 75%, and Item 2. “I would recommend this guideline for use” was answered Yes by 3 of the 6 appraisers and “Yes, with modifications” by the other 3 appraisers; none answered *No*.

Summary

The 2017 version of the Clinical Practice Guidelines for Liver Cancer was externally reviewed using the AGREE II tool. Assessments thought to be valuable for the next review process are listed below.

・The Revision Committee needs to (1) include palliative care specialists, nurses, and patients as members, and (2) specifiy their financial and academic COIs in addition to the role of individual committee members.

・Recommendations for each CQ need to be specific and practical.

・Facilitators and barriers (cost, etc.) to the application of the Guidelines (e.g., in liver transplantation, molecular-targeted therapy, and particle therapy) need to be discussed from the perspective of facility resources and health economics.

・Methods used to evaluate the versatility and utility of the Guidelines need to be described.

References

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4) Brouwers M, Kho ME, Browman GP, et al. AGREE II: Advancing guideline development, reporting and evaluation in health care. *J Clin Epidemiol* 2010; 63: 1308-11. PMID: 20656455

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6) Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med* 2003; 139: 493-8. PMID: 13679327

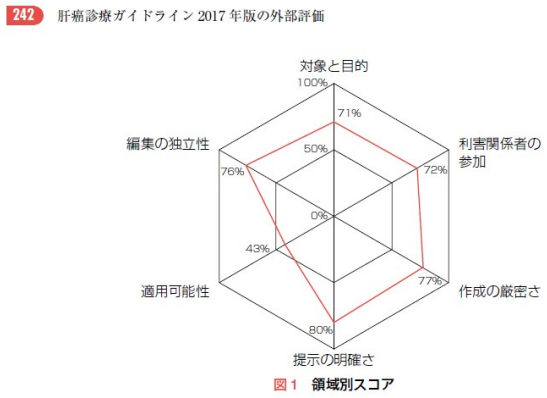
Table 1. Scores and percentages for the different AGREE II items

Domain	Item	
1 Scope and Purpose	1	The overall objective (s) of the guideline is (are) specifically described.
	2	The health question (s) covered by the guideline is(are) specifically described.
	3	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
2 Stakeholder Involvement	4	The guideline development group includes individuals from all relevant professional groups.
	5	The views and preferences of the target population (patients, public, etc.) have been sought.
	6	The target users of the guideline are clearly defined.
3 Rigour of Development	7	Systematic methods were used to search for evidence.
	8	The criteria for selecting the evidence are clearly described.
	9	The strengths and limitations of the body of evidence are clearly described.
	10	The methods for formulating the recommendations are clearly described.
	11	The health benefits, side effects, and risks have been considered in formulating the recommendations.
	12	There is an explicit link between the recommendations and the supporting evidence.
	13	The guideline has been externally reviewed by experts prior to its publication.
	14	A procedure for updating the guideline is provided.
4 Clarity of Presentation	15	The recommendations are specific and unambiguous.
	16	The different options for management of the condition or health issue are clearly presented.
	17	Key recommendations are easily identifiable.
5 Applicability	18	The guideline describes facilitators and barriers to its application.
	19	The guideline provides advice and/or tools on how the recommendations can be put into practice.
	20	The potential resource implications of applying the recommendations have been considered.
	21	The guideline presents monitoring and/or auditing criteria.
6 Editorial Independence	22	The views of the funding body have not influenced the content of the guideline.
	23	Competing interests of guideline development group members have been recorded and addressed.

Overall Guideline Assessment	1	Rate the overall quality of this guideline.
	2	I would recommend this guideline for use.

Specialist in liver cancer			Specialist in other area			Overall		
Points	Rate of agreement	Score by domain	Points	Rate of agreement	Score by domain	Points	Rate of agreement	Score by domain
15	67%	72 %	17	78 %	70 %	32	72 %	71 %
21	100%		19	89%		40	94 %	
12	50%		11	44 %		23	47%	
20	94%	83%	15	67%	61%	35	81%	72%
14	61%		9	33%		23	47%	
20	94%		18	83%		38	89%	
14	61%	78%	12	50%	76%	26	56%	77%
14	61%		14	61%		28	61%	
18	83%		16	72%		34	78%	
19	89%		19	89%		38	89%	
16	72%		15	67%		31	69%	
15	67%		16	72%		31	69%	
21	100%		21	100%		42	100%	
19	89%		21	100%		40	94%	
19	89%	83%	14	61%	76%	33	75%	80%
15	67%		16	72%		31	69%	
20	94%		20	94%		40	94%	
15	67%	42%	11	44%	44%	26	56%	43%
18	83%		16	72%		34	78%	
6	17%		11	44%		17	31%	
3	0%		6	17%		9	8%	
19	89%	78%	19	89%	75%	38	89%	76%
15	67%		14	61%		29	64%	
17	78%		16	72%		33	75%	
Yes		2	Yes		1	Yes		3
Yes, with modification		1	Yes, with modification		2	Yes, with modification		3
No		0	No		0	No		0

Figure 1. Domain-based scoring



242 External review of the Clinical Practice Guidelines for Liver Cancer 2017

Scope and Purpose

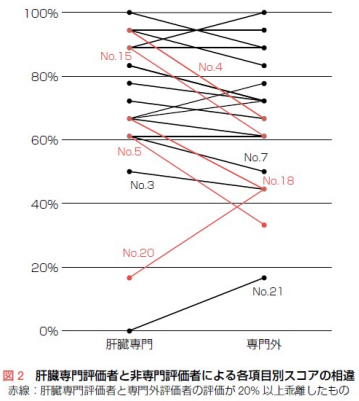
Editorial Independence Stakeholder Involvement

Applicability Rigour of Development

Clarity of Presentation

Figure 2. AGREE II items scored differently by hepatologists and non-hepatologists

Red lines indicateI items with ≥ 20% difference in scores.



Hepatologists Non-hepatologists