General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Nationwide Follow-Up Survey and Clinical Practice Guidelines: The Outstanding Achievements of the Liver Cancer Study Group of Japan

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Introduction

As for other cancers, general rules and clinical practice guidelines have been developed for hepatocellular carcinoma (HCC). Historically, the general rules for HCC have been published by the Liver Cancer Study Group of Japan (LCSGJ), under the title ‘General Rules for the Clinical and Pathological Study of Primary Liver Cancer’. After the publication of the first edition on June 20, 1983, subsequent editions were published in 1987 (2nd edition), 1992 (3rd edition), 2001 (4th edition) and 2008 (5th edition), followed by a revision of the current fifth edition on July 7, 2009 [1, 2]. The sixth edition is scheduled for publication in 2015. While the general rules for other cancers have been compiled primarily by the respective large medical societies, the general rules for primary liver cancer were published by the LCSGJ.

In terms of the clinical practice guidelines for HCC, the Clinical Practice Guidelines Committee for Liver Cancer (Chairman, Dr. Masatoshi Makuuchi), sponsored by the Ministry of Health, Labour and Welfare, played a central role in establishing the first edition of the Evidence-based Clinical Practice Guidelines for HCC in 2005. The committee consisted mainly of executive council members of the LCSGJ. Thereafter, the Japan Society...
of Hepatology (JSH) sponsored the publication of the second edition of the guidelines in 2009 and the latest edition in 2013 [3]. JSH also published the first and second editions of the Clinical Practice Manual for HCC, ‘Management of Hepatocellular Carcinoma in Japan: Consensus-Based Clinical Practice Manual’ in 2007 and the revised version in 2010, respectively [4, 5]. The third edition was published in 2015 [6, 7]. This manual is useful as it incorporates recommendations with a high level of evidence that are presented in the aforementioned Evidence-based Clinical Practice Guidelines for HCC [8–10], while also explaining diagnoses and treatments relevant to routine clinical settings that are in line with expert opinion and consensus.

**General Rules for the Clinical and Pathological Study of Primary Liver Cancer**

The first edition of General Rules for the Clinical and Pathological Study of Primary Liver Cancer was published to provide physicians specializing in liver cancer with specific terminology and abbreviations for noting the macroscopic findings of HCC, tumor stage, pathological findings, important terminology and the accompanying cirrhosis state and also for enabling discussions using ‘common language’. Every time a subsequent edition was published, the TNM classification system became unique to Japan, and owing to advances in pathological studies, the definition of pathological early well-differentiated HCC [11] was clearly stated already in the third edition published in 1992. Moreover, Japan has adopted the liver damage to reflect degree of liver functional reserve, instead of the Child-Pugh classification, which is a global standard. This unique approach has arisen because the indocyanine green retention test is frequently performed before surgical resection in Japan. In that sense, liver damage is more of an HCC-oriented liver functional reserve classification than Child-Pugh classification, where the latter was originally developed to predict the prognosis of cirrhotic patients [12, 13].

With the publication of the General Rules for the Clinical and Pathological Study of HCC and Intrahepatic Cholangiocarcinoma in Japanese and English, unique advances have been made. The TNM classification of HCC and intrahepatic cholangiocarcinoma is easy to remember and judge because the staging of T1–T4 tumors involves only 3 criteria: <2 or ≥2 cm, the presence or absence of vascular invasion and single or multiple tumors (Table 1). This innovative staging system is again unique to Japan and differentiates itself from the TNM classification system used worldwide that was developed by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer. A study that used the TNM classification systems proposed by the LCSGJ and the UICC to examine Japanese patients showed that the former system allowed for more accurate stratification [14]. This also demonstrates that Japan’s General Rules for the Clinical and Pathological Study of Primary Liver Cancer have developed in a unique way.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T factor (fulfilling T factors)</th>
<th>N</th>
<th>M</th>
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<tr>
<td>I</td>
<td>T1 (fulfilling 3 T factors)</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>II</td>
<td>T2 (fulfilling 2 T factors)</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>III</td>
<td>T3 (fulfilling 1 T factors)</td>
<td>N0</td>
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<tr>
<td>IV-A</td>
<td>T4 (fulfilling 0 T factors)</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>IV-B</td>
<td>Any T N0–1 M1</td>
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T factor: (1) single, (2) <2 cm and (3) no vascular involvement.
ing the treatment response of HCC. Therefore, the LCSGJ has developed unique criteria to evaluate the direct treatment effects by locoregional therapies such as ablation or TACE. However, following recent advances in systemic chemotherapy using the molecular targeted agent, sorafenib, the fifth edition was revised to include the response evaluation of systemic therapy and was re-issued under the title ‘Response Evaluation Criteria in Cancer of the Liver’ (RECICL) [25] in order to apply the criteria and to evaluate the outcome of systemic chemotherapy.

The forthcoming sixth edition of the general rules in 2015 will include the revision of the TNM classification system for intrahepatic cholangiocarcinoma, descriptions of lymph node metastasis and HCC rupture and more sophisticated revised response evaluation criteria, namely, RECICL version 1.1 [26]. These revisions will also improve the descriptions used in the follow-up survey, thus making all the revision efforts worthwhile.

**Clinical Practice Guidelines**

The essential elements of the Evidence-Based Clinical Practice Guidelines for Liver Cancer are the surveillance, diagnostic and treatment algorithms for HCC. The guidelines also cover prevention, diagnosis, surveillance, surgery, ablation therapy, TACE, systemic chemotherapy [27, 28], radiation therapy [29, 30], post-treatment follow-up, prevention of recurrence after curative treatment.
Extrahepatic spread

Liver function

Vascular invasion

Number

Size

Treatment

• Intensive follow-up
• Ablation

• Resection
• TACE
• TACE + Ablation

• TACE
• HAIC
• Resection
• Ablation

• HAIC (Vp1–4)
• Sorafenib (Vp1–3)
• TACE (Vp1,2)
• Resection (Vp1,2)

• Transplantation
• TACE/Ablation for Child-Pugh C pts

Palliative care

Sorafenib

Fig. 2. JSH-LCSGJ consensus-based treatment algorithm for HCC revised in 2014. 1. Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. 2. Sorafenib is the first choice of treatment in this setting as a standard of care. 3. Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (1) when the nodule is diagnosed pathologically as early HCC; (2) when the nodules show decreased uptake on hepatocyte phase Gd-EOB-MRI; (3) when the nodules show decreased portal flow by CTAP or (4) decreased uptake is shown on Kupffer phase of Sonazoid enhanced US, since these nodules are known to frequently progress to the typical hypervascular HCC. 4. Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated. 5. Transcatheter arterial chemoembolization (TACE) is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (HAIC) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5FU + CDDP) or intraarterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also a treatment of choice for TACE refractory patients with Child Pugh A liver function. 6. Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. 7. Milan criteria: Tumor size <3 cm and tumor numbers <3; or solitary tumor <5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. 8. Sorafenib and HAIC are recommended for HCC patients with Vp1,2 (minor portal vein invasion), Vp3 (portal invasion at the 1st portal branch), whereas HAIC is recommended for such patients with tumor thrombus in the main portal branch. 9. Resection and TACE is frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the 3rd or more peripheral portal branch) or Vp2 (portal invasion at the 2nd portal branch). 10. Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (<3.0 mg/dl). Although it is as a well accepted treatment in the routine clinical setting, there is no evidence of its survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child-Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments.
and treatment for recurrence. These issues are introduced in a ‘Clinical Questions’ format, in which questions routinely asked in daily clinical practice are answered based on facts with a high level of evidence that are reported in scientific articles selected during an extensive review of the literature. Evidence levels and recommended grades are listed to assist the diagnosis and treatment of HCC in daily clinical practice. The surveillance and diagnostic algorithm, the most important part of the clinical practice guidelines, recommends regular ultrasound and tumor marker screening using 3 markers (AFP, AFP-L3 and PIVKA-II) [31–33] or annual-to-semiannual CT or MRI depending on whether the patients are categorized as very high-risk or high-risk patients. The treatment algorithm presents treatment strategies that are in line with the severity of liver damage and the number and size of tumors [8, 9]. The 2013 edition states that the Child-Pugh classification can be used when non-surgical therapy is applied [3, 10].

But, it should be noted that, since the consensus-based surveillance and diagnostic algorithm is relatively complex, it is scheduled to be simplified considerably in the 2015 edition (fig. 1) [7]. This was the results of consensus meeting at the 50th Annual Meeting of LCSGJ (Congress President: Prof. Masatoshi Kudo). In addition, the proposed treatment algorithm provides extremely useful guidance for daily clinical practice because it contains a list of practical treatment strategies that are being performed in accordance with current treatment policies developed based on expert opinion and consensus (fig. 2). The criteria for TACE failure/refractoriness were also included in the third edition of the guidelines (table 2) [34].

It was revealed at the 48th LCSGJ Congress (Congress President, Prof. Osamu Matsui, Kanazawa University) [35] that over 90% of physicians specializing in liver cancer who diagnose and treat liver cancer refer to the JSH’s Evidence-based Clinical Practice Guidelines for HCC or Consensus-based Clinical Practice Guidelines for HCC. This indicates how well these guidelines complement each other and assist in optimizing diagnosis and treatment of liver cancer in Japan.

### Conclusion

This review outlines the significance of establishing general rules, a nationwide follow-up survey and clinical practice guidelines for liver cancer in Japan. The general rules are an essential part of HCC treatment, enabling a ‘common language’ to be used in daily clinical practice and for the nationwide follow-up survey. The Japanese General Rules for the Clinical and Pathological Study of Primary Liver Cancer [2], which provide detailed descriptions of HCC, are excellent and are unique to Japan. Items in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer are used substantially in another important project, the Nationwide Follow-Up Survey of Primary Liver Cancer which has been rigorously undertaken with great effort by the LCSGJ biannually since 1969.

Both the evidence-based and consensus-based treatment algorithms for HCC are used to complement each other in clinical practice in Japan. The most important point going forward is that prospective clinical trials are needed to accumulate solid evidence for the recommendations proposed in the consensus-based treatment algorithm, which are not included in the evidence-based clinical practice guidelines because of the lack of such evidence. In fact, clinical trials are now looking for evidence, and include the SURF trial (UMIN No. UMIN000001795), SILIUS trial (NCT Trial No. 01214343), TACTICS trial (NCT Trial No. 01217034) and DELICATE trial. Their results are eagerly awaited.

### Disclosure Statement

The authors declare that they have no conflict of interest.
References