Clinics in Oncology

Limitation of Modified RECIST - Two Hepatocellular Carcinoma Cases Achieving Radiological Response Incompatible with Histopathological Analysis

Soo Ki Kim[1], Takako Fujii[1]*, Hisato Kobayashi[2], Soo Ryang Kim[1], Yu-ichiro Koma[3], Tsutomu Kumabe[4], Osamu Nakashima[5] and Takamichi Murakami[6]

[1]Department of Gastroenterology, Kobe Asahi Hospital, Japan

[2]Department of Radiology, Kobe Asahi Hospital, Japan

[3]Department of Pathology, Kobe University Graduate School of Medicine, Japan

[4]Kumabe Clinic, Japan

[5]Department of Clinical Laboratory Medicine, Kurume University Hospital, Japan

[6]Department of Radiology, Kobe University Graduate School of Medicine, Japan

Abstract

We encountered two cases of Hepatocellular Carcinoma (HCC) treated with molecular-targeted therapy such as Lenvatinib (LEN), assessed as complete responders through radiological evaluation with Contrast Enhanced Computer Tomography (CECT) and gadolinium Contrast Enhanced Magnetic Resonance Imaging (CEMRI) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). Nonetheless, the response was incompatible with histopathological analysis.

In both cases, more than 6 weeks of post-LEN treatment, CECT and CEMRI revealed complete absence of intratumoral arterial contrast enhancement; however, ultrasound guided biopsy revealed moderately differentiated HCC with or without coagulation necrosis.

Subsequent to the total absence of intratumoral arterial contrast enhancement, MRI revealed hyper intensity on Diffusion-Weighted Imaging (DWI) and hypointensity on the Apparent Diffusion Coefficient (ADC) -map.

mRECIST depends on only complete absence of intratumoral arterial enhancement, and has limitations in tumor response assessment of post-molecular-targeted therapy.

MRI on DWI and ADC-map may be useful and more effective when complemented with mRECIST in order to improve the diagnostic accuracy and viability of HCC.

Keywords: Modified RECIST; Complete response; Coagulation necrosis; Molecular-targeted therapy; Diffusion-weighted imaging

Introduction

In 2010, modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria were recommended as a method of adapting the RECIST criteria to the particularities of Hepatocellular Carcinoma (HCC) [1-7]. They were aimed at correcting some limitations of RECIST in measuring tumor shrinkage with local and systemic treatments, and to refine the assessment of progression that could be misconstrued under routine RECIST [1-4], due to clinical events related to the clinical course of chronic liver disease (appearance of ascites, enlargement of lymph nodes, etc.) [8-11]. mRECIST has used well since being used or included in clinical practice guidelines (European, American and Asian) for the management of HCC. With molecular-targeted therapy at advanced stages of HCC, guidelines propose the use of both methods. mRECIST has been proven to capture high Objective Response (OR) rates in tumors treated with molecular-targeted therapy and those rates have been independently related to better prognosis [8-11].

According to mRECIST criteria used for the assessment of HCC treatment with molecular-targeted procedures, complete absence of intratumoral arterial contrast enhancement found with the use of Contrast Enhanced Computed Tomography (CECT) or by gadolinium Contrast Enhanced Magnetic Resonance Imaging (CEMRI) clarifies tumor necrosis and indicates Complete

Response (CR) [8-11].

Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth receptors 1-3, fibroblast growth factors 1-4, platelet-derived growth factor receptor-α, RET, and KIT [12,13].

Data from the REFLECT study of LEN versus sorafenib was statistically evidenced by non-inferiority Overall Survival (OS) [14-16].

We experienced two HCC patients administered molecular-targeted therapy LEN, evaluated as CR through radiological evaluation with mRECIST, but incompatible with histological analysis.

Case Presentation

Case 1

History of past illness: An 82-year-old woman who had been treated with Pegylated interferon for hepatitis C virus infection had achieved sustained virological response 10 years earlier, demonstrated Child-Pugh class A Liver Cirrhosis (LC).

Imaging examination: In 2019 CEMRI revealed several HCC nodules up to 4.5 cm in both lobes (Figure 1A). Pre-LEN treatment, MRI on DWI (b value = 200 s/mm^2) revealed hyper intensity (Figure 1B) and hypointensity on ADC-map (ADC measurements = 0.995 × 10^{-3} mm^2/sec) in both lobes (diffusion restricted).

CECT 7 week's post-LEN treatment and CEMRI 11 weeks post-treatment revealed complete absence of intratumoral arterial contrast enhancement in all nodules (Figure 1C). Additionally, 11 weeks post-LEN treatment, subtraction imaging by CEMRI revealed no enhancement.

Eleven weeks post-LEN treatment, MRI on DWI (b value = 1200 s/mm^2) revealed hyper intensity, and hypointensity on ADC-map (ADC measurements = 0.873 × 10^{-3} mm^2/sec) in all nodules (diffusion restricted), and MRI on DWI revealed shrinkage of tumors in all nodules: the nodule in S2 shrank from 4.5 cm to 3 cm, and that in S5 from 2.1 cm to 1.5 cm (Figure 1D).

Laboratory examination: Seven weeks post-oral administration of LEN at 8 mg/day, Alpha-Fetoprotein (AFP) decreased from 30333 ng/ml to 13460 ng/ml.

Histopathological examination: At the start of LEN treatment, Ultrasound (US) guided biopsy revealed moderately differentiated HCC with trabecular structure and coagulation necrosis in specimens obtained from Segment (S) 2 (4.5 cm) (Figure 2A), and moderately differentiated HCC with trabecular structure without coagulation necrosis in specimens obtained from S5 (2.1 cm) (Figure 2B).

Eleven weeks post-treatment, US guided biopsy revealed moderately differentiated HCC and coagulation necrosis in specimens obtained from S2 and S5 (Figure 2C).

Outcome: LEN was interrupted at 12 weeks of administration due to adverse events. CECT revealed several recurrent hyper vascular HCC nodules in both lobes 2 weeks post-LEN discontinuation (Figure 1E).

Case 2

History of past illness: Hepatitis B virus related LC in a 59-year-
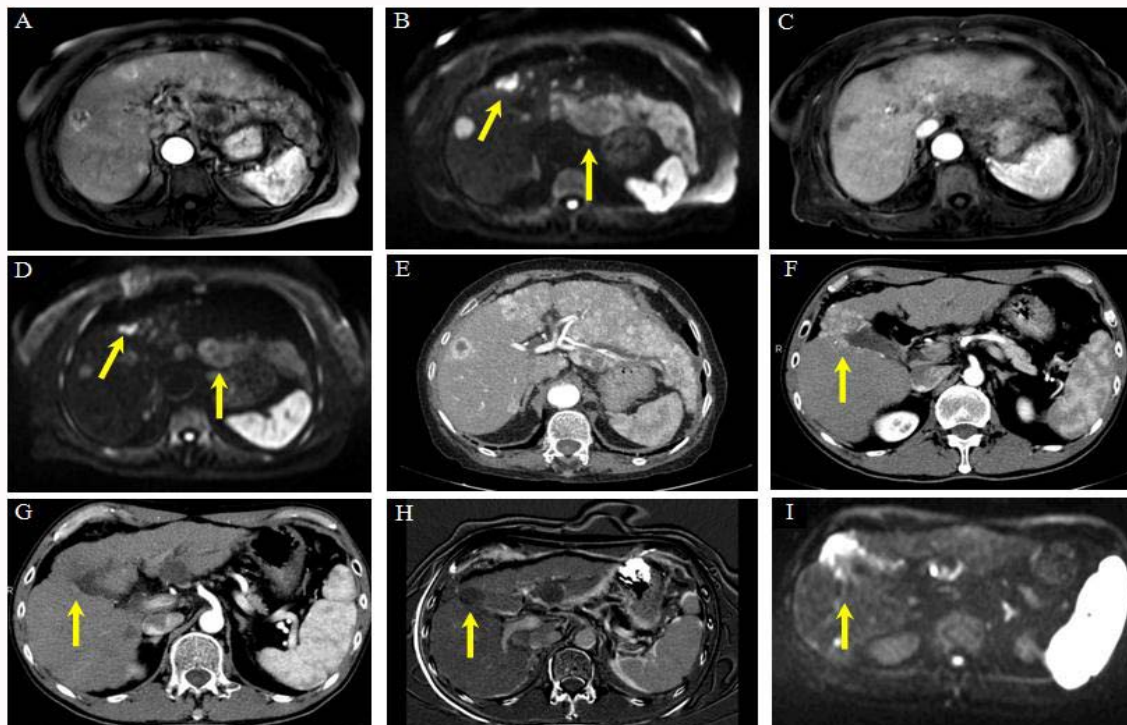

Figure 1: Case 1: (A) Pre-LEN treatment: CEMRI reveals several hyper vascular HCC nodules in both lobes. (B) Pre-LEN treatment: MRI on DWI reveals hyper intensity (diffusion restricted). Arrows indicate a 4.5 nodule in S2 and a 2.1 cm nodule in S5. (C) Eleven weeks post-LEN treatment: CEMRI reveals total absence of intratumoral arterial contrast enhancement. (D) Eleven weeks post-LEN treatment: MRI on DWI reveals hyper intensity (diffusion restricted) and tumor shrinkage. Arrows indicate a 3 cm nodule in S2 and a 1.5 cm nodule in S5. (E) CECT reveals several recurrent hyper vascular HCC nodules in both lobes (2 weeks post-LEN discontinuation). Case 2: (F) Pre-LEN treatment: CECT reveals several hyper vascular HCC nodules in S4 and S5. (G) Ten weeks post-LEN treatment: CECT reveals complete absence of intratumoral arterial contrast enhancement. (H) Ten weeks post-LEN treatment: CECT including subtraction imaging reveals no enhancement. (I) Ten weeks post-LEN treatment: MRI on DWI reveals hyper intensity (diffusion restricted).
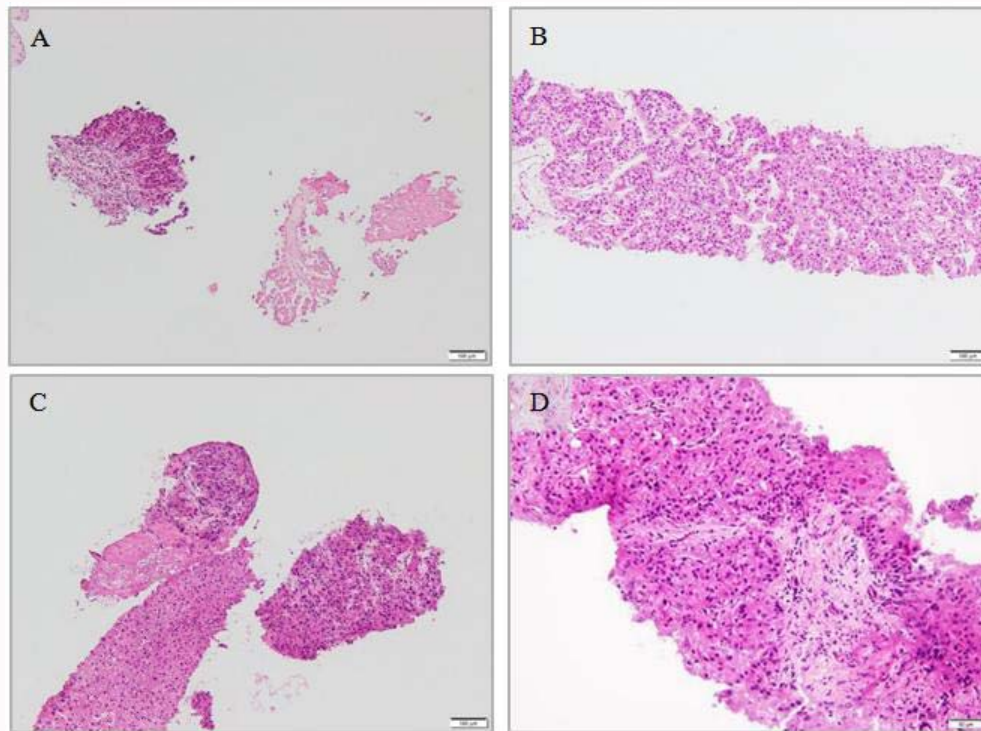
Figure 2: Case 1: (A) Pre-LEN treatment: Specimen obtained from S2 reveals moderately differentiated HCC with trabecular structure and coagulation necrosis (HE staining). (B) Pre-LEN treatment: Specimen obtained from S5 reveals moderately differentiated HCC with trabecular structure and without coagulation necrosis (HE staining). (C) Eleven weeks post-LEN treatment: Specimen obtained from S5 reveals moderately differentiated HCC and coagulation necrosis (HE staining). Case 2: (D) Ten weeks post-LEN treatment: Specimen obtained from S5 reveals moderately differentiated HCC with fibrous stroma. No coagulation necrosis is observed (HE staining).

old man had been controlled with nucleotide analogue such as tenofovir, and he remained in Child-Pugh class A LC state.

Imaging examination: In 2019 CECT (Figure 1F) and CEMRI disclosed several HCC nodules up to 1 cm in S4 and S5. Pre-LEN treatment MRI on DWI (b value = 800 s/mm^2) revealed hyper intensity and hypointensity on ADC-map (ADC measurements = 1.017×10^{-3} mm^2/sec) in all nodules in S4 and S5 (diffusion restricted).

Laboratory examination: Pre-LEN treatment, the AFP level which stood at 53.2 ng/ml decreased to 9.2 ng/ml 6 weeks post-treatment with LEN administered orally at 12 mg/day.

Further diagnostic work-up: CECT 10 weeks post-LEN treatment (Figure 1G), and CEMRI 7 weeks post-LEN treatment revealed complete absence of intratumoral arterial contrast enhancement in all nodules in S4 and S5. Additionally, CECT including subtraction imaging 10 weeks post-LEN treatment, and CEMRI including subtraction imaging 7 weeks post-LEN treatment revealed no enhancement (Figure 1H).

Histopathological examination: Nonetheless, US guided biopsy 10 weeks post-LEN treatment, revealed moderately differentiated HCC with fibrous stroma in specimens obtained from S5. No necrosis was observed in these specimens (Figure 2D).

Outcome: Ten weeks post-LEN treatment, MRI on DWI (b value = 1200 s/mm^2) revealed hyper intensity (Figure 1I) and hypointensity on ADC-map (ADC measurements = 1.052×10^{-3} mm^2/sec) in all nodules (diffusion restricted).

Discussion

The RECIST criteria are evaluated the standard method for tumor response assessment in clinical settings. Specifically, they obtain the impact on survival outcome in patients with solid tumors [5-7].

The mRECIST guideline clarifies response as complete absence of any intratumoral arterial enhancement [1-4]. A change from hypervascularity to hypovascularity does not denote tumor necrosis. Reduced arterial perfusion, either involving the whole tumor mass or circumscribed to intratumoral areas, must be carefully differentiated from necrosis [8-11].

As in clinical radiological practice, subtraction imaging or quantitative determinations of contrast uptake obtained by comparing related regions of interest measurements on pre-contrast and post-contrast scans can serve, whenever considered appropriate, to support the assessment.

In the present study, biopsy samples of all the nodules assessed radiologically as "CR" in cases 1 and 2 were found to include viable HCC cells by histopathological evaluation.

Ten (case 2) and 11 weeks (case 1) post-LEN treatment, viable HCC cells were detected through histopathological analysis, irrespective of the complete absence of intratumoral arterial contrast enhancement as ascertained through imaging studies with CECT and CEMRI including subtraction imaging. In the assessment of HCC treatment, any discrepancy between radiological and histopathological findings should be noted.

In case 1, histopathological analysis disclosed necrosis, to some extent, 11 weeks post-LEN treatment. Indeed, MRI on DWI displayed shrinkage of HCC in S2 (from 4.5 cm to 3 cm) and in S5 (from 2.1 cm to 1.5 cm). In case 2, however, despite precise histopathological

analysis, no necrosis was observed 10 weeks post-LEN treatment, which might be attributed to the limitations of the biopsy sample.

In case 1 pre-LEN treatment, necrosis in S2 indicated spontaneous necrosis attributed to ischemia by the large (4.5 cm) HCC. Post-LEN treatment, the necrosis evinced spontaneous or treatment-induced necrosis, or both. The necrosis in S5 post-LEN treatment indicated treatment-induced necrosis, because no necrosis was observed pre-LEN treatment.

Based on the radiological and histopathological findings of case 1, two hypotheses regarding the outcome of HCC viability and treatment efficacy need to be considered. First, if treatment continues for a long time beyond 7 to 11 weeks, total necrosis could occur. Second, radiological assessment with mRECIST is useful to some extent; however, it does not necessarily reflect the real efficacy of the treatment.

Some cases have revealed tumor reperfusion when LEN is discontinued; therefore, staining criteria should be carefully assessed in treatment with LEN. Although a good early response has been reported, Progressive Disease (PD) often follows post-LEN discontinuation. Based on these findings, the authors have suggested that additional studies are required to identify the optimal time point for evaluating a radiological response [17-20]. That observation and the recurrence of HCC confirmed by CECT 2 week's post-LEN discontinuation in case 1 support our second hypothesis.

The discrepancy between a good early response and PD post-LEN discontinuation cannot be explained without the histopathological studies that the authors did not implement.

Of note is that the arterial phase (bi- or tri-phasic dynamic imaging technique), although not served for density measurement, is also requisite for optimizing the visualization of all tumors and to record changes in tumor vascularity and the pattern of enhancement pre- and post-LEN treatment. It is also suggested that such an evaluation tool is also useful for liver tumors [21,22].

Three criteria have been studied regarding radiological response on survival in patients with HCC treated with LEN.

OS and OR are assessed under three different criteria - RECIST, m-RECIST, and Choi criteria - that have been described as useful therapeutic evaluation methods in LEN treatment of unresectable HCC. The precise evaluation of the effect and follow-up of LEN treatment might lead to a better prognosis [17-20].

In our two cases, although CECT and CEMRI including subtraction imaging evinced complete absence of intratumoral arterial contrast enhancement, MRI revealed hyper intensity on DWI and hypointensity on ADC-map.

Recommended clinical uses of DWI include: Assessing prognosis, predicting response, monitoring response to treatment, and differentiating tumor recurrence from treatment effect. Ideally, DWI would help high-risk patients and would play a role in prognostic modeling [23-26].

In clinical settings the main merit of DWI is heightening confidence in the diagnosis of HCC, especially when intravenous administration of contrast mediums is not possible or when small tumors are attached to vessels [23-26].

Moreover, tumor hyper intensity on DWI and hypointensity on ADC-map (diffusion restricted) are thought to be ancillary features of

malignant character according to LI-RADS (Liver Imaging Reporting and Data System) [27-30].

Conclusion

mRECIST depends on only complete absence of intratumoral arterial enhancement, as assessed by CECT and CEMRI, and has limitations in tumor response assessment of post-molecular-targeted therapy.

MRI on DWI and ADC-map may be important and more effective when complemented with mRECIST in order to improve the diagnostic accuracy and viability of HCC.

References

1. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.

2. Bogaerts J, Ford R, Sargent D, Schwartz LH, Rubinstein L, Lacombe D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. Eur J Cancer. 2009;45(2):248-60.

3. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711.

4. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer. 2009;115(3):616-23.

5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205-16.

7. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35(3):421-30.

8. Lencioni R, Montal R, Torres F, Park JW, Decaens T, RaoulJL, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. J Hepatol. 2017;66(6):1166-72.

9. Llovet JM, Montal R, Villanueva A. Randomized trials and endpoints in advanced HCC: Role of PFS as a surrogate of survival. J Hepatol. 2019;70(6):1262-77.

10. Llovet JM, Lencioni R. mRECIST for HCC: Performance and novel refinements. J Hepatol. 2020;72(2):288-306.

11. Vincenzi B, Di Maio M, Silletta M, D'Onofrio L, Spoto C, Piccirillo MC, et al. Prognostic relevance of objective response according to EASL criteria and mRECIST criteria in hepatocellular carcinoma patients treated with loco-regional therapies: A literature-based meta-analysis. PLoS One. 2015;10(7):e0133488.

12. Matsui J, Yamamoto Y, Funahashi Y, Tsuruoka A, Watanabe T, Wakabayashi T, et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer. 2008;122(3):664-71.

13. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of Vascular Endothelial Growth Factor-Receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res. 2008;14(17):5459-65.

14. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, et al. Antitumor activity of lenvatinib (e7080): An angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res. 2014;2014:638747.

15. Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.

16. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163-73.

17. Kaneko S, Tsuchiya K, Kurosaki M, Kirino S, Inada K, Yamashita K, et al. Three criteria for radiological response on survival in patients with hepatocellular carcinoma treated with lenvatinib. Hepatol Res. 2020;50(1):137-43.

18. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-Multicenter analysis. Cancer Med. 2019;8(8):3719-28.

19. Ikeda M, Kobayashi M, Tahara M, Kaneko S. Optimal management of patients with hepatocellular carcinoma treated with lenvatinib. Expert Opin Drug Saf. 2018;17(11):1095-105.

20. Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Itobayashi E, Shimada N, et al. Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: Multicenter analysis. Hepatol Res. 2019;49(1):111-7.

21. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: Proposal of new computed tomography response criteria. J Clin Oncol. 2007;25(13):1753-9.

22. Choi H, Charnsangavej C, Faria SC, Tamm EP, Benjamin RS, Johnson MM, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: A quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol. 2004;183(6):1619-28.

23. Gluskin JS, Chegai F, Monti S, Squillaci E, Mannelli L. Hepatocellular carcinoma and diffusion-weighted MRI: detection and evaluation of treatment response. J Cancer. 2016;7:1565-70.

24. Sugahara T, Korogi Y, Kochi M, Ikushima I, Shigematu Y, Hirai T, et al. Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. J Magn Reson Imaging. 1999;9(1):53-60.

25. Park MS, Kim S, Patel J, Hajdu CH, Do RKG, Mannelli L, et al. Hepatocellular carcinoma: Detection with diffusion-weighted versus contrast-enhanced magnetic resonance imaging in pretransplant patients. Hepatology. 2012;56(1):140-8.

26. Xu PJ, Yan FH, Wang JH, Shan Y, Ji Y, Chen CZ. Contribution of diffusion-weighted magnetic resonance imaging in the characterization of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver. J Comput Assist Tomogr. 2010;34:506-12.

27. Chernyak V, Fowler KJ, Kamaya A, Kielar AZ, Elsayes KM, Bashir MR, et al. Liver Imaging Reporting and Data System (LI-RADS) version 2018: Imaging of hepatocellular carcinoma in at-risk patients. Radiology. 2018;289(3):816-30.

28. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-50.

29. Fowler KJ, Potretzke TA, Hope TA, Costa EA, Wilson SR. LI-RADS M (LR-M): Definite or probable malignancy, not specific for hepatocellular carcinoma. Abdom Radiol (NY). 2018;43:149-57.

30. Chernyak V, Santillan CS, Papadatos D, Sirlin CB. LI-RADS° algorithm: CT and MRI. Abdom Radiol (NY). 2018;43:111-26.