New approaches for precise response evaluation in hepatocellular carcinoma

Koichi Hayano, Jorge M Fuentes-Orrego, Dushyant V Sahani

Abstract
With the increasing clinical use of cytostatic and novel biologic targeted agents, including World Health Organization criteria and Response Evaluation Criteria in Solid Tumors, are confronting limitations because of their difficulties in distinguishing viable tumor from necrotic or fibrotic tissue. Therefore, the investigation for reliable quantitative biomarkers of therapeutic response such as metabolic imaging or functional imaging has been desired. In this review, we will discuss the conventional and new approaches to assess tumor burden. Since targeted therapy or locoregional therapies can induce biological changes much earlier than morphological changes, these functional tumor burden analyses are very promising. However, some of them have not gone thorough all steps for standardization and validation. Nevertheless, these new techniques and criteria will play an important role in the cancer management, and provide each patient more tailored therapy.

INTRODUCTION
Accurate assessment of tumor burden is an important component of cancer patient management and the investigation of new therapies. Traditionally, therapeutic response has been assessed by serial tumor size measurements according to World Health Organization criteria or Response Evaluation Criteria in Solid Tumors (RECIST)\textsuperscript{1-3}. These criteria, which are based on anatomical measurement, are well established tool, and easy to

Correspondence to: Dushyant V Sahani, MD, Division of Abdominal Imaging and Intervention, Department of Radiology, Massachusetts General Hospital, 55 Fruit St, White 270, Boston, MA 02114, United States. dsahani@partners.org
Telephone: +1-617-7268361 Fax: +1-617-7264891
Received: September 28, 2013 Revised: November 26, 2013
Accepted: January 6, 2014
Published online: March 28, 2014

Key words: Hepatocellular carcinoma; World Health Organization criteria; Response Evaluation Criteria in Solid Tumors; European Association for the Study of Liver; Computed tomography perfusion; Dynamic contrast-enhanced-magnetic resonance imaging; Diffusion-weighted imaging; Positron emission tomography

INTRODUCTION
Accurate assessment of tumor burden is an important component of cancer patient management and the investigation of new therapies. Traditionally, therapeutic response has been assessed by serial tumor size measurements according to World Health Organization (WHO) criteria or Response Evaluation Criteria in Solid Tumor (RECIST)\textsuperscript{1-3}. These criteria, which are based on anatomical measurement, are well established tool, and easy to
apply for assessment of tumor burden. However, these morphological evaluations have substantial limitations, including the presence of tumors that cannot be measured, poor measurement reproducibility and mass lesions of unknown activity that persist following therapy\(^3\). They also have a difficulty in distinguishing viable tumor from necrotic or fibrotic tissue and recognizing the delay between cell kill and tumor shrinkage. Faced with these limitations, more sophisticated measurements (including tumor volume and lesion regression rates) have been applied to the evaluation of the tumor response to therapy.

With the increasing clinical use of cytostatic and novel biologic targeted agents or locoregional therapies (LRTs) such as ablation and transarterial chemoembolisation (TACE) in the management of hepatocellular carcinoma (HCC), it has become increasingly recognized that new methods of therapy assessment need to be developed urgently. For example, antiangiogenic agents are known to rapidly decrease contrast enhancement on computed tomography (CT)/magnetic resonance imaging (MRI) scans that occur within days of initiation of reduced vascular permeability to contrast agents rather than a true antitumor effect\(^6\). Faced with these limitations, the investigation for reliable quantitative biomarkers to assess tumor burden and therapeutic response including blood surrogate parameters, metabolic imaging and functional imaging based on CT, MRI, or positron emission tomography (PET) has been desired\(^4-7\). In this review, we discuss various conventional and new approaches to determine tumor burden in the current clinical practice of HCC.

MORPHOLOGIC TUMOR BURDEN ANALYSIS

In 1981, the WHO first published tumor response criteria, mainly for use in trials where tumor response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumor burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment. Subsequently, RECIST was introduced and approved for clinical use in 2000\(^9\). RECIST criteria were primarily conceived to provide specific guidelines for tumor burden measurement. After extensive experience and validation in several chemotherapeutic trials in solid tumors, it was revised in 2009 as RECIST 1.1\(^8\). RECIST 1.1 relies on the measurement of a maximum of five target lesions, not exceeding two per organ; subsequently, the sum of the greatest diameters is recorded followed by a final classification\(^9\). On the other hand, it has been questioned if these unidimensional measurements can reflect total tumor burden accurately. With the advent of imaging technologies such as workstation and 3D software, longitudinal or oblique measurements readily can be determined, and tumor volumes can be computed algorithmically. Sohaib et al\(^10\) reported that CT volumetric measurements were accurate and reproducible in their phantom study. Welsh et al\(^10\) reported that RECIST might overestimate tumor burden compared with volumetric measurements in HCC and pancreatic cancer, and they concluded that volumetric analysis might be the preferred method to detect tumor progression. However, the practical clinical value of tumor volumetric analysis remains controversial. There is no consensus about the recommended volume equivalents converted from diameter thresholds, which can be effectively applied without sacrificing either reproducibility or sensitivity to tumor progression or partial response.

TUMOR BURDEN ANALYSIS ACCORDING TO VIABILITY AND DENSITY

Recent studies have demonstrated poor correlations between the clinical benefit provided by targeted therapy agents or LRTs and conventional morphologic tumor burden analysis\(^11-14\). Unlike cytotoxic agents that may induce rapid tumor shrinkage, targeted therapy agents are acknowledged to yield sustained tumor stabilization and delay tumor progression. For example, antiangiogenic agents can reduce tumor vascularization, provoke areas of necrosis, and sometimes cause cavitation in solid tumors. These peculiar features have been reported with bevacizumab, sorafenib, and sunitinib in HCC\(^15-18\). In addition, the main objective of all effective LRTs is to induce necrosis of the tumor regardless of the shrinkage of the lesion. Therefore, in 2000, a panel of experts on HCC of the European Association for the Study of Liver (EASL) amended the response criteria to take into account tumor necrosis induced by treatment\(^19\). In 2008, The American Association for the Study of Liver Disease developed a set of guidelines that included a formal modification of the response assessment based on the RECIST criteria and aimed to translate into the concept of viable tumor (tumoral tissue showing arterial uptake in the arterial phase of the contrast-enhanced imaging techniques), which are referred to as modified RECIST (mRECIST) criteria (Figure 1)\(^20,21\). These criteria are summarized in Table 1. Forner et al\(^21\) reported that overall response rates of 21.8% for RECIST criteria and 81.8% for EASL in 55 HCC patients treated with a variety of LRTs. Similar findings about overall response rates were reported by Keppke et al\(^23\) (RECIST 23%, WHO 26%, and necrotic area 59%), Riaz et al\(^23\) (RECIST 42.4%, WHO 42.4%, and EASL 70.2%), and Prajapati et al\(^23\) (RECIST 10.8%, WHO 4.1%, EASL 39.2%, and mRECIST 52.5%).

A question then arises which response criteria have the strong association with survival. Previous reports have shown that WHO, RECIST, and EASL responses are associated with improved survival\(^22,23\), but these studies didn’t make the comparison at a single time point. In the phase II study of brivanib in advanced HCC, mRECIST was able to demonstrate a higher response and disease control rate and longer time to progression.
than the WHO criteria\textsuperscript{[20]}. In a recent retrospective study of HCC patients treated with sorafenib, patients categorized as responder according to mRECIST had a longer overall survival (OS) than non-responder\textsuperscript{[27]}. Prajapati \textit{et al}\textsuperscript{[24]} reported that mRECIST and EASL had significant correlation with survival, whereas WHO and RECIST 1.1 had poor correlation. Another key issue is that radiological assessments with EASL and mRECIST can be carried out at an early time point, in comparison with WHO and RECIST\textsuperscript{[12,22,23]}. Therefore, response evaluation based on the concept of viable tumor may be valuable for making early decisions regarding further therapy.

The tumor density analysis based on contrast enhanced CT attenuation measurement can serve as an additional method for response assessment in solid tumors\textsuperscript{[28]}. Choi \textit{et al}\textsuperscript{[28]} reported that gastrointestinal stromal tumors treated with imatinib mesylate, reduced tumor density on the portal venous phase CT, which had a correlation with the tumor necrosis, or cystic or myxoid degeneration without changes in tumor size. The tumor density is measured by drawing a region of interest (ROI) circumscribing the boundary of the tumor in the portal venous phase\textsuperscript{[29]}. In gastrointestinal stromal tumors, a decrease in tumor Hounsfield units $> 15\%$ correlated with progression free survival\textsuperscript{[30]}. In HCC, a recent studies showed that tumor density measurement on the portal venous phase CT images was more sensitive than RECIST in detecting patients with longer time to progression after sunitinib therapy (Figure 2)\textsuperscript{[31]}.

### PERFESSIONAL ANALYSIS

As discussed earlier, the morphologic tumor burden assessment has a difficulty in distinguishing viable tumor from necrotic or fibrotic tissue because molecular targeted agents suppress tumor growth by downregulating angiogenesis without causing much morphologic change. In this sense, the investigation for reliable quantitative assessment of therapeutic response including blood surrogate parameters, metabolic imaging and functional imaging has been desired\textsuperscript{[24,33]}. Perfusion technique, which enables quantification of tumor vascularity by measuring the temporal changes in tissue density following intravenous contrast administration, are readily incorporated into the existing CT and MRI protocols that continue to provide the mainstay for anatomical imaging in oncol-

---

**Table 1  Summary of response criteria**

| WHO | RECIST 1.1 | EASL | mRECIST |
|-----|----------------|--------|---------|
| Complete response (CR) | Disappearance of all lesions | Disappearance of all lesions and pathologic lymph nodes | Disappearance of intratumoral arterial enhancement | Disappearance of all lesions and pathologic lymph nodes |
| Partial response (PR) | $\geq 50\%$ decrease in the sum of the area (longest diameters multiplied by longest perpendicular diameters) | $\geq 30\%$ decrease in the sum of the longest diameters | $\geq 50\%$ decrease in the sum of the arterial enhancing areas (longest diameters multiplied by longest perpendicular diameters) | At least a $30\%$ decrease in the sum of diameters viable (enhancing) target lesions, taking as reference the baseline sum of the target lesions |
| Stable disease (SD) | Neither PR nor PD | Neither PR nor PD | Neither PR nor PD | Neither PR nor PD |
| Progressive disease (PD) | $\geq 25\%$ increase in the sum of the area | $\geq 20\%$ increase in the sum of the longest diameters and $\geq 5$ mm absolute increase in the sum of the longest diameters | $\geq 25\%$ increase in the size of the arterial enhancing areas or development of a new lesions | $\geq 20\%$ increase in the sum of diameters of viable target lesions recorded since treatment started or development of new lesions |

WHO: World Health Organization; EASL: European Association for the Study of Liver; mRECIST: Modified Response Evaluation Criteria in Solid Tumors.
ogy\(^{[32]}\). Most scanners now come equipped with sophisticated hardware platforms coupled with powerful and user-friendly software packages for tissue perfusion analysis. Perfusion parameters are dependent on the scan protocol and the mathematical model for perfusion analysis\(^{[13,14]}\), but the commonly described perfusion CT parameters include blood flow (BF), blood volume (BV), mean transit time (MTT), and permeability surface area product (PS)\(^{[15,16]}\). Similarly for dynamic contrast-enhanced (DCE)-MRI, transfer constant (Ktrans) is the most accepted quantitative surrogate end point from compartment models\(^{[15-17]}\).

Several studies have demonstrated the value of perfusion imaging for monitoring the effect of antiangiogenic agents advocating various imaging tools in various solid tumors\(^{[14,15,39-43]}\). Several papers reported that BF or BV decreased even after 2 wk of antiangiogenic therapy (Figure 3)\(^{[15,40]}\). Moreover, perfusion imaging has a potential to be a biomarker of antiangiogenic therapy\(^{[34,41-43]}\). In perfusion CT, Jiang et al\(^{[40]}\) demonstrated that HCC with higher baseline MTT correlated with favorable clinical outcome. In DCE-MRI study of renal cell carcinoma, high baseline Ktrans and reduction in Ktrans after treatment were related to progression free survival (PFS)\(^{[15,42]}\).

In advanced HCC, DCE-MRI demonstrated reduction in Ktrans during antiangiogenic treatment and the change of Ktrans during treatment was related to better PFS and OS in clinical trials of tyrosine kinase inhibitors\(^{[14,17,43]}\). Considering the accessibility and availability, Perfusion CT is superior to DCE-MRI. However, relatively high radiation dose and limited coverage of the anatomy are two major draws backs of perfusion CT. Therefore, several efforts are being made with low dose scanning technique\(^{[34]}\). In addition, there is no consensus on a scanning protocol or a mathematical model in abdominal lesion. The definition of the tumor ROI and the acquisition time is also a subject to similar consideration\(^{[34,45]}\).

On the other hand, DCE-MRI has the advantage of lack of ionizing radiation, good spatial resolution and soft-tissue contrast. However, it is one of the most expensive and still technically challenging imaging modalities, requiring longer image acquisition times and provides smaller interscan reproducibility, as compared with CT\(^{[46,47]}\). DCE-MRI also lacks the standard protocol and the established response evaluation criteria.

Regardless of these limitations, perfusion technique must be a potentially powerful tool for HCC patient management, which may enable prediction or early detection of therapy responder.

**DIFFUSION-WEIGHTED MRI**

Molecular diffusion, or Brownian motion, was first formally described by Einstein\(^{[48]}\) in 1905. Various tissue types have unique diffusion characteristics, as measured by the apparent diffusion coefficient (ADC), which can be calculated by the diffusion-weighted imaging (DWI) measurements acquired with a different gradient duration and amplitude (b-values). The movement of water molecules in biological tissues within the body is typically limited by interactions with cell membranes macromolecules, and fibers in tissue compartments. Therefore, DWI has been suggested as a tool to distinguish different tissue compartments and detect changes in cellular tissue structures and viability, which could be used to monitor the response to treatment. DWI has been discussed as cancer biomarker in a consensus meeting and a publication on consensus and recommendations for DWI as a cancer biomarker has been published recently highlighting the potential of this promising technique in cancer patients\(^{[49]}\). In lung cancer, a previous study reported that ADC values differ based on histological type, which suggested a possible correlation between ADC values and tumor characteristics, such as histology, response to therapies and prognosis\(^{[50]}\). Monitoring effectiveness of treatment is often challenging, especially following liver directed therapy. In HCC, the usefulness of DWI in the evaluation of therapeutic efficacy after targeted therapy or TACE has already been reported in several studies\(^{[51-55]}\). Some of those studies reported that the ADC value in HCC showed significant increases after TACE\(^{[51-53]}\). Yuan et al\(^{[49]}\) reported that high baseline ADC value of HCC could predict poor response to TACE and that responding lesions had a significant increase in %ADC values than nonresponding during TACE. They demonstrated...
that an alteration %ADC value $\geq 16.21\%$ could be used to identify HCC to early response to chemoembolization. In HCC treated with an antiangiogenic agent (sorafenib), Schraml et al.\cite{54} reported that early decrease in ADC of tumor after therapy was followed by an increase (Figure 4). However, there are some limitations regarding ADC values reproducibility, which depend on magnetic field strength, technical factors (e.g., b-value selection) and on the ROI localization on ADC maps.\cite{56,57} In addition, particularly in abdomen, DWI still represents a technical challenge because of the strong influence of motion caused by breathing and vascular pulsation, resulting in image artifacts that may lead to inaccurate ADC measurements.\cite{58} Nevertheless, DWI is one of the promising techniques for the noninvasive assessment of tumor burden. Future studies are necessary to correlate the time course of ADC changes with HCC therapy response, and additional technical developments are necessary to improve DWI quality and spatial resolution.

PET

PET is a quantitative imaging modality using various tracers such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG),\cite{59-63} $^{11}$C-acetate ($^{11}$C-Act),\cite{64-67} $^{11}$C- or $^{18}$F-F-choline ($^{11}$C-Cho, $^{18}$F-F-Cho)\cite{68} and $^{18}$F-fluorothymidine ($^{18}$F-FLT)\cite{69} to assess metabolism, lipogenesis, cellular membrane metabolism and proliferation respectively.

$^{18}$F-FDG, which can be used for assessing glucose metabolism of tumors, is the most widely available clinical PET tracer (Figure 5). Generally, malignant tumors show increased $^{18}$F-FDG uptake due to the increased number of glucose transporters and the increased hexokinase activity. Nevertheless, FDG-PET shows poor sensitivity for the detection of HCC with reports ranging from 50% to 55%.\cite{70,71-74} In spite of the poor sensitivity of $^{18}$F-FDG PET in HCC, Song et al.\cite{75} reported that the increase of $^{18}$F-FDG uptake in HCC was significantly associated with tumor burdens such as size and number of tumors, and they concluded that $^{18}$F-FDG PET could provide effective information on the prognosis of the treatment response. In addition, it has been demonstrated that $^{18}$F-FDG uptake after TACE might be a favorable marker to assess tumor viability after TACE.\cite{66-76} Similar findings have been reported in detecting local tumor progression following radiofrequency ablation of HCC.\cite{77}

Despite the rapid integration of PET with $^{18}$F-FDG into clinical practice, there has been relatively little systematic integration of PET into clinical trials of new cancer treatments. Given the clinical importance and quantitative nature of PET, it is important to have methods to allow inclusion of PET response criteria into clinical trials. Therefore, the European Organization for Research and Treatment of Cancer (EORTC) has defined response assessment criteria for PET in 1999.\cite{78} Although some use the EORTC criteria, methods for PET performance and

![Perfusion maps of 53-year-old man with hepatocellular carcinoma. Parameters measure by perfusion computed tomography showed substantial changes in comparison with tumor size and density at only 2 wk after antiangiogenic treatment. Blood flow (BF), blood volume (BV) were -75.5% and -59.5%. On the other hand, those of size and density were not so obvious (-3.0% and -18.1%).](image)
interpretation are typically highly variable across studies and typically only exploratory. Therefore, in 2009, Wahl et al. described the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0 to standardize therapy-monitoring method with PET. They classified responses by use of percentage changes in SUVs in the “hottest” lesions per scan. The basics of PERCIST 1.0 are shown in Table 2, where they are contrasted with the EORTC criteria. It is clear that further efforts are needed to validate usefulness of SUV as a sensitive biomarker to assess tumor burden, response and clinical outcome. At present, PET still plays a small role in imaging assessment of HCC tumor burden, compared with other modalities, but tumor-specific tracers may be the key in future.

CONCLUSION

Accurate tumor burden assessment is a critical component of patient management and the investigation of new therapies. Morphological tumor burden analysis has been served as golden standard. However, with the increasing clinical use of novel biologic targeted agents or LRTs,
morphological analysis confronted limitations, and new methods to assess tumor burden were desired. Advances in software and hardware of imaging technique enable us to assess tumor function such as viability, vascular physiology, or metabolism. Since targeted therapy or LRTs can induce biological changes much earlier than morphologically changes, these functional tumor burden analyses are very promising. However, some of them have not gone thorough all steps for standardization and validation. Nevertheless, these new techniques and criteria will play an important role in the cancer management, and provide each patient more tailored therapy.

REFERENCES

1. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. 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: 205-216 [PMID: 10655437]

2. Nishino M, Jackman DM, Hatabu H, Yeap BY, Cioffredi LA, Yap JT, Jänne PA, Johnson BE, Van den Abbeele AD. New Response Evaluation Criteria in Solid Tumors (RECI ST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. AJR Am J Roentgenol 2010; 195: W221-W228 [PMID: 20729419 DOI: 10.2214/ AJR.09.3928]

3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Danayce J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

4. Taylor M, Rössler J, Geoerger B, Vassal G, Farace F. New anti-angiogenic strategies in pediatric solid malignancies: agents and biomarkers of a near future. Expert Opin Investig Drugs 2010; 19: 859-874 [PMID: 20470190 DOI: 10.1517/13543784.2010.487654]

5. Murakami T, Imai Y, Okada M, Hyodo T, Lee WJ, Kim MJ, Kim T, Choi BI. Ultrasonography, computed tomography and magnetic resonance imaging of hepatocellular carcinoma: toward improved treatment decisions. Oncology 2011; 81 Suppl 1: 86-99 [PMID: 22212941 DOI: 10.1159/000333267]

6. Hennedige T, Venkatesh SK. Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. Cancer Imaging 2013; 12: 530-547 [PMID: 23400006 DOI: 10.1102/1470-7730.2012.0044]

7. Shields AF. Positron emission tomography measurement of tumor metabolism and growth: its expanding role in oncology. Mol Imaging Biol 2006; 8: 141-150 [PMID: 16534552 DOI: 10.1007/s11307-006-0039-2]

8. Miller AB, Hoogstraten B, St Tauquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214 [PMID: 7459811]

9. Sohaib SA, Turner B, Hanson JF, Farquharson M, Oliver RT, Reznik RH. CT assessment of tumour response to treatment: comparison of linear, cross-sectional and volumetric measures of tumour size. Br J Radiol 2000; 73: 1178-1184 [PMID: 11144795]

10. Welsh JL, Bodeker K, Fallon E, Bhatia SK, Buatti JM, Cullen J]. Comparison of response evaluation criteria in solid tumors with volumetric measurements for estimation of tumor burden in pancreatic adenocarcinoma and hepatocellular carcinoma. Am J Surg 2012; 204: 580-585 [PMID: 22982100 DOI: 10.1016/j.amjsurg.2012.07.007]

11. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane C, Blanc JF, de Oliveira AC, Santoro A, Raoul J, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Gallo PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shor M, Moscovi C, Volioti D, Bruix J, Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

12. Gillmore R, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, Meyer T. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol 2011; 55: 1309-1316 [PMID: 21703196 DOI: 10.1016/j.jhep.2011.03.007]

13. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of
tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer 2009; 115: 616-623 [PMID: 19117042 DOI: 10.1002/cncr.24050]

14 Sahani DV, Jiang T, Hayano K, Duda DG, Catalano OA, Ancukiewicz M, Jain RK, Zhu AX. Magnetic resonance imaging biomarkers in hepatocellular carcinoma: association with response and circulating biomarkers after sunitinib therapy. J Hepatol Oncol 2013; 6: 51 [PMID: 23842041 DOI: 10.1186/1756-7722-6-51]

15 Zhu AX, Holalkere NS, Muzikansky A, Horgan K, Sahani DV. Early antiangiogenic activity of bevacizumab evaluated by computed tomography perfusion scan in patients with advanced hepatocellular carcinoma. Oncologist 2008; 13: 120-125 [PMID: 18305056 DOI: 10.1634/theoncologist.2007-0174]

16 Jiang T, Kambadakone A, Kulkarni NM, Zhu AX, Sahani DV. Monitoring response to antiangiogenic treatment and predicting outcomes in advanced hepatocellular carcinoma using image biomarkers, CT perfusion, tumor density, and tumor size (RECIST). Invest Radiol 2012; 47: 11-17 [PMID: 21512936 DOI: 10.1097/RLI.0b013e3182199f65]

17 Zhu AX, Sahani DV, Duda DG, di Tomaso E, Ancukiewicz M, Catalano OA, Sondhiwani V, Blaskowsky LS, Yoon SS, Lahdenranta J, Bhargava P, Meyerhardt J, Clark JW, Kwak EL, Hezel AF, Miksad R, Abrams TA, Enzinger PC, Fuchs CS, Ryan DP, Jain RK. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol 2009; 27: 3027-3033 [PMID: 19470923 DOI: 10.1200/JCO.2008.20.9008]

18 Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figar A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Salz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006; 24: 4293-4300 [PMID: 16908937 DOI: 10.1200/JCO.2005.01.3441]

19 Bruix J, Sherman M, Llovet JM, Beaumard M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of theLiver. J Hepatol 2001; 35: 421-430 [PMID: 11592607]

20 Lencioni R, Llovet JM. Modified RECIST (mRECIST) for assessment of hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]

21 Llovet JM, D’Arteaga CE, Biegergie AM, Bruix J, Krane RE, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ. Design and endpoints of clinical trials in hepatocellular carcinoma. Nat Cancer Inst 2008; 100: 698-711 [PMID: 18477802 DOI: 10.1093/jnci/djn134]

22 Keppke AL, Salem R, Reddy D, Huang J, Jin J, Larson AC, Miller FH. Imaging of hepatocellular carcinoma after treatment with yttrium-90 microspheres. AJR Am J Roentgenol 2007; 188: 768-775 [PMID: 17312067 DOI: 10.2241/ AJR.06.0706]

23 Riaz A, Miller FH, Kulik LM, Nikolaidis P, Yaghmai V, Lewandowski RJ, Mulcahy MF, Ryu RK, Sato KT, Gupta R, Wang E, Baker T, Abecasis M, Benson AB, Nemecck AA, Omary R, Salem R. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA 2010; 303: 1062-1069 [PMID: 20253824 DOI: 10.1001/jama.2010.262]

24 Prapajati HJ, Spivey JR, Hanish SI, El-Rayes BF, Kauh JS, Chen Z, Kim HS. mRECIST and EASL responses at early time point by contrast-enhanced dynamic MRI predict survival in patients with unresectable hepatocellular carcinoma (HCC) treated by doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE). Ann Oncol 2013; 24: 965-973 [PMID: 23223331 DOI: 10.1093/annonc/mds605]

25 Llovet JM, Real MI, Montañá X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodes J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359: 1734-1739 [PMID: 12049862 DOI: 10.1016/S0140-6736(02)60649-X]

26 Park JW, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, Thomsen M, Harris R, Baudelet C, Walters I, Raoul JL. Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2011; 17: 1973-1983 [PMID: 21349999 DOI: 10.1186/1747-0432-CCR-10-2011]

27 Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, Le Roux C, Raoul JL. Comparison of tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer 2012; 118: 147-156 [PMID: 21713764 DOI: 10.1002/cncr.26255]
March 28, 2014 | Volume 20 | Issue 12
Hayano K et al. New response evaluation for HCC

10.2967/jnumed.106.103667]

64 Ho CL, Yu SC, Yeung DW. 11C-acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 2003; 44: 213-221 [PMID: 12571212]

65 Hwang KH, Choi DJ, Lee SY, Lee MK, Choe W. Evaluation of patients with hepatocellular carcinomas using [(11)C]acetate and [(18)F]FDG PET/CT: A preliminary study. Appl Radiat Isot 2009; 67: 1195-1198 [PMID: 19342249 DOI: 10.1016/j.apradiso.2009.02.011]

66 Salem N, Kuang Y, Corn D, Erokwu B, Kolthammer JA, Tian H, Wu C, Wang F, Wang Y, Lee Z. [(Methyl)-1-(11)]-acetate metabolism in hepatocellular carcinoma. Mol Imaging Biol 2011; 13: 140-151 [PMID: 20401538 DOI: 10.1007/s11307-010-0308-y]

67 Yun M, Bang SH, Kim JW, Park JY, Kim KS, Lee JD. The importance of acetyl coenzyme A synthetase for 11C-acetate uptake and cell survival in hepatocellular carcinoma. J Nucl Med 2009; 50: 1222-1228 [PMID: 19617323 DOI: 10.2967/jnumed.109.062703]

68 Salem N, Kuang Y, Wang F, Maclennan GT, Lee Z. PET imaging of hepatocellular carcinoma with 2-deoxy-2[18F]fluoro-D-glucose, 6-deoxy-6[18F]fluoro-D-glucose, [1-11C]-acetate and [N-methyl-11C]-choline. Q J Nucl Med Mol Imaging 2009; 53: 144-156 [PMID: 19039303]

69 Eckel F, Herrmann K, Schmidt S, Hillerer C, Wieder HA, Krause B, Schuster T, Langer R, Wester HJ, Schmid RM, Schweiger M, Back AK. Imaging of proliferation in hepatocellular carcinoma with the in vivo marker 18F-fluorothymidine. J Nucl Med 2009; 50: 1441-1447 [PMID: 19690030 DOI: 10.2967/jnumed.109.058596]

70 Takayasu K, Arii S, Matsuo N, Yoshikawa M, Ryu M, Takanari K, Sato M, Yamanaka N, Shimamura Y, Ohito M. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. AJR Am J Roentgenol 2000; 175: 699-704 [PMID: 10954453 DOI: 10.2214/ajr.175.3.1750699]

71 Guan YS, Sun L, Zhou XP, Li X, Zheng XH. Hepatocellular carcinoma treated with interventional procedures: CT and MRI follow-up. World J Gastroenterol 2004; 10: 3543-3548 [PMID: 15534903]

72 Strauss LG, Conti PS. The applications of PET in clinical oncology. J Nucl Med 1991; 32: 623-48; discussion 649-50 [PMID: 2013803]

73 Okazumi S, Isono K, Nomoto K, Kikuchi T, Ozaki M, Yamamoto H, Hayashi H, Asano T, Ryu M. Evaluation of liver tumors using fluorine-18-fluorodeoxyglucose PET: characterization of tumor and assessment of effect of treatment. J Nucl Med 1992; 33: 333-339 [PMID: 1311035]

74 Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolkensk MK, Solomon H, Collins BT, Bi Biseglie AM. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. J Hepatol 2000; 32: 792-797 [PMID: 10845666]

75 Song MJ, Bae SH, Yoo JH, Park CH, Jang JW, Chun HJ, Choi BG, Lee HG, Choi JY, Yoon SK. Predictive value of 18F-fluorodeoxyglucose PET/CT for transarterial chemolipiodolization of hepatocellular carcinoma. World J Gastroenterol 2012; 18: 3215-3222 [PMID: 22783045 DOI: 10.3748/wjg.v18.i25.3215]

76 Torizuka T, Tamaki N, Inokuma T, Magata Y, Yonekura Y, Tanaka A, Yamaoka Y, Yamamoto K, Konishi J. Value of fluorine-18-FDG-PET to monitor hepatocellular carcinoma after interventional therapy. J Nucl Med 1994; 35: 1965-1969 [PMID: 7989978]

77 Kuehl H, Stattaus J, Hertel S, Hulond P, Kaiser G, Bockisch A, Forsting M. Mid-term outcome of positron emission tomography/computed tomography-assisted radiofrequency ablation in primary and secondary liver tumours—a single-centre experience. Clin Oncol (R Coll Radiol) 2008; 20: 234-240 [PMID: 1815453 DOI: 10.1016/j.cionc.2007.11.011]

78 Young H, Baum R, Cremerius U, Herholz K, Hoeckstra O, Lammertsma AA, Pruim J, Price P. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and subclinical tumour response using [18F]-fluorodeoxyglucose PET/CT: A preliminary study. AJR Am J Roentgenol 2000; 175: 699-704 [PMID: 10954453 DOI: 10.2214/ajr.175.3.1750699]

79 Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009; 50 Suppl 1: 122S-150S [PMID: 19403881 DOI: 10.2967/jnumed.108.057307]
