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TOPIC HIGHLIGHT

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Evaluation of cancer treatment in the abdomen: Trends and advances

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Abstract

Response evaluation in Oncology has relied primarily on change in tumor size. Inconsistent results in the prediction of clinical outcome when size based criteria are used and the increasing role of targeted and locoregional therapies have led to the development of new methods of response evaluation that are unrelated to change in tumor size. The goals of this review are to expose briefly the size based criteria and to present the non-size based approaches that are currently applicable in the clinical setting. Other paths that are still being explored are not discussed in details.

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Key words: Evaluation; Cancer treatment; Abdomen

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INTRODUCTION

Evaluation of treatment outcome is a crucial task in oncology, one shared by clinicians, radiologists and pathologists. Pathological response to preoperative therapy has proven to be a predictor of survival for patients with solid tumors[1,2]. Imaging that provides a noninvasive and yet objective measure of response is the cornerstone of response evaluation, but the performance of imaging at predicting outcome remains inconsistent.

The established and most widely used method of radiological response evaluation relies on changes in tumor size as defined by the World Health Organization (WHO) and Response Evaluation of Criteria in Solid Tumors (RECIST) criteria[3]. The advent of targeted and locoregional therapies and progress in molecular imaging, however, are increasingly drawing attention to the shortcomings of this method. Approaches that do not rely exclusively on change in tumor size are developed[4].

Optimal response criteria need to be simple, reproducible, standardized, quantifiable and need to provide an early indication of treatment efficacy. In addition, response should be a reliable and meaningful indicator of clinical outcome. Quantification of the response can be subjective or objective, the latter needed in the context of clinical trials[5]. Although many new methods to explore response to treatment have been proposed, such as perfusion studies, magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) and texture evaluation, these are complex and not ready for routine use[6-8]. The goals of this review are to review briefly the size-based methods and to present the non-size-based approaches that have so far been developed for several tumor types and are applicable in the clinical setting.

In clinical practice, tumor response can be approached from three different perspectives: change in tumor size, morphological change unrelated to size, and functional imaging, essentially ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET).

CHANGES IN TUMOR SIZE

The WHO criteria, introduced in 1979 in an attempt to standardize treatment response, are based on changes in bidimensional measurement of the largest diameters of the target lesions. Response is categorized into four groups: complete response (CR), partial response (PR) (50% decrease in target lesions, without a 25% increase in any one target lesion), progressive disease (PD) (25% increase in the size of measurable or unequivocal progression of non-target lesions) and stable disease (SD) (neither PR nor PD)[3].

RECIST was introduced in 2000 by the European Organization for Research and Treatment of Cancer, the National Cancer Institute of the United States and the National Cancer Institute of Canada to increase standardization and simplify data collection[9]. RECIST relies on unidimensional measurement of the tumor's largest diameter. Tumor response is classified into the same four categories as for the WHO criteria, but PR and PD are defined differently: for PR, a 30% decrease in the sum of the longest diameters of target lesions; for PD, a 20% increase in the sum of the longest diameter, appearance of new lesions, or unequivocal progression of non-target lesions.

RECIST criteria were revised in 2009 to clarify the evaluation of nodal disease, refine the definition of PD, and simplify data collection[3].

While change in tumor size is a strong, simple indicator of treatment effect, it has shortcomings. RECIST and WHO criteria are best adapted to gauge the effect of cytotoxic chemotherapy and are poor indicators of outcome with drugs that have a cytostatic effect or with locoregional therapy[10-13].

Attempts to improve the sensitivity of the RECIST criteria are under way. The choice of threshold values to define the response categories PR, PD and SD is increasingly challenged. Recent studies suggest that a decrease in size smaller than the one required by RECIST is a reliable predictor of favorable outcome. This has been shown with colorectal carcinoma (CRC), renal cell carcinoma (RCC) and the Choi criteria in gastro intestinal tumors (GIST), which specify a 10% decrease in size[14-17].

These observations underscore the need to revisit the threshold values used to define treatment response and suggest that early tumor shrinkage could identify responders earlier than with the RECIST criteria and may be a better indicator of improvement.

NON-SIZE-BASED MORPHOLOGICAL CRITERIA

Another important limitation of RECIST is the assumption that an overall decrease in tumor size reliably indicates a decrease in the number of viable tumor cells. This assumption is not valid when intratumoral necrosis or hemorrhage is associated with treatment or when response to chemotherapy is not uniform within a mass, for example, with hepatocellular carcinoma (HCC)[18]. In these situations, the response cannot be approached globally and tumors need to be scrutinized to identify areas that may be responding in the midst of nonresponding tissues. Likewise, such an assumption is not valid with targeted therapy, since these drugs tend to have a cytostatic effect. New criteria have been established for GIST, hepatic colorectal metastasis, RCC and HCC treated with targeted or loco regional therapy. These criteria are discussed in the following pages[16-19].

FUNCTIONAL IMAGING

While anatomical imaging remains the standard for objective tumor response assessment, functional imaging serves an important role in response assessment, helping to overcome the limitations of size-based criteria. The wide acceptance of ^{18}F-FDG-PET imaging has brought a new means for identifying tumor and assessing treatment responses. Although subject to false positive findings, frequently due to inflammation or physiological variations in uptake, PET provides valuable data directly influencing clinical management.

The National Oncologic PET Registry (NOPR), the framework created to facilitate evaluation of PET clinical impact, showed an overall change in management in 36.5% of cases based upon PET findings[20]. This effect is seen across multiple cancer types, including but not limited to ovarian and cervical carcinomas, renal tumors, gastric tumors, hepatic tumors and even prostate cancer[21]. These results led to increased coverage of PET imaging by the Centers for Medicare and Medicaid Services, which now includes ovarian and cervical carcinomas and myeloma, and to continued coverage of PET imaging for other solid tumors under the NOPR.

Much of the clinical benefit of PET is through identification of additional sites of disease involvement, clinically silent and not conspicuous by other imaging modalities, and through evaluation of post-therapy abnormalities, for example after radiation therapy. However, the inclusion of PET imaging into response criteria remains slow in coming, in part due to technical variations in how it is performed and the lack of widespread use throughout the world. In 1999, the EORTC proposed the inclusion of PET criteria but concluded that further study was necessary to assess their accuracy[22]. Although PET was not included in the first version of RECIST[9], the revised criteria published in 2009 acknowledge a potential role of PET in identifying PD but reiterate the need for better standardization and more widespread availability[3]. However, PET has been incorporated into lymphoma response criteria based upon the visual interpretation of findings. Quantitative assessment of PET, although widely used in the literature, has not been accepted into tumor response criteria.

The ability to quantify tumor metabolic activity provides another metric for target lesions in addition to the RECIST criteria and can also be applied to unmeasurable disease sites, such as bone metastases[23]. In addition, studies have reported that PET imaging can detect tumor responses earlier than conventional imaging. These potential advantages helped prompt the creation of PERCIST, PET Response Criteria in Solid Tumors[24]. Within this framework, tumor activity is measured using the SUL peak, which is designed to minimize factors lending to variation in quantitative measurements. Also of note, standardization of patient preparation and imaging technique is required for comparison with subsequent studies. Although the details of this proposal are too complex to discuss here, and also perhaps too cumbersome for routine use, PERCIST stands out as a framework to begin standardized and systematic evaluation of PET findings for determining treatment response.

This review will address response evaluation from the perspectives defined above, their respective roles and how they apply to the following tumors: HCC, CRC, lymphoma, RCC.

HCC

The curative options for patients diagnosed with HCC are resection, transplantation and ablation. Surgery is indicated only for a small percentage of patients who are seen at an early stage of disease and who have a preserved liver function. Ablation is performed in small tumors. Transplantation is restricted to patients who meet the Milan criteria and is limited by the shortage of liver donors[18].

Consequently, for the majority of patients who present with disease at more advanced stages, these therapies are not indicated. Systemic cytotoxic chemotherapy can be offered but has little effect on survival, although sorafenib, a multitarget kinase inhibitor, has been shown recently to improve survival[12,13,25]. Trials are under way with other targeted agents[26].

In this context, alternative therapeutic options to control the disease locally are crucial and dominated by embolization techniques, transarterial chemoembolization (TACE) and increasingly radioembolization[18,27]. Locoregional treatments, such as ablation and embolization, as well as targeted therapy induce necrosis and decrease tumor vascularity and do not necessarily induce a significant decline in tumor size. Therefore, tumor response in this setting is best judged on the extent of residual viable tumor seen as enhancing tissue on contrast-enhanced computed tomography (CT) or MRI[28-30]. Other methods of response evaluation such as DW MRI, CT or MRI perfusion, and PETCT are being explored and may play a role in the future but are still in the development phase[31].

RESPONSE EVALUATION AFTER TUMOR ABLATION

Ablative techniques, such as ethanol injection and radiofrequency ablation (RFA), are indicated in patients with small tumors and early stage A disease who are not surgical candidates[18,27]. Intratumoral instillation of ethanol under ultrasound guidance is a simple, safe and inexpensive method to ablate small tumors. RFA, which destroys tumors by heating tissue to temperatures that exceed 60 ℃, has been shown to be more effective and is currently the standard of care for nonsurgical patients with lesions smaller than 3 cm[27,32]. RFA achieves a survival rate similar to that for surgical resection[33,34]. It can also be used as a bridge to transplantation[35].

RFA is not indicated for tumors larger than 5 cm. Its role in the treatment of tumors 3 to 5 cm is debated[36]. In addition to tumor size, the proximity of large vessels, the lack of ablative margins in lesions close to the liver surface, and proximity to liver hilum are anatomical parameters that are associated with recurrence[37].

The goal of ablation, regardless of the method, is to achieve complete necrosis of the tumor and also to prevent local recurrence from satellite nodules by ensuring adequate ablative margins[38].

Radiographic findings after ablation with ethanol injection or RFA are similar, as both lead to coagulation necrosis. Complete ablation is defined by the disappearance of tumoral enhancement indicative of viable tumor, which can be demonstrated by contrast-enhanced ultrasound (CEUS), CT or MRI.

While CEUS has been shown to be effective in detecting residual tumor vascularity after ablation, it cannot be the primary imaging modality for response evaluation because contrast is not available to all practices and because the technique is operator dependent[39].

Response is evaluated with CT or MRI, typically 1 to 2 mo after the procedure; earlier evaluation may be rendered more difficult by the development of arteriovenous shunting. Restaging is performed every 3 mo during the first 2 years and every 4 to 6 mo thereafter, as local recurrence most frequently occurs during the first 2 years[40].

The quality of the ablation is first judged morphologically, based on the size and position of the RFA defect in comparison to the pretreatment scan. This correlation allows estimation of the width of the ablative margin. A margin of 0.5 to 1 cm is recommended[32,40]. Poor centering of the defect over the tumor should prompt a thorough search for subtle areas of residual disease where the ablative margin is considered suboptimal.

Complete ablation is characterized by lack of enhancement on contrast-enhanced CT or MRI, while residual tumor appears as areas of nodular eccentric arterial enhancement followed by wash-out on the portal or delayed phase. Residual tumor is generally seen at the margin of the ablation defect. Three morphological patterns of local recurrence have been described, a nodular type or nodules at the periphery (67%), a halo type or presence of active tumor on all edges of the ablation zone (38%), and gross enlargement type or recurrence associated with an overall increase in the ablation zone (33%)[37,41-43].

Benign perilesional enhancement is a physiological

response to thermal injury that mimics residual tumor. Unlike tumor nodules, it is typically concentric, symmetrical and uniform and usually disappears within a month, although it can persist for up to 6 mo[32,37,40,44]. In difficult cases, short-term follow-up may be needed to differentiate residual disease and post-ablative hyperemia.

Tiny air bubbles are produced during the ablation that may be seen on immediate follow-up imaging and which will disappear within 1 mo[43].

With MRI, in addition to the morphological and enhancement patterns, changes in signal intensity are observed. The ablation zone is hypointense on both T1 and T2 images, although variations occur based on the presence of blood products and the type of necrosis. On T1 images, a peripheral hyperintense rim may be present[44].

On serial follow-up, the ablation zone should gradually decrease in size although it may remain stable. An increase in size is indicative of recurrence[40].

RESPONSE EVALUATION AFTER CHEMOEMBOLIZATION AND RADIOEMBOLIZATION

TACE is the standard treatment for patients with intermediate stage B HCC and can also act as a bridge for liver transplantation. Effectiveness is related to the hypervascular nature of HCC[45,46]. Chemotherapy with or without embolic materials is administered intraarterially as selectively as possible. The purpose is to achieve tumor necrosis and control while preserving normal liver tissue. Doxorubicin and cisplatin (with mytomycin c in the United States) have been traditionally mixed with lipiodol to increase local concentration and slow release[45,46]. In recent years, doxorubicin-eluting beads have been introduced as a novel embolic agent and a new form of embolization using radioactive particles containing yttium-90 is gaining rapid clinical acceptance[47].

Response to TACE is evaluated on serial contrast-enhanced CT or MRI with a first restaging at 4 to 6 wk. Several groups have reported good results with CEUS but the known limitations of ultrasound, discussed above, restrict its application.

Response to TACE is judged based on the extent of necrosis induced by the embolization, the disappearance of enhancing tissue on the arterial phase, or solid lipiodol uptake. The focus is the identification enhancing tumor on the arterial phase rather than the tumor size. This concept has led to an amendment of the RECIST criteria specific to HCC, referred to as modified RECIST. PR is defined by a decrease of at least 30% in the sum of the diameters of enhancing tissues compared with baseline, while progression is defined by an increase of 20% compared with baseline[28,30].

Indications for retreatment are based on the tumor response judged on CT or MRI or the development of new tumors, but progression after two sessions usually leads to interruption.

Intraarterial administration of yttrium-90-embedded microspheres is an emerging therapy that aims to provide high-dose radiation to the tumor. The effect of treatment on the tumor is similar to that of TACE, with reduction of enhancement and necrosis. Imaging findings, however, differ from those for TACE because of the internal radiation effect that can lead to radiation hepatitis, perivascular edema and inflammatory-based enhancement at the margins of the treated tumors. Response is judged similarly on the measurement of residual enhancing tissue, taking into consideration the findings attributable to radiation hepatitis[48]. Optimal imaging strategy after yttrium-90 is not yet known. The effect of treatment is evaluated by most practices at 2 to 3 mo, although earlier imaging may be performed to assess progression in patients with bilobar disease who may be candidates for sequential lobar treatment.

RESPONSE AFTER TARGETED THERAPY

There is no effective conventional systemic chemotherapy for HCC, but recent clinical trials with targeted therapy have demonstrated some response in patients with advanced disease. A phase Ⅲ randomized trial of sorafanib, a multitarget kinase inhibitor, has shown improved survival and a doubling of time to progression in patients with advanced HCC. It was noticed, however, that clinical improvement after Sorafenib did not correlate with the radiographic response evaluated by RECIST[12,13,49].

Sorafenib tends to induce decreased vascularity and necrosis with limited change in tumor size. Size has even been reported to temporarily expand with the proportion of necrotic tissue[25]. The focus again is to assess enhancement and necrosis rather than size (Figure 1). MRI has been shown in one study to document changes in signal-reflecting necrosis[50]. New guidelines that take into consideration the anti-angiogenic action of these new drugs need to be developed[51,52].

In summary, as with other tumors, response evaluation in HCC cannot be limited to size measurement any longer. It needs to take into consideration the type of treatment and include an analysis of the morphology and enhancement.

COLORECTAL LIVER METASTASIS

Advancements in chemotherapy and the increased use of hepatic resection over the last decade have improved the outcome for patients with metastatic CRC[53].

Chemotherapy for CRC includes cytotoxic drugs (irinotecan, oxaliplatin, capecitabine, 5-fluorouracil, leucovorin) often used in combination with targeted therapy (bevacizumab, cetuximab or panitumumab).

Tumor response can be judged on change in tumor size, change in tumor morphology other than size, and change in metabolic activity.

CHANGE IN TUMOR SIZE

RECIST criteria are the mainstay for response evaluation in CRC. With RECIST, response is categorized in one of

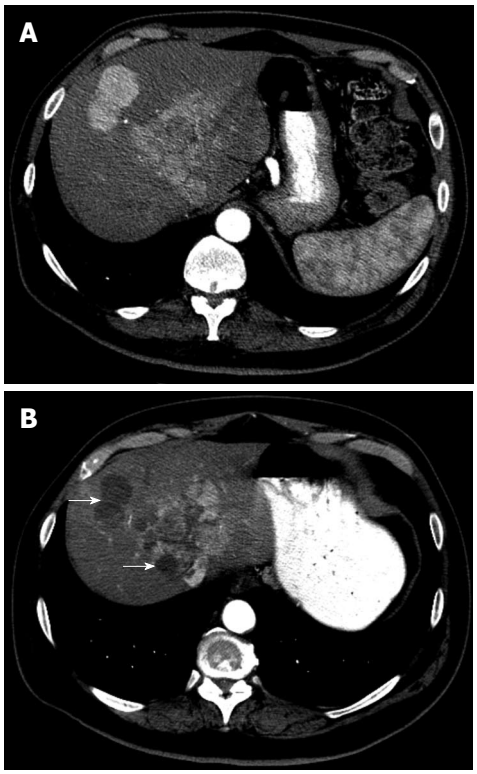

Figure 1 A 62-year-old man with multifocal hepatocellular carcinoma. A: Baseline contrast enhanced computed tomography (CT) in the arterial phase shows enhancing nodules in segment Ⅷ and Ⅳ; B: Contrast enhanced CT after Sorafenib shows decreased tumor enhancement with near complete disappearance of enhancement in some nodules (arrows) and only marginal decreased tumor size.

four groups based on the percentage of decrease in the sum of the largest diameters of the target lesion[3].

Recent studies have questioned the clinical value of the categorical definitions of RECIST, the optimal time point to assess response in metastatic CRC, and the choice of threshold values that were developed in an era when precise measurements were not feasible.

Suzuki *et al*[14] retrospectively reviewed 567 patients treated with conventional chemotherapy and showed that a decrease of only 10% in the tumor size after two cycles of chemotherapy was a positive indicator of progression-free survival (PFS) and overall survival.

In another study of 329 patients treated with cetuximab, Piessevaux *et al*[15] showed similarly that a decrease of at least 10% in tumor size at 6 wk was a strong predictor of time to progression and overall survival.

Additional studies are needed to confirm and explore this model with other regimens. Nonetheless these studies and others in RCC and gastrointestinal stromal tumors support the need to reappraise the threshold values that define response based on changes in tumor size.

Importantly, one needs to bear in mind that a complete radiographic response by RECIST, observed in 7% to 9% of patients after neoadjuvant chemotherapy, is not a definite indicator of complete pathological response. According to Benoist *et al*[54], viable tumor was present in 83% of lesions that had disappeared, while Auer *et al*[55] showed that 66% of disappearing lesions were CRs.

CHANGES IN TUMOR MORPHOLOGY

Lack of congruence between radiographic and clinical responses has been observed with bevacizumab-containing chemotherapy[11,56]. Bevacizumab, a humanized monoclonal antibody against VEGFA, inhibits angiogenesis and is used as a first-line chemotherapy in combination with FOLFOX or FOLFIRI[11,53].

With this combination, responding metastases in the liver that are heterogeneous with ill-defined margins on CT before treatment become homogeneous and develop a sharp interface with the normal liver (Figure 2). On the basis of these morphological observations, new non-size-based criteria were developed. The criteria solely consider changes in tumor attenuation and margins. Response is classified into three groups: optimal response, incomplete response and no response.

In a study of 234 liver metastases from 50 patients with colorectal cancer treated with bevacizumab, RECIST and the new non-size-based morphological criteria were compared with pathological response. Pathological response was stratified into three categories: CR (no residual tumor cells), major response (1%-49% residual tumor cells) and minor response (more than 50% residual tumor cells). Chun *et al*[19] found that morphological response was a better predictor of minor pathological response and correlated with overall survival, whereas response by RECIST did not. These criteria are very promising and need to be validated by other groups[19,57].

The morphological criteria point to the importance of the interface of the tumor and normal liver in evaluating response and this observation is supported by the correlation with pathology. The maximal thickness of the uninterrupted layer of tumor cells observed at the tumor-normal interface (TNI) was shown to correlate with the morphological radiographic response, the percentage of residual tumor cells and PFS. The measure of the maximal thickness of the uninterrupted layer of residual tumor cells was proposed as a new prognostic indicator of response. A thin TNI indicates a better 4-year PFS, TNI < 0.5 mm thickness yields 70% PFS, TNI ≥ 0.5 mm to 5 mm thickness yields 51% PFS, and TNI > 5 mm thickness yields 35% PFS. Of note, TNI was less in patients treated with bevacizumab than in patients not given bevacizumab[58].

CHANGES IN METABOLIC ACTIVITY

Demonstration of abnormal biology in cancer cells is the basis for functional imaging. ^{18}F-FDG is a glucose analogue used as a marker of the increased glycolytic activity in malignant cells and its reduction after treatment. Quantitative evaluation of changes in metabolic activity can be performed using standardized uptake value (SUV) measurement[59].

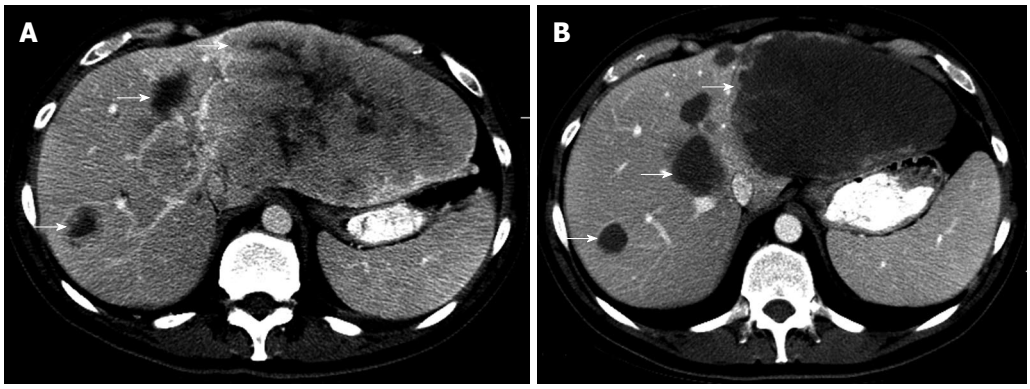

Figure 2 Axial computed tomography images in the portovenous phase of a 50-year-old female with colorectal liver metastases. A: Pretreatment evaluation showed multiple heterogeneously enhancing hepatic masses that are compatible with known hepatic metastases. The entire left hepatic lobe was occupied by the masses. Note the thickened nodular interface between the mass and normal liver (arrow); B: Liver metastases became more homogenous and showed well-defined interfaces with the normal liver parenchyma after Folfox and Avastin, corresponding to treatment response. Note the well defined interface (arrows).

Several publications have indicated the potential value of PET in monitoring the response to chemotherapy in CRC metastases. Response in colorectal metastases is associated with a decrease in ^{18}F-FDG uptake. The role of PET in response evaluation, however, remains to be defined as currently available data are from small series and there are controversies in the results[59,60]. The most recent publication on the subject indicates that PET can identify patients that will not benefit from treatment after only one cycle of chemotherapy[61].

Because ^{18}F-FDG uptake decreases with effective chemotherapy, PET is not reliable for preoperative staging after neoadjuvant chemotherapy[62]. Importantly, complete PET response, like complete radiographic response, is not indicative of complete pathological response[63].

DW MRI indirectly assesses cellularity. Water molecules that move freely in normal tissue have a restricted motion within hypercellular tissues. Preliminary studies have suggested that DW MRI can be used as an early marker for treatment response since changes at the cellular level typically precede changes in size[6,64].

Angiogenesis is necessary for tumor growth and the antitumor efficacy of targeted therapy derives from its anti-angiogenic effect. A number of techniques allow assessment of *in vivo* vascular features. Dynamic contrast-enhanced CT and MRI can detect perfusion changes indicative of response. Although these techniques can detect response, they are not yet established for clinical use[65].

In summary, the approach to response evaluation in metastatic CRC is evolving. The criteria that defined response based on changes in tumor size are being revisited, while new morphological and physiological criteria are emerging. The combination of these methods allows for a more refined judgment of response compared with the simple, somewhat crude, and yet still very important size criteria.

LYMPHOMA

Evaluation of lymphoma has changed significantly since the original Ann Arbor staging system was created in the early 1970s[66,67]. Multidetector CT has replaced chest radiographs and physical exams, resulting in more precise measurements of tumor size. Bi-dimensional measurements of enlarged lymph nodes are used to calculate the sum of the products of the greatest diameters (SPD) as a qualitative measurement of tumor response[68,69]. However, response criteria have been recognized as imperfect as there is no consensus on what is a normal (or abnormal) lymph node size[70], the frequent occurrence of post-residual masses after successful treatment[71,72], and difficulty in evaluating bone marrow involvement[73]. Imaging techniques have also improved and gallium scans have been replaced with ^{18}F-FDG-PET (or PET) and PET/CT hybrid imaging, which has made identification of lymphoma much easier and provides valuable information for treatment responses. This led to incorporation of PET imaging information into lymphoma response criteria[69] but at the same time has stirred up new controversies.

In using PET/CT to evaluate lymphoma, it is important to know whether the particular type of lymphoma is typically "hot" or "cold" in terms of FDG uptake. The aggressive lymphomas, *e.g.*, Hodgkin's lymphoma, diffuse large B-cell lymphoma and mantle cell lymphoma, tend to have high uptake of FDG, making them readily visible on PET (Figure 3A). In contrast, indolent lymphomas such as chronic lymphocytic leukemia/small cell lymphoma and marginal zone lymphoma have a more variable appearance on PET; when presented with a lymphoma with low FDG-avidity, the interpreting physician becomes dependent upon the anatomic imaging to identify sites of involvement and to determine treatment response (Figure 3B and C). In addition, lymphomas which typically have high FDG-avidity may be difficult to identify when they present in unusual locations, such as in the skin, vitreous eye or in an effusion. A recent study reported on the FDG-avidity of different lymphoma subtypes for a large number of patients[74]; however, given the variable uptake, it is preferred to have a baseline PET study for an individual patient before initiation of a new therapy.

As mentioned, the addition of PET information has improved lymphoma staging and response assessment.

Table 1 Changes in lymphoma response definitions for clinical trials

	1999 response criteria	2007 response criteria
CR	Resolution of clinical and radiographic evidence of disease	Disappearance of disease; residual masses are allowed if previously PET positive and now PET negative
CR unconfirmed	May have a residual node greater than 1.5 cm in longest dimension, but SPD must be decreased by > 75%; or has indeterminate bone marrow	Category no longer used
PR	⩾ 50% decrease in SPD, and no new or progressive sites of disease	⩾ 50% decrease in SPD; may still be positive on PET, but no new lesions
Stable disease	Less than PR but more than PD	Not CR, PR, or PD
Relapsed or PD	Any new lesion or ⩾ 50% increase in SPD from nadir	New lesion, PET positive or > 1.5 cm, or ⩾ 50% increase in SPD or longest diameter of a previously involved node

PD: Progressive disease; PR: Partial response; CR: Complete response; PET: Positron emission tomography; SPD: Sum of the products of the greatest diameters.

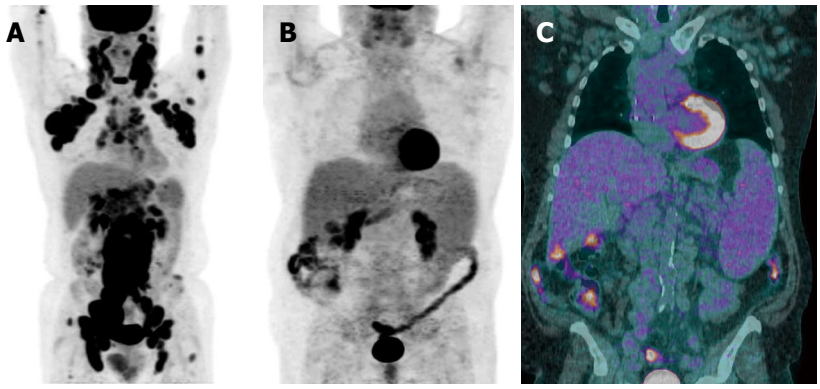

Figure 3 The fluorodeoxyglucose activity of lymphoma can be variable. A: A positron emission tomography (PET) image of a 62-year-old male with untreated grade 2 follicular lymphoma showed strong fluorodeoxyglucose (FDG) avid lymph nodes above and below the diaphragm; B, C: A whole body PET image of a 65-year-old male with untreated chronic lymphocytic leukemia or small lymphocytic leukemia showed no FDG uptake (B) but a PET/computed tomography fusion image demonstrated retroperitoneal lymphadenopathy (C).

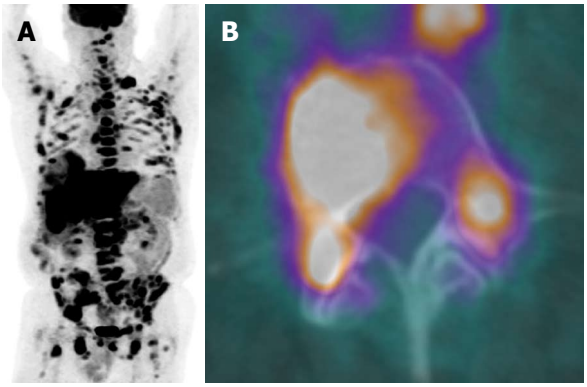

Figure 4 A whole body positron emission tomography image of a 67-year-old male with marginal zone lymphoma showed extensive disease involving lymph nodes above and below diaphragm, osseous structures and liver (A). The bone marrow biopsy was negative but the direct biopsy from L4, which was positive on the positron emission tomography/computed tomography fusion image (B), confirmed bone marrow involvement.

PET can identify lymphomatous involvement of normal sized nodes and can help identify focal sites of bone marrow involvement, leading to alterations in stage assignment and therapy (Figure 4)[75-77]. Moreover, it has been shown that PET information is a better prediction of treatment response. In one early study, 84% of patients with a negative PET after therapy were still in remission over a year later, whereas all 26 (100%) of patients with a positive PET after therapy had relapsed; in the same set of patients, conventional imaging studies identified a good treatment response, 75%, but correctly predicted treatment failure in only 50% of cases[78]. The improved response prediction is, in part, due to the frequent occurrence of a residual mass after therapy, which contributes to calculation of the SPD used for classifying responses. It was already known that the majority of these are post-therapy fibrotic masses; however, PET imaging identifies which are more likely to represent a residual viable tumor (Figure 5)[79]. Subsequent work showed that the inclusion of PET information resulted in a more accurate prediction of clinical response to therapy[80] and in 2007, lymphoma response criteria were modified to incorporate PET imaging and reduced the number of response categories, as shown in Table 1[68,69].

PET interpretation, however, is not without pitfalls. There are a myriad of potential false positive findings, including thymic rebound and physiological bone marrow activation which can be difficult to distinguish from tumor involvement[81]. Response is based upon visual interpretation and scans are reported as either positive or negative. There may still be significant variation in interpretation and a recent study reported disagreement in about one-

Table 2 Traditional response evaluation criteria of solid tumors

Criteria	WHO[7]	RECIST[9]	RECIST 1.2[12]
CR	Disappearance of all known lesions	Disappearance of all target and non-target lesions - confirm at 4 wk	Disappearance of all target and non-target legions[1]
PR	⩾ 50% decrease in sum of products of all lesions - confirm at 4 wk; no new lesions; no progression of any lesions	⩾ 30% decrease from the baseline of the sum of max diameter of all lesions - confirm at 4 wk; no new lesions; no progression	⩾ 30% decrease from the baseline of the sum of max diameter of all lesions; no new lesions; no progression[1]
SD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD	⩾ 25% increase of a single lesion over the smallest measurement or any new lesions	⩾ 20% increase over the smallest sum of maximum diameter observed or any new lesions	⩾ 20% increase over the smallest sum of maximum diameter and at least 5 mm increase or any new lesions

[1]Confirmation at 4 wk required only for non-randomized trials with the primary end-point of response. CR: Complete response; PR: Partial response; PD: Progressive disease; SD: Stable disease; WHO: World Health Organization; RECIST: Response Evaluation of Criteria in Solid Tumors.

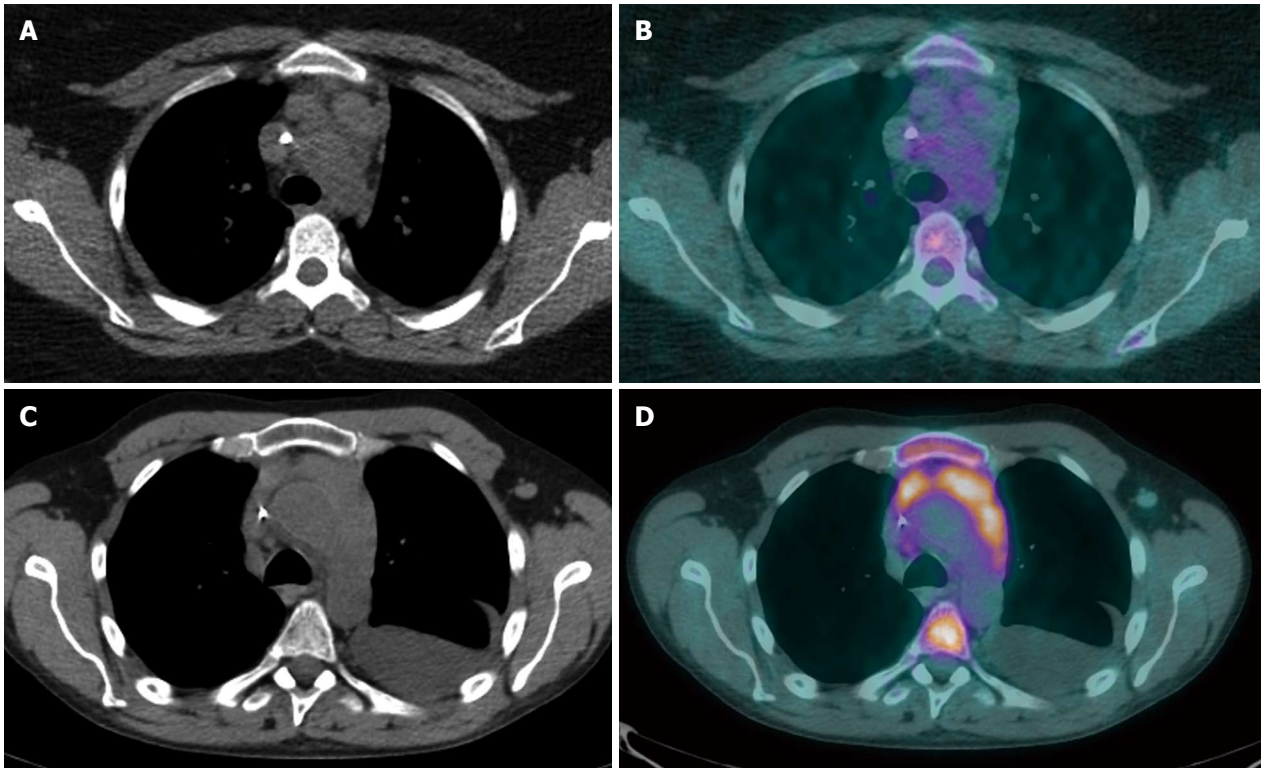

Figure 5 A computed tomography image of a 22-year-old female with Hodgkin's lymphoma after 4 cycles of chemotherapy demonstrated residual mediastinal lymphadenopathy (A) that is not metabolically active, as seen on positron emission tomography/computed tomography fusion images, and consistent with post-therapy fibrosis (B). A computed tomography image of a 50-year-old male with diffuse large B-cell lymphoma after 6 cycles of chemotherapy showed a residual mediastinal abnormality that represents viable tumor as shown by the abnormal actiivty on the positron emission tomography/computed tomography fusion image. Also note left pleural effusion and bone marrow activation (D).

third of cases reviewed by a panel of three expert readers[82]. This report highlights the need for standardization of technique and reporting criteria across the field. Moreover, the role for semi-quantitative measurements (*e.g.*, SUVs) has yet to be defined. One retrospective study found that the positive predictive value for overall survival was only 38% using visual analysis, whereas an SUV-based approach had a PPV up to 92%[83]. The negative predictive value was around 85% by either analysis, suggesting the main power in PET is in identifying treatment failures.

The metabolic changes in tumors may occur rapidly after starting therapy; it has been reported that a scan can go from positive to negative even after 1 d of chemotherapy - far too short a time to expect significant anatomic change[84]. Subsequent work indicated PET scans performed after a few cycles of chemotherapy are also able to predict treatment response; these have also been referred to as early response or interim PET (iPET). One widely discussed study found that PET performed after 2 cycles of chemotherapy (typically a total of 4-8 cycles are given) was better able to predict clinical outcome of Hodgkin's lymphoma patients compared to an accepted clinical model, the international prognostic score[85]. However, another study reported that PET performed after 4 cycles with a different chemotherapy regimen used in non-Hodgkin's lymphoma frequently resulted in false

positive findings and the use of this information to escalate therapy did not result in improved outcome[86]. Thus, the significance of a positive iPET remains under debate and studies are ongoing to test the reliability of early PET imaging to predict treatment response.

Despite the lack of clear evidence-based guidance on how to use iPET scan results, many clinicians continue to request these studies before the completion of planned therapy. These are frequently negative, likely a tribute to the improvements in chemotherapy regimens developed for lymphoma. In contrast, the presence of new sites of involvement or an enlarging persistent FDG-avid mass is an indication of treatment failure. However, patients with decreasing tumor size and decreasing but persistent abnormal activity on an iPET study remain a diagnostic and management dilemma. It remains to be determined whether semi-quantitative assessment, better standardization of technique and reporting criteria, or the intrinsic biology of the tumors will be most important in interpreting PET scans obtained for lymphoma treatment response.

TREATMENT RESPONSE OF GASTROINTESTINAL STROMAL TUMORS

Historically, the response evaluation of solid tumors has been based on anatomical information or changes in tumor size measured on cross-sectional images of CT or MRI. Despite the reported discrepancies in response rates between the traditional size-based response evaluation criteria (WHO criteria and RECIST) and its impact on the survival outcome[87-89], these have been well accepted and used in numerous clinical trials for testing new anticancer drugs, from the cytotoxic to newly available molecularly targeted drugs, often with some modifications.

Recently, however, there has been increasing concern about the use of the traditional size-based tumor response criteria[90-92]. The most dramatic such observation was first reported in patients with advanced GISTs treated with imatinib[93].

The stromal tumor is rare but the most common sarcoma along the gastrointestinal (GI) tract. The tumor used to be misclassified as smooth muscle tumor, such as leiomyosarcoma, without any effective way of treatment. Identification of C-Kit, a tyrosine receptor protein, at the interstitial cells of Cajal within the GI wall in stromal patients and development of Kit receptor blocker with a dramatic response have led to significant prolonging of PFS. The stromal tumor is a highly vascular tumor that occurs anywhere along the GI tract and rarely in the peritoneal cavity or retroperitoneum. The tumor metastasizes most to the liver and peritoneum, occasionally to the lungs, soft tissue and rarely to the bones.

When the tumor responds to the TKI blocker, the tumor becomes homogenous with a significant decrease in degree of enhancement on CT images within a month, regardless of tumor size change (Figure 6). In some responding tumors, the size increases due to development of intratumoral hemorrhage. Note should be made that there is a significant lag time (*e.g.*, 6 mo) between these subjective changes in intratumoral characteristics in responding GIST and the tumor shrinkage to the degree to fulfill, so called, RECIST, the international response evaluation criteria in solid tumors. Choi *et al*[92] evaluated the responses of 40 patients with metastatic or recurrent GISTs by FDG-PET and contrast-enhanced CT. While the responding tumors demonstrated dramatic changes in their CT enhancement characteristics and significant decreases in FDG uptake on PET images at 8 wk, the tumor size change did not meet the PR criteria by RECIST in 75% of best responders by FDG-PET. On the basis on these observations, the same authors first proposed new CT criteria for response evaluation of GIST using the combination of tumor density (degree of enhancement) and unidimensional measurement of tumor size, named "Choi criteria". The criteria, a 10% decrease in the sum of the unidimensional tumor size or a 15% decrease in tumor density, as determined by the CT attenuation coefficient in HU, at the first follow-up (8 wk) following treatment, could best separate the good and poor responders and that response at this time is an excellent predictor of PFS[16]. These criteria have been validated in an extended group of patients (a total of 98 patients) and the early responses at 8 wk, time-to-tumor progression (TTP) and disease specific survival (DSS) up to 60 mo were compared with the response evaluated by RECIST[94]. The good responders by Choi's response criteria had significantly longer TTP and better DSS than the responders by RECIST. In addition, the early response by Choi's criteria predicted the DSS significantly more accurately than that by RECIST.

Identification of progression of disease is as important as identification of correct responses in response evaluation of solid tumors. Traditional criterion of recurrence or progression includes a tumor size increase and appearance of new lesions. In progressing GIST, almost half of progression occurs within the treated tumors (unpublished data) (Figure 7) with no change in tumor size. This unique feature of intratumoral tumor progression is included in the new modified CT criteria (Table 2). Several investigators have applied the modified CT criteria to other tumors, such as renal cell tumors, metastatic colon cancer and other types of sarcomas undergoing TKI treatments with promising results[95,96].

METASTATIC RCC

RCC is the most lethal urological malignancy that shows remarkable resistance to conventional chemotherapy/radiation with a poor 5-year survival rate of less than 10% and a median survival of 7-11 mo[97]. Approximately 30% of patients with RCC initially present with locally advanced or metastatic disease[98,99] to the lung, bone, liver and brain[100]. In addition, 20%-40% of patients who undergo surgery for localized disease develop a relapse.

Recent advances in pathology and genetics have led to better understanding of histological and biological diversity of RCCs. Clear cell RCC is the most common

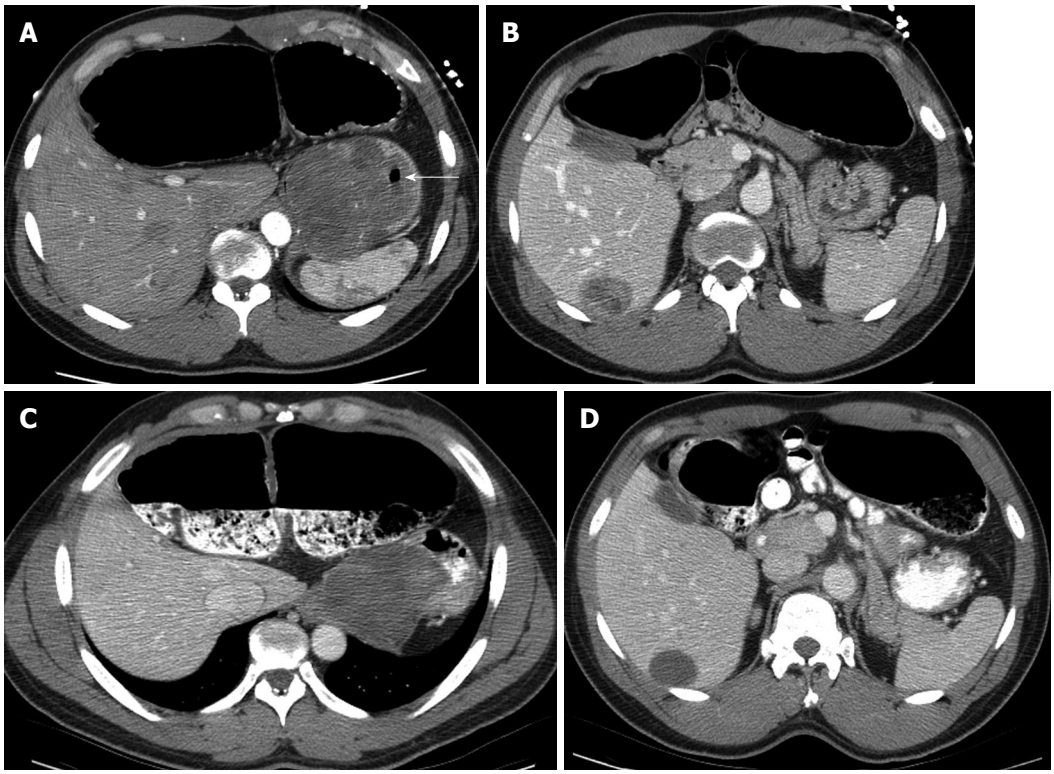

Figure 6 A computed tomography image of a 64-year-old male with metastatic gastro intestinal tumors prior to the imatinib shows a large heterogeneously enhanced gastric mass compatible with gastric gastro intestinal tumors (A) and a segment 6 hepatic metastasis (B). The primary tumor and hepatic metastasis showed decreases in tumor size and became homogeneous in internal appearance after the targeted therapy (C, D). Note the stomach air bubble (arrow in A).

histological subtype of sporadic RCCs that comprises 90%-95% of all metastatic RCCs (mRCCs). It is now well established that all hereditary RCCs in patients with von-Hippel Lindau (VHL) disease and most sporadic clear cell RCCs develop due to genetic or epigenetic "silencing" of the tumor suppressor gene, *VHL*. The VHL protein is an integral part of a complex that hydroxylates hypoxia inducible factors (HIFs) in oxygen and iron-replete states that subsequently lead to ubiquitin-mediated degradation. In clear cell RCCs with inactivation of the *VHL* gene, there is uncontrolled activation of HIF and related pathways such as mammalian target of rapamycin (mTOR) leading to downstream up-regulation of vascular and somatic growth factors[101]. Based on this information, several "small" molecules have been developed that target these specific tumor signaling pathways, thereby markedly reducing angiogenesis and/or tumor growth[102].

Immunotherapy with interleukin 2 (IL-2) and interferon α (IFN-α) were the mainstays of therapy in patients with mRCCs before the advent of targeted therapeutics[100,103,104]. IL-2 induces sustainable complete remission in 5%-10% patients[105] and IFN-α showed an overall response rate of 15%, but the response was short and partial[106-108]. Also, because of significant clinical toxicity profiles and limited clinical indications, the treatment options for patients with mRCCs were markedly limited[102,109]. Over the past 15 years, a number of anti-VEGF agents, tyrosine kinase inhibitors and mTOR-inhibitors, such as Bevacizumab, Sunitinib, Pazopanib, Sorafenib and Everolimus, have been approved by the Food and Drug Administration for the treatment of mRCCs based on superior response rates of 20%-40% and/or better PFS rates.

IMAGING EVALUATION OF TREATMENT RESPONSE

The targeted agents interfere with tumor angiogenesis and/or growth and may not necessarily be associated with meaningful decrease in tumor size (Figure 8)[10]. Thus, the conventional size-based criteria such as WHO, RECIST, RECIST 1.1 or volumetric evaluation that may be appropriate to evaluate solid tumors treated with conventional cytotoxic chemotherapy, may not be applicable for assessing response in mRCC patients treated with targeted therapy[110,111]. A recent study of 61 mRCC patients treated by targeted therapy concluded that greater than 30% decrease in size (PR by RECIST guidelines) is extremely rare[112]. Some pilot studies have shown that 10% reduction in size is a more appropriate threshold to identify PR than 30%[113]. Similar results for 10% cut-off value and overall patient outcomes have been recently reported[114,115]. Interestingly, the 10% cut-off value is similar to the Choi criteria that was used to assess treatment response in mGIST treated with imatinib[16]. Other imaging based criteria that incorporate changes in tumor size and morphology such as Choi/modified Choi criteria, SACT criteria (Size and Attenuation CT criteria) and MASS (Morphology, Attenuation, Size and Structure) criteria have been recently proposed. A study in 2010 found that the SACT criteria

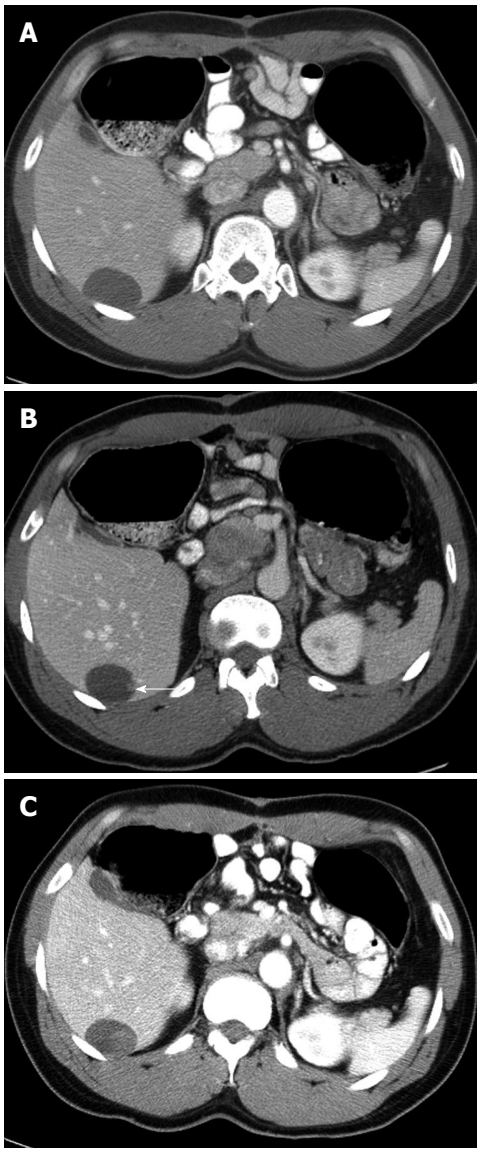

Figure 7 Axial computed tomography images of the same patient in Figure 6 at a later time showed progression of metastatic disease. Immediately following the second course of targeted therapy, the hepatic metastasis showed homogenous hypoenhancement compatible with treatment response (A). A small nodular enhancing focus within the lesion is the radiographic finding of recurrent disease (arrow in B) which had progressed and appeared more conspicuous (C).

markedly improved therapeutic response assessment. PFS of > 250 d was predicted in 75% of cases with the SACT criteria and only 16% with RECIST. CT findings suggestive of poor outcomes included a central fill-in pattern and a new enhancing focus within the treated mass[17]. Because the SACT criteria are cumbersome, MASS criteria were introduced by Smith *et al*[17]. This new criteria incorporated specific morphological and structural changes such as tumor necrosis. A favorable response group in MASS criteria had 86% sensitivity and 100% specificity in identifying patients with PFS of > 250 d, while only 17% sensitivity and 100% specificity for RECIST PR. Although PPV for RECIST PR, SACT and MASS favorable response approached 100%, RECIST had the lowest

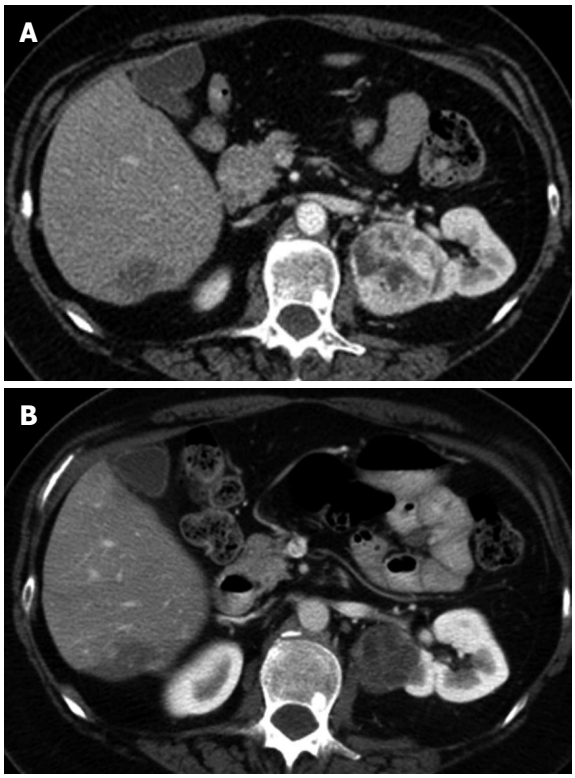

Figure 8 A computed tomography image of a 45-year-old man with clear cell type renal cell carcinoma who had received pre-operative Sorafenib. An exophytic heterogeneously hyperenhanced right renal mass (A) demonstrated homogenous hypoenhancement after the targeted therapy (B). Note an atypical segment 6 hepatic hemangioma and a L1 bone island.

NPV and accuracy, 20% and 30%. The authors concluded that MASS criteria is more accurate than SACT, mChoi and RECIST in evaluation of tumor response in mRCC patients treated with targeted therapy and may predict disease outcome as measured by PFS[110].

Angiogenesis is an important mechanism of tumor growth and metastasis. There are a large number of ongoing research trials that have applied dynamic contrast enhanced (DCE) with US, CT and MRI techniques to detect changes in tumor vascularity[116]. The basic principle of CT perfusion is that the contrast enhancement is linearly proportional to the iodine concentration; thus, quantitative analysis of tumor vascular parameters is relatively straightforward[117-119]. CT perfusion software installed in new generation CT scans are able to calculate CT perfusion parameters[120,121]. Although preliminary studies have shown impressive results and perfusion parameters can be used as biomarkers of prognosis and tumor response in mRCC[122-124], there are some limitations, including limited sample volume, patient motion and, the most important, a high radiation dose, a major drawback[116]. DCE MRI, albeit with more complex algorithm than CT-perfusion technique, is an emerging tool for assessment of tumor vascularity[125-128]. Flaherty *et al*[129] found inhibition of tumor vascular permeability in mRCC patients treated with sorafenib was associated with improved outcome and was a predictive marker of the response to therapy. However, Hahn *et al*[130] found that although calculated MRI param-

eters are useful biomarkers of sorafenib, the variability is high and therefore cannot serve as surrogate end points. While potential pitfalls of DCE MRI include lack of standard protocols and complex analysis of data due to variable MRI parameters, the important advantage is the lack of radiation exposure[120,121]. DCE US is one of the functional imaging tests that uses microbubble contrast agents and Doppler ultrasound to assess tumor perfusion[120,131,132]. A pilot study conducted in 30 mRCC patients receiving sorafenib concluded that DCE US might be an effective tool for evaluating antiangiogenesis drugs in RCCs[133]. A subsequent study in 38 mRCC patients receiving sunitinib confirmed the value of DCE US in predicting early drug efficacy and also to provide robust correlation with DFS and OS[134]. Several advantages include the low cost, its ease of use and lack of radiation. Of note, the US beam cannot penetrate aerated lesions such as lung metastasis, a potential shortcoming since lung is the most common site of mRCC[121].

The basic principle of DW MRI is detecting random motion of water molecules in the tissues using a heavily T2-weighted technique. ADC values can be calculated by acquiring images with a different gradient duration and amplitude (*b*-value)[116]. Hypercellularity in tumor tissues causes a decrease of interstitial space, decreased ACD value and subsequently restricted diffusion[121]. Due to this important characteristic of most tumors, DW MRI can be used to differentiate highly cellular areas from acellular areas, which imply tumor response to therapy[135,136]. A few studies related to RCC primarily for characterization of primary tumor[135,137-139] exist in the literature. There is no data of DWI on RCC response.

Increased glycolytic activity and abundant GLUT 1-2 in the tumor tissues is the basic concept of application of ^{18}F-FDG PET for assessing tumors. Integration of FDG PET with CT permits better anatomic detail and soft tissue resolution. Although FDG PET plays an important role in oncology as a tool to evaluate tumor response and patient outcomes, the role of ^{18}F-FDG PET for detection and localization of RCCs, mRCCs and recurrent RCCs is limited because the majority of RCCs are not FDG-avid[140-143]. In cases of FDG avid RCC, FDG PET/CT can be used as a monitoring tool for tumor response in mRCC patients treated with targeted and cytokine therapies[144-148].

In conclusion, patients with mRCCs are being treated by a wide array of targeted therapeutics based on burgeoning knowledge of genetic and pathological data. Many "small" molecules continue to play a "big" role in the management of mRCC by improving response rates with resultant better survival rates and patient outcomes. Parallel to this, there is continued evolution of imaging criteria for determining and quantifying tumor response. Several imaging based hybrid criteria that incorporate tumor size and morphology, such as mChoi, SACT and MASS, enable better assessment of response and help predict patient outcomes. There are continued efforts to develop and validate advanced functional imaging studies, such as CT/MRI perfusion, diffusion MRI and PET, to monitor treatment response.

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