

IMAGE-BASED EVALUATION OF TUMOR RESPONSE TO TREATMENT: WHERE IS RADIOLOGY TODAY?

*Siarhei Kharuzhyk^{1, 2, *}, Michael Fabel³, Hendrik von Tengg-Kobligh⁴, Hans-Ulrich Kauczor^{4, 5}*

¹*Department of Diagnostic Radiology, Republican Scientific-Practical Center of Oncology and Medical Radiology Named for N.N. Alexandrov, 223040 Minsk, Belarus*

²*Chair of Diagnostic Imaging, Belarusian Medical Academy of Postgraduate Education, 220013 Minsk, Belarus*

³*Clinic for Diagnostic Radiology, University Hospital Schleswig-Holstein, 24105 Kiel, Germany*

⁴*Department of Radiology, German Cancer Research Center, 69120 Heidelberg, Germany*

⁵*Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, 69120 Heidelberg, Germany*

Oncological patient care requires long term follow-up in order to estimate effectiveness of existing and new treatment choices. Image-based assessment of whole body tumour burden is commonly used for that purpose. The WHO response criteria were established in 1979 proposing bi-dimensional tumor measurements. New RECIST guidelines appeared in 2000 relying on only the longest diameter (uni-dimensional) measurements. Obviously, a change in tumour size is only one potential surrogate for therapy response which not necessarily reflects the biologic activity of the tumour or the effect of particular therapy. Thus, the evaluation of biological, metabolic or molecular properties of a tumor and its changes might be an attractive means to assess the response to therapy sensitively and early. **Key Words:** tumor burden, response to treatment, RECIST, volumetric analysis, CAD.

Many cancer types are still on the upslope of the incidence curve with high mortality rates and long lasting histories of different treatment choices [1]. Oncological patient care often requires long term follow-up of the primary tumour and its metastases, which can be spread throughout the whole body. Thus, an image-based assessment of whole body tumour burden is required. The vast availability of cross-sectional imaging plays an increasing role for the oncologist who has to decide if the therapy is successful or not. Ideally, response to therapy should be assessed as early as possible to optimize patient care, i. e. to lower complication rates and adverse effects as well as to reduce costs for the healthcare system. Tumour markers might help to decide if a therapy works but they are often unreliable and sometimes do not correlate with the actual tumour response to therapy [2]. To establish or evaluate new therapy regimens the response to treatment needs to be monitored and documented in a highly standardized and non-invasive manner to ensure comparability among clinical trials.

Solid tumours are defined by the National Cancer Institute in the United States as benign or malignant abnormal masses of tissue that usually does not contain cysts or liquid areas. Examples of solid tumours are sarcomas, carcinomas and lymphomas. Response criteria for solid tumours have already been developed

in the late 70s by the Union Internationale Contre le Cancer (UICC) and the World Health Organization (WHO). They introduced specific criteria for the codification of tumour response evaluation based on the available imaging modalities (plain film radiography and computed tomography, CT) [3]. Due to an increasing number of clinical oncological trials and improved imaging technology the WHO-response criteria did not fulfil the required level of standardization and practicability. Therefore, the Response Evaluation Criteria in Solid Tumours (RECIST) were developed by the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) in the United States and the National Cancer Institute of Canada Clinical Trials in the late 90's paying more attention to modern cross-sectional imaging modalities [4, 5]. The WHO and the RECIST criteria were supposed to simplify the response assessment and allow for a more objective evaluation during follow-up examinations and they were used within different clinical trials since their introduction [6, 7].

Criteria of the World Health Organization. The WHO response criteria were established in 1979 and published by Miller in 1981 [3]. All tumour lesions were divided into uni-dimensional and bi-dimensional as well as measurable and non-measurable.

For bi-dimensionally measurable tumours, e. g. lung metastases, the product of two maximum perpendicular diameters should be calculated resulting in a surface area (Fig. 1). In case of multiple lesions surface areas are summed. Depending on percentage tumour area change responses are categorized as complete or partial response, no change or progressive disease (Table 1). The same response criteria need to be applied for uni-dimensionally measurable tumours, especially using plain film radiography. In

Received: May 11, 2008.

*Correspondence: Fax: +375-17-2654704

E-mail: skharuzhyk@nld.by

Abbreviations used: CAD – computer aided detection; CT – computed tomography; FDA – Food and Drug Administration; FDG – fluorodeoxyglucose; MRI – magnetic resonance imaging; MRS – magnetic resonance spectroscopy; MSCT – multislice computed tomography; PACS – picture archiving and communication system; PET – positron emission tomography; RECIST – Response Evaluation Criteria in Solid Tumours; WHO – World Health Organization.

non-measurable but recorded/documented tumour lesions, e. g. lymphangitic lung metastases, no precise (quantitative) tumour measurements can be obtained and response is categorized depending on estimated increase, decrease or disappearance of the tumour manifestation.

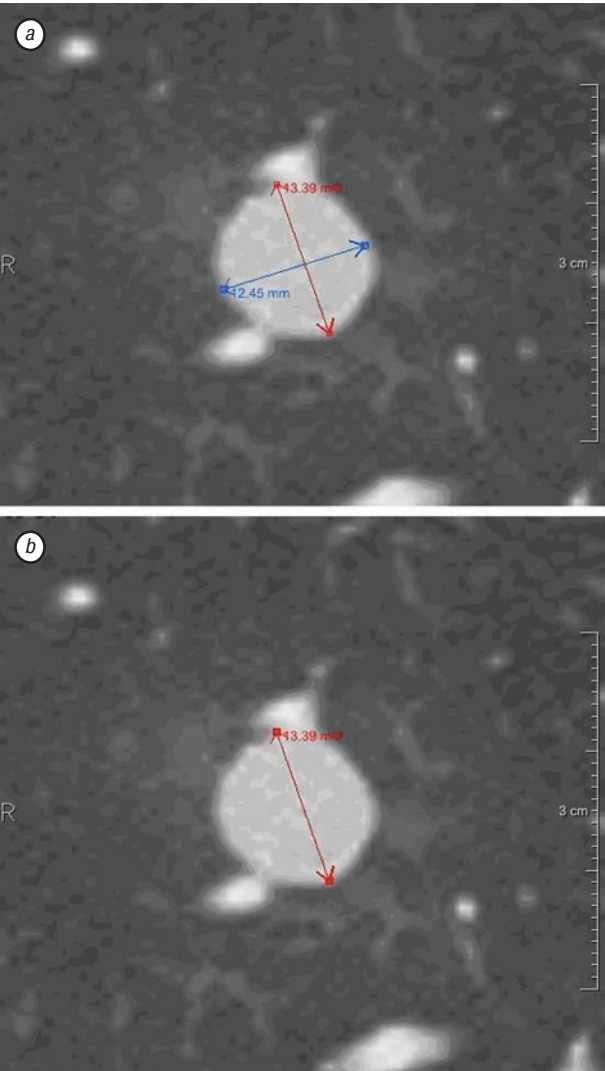


Fig. 1. Tumor assessment using (a) WHO and (b) RECIST, pulmonary nodule, 1 mm axial slices, lung kernel

Table 1. Definition of best response according to WHO and RECIST criteria [8]

Best Response	WHO (change in sum of products)	RECIST (change in sum of longest diameters)
Complete Response	Disappearance of all lesions; confirmed at four weeks	Disappearance of all lesions; confirmed at four weeks
Partial Response	50% or more decrease in target lesions without an increase of 25% in any one target lesion; confirmed at four weeks	At least 30% reduction in the sum of the longest diameters; reference baseline study; confirmed at four weeks
Stable Disease	Neither progressive disease nor partial response	Neither progressive disease nor partial response; reference smallest sum of longest diameters since treatment started
Progressive Disease	Increase of 25% or more in the size of measurable lesions; appearance of new lesions	At least 20% increase in the sum of the longest diameters of target lesions; new lesions; reference smallest sum of longest diameters since treatment started

Imaging modalities or measurement techniques were not defined by the WHO. Radiography has been

used in most occasions. Although these criteria are known for many years one might wonder why only few radiologists are actually using them in daily clinical routine. One major reason might be that the WHO criteria requested accurate measurements of every possible lesion in each involved organ. It is very cumbersome not only to measure every lesion on films but also to document this data.

Response Evaluation Criteria in Solid Tumours.

In 2000 the RECIST were published to help the radiologist to perform a response calculation, and more importantly, to standardize imaging procedures for evaluation of tumour burden and therapy response in routine diagnostics as well as in clinical trials [4, 5, 8]. The RECIST guidelines consist of a lower number of measurements for each examination when compared to WHO. For the documentation of response to treatment using RECIST the measurements of tumour lesions are only based on the longest (uni-dimensional) diameter (see Fig. 1) [4]. Tumour lesions are defined as measurable (target lesions) considering that their longest diameter is ≥ 2 cm when measured with plain film radiography or ≥ 1 cm when measured by CT. Measurements can be performed on axial slices of a CT scan as well as on coronal reformats from multislice CT (MSCT). In these cases the type of measurement has to be documented for follow-up measurements. Bone lesions, meningeal diseases, fluid collections, such as ascites, pleural or pericardial effusion, lymphangitis and cystic lesions are defined as non-measurable (non-target lesions). Up to a maximum of five target lesions per organ and ten lesions in total need to be identified on one examination; non-target lesions are only recorded. The sum of the longest diameters of all target lesions represents the status and is used to assess the response to treatment (see Table 1; Table 2). WHO response categories, defined as complete response, or partial response, stable disease or progressive disease, were preserved while threshold values were changed (see Table 1). The findings of partial and complete response should be confirmed after a minimum interval of 4 weeks. After the introduction of RECIST extensive discussions about imaging techniques resulted also in imaging guidelines. CT and increasingly magnetic resonance imaging (MRI) are recommended as the most suitable techniques, provided that the same acquisition techniques (slice thickness; volume, type and delay time of contrast media; reconstruction kernel; MRI-sequences and slice orientation) are used during follow-up examinations. In addition, different archiving and documenting systems (film, compact discs, picture achieving and communication system (PACS), etc.) exist throughout different institutes. To ensure comparability and standardization between follow-up examinations a digital form facilitates the monitoring of tumour burden including an automated calculation of tumour growth or shrinkage. Each measurement can be documented in this database (series number, table and slice position) for every exam. Such a digital form is exemplified in Table 2.

Table 2. Example for RECIST documentation during follow-up (baseline, 3 and 6 months). Target lesions, their change in diameter and the relative increase (or decrease) are documented. Registration of target and non-target lesions is done by documenting slice position and number of series

Nr.	Examination	Baseline			3 Months			6 Months		
		Ser	SL	LD (mm)	Ser	SL	LD (mm)	Ser	SL	LD (mm)
1	Lymph node right inguinal	3	152	23	4	144	29	4	148	27
2	Lymph node right iliac	3	123	24	4	121	32	4	125	30
3	Liver segment 4a	3	42	44	4	46	52	4	51	52
4	Liver segment 8	3	44	25	4	43	35	4	48	36
5	Lung segment 2 right	2	39	22	3	38	27	3	42	26
...										
10	Status									
	Sum of LD			138			175			171
	Difference to last exam						27%			–2%
	Difference to first exam									+24%
	Difference to lowest sum									+24%
	Therapy				Chemotherapy A			Chemotherapy B		
					new	prog	const	new	prog	const
	Non-target lesions		present							
1	Multiple pulmonary nodules	x				x			x	
2	Pleural effusion					x				x
3	Ascites	x					x			
	Overall Response				Progressive disease			Stable disease		

Ser = series, SL = slice position, LD = longest diameter, prog = progressive, const = constant.

RECIST vs WHO. Despite the fact that the RECIST was published already about 10 years ago there is still controversy and need for discussion about them and their alternatives [9]. In order to be uniformly accepted, the RECIST guidelines should demonstrate at least comparable results with the WHO guidelines in the evaluation of response. This is important to allow for a comparison between current, recent and older trials.

Retrospective analysis of 4613 cancer patients recruited in 14 different trials (1417 with breast cancer, 1221 with lung cancer, 1127 with colon cancer, 599 with ovarian carcinoma, 190 with melanoma, 31 with brain tumours and 28 with sarcoma) showed perfect agreement between WHO and RECIST in terms of response rate calculation (25.6% vs 25.4%). Complete response, partial response, stable disease and progressive disease were found in 3.8%, 26.2%, 39.7% and 30.3% of 794 patients if WHO criteria were applied, and in 3.8%, 24.9%, 42.3% and 29.0% if RECIST criteria were used [4].

Partial response on RECIST is defined as at least 30% decrease of the longest diameter (see Table 1). This threshold is obtained by simple mathematical recalculation from WHO's 50% bi-dimensional product decrease assuming the tumour is spherical in shape, i. e. the ratio of two diameters does not exceed 1.5. This is not always true as tumours may vary in shape considerably before and after treatment, and even in different ways. In such a case response to treatment might be judged differently comparing WHO and RECIST. In one study five of 569 patients ($0.88 \pm 0.8\%$) with varying tumour histologies had partial response measured with WHO criteria and stable disease with RECIST, another five patients ($0.88 \pm 0.8\%$)

had stable disease with WHO and partial response using RECIST [10]. In a different study only two of 164 non-small cell lung cancer patients were judged responders using WHO but not with RECIST (1,2%) and another two were judged responders by RECIST but not with WHO (1,2%) [11]. The discordance found between bi-dimensional and uni-dimensional measurements in discriminating partial response vs stable disease was judged as non significant in the above mentioned studies.

The different percentage values for tumour growth or regression with the two systems of criteria may also shift some patients from category "stable" to "progressive disease" and vice versa. RECIST's 20% or more increase in longest diameter is equal to approximately 44% increase in bi-dimensional product vs 25% as defined by WHO (Table 3).

Table 3. Change in diameter, product of longest diameter and volume of spherical lesion [8]. An increase of the longest diameter by 20% or more in RECIST is equal to an increase of the bi-dimensional product by approximately 44% instead of 25% as defined by the WHO criteria

Response	Diameter (2r)	Product (2r ²)	Volume ($\frac{4}{3}\pi r^3$)
Decrease	30%	50%	65%
	50%	75%	87%
Increase	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

Gurland and Jonson already recorded in the 60's that adding the greatest perpendicular diameter of a lesion to the maximum diameter increases the measurement error since multiplication of two diameters multiply measurement error as well [12]. A good correlation of the maximum lesion diameter with the greatest perpendicular diameter and the product of two diameters allowed them to recommend to only using one maximum diameter for response evaluation. The mathematical observation that changes in maximum tumour diameter relate more closely to the proportion of cells killed by chemotherapy compared to bi-dimensional product also favoured usage of a single tumour diameter measurement [10]. Mazumdar et al. describe the discordance between WHO criteria and the RECIST guidelines within a statistical simulation study. The response assessment as measured by RECIST often results in different categorization of response compared to WHO. The difference in response categorization may be problematic in the comparison between response rates in new experimental therapies and conventional agents whose response rates have been established in historical trials [13].

RECIST Limitations. Although the RECIST are an improvement compared to the WHO criteria there are still major challenges that are not well enough addressed and need to be taken into account during evaluation and documentation of tumour burden. Some solid tumour lesions might have a morphology that makes a clear and accurate radiological measurement impossible, i. e. they can have a diffuse margin, contain partially necrotic, hemorrhagic or calcified areas. Sometimes they merge with adjacent tissues including a perifocal edema or show inhomogeneous contrast media uptake. According to RECIST such lesions could also be classified as non-target lesions or cannot be

classified at all with the current official criteria. Thus, adapted RECIST criteria were created for some tumour entities, e. g. considering particular growth patterns such as in malignant pleural mesothelioma [14–17]. A further challenge is the lack of standardization in global image acquisition concerning tumour monitoring with varying standards of scan parameters such as collimation, slice thickness, contrast media and bolus timing as well as varying sequences. Also the number of evaluated lesions according to RECIST criteria has to be reconsidered. A study by Schwartz et al. has shown that measuring a larger number of lesions will result in a decreased variability. In an evaluated population, the variance decreased by at least 90% when six or more lesions were measured bi-dimensionally [18].

Based on the fact that usually most of the tumour lesions are inhomogeneous and irregular, a uni-dimensional measurement technique sometimes gives a non-adequate estimation of tumour growth or shrinkage. In addition, two different readers can measure the diameters on different slices or with different angles resulting in lower accuracy and reproducibility. Erasmus et al. state in an inter- and intraobserver study that in approximately 25% of all cases repeated manual measurements performed by independent and experienced readers lead to misclassification of therapy responders between progressive disease and partial response [19]. Even for well delineated lung nodules manual measurements might not be accurate or reliable enough following the RECIST or WHO criteria [19]. Regarding the interobserver variability described in an amendment to the WHO and RECIST guidelines all serial measurements need to be performed by the same reader during intraindividual follow-up examinations. In clinical routine, this is almost impossible to achieve. The intention of volumetric analysis of tumour burden is to provide a more accurate and precise method in the assessment of changes in solid tumour growth. Clinical studies showed that a volumetric analysis of tumours is more accurate compared to a RECIST assessment [20].

Volumetric analysis / Computer aided detection (CAD) of tumour lesions. The volumetric analysis of different organs and tumours has been assessed throughout many clinical trials, especially for lung nodules and in surgical planning of liver transplantations or portal vein embolisations [21–23]. But a successful translation into clinical routine is still missing. This is due to the time required for manual segmentation in combination with an increasing number of images produced by whole body MRI and MSCT. Computer-aided detection software systems are already available for different tumour lesion types and various organs. They were developed to simplify the radiological workflow. The first CAD systems were introduced for the screening of lung nodules and evaluated in the early 90s [24]. CAD systems were also introduced to aid in the interpretation of mammography. The first system was approved for screening mammography by the Food and Drug Administration (FDA) in 1998 and evaluated in initial clinical trials [25]. In 2004, the first system for the detection of

lung nodules received clearance by the FDA [26]. The assessment of lung nodules is an extremely attractive target for volumetric analysis as the nodules are often clearly circumscribed with high contrast against the surrounding lung parenchyma [27]. Intrapulmonary nodules are easy candidates for software algorithms which are mainly based on fixed thresholds (Fig. 2). However, lung nodules adjacent to mediastinal or pleural structures are more challenging.



Fig. 2. Volumetric analysis of (a) pulmonary nodule, (b) right axillary lymph node metastasis and (c) liver metastasis on axial slices, lung and soft tissue kernel respectively in 1 mm and 3D Volume Rendering (VR), visual control of the volumetric result in axial, coronal, and sagittal reformation

Tumour lesions beyond the lung require more sophisticated software algorithms. In an advanced approach volumetric analysis was adapted for segmenta-

tion of liver lesions. These lesions are more challenging compared to lung nodules because the parenchyma of the liver changes its density depending on the contrast phase and the amount of contrast. Liver lesions also can be of high or low intensity/density and are often inhomogeneous. Therefore, the a priori determination of lower and upper thresholds which are important to separate adjacent tissues automatically is difficult. Some first results were shown by different groups, e.g. by Mahr et al. in a phantom study [28]. Currently, semi-automated segmentation and volumetric analysis of hypo- and hyperdense liver lesions [29] as well as lymph nodes [30] is studied within clinical trials with promising results (see Fig. 2). Some of the software tools allow for visualization of tumour growth during follow-up (Fig. 3). Although automatic segmentation and volume calculation are needed, software tools for volumetric analysis must offer additional options for manual correction to control and improve segmentation results.

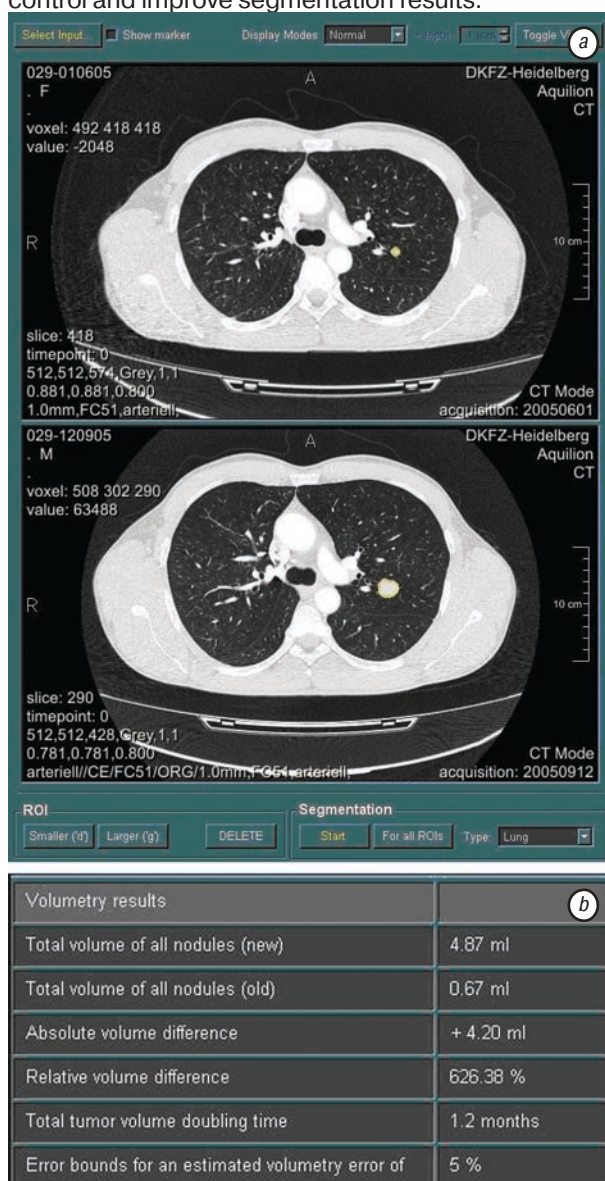


Fig. 3. (a) Volumetric analysis of a pulmonary nodule during follow-up on axial slices, previous examination (top), follow-up (bottom), lung kernel in 1 mm and 3D VR. (b) Tumour growth assessment (differences in volume, doubling time) during follow-up given in a table

To make RECIST or tumour volumetry widely available in clinical routine the capabilities of PACS, radiology information systems and CAD tools must be fully exploited. PACS facilitates the quantitative evaluation of tumour burden affecting the whole human body. Softcopy reading is of eminent importance since reconstruction of isotropic 1 mm cross-sectional slices from MSCT or whole body coverage with high spatial resolution by MRI produce a huge amount of data. This poses an enormous challenge to software engineers in order to develop smart post processing tools allowing for fast and reliable tumour segmentation in every region of the body including multiple longitudinal follow-up examinations. Automated matching of follow-up studies, support in lesion detection, semi-automatic volumetry, digital archiving of measured target lesions as a separate series on PACS, automatic identification of target lesions on follow-up scans [31], as well as automatic integration of size and volumetry measurements into a standardized report are favoured among other tools by the imaging community. If this can be achieved, RECIST will be easy to handle supporting clinical trials and can also be introduced into broad clinical routine. This will facilitate the workflow for radiologists and strengthen the recognition by oncologists.

There is still need for improvement, evaluation, validation and comparison of existing segmentation software tools in larger clinical trials, also defining the necessary technical parameters for an effective volumetry. Different technical parameters are able to influence the volumetric result and are evaluated within different phantom studies [32, 33].

Functional assessment of response to therapy. There are some caveats when using RECIST or volumetric analysis for the assessment of tumour response. They only consider the morphological aspect of tumour growth [34]. Obviously, a change in tumour size is only one potential surrogate for therapy response which not necessarily reflects the biologic activity of the tumour or the effect of particular therapy. Thus, the evaluation of biological, metabolic or molecular properties of a tumor and its changes might be an attractive means to assess the response to therapy sensitively and early [35]. Numerous approaches for such “functional”, “metabolic” or “molecular” imaging have been developed, proposed or are still under investigation. In the following, the most common are reviewed.

In oncology positron emission tomography (PET) and hybrid PET/CT systems have been increasingly used for the diagnosis and staging of tumors as well as monitoring response to treatment during the last few years [36–38]. Since glycolysis is increased in most malignant tumors, the fluorine-18- (^{18}F -) labeled glucose analog fluorodeoxyglucose (FDG) is generally used as a tracer in oncology imaging. The use of FDG-PET before and after therapy assessing a decrease of glycolysis instead of a reduction in size as a marker of response is promising. In gastrointestinal stromal

tumors PET/CT has an important role in the assessment of response to the anti-angiogenic drug imatinib (Gleevec®), as CT alone may not reveal a response until several months after the start of treatment. In 20 gastrointestinal stromal tumor patients the response to imatinib at 1 month was accurately assessed by PET/CT in 95% of patients, compared to only 44% by CT. At 3 and 6 months PET/CT diagnosed tumor response in 100% of patients, whereas CT was found to be accurate in only 60% at 3 months and 57% at 6 months. At the same time hybrid PET/CT was superior to fused images of PET and CT as well as PET alone [39]. In lymphoma, PET/CT more accurately reflects treatment outcome in patients with aggressive non-Hodgkin's lymphoma than CT. The difference in 18-month progression-free survival between patients with complete remission and those with partial remission as judged by CT was not significant, whereas using PET/CT, this difference was highly significant. Moreover, there was a statistically significant difference in 18-month progression-free survival between patients with partial remission by PET/CT vs CT alone (22% vs 70%) [40]. As more evidence becomes available it will be possible to integrate findings from PET/CT using FDG into a new scheme to assess tumor response. With new radiopharmaceuticals become available even more specific assessment of tumor response might be possible, e. g. ^{18}F -thymidine and ^{18}F -methionine for brain tumors, or ^{18}F -choline for prostate cancer [41].

Beyond PET, MRI can also deliver “functional” information to characterize individual tumor biology. Where PET needs CT as its morphological counterpart, MRI will provide the morphological information by itself, most commonly from T1- and T2-weighted sequences. Complementary “functional” information might be gained with use of perfusion, spectroscopy and diffusion-weighting MRI techniques.

The assessment of blood supply of tumors on the macro- and microvascular levels is highly attractive, especially since the importance of angiogenesis and anti-angiogenic treatment has become clear. Time-resolved MR angiography and contrast-enhanced dynamic T1- or T2*-MRI provide such information. These techniques have been applied to many different tumors, such as cancers of breast (Fig. 4), prostate, cervix, rectum, liver, as well as gliomas, pulmonary nodules, malignant pleural mesothelioma and multiple myeloma [41]. Beyond the simple visual assessment of a signal intensity time curve, descriptive parameters such as lag time, amplitude, slope, and area under the curve (wash-out) can be calculated [42]. They are determined by perfusion and flow towards the tumor and related to microvascular density and permeability. Perfusion itself can be quantified by the introduction of pharmacokinetic compartmental models which take the different properties of the contrast agents and the tissue of interest into consideration [43, 44] in order to quantify regional blood volume, regional blood flow

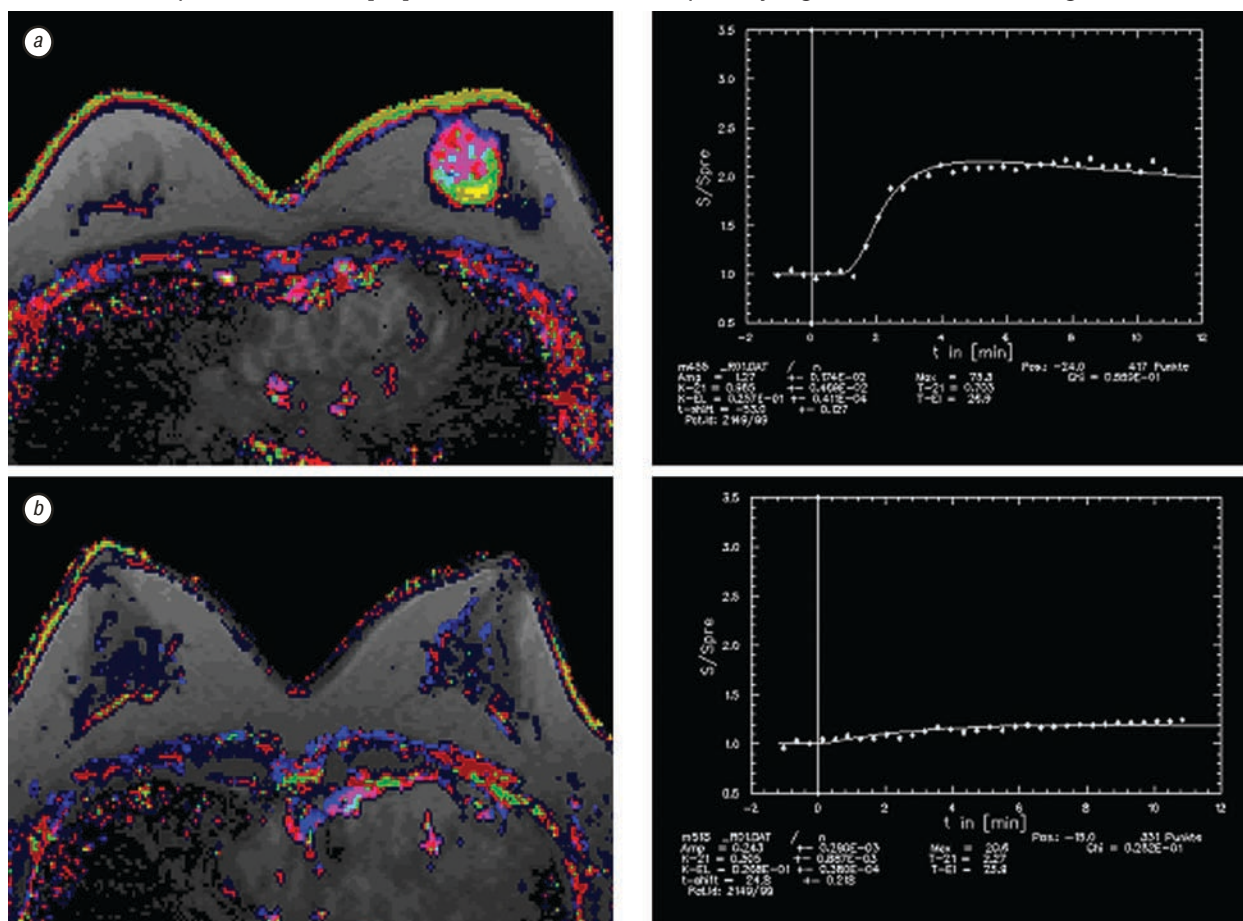


Fig. 4. MRI-based perfusion map in breast cancer. (a) High perfusion indicated by high amplitude and exchange rate before chemotherapy. (b) No spot of increased perfusion after chemotherapy, i. e. “complete regression”

and mean transit time. It has been demonstrated that the amplitude of the signal correlates with the microvascular density of the tumor whereas the exchange rate points towards an increased permeability of the tumor vasculature [45, 46]. These parameters are also helpful to assess the angiogenic potential of tumors and are well-suited to follow-up therapies with anti-angiogenic compounds such as thalidomide for the treatment of multiple myeloma [47] as well as to predict response and outcome early.

MR spectroscopy (MRS), either single-voxel or chemical shift imaging, is capable to provide metabolic information about tumor cells and the surrounding tissue. Shifts in the distribution of certain metabolites provide important hints towards the differential diagnosis and the tumor biological behavior at the same time. Clinically, MRS is mainly applied in suspicious intracranial masses and prostate cancer. In the brain, MRS is helpful for the differential diagnosis between gliomas and metastases or tumor recurrence and radionecrosis [48], where the appearance of lipid peaks is related to necrosis. Citrate is a typical metabolic product of the normal prostate gland, whereas the loss of citrate and the increase of the choline/citrate ratio is an important indicator for prostate cancer [49].

Diffusion-weighted MRI has gained increased importance for planning stereotactic procedures, such as biopsies or radiotherapy, but might be a very attractive tool for follow-up studies as well. As the magnitude of diffusion in the tissues is dependent of cellularity indicating viable tumor, changes in diffusion signal after therapy may reflect its effectiveness (Fig. 5) or failure [50]. Diffusion-weighted MRI can also be used to assess the fractional anisotropy of tissues. Fractional anisotropy detects suspicious changes within brain tissues adjacent to the tumor which might predict the future infiltration paths [51]. Such structures seem to be at a higher risk for tumor infiltration or recurrence during follow-up and will deserve increased attention.

Future perspectives. Imaging assessment of tumor response becomes more and more important because multimodal treatment regimes are rather complex and expensive. Thus, imaging and its future development has to meet definite requirements. RECIST is far from being perfect, but it is the agreed current standard in oncology. An optimized radiological workflow within the electronic information systems will make RECIST evaluation available under time- and cost-efficient conditions. At the same time, more standardization will be highly appreciated by all clinicians involved in oncology. With software tools for volumetric analysis becoming more widely available they can be integrated and expand RECIST to the third dimension. However, the assessment will still merely rely on morphological structure. Currently, the different techniques of “functional” assessment of therapy response are in different phases of development and clinical availability. More evidence has to be generated by clinical trials before such techniques will be officially accepted as a complement or substitute of

RECIST. We assume that the selection of the appropriate functional imaging techniques or a combination of them will either be determined by the tumor entity or the type of treatment. PET and MRI come up with techniques tailored for the assessment of proliferation, amino acid- or tissue-specific metabolism, angiogenesis, or fiber structure. Thus, they can be applied according to the expected properties of the tumor tissue, such as MRS or choline PET in prostate cancer or perfusion MRI in gliomas or multiple myeloma. For assessment of potential or actual treatment response the techniques should be selected according to the mechanism of action of the therapy, such as perfusion MRI for anti-angiogenic treatment or hypoxia imaging for radiotherapy.

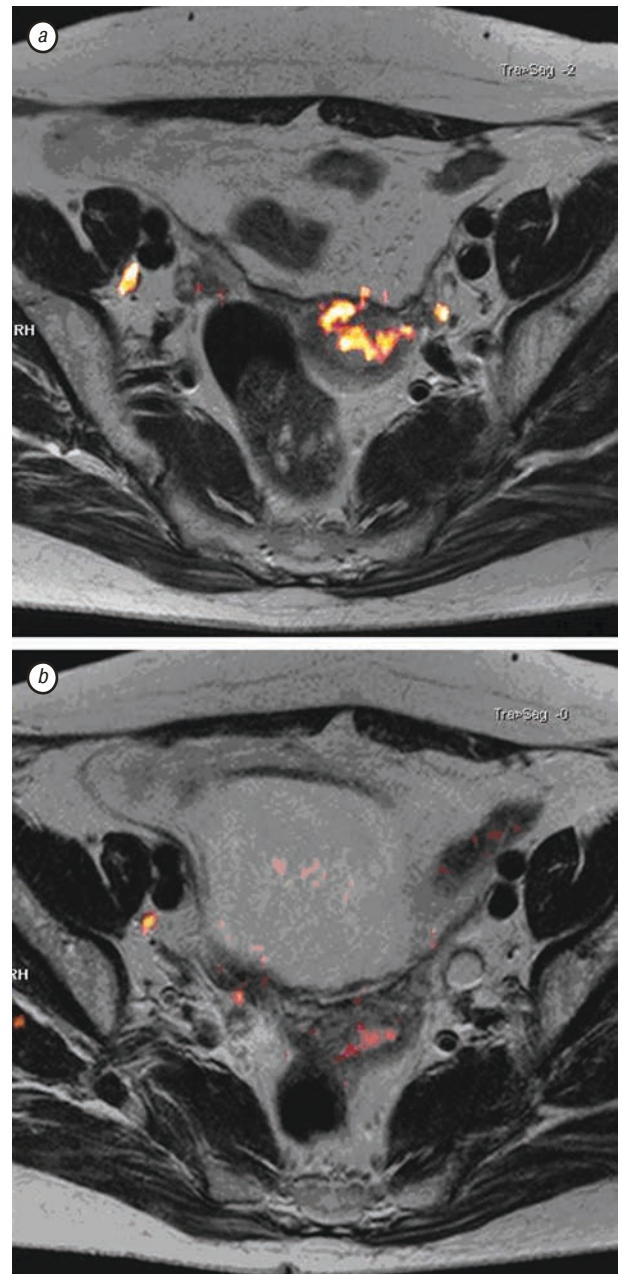


Fig. 5. Fused anatomical T2-weighted MR-images and MR-diffusion maps in endometrial carcinoma. (a) High diffusion signal before chemoradiotherapy. (b) Marked decrease of diffusion signal both in endometrium and right iliac lymph node after chemoradiotherapy, i. e. “partial regression”

ACKNOWLEDGMENTS

We would like to thank Lars Bornemann, Volker Dicken (MeVis GmbH, Bremen, Germany), Klaus Wasser (Dept. of Radiology, University Clinic Mannheim, Mannheim, Germany), and Frederik Giesel (Department of Radiology, German Cancer Research Center, Heidelberg, Germany) for image support. Sjarhei Kharuzhyk was supported by International Atomic Energy Agency grant No. BYE/06001.

REFERENCES

- Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005; **16**: 481–8.
- Kumar P, Rehani MM, Kumar L, *et al.* Tumor marker CA-125 as an evaluator and response indicator in ovarian cancer: its quantitative correlation with tumor volume. *Med Sci Monit* 2005; **11**: 84–9.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
- Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92**: 205–16.
- Husband JE, Schwartz LH, Spencer J, *et al.* Evaluation of the response to treatment of solid tumours - a consensus statement of the International Cancer Imaging Society. *Br J Cancer* 2004; **90**: 2256–60.
- Stroszczynski C, Jost D, Reichardt P, *et al.* Follow-up of gastro-intestinal stromal tumours (GIST) during treatment with imatinib mesylate by abdominal MRI. *Eur Radiol* 2005; **15**: 2448–56.
- Krix M, Plathow C, Essig M, *et al.* Monitoring of liver metastases after stereotactic radiotherapy using low-MI contrast-enhanced ultrasound — initial results. *Eur Radiol* 2005; **15**: 677–84.
- Padhani AR, Ollivier L. The RECIST (Response Evaluation Criteria in Solid Tumors) criteria: implications for diagnostic radiologists. *Br J Radiol* 2001; **74**: 983–86.
- Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. *J Clin Oncol* 2006; **24**: 3245–51.
- James K, Eisenhauer E, Christian M, *et al.* Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999; **91**: 523–8.
- Cortes J, Rodriguez J, az-Gonzalez JA, *et al.* Comparison of unidimensional and bidimensional measurements in metastatic non-small cell lung cancer. *Br J Cancer* 2002; **87**: 158–60.
- Gurland J, Johnson RO. Case for using only maximum diameter in measuring tumors. *Cancer Chemother Rep* 1966; **50**: 119–24.
- Mazumdar M, Smith A, Schwartz LH. A statistical simulation study finds discordance between WHO criteria and RECIST guideline. *J Clin Epidemiol* 2004; **57**: 358–65.
- Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Ann Oncol* 2004; **15**: 257–60.
- Plathow C, Klopp M, Thieke C, *et al.* Therapy response in malignant pleural mesothelioma-role of MRI using RECIST, modified RECIST and volumetric approaches in comparison with CT. *Eur Radiol* 2008; DOI 10.1007/s00330-008-0918-9.
- Oxnard GR, Armato SG, Kindler HL. Modeling of mesothelioma growth demonstrates weaknesses of current response criteria. *Lung Cancer* 2006; **52**: 141–8.
- Van Schil P. Malignant pleural mesothelioma: staging systems. *Lung Cancer* 2005; **49** (Suppl 1): S45–8.
- Schwartz LH, Mazumdar M, Brown W, *et al.* Variability in response assessment in solid tumors: effect of number of lesions chosen for measurement. *Clin Cancer Res* 2003; **9**: 4318–23.
- Erasmus JJ, Gladish GW, Broemeling L, *et al.* Inter-observer and intraobserver variability in measurement of non-small-cell carcinoma lung lesions: implications for assessment of tumor response. *J Clin Oncol* 2003; **21**: 2574–82.
- Marten K, Auer F, Schmidt S, *et al.* Automated CT volumetry of pulmonary metastases: the effect of a reduced growth threshold and target lesion number on the reliability of therapy response assessment using RECIST criteria. *Eur Radiol* 2007; **17**: 2561–71.
- Covey AM, Tuorto S, Brody LA, *et al.* Safety and efficacy of preoperative portal vein embolization with polyvinyl alcohol in 58 patients with liver metastases. *AJR Am J Roentgenol* 2005; **185**: 1620–6.
- Denys A, Lacombe C, Schneider F, *et al.* Portal vein embolization with N-butyl cyanoacrylate before partial hepatectomy in patients with hepatocellular carcinoma and underlying cirrhosis or advanced fibrosis. *J Vasc Interv Radiol* 2005; **16**: 1667–74.
- Marten K, Grillhosi A, Seyfarth T, *et al.* Computer-assisted detection of pulmonary nodules: evaluation of diagnostic performance using an expert knowledge-based detection system with variable reconstruction slice thickness settings. *Eur Radiol* 2005; **15**: 203–12.
- Matsumoto T, Yoshimura H, Giger ML, *et al.* Potential usefulness of computerized nodule detection in screening programs for lung cancer. *Invest Radiol* 1992; **27**: 471–5.
- Sitteck H, Perlet C, Helmlinger R, *et al.* Computer-assisted analysis of mammograms in routine clinical diagnosis. *Radiologie* 1998; **38**: 848–52 (in German).
- Peldschus K, Herzog P, Wood SA, *et al.* Computer-aided diagnosis as a second reader: spectrum of findings in CT studies of the chest interpreted as normal. *Chest* 2005; **128**: 1517–23.
- Kostis WJ, Reeves AP, Yankelevitz DF, Henschke CI. Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images. *IEEE Trans Med Imaging* 2003; **22**: 1259–74.
- Mahr A, Levegrun S, Bahner ML, *et al.* Usability of semiautomatic segmentation algorithms for tumor volume determination. *Invest Radiol* 1999; **34**: 143–50.
- Yim PJ, Vora AV, Raghavan D, *et al.* Volumetric Analysis of Liver Metastases in Computed Tomography With the Fuzzy C-Means Algorithm. *J Comput Assist Tomogr* 2006; **30**: 212–20.
- Fabel M, von Tengg-Kobligh H, Giesel FL, *et al.* Semi-automated volumetric analysis of lymph node metastases in patients with malignant melanoma stage III/IV-A feasibility study. *Eur Radiol* 2008; DOI 10.1007/s00330-008-0866-4.
- Bornemann L, Kuhnigk JM, Dicken V, *et al.* Informatics in radiology (infoRAD): new tools for computer assistance in thoracic CT part 2. Therapy monitoring of pulmonary metastases. *Radiographics* 2005; **25**: 841–8.
- Goo JM, Tongdee T, Tongdee R, *et al.* Volumetric measurement of synthetic lung nodules with multi-detector row CT: effect of various image reconstruction parameters and segmentation thresholds on measurement accuracy. *Radiology* 2005; **235**: 850–6.
- Winer-Muram HT, Jennings SG, Meyer CA, *et al.* Effect of varying CT section width on volumetric measurement of lung tumors and application of compensatory equations. *Radiology* 2003; **229**: 184–94.

34. Suzuki C, Jacobsson H, Hatschek T, *et al.* Radiologic Measurements of Tumor Response to Treatment: Practical Approaches and Limitations. *RadioGraphics* 2008; **28**: 329–44.
35. Kauczor HU. Multimodal imaging and computer assisted diagnosis for functional tumour characterisation. *Cancer Imaging* 2005; **5**: 46–50.
36. Sachelarie I, Kerr K, Ghesani M, Blum RH. Integrated PET-CT: evidence-based review of oncology indications. *Oncology (Williston Park)* 2005; **19**: 481–90.
37. Lardinois D, Weder W, Hany TF, *et al.* Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003; **348**: 2500–7.
38. Israel O, Mor M, Guralnik L, *et al.* Is 18F-FDG PET/CT useful for imaging and management of patients with suspected occult recurrence of cancer? *J Nucl Med* 2004; **45**: 2045–51.
39. Antoch G, Kanja J, Bauer S, *et al.* Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. *J Nucl Med* 2004; **45**: 357–65.
40. Juweid ME, Wiseman GA, Vose JM, *et al.* Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 2005; **23**: 4652–61.
41. Knopp MV, von Tengg-Kobligh H, Choyke PL. Functional magnetic resonance imaging in oncology for diagnosis and therapy monitoring. *Mol Cancer Ther* 2003; **2**: 419–26.
42. Padhani AR, Dzik-Jurasz A. Perfusion MR imaging of extracranial tumor angiogenesis. *Top Magn Reson Imaging* 2004; **15**: 41–57.
43. Schnall MD, Blume J, Bluemke DA, *et al.* Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. *Radiology* 2006; **238**: 42–53.
44. Furman-Haran E, Degani H. Parametric analysis of breast MRI. *J Comput Assist Tomogr* 2002; **26**: 376–86.
45. Kiessling F, Farhan N, Lichy MP, *et al.* Dynamic contrast-enhanced magnetic resonance imaging rapidly indicates vessel regression in human squamous cell carcinomas grown in nude mice caused by VEGF receptor 2 blockade with DC101. *Neoplasia* 2004; **6**: 213–23.
46. Kiessling F, Huber PE, Grobholz R, *et al.* Dynamic magnetic resonance tomography and proton magnetic resonance spectroscopy of prostate cancers in rats treated by radiotherapy. *Invest Radiol* 2004; **39**: 34–44.
47. Wasser K, Moehler T, Neben K, *et al.* Dynamic MRI of the bone marrow for monitoring multiple myeloma during treatment with thalidomide as monotherapy or in combination with CED chemotherapy. *Rofo* 2004; **176**: 1285–95 (in German).
48. Lichy MP, Plathow C, Schulz-Ertner D, *et al.* Follow-up gliomas after radiotherapy: 1H MR spectroscopic imaging for increasing diagnostic accuracy. *Neuroradiology* 2005; **47**: 826–34.
49. van Dorsten FA, van der GM, Engelbrecht MR, *et al.* Combined quantitative dynamic contrast-enhanced MR imaging and (1)-H MR spectroscopic imaging of human prostate cancer. *J Magn Reson Imaging* 2004; **20**: 279–87.
50. Hamstra DA, Chenevert TL, Moffat BA, *et al.* Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. *PNAS* 2005; **102**: 16759–64.
51. Stieltjes B, Schluter M, Didinger B, *et al.* Diffusion tensor imaging in primary brain tumors: Reproducible quantitative analysis of corpus callosum infiltration and contralateral involvement using a probabilistic mixture model. *Neuroimage* 2006; **31**: 531–42.

ОЦЕНКА ОПУХОЛЕВОГО ОТВЕТА НА ЛЕЧЕНИЕ: ГДЕ НАХОДИТСЯ ЛУЧЕВАЯ ДИАГНОСТИКА СЕГОДНЯ?

Лечение онкологических пациентов требует длительного наблюдения для оценки эффективности существующих и новых способов терапии. Обычно для этого определяют регрессию опухоли, используя методы лучевой диагностики. В 1979 г. ВОЗ предложила критерии оценки регрессии опухоли, основанные на измерении двух максимальных размеров. Новые критерии RECIST появились в 2000 г. и основаны на определении только одного максимального размера. Не вызывает сомнения, что изменение размеров опухоли является только одним из способов оценки ее ответа на лечение, не обязательно отражающим биологическую активность опухоли или эффективность конкретного метода противораковой терапии. Исследование биологических, метаболических и молекулярных свойств опухоли и их изменения в процессе лечения может послужить более чувствительным и ранним способом оценки опухолевого ответа.

Ключевые слова: опухоль, ответ на лечение, RECIST, анализ объема, компьютер-ассистированная диагностика.