Journal of Cancer Research and Practice 3 (2016) 97–103

Contents lists available at ScienceDirect

Journal of Cancer Research and Practice

journal homepage: http://www.journals.elsevier.com/journal-of-cancer-research-and-practice

Review article

Angiogenesis in hematological malignancy – Evaluated by dynamic contrast-enhanced MRI

Tiffany Ting-Fang Shih [a, b, *]

[a] Department of Radiology and Medical Imaging, National Taiwan University Medical College and Hospital, Taipei, Taiwan
[b] Department of Medical Imaging, Taipei City Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 6 April 2016
Accepted 8 June 2016
Available online 24 June 2016

Keywords:
Dynamic-Contrast Enhancement
MRI
Angiogenesis
Leukemia
Multiple myeloma

ABSTRACT

Bone marrow angiogenesis can be measured by DCE-MRI. DCE-MRI is an imaging technique that appears to provide quantitative and biologically relevant information related to tumor vasculature and angiogenesis, which can inform novel drug efficacy, monitor treatment response and act as an imaging biomarker to predict treatment outcome and survival in hematological malignant patients. Increased bone marrow perfusion as reflected by higher Peak value can independently predict adverse clinical outcome in patients with acute myeloid leukemia (AML). In addition, DCE-MRI derived data of bone marrow in AML patients at remission status provides useful information on clinical outcome of patients who might have relapse or not. Patients with a higher value for Kep at remission status would have shorter relapse-free duration and may need to undergo additional therapy. In multiple myeloma, DCE-MRI data correlate strongly with marrow tissue microvessel density. Studies identify high Amplitude values as a possible risk factor associated with the development of extra-medullary disease in multiple myeloma patients; these findings partly support the hypothesis that bone marrow angiogenesis may play role in the development of extra-medullary disease in multiple myeloma. DCE-MRI derived-parameters could serve as a guidance for the selection of optimal management plans, thereby contributing to the development of "personalized medicine" for patient.

1. Introduction

Personalized medicine is the major goal of translational research in the post-genomic era.[1] Numerous biomarkers have been identified by genomic or proteomic approach that can reclassify the disease phenotype and predict clinical outcome.[2] However, to define a specific disease phenotype, it is not necessarily depend on molecular or genomic technologies.

Angiogenesis is one of the factors that correlate with the tumor aggressiveness and clinical outcome of patients with malignant solid tumors such as melanoma,[3–6] prostate cancer,[7] breast cancer,[8] and also in so called "liquid tumors" such as leukemia or lymphomas[9,10] and multiple myeloma.[11–13] Microvessel density (MVD) is traditional "gold standard" for quantification of angiogenesis in tumor tissue. MVD increased in patients with acute leukemia with active disease in comparison to healthy controls or patients in remission. It is also known that various parameters such as age, karyotype, and performance status are prognostic factors in acute myeloid leukemia (AML) patients before they receive chemotherapy.[14,15] However, MVD can be measured only in the limited area of the bone marrow (BM) biopsy specimen; thus, it cannot be used to assess the global or in vivo tumor angiogenesis. None of the functional status of the tumor blood vessel (such as permeability, elimination rate) could be determined by the above-mentioned immunohistochemical methods of MVD.[16–19]

On the other hand, once patients achieve complete remission (CR) after standardized treatment, an ideal prognostic predictor that should be rapidly and easily measurable and reproducible to be adopted into routine clinical practice is still absent.[20] Although the likelihood of relapse declines sharply to less than 10% once CR persists for 3 years,[21] the challenge remains of maintaining remission. The ability to detect patients at high risk of relapse may help in the design of therapeutic strategies to improve the duration of remission. Therefore, an accurate assessment of bone marrow microenvironment in these patients in whom CR is achieved is

* Department of Radiology and Medical Imaging, National Taiwan University Medical College and Hospital, No.7, Chung-Shan S. Rd., Taipei 10002, Taiwan.
E-mail address: ttfshih@ntu.edu.tw.
Peer review under responsibility of The Chinese Oncology Society.

http://dx.doi.org/10.1016/j.jcrpr.2016.06.001

essential to detect early relapse and evaluate treatment effectiveness.

Because the BM microenvironment should change considerably after the initial induction chemotherapy,[22] it is reasonable that the data collected at CR status would be more useful than pretreatment data to predict the survival outcome of these patients. For example, findings in a recent study suggested that neutrophil count and platelet count at the time of CR can serve as independent factors for prediction of relapse-free survival (RFS).[23] Another study described that the cytogenetic analysis performed at the time of CR is a predictor of overall survival (OS), RFS, and relapse rate in AML patients.[24]

The aggressiveness of angiogenesis is not only well known in acute leukemia, but also noted in multiple myeloma. Multiple myeloma (MM) is a malignant plasma cell proliferation typically found in BM.[25] Although MM cells (MCs) depend on the BM microenvironment to provide the signals essential for their growth and survival, in a fraction of patients MCs acquire the ability to proliferate in sites outside the BM. Such occurrences appear as extramedullary disease (EMD), indicating that MCs have become independent of the BM microenvironment.[25] The exact mechanism underlying the development of EMD in MM patients is not clear. One hypothesis suggests an alteration in the interaction between MCs and the BM microenvironment.[26,27] Therefore, the BM "angiogenesis" might also play a major role in not only promoting the growth and survival of MCs but also the disease progression itself.[26–28] The interaction between MCs and BM endothelial cells upregulates a number of angiogenic cytokines, such as vascular endothelial growth factor or matrix metalloproteinases. Such cytokines further stimulate BM angiogenesis and myeloma progression,[29,30] as well as possible extramedullary dissemination.[28]

New technologies for cancer image with functional assessment are now possible in vivo by Doppler sonography, dynamic contrast-enhanced (DCE)-MRI, DCE computed tomography (CT), and fluorodeoxyglucose-18 positron emission tomography (PET).[31–33] DCE-MRI is a noninvasive and quantitative method of investigating microvascular structure and function by tracking the pharmacokinetics of injected low-molecular-weight contrast agents as they pass through the tumor vasculature.[34] This technique provides a direct quantification of blood vessel density, vascular flow, and permeability.[35–37] Up to date, DCE-MRI is one of the most widely used noninvasive methods of measuring the perfusion and permeability of a biological tissue in the body, such as vertebral BM.[38] In addition, functional imaging biomarkers may be used to assess treatment response earlier.[39] This modality is being increasingly used in many oncological studies, including those of patients with hematologic cancers,[14,15,40–42] to characterize tumor angiogenesis and invasiveness and to monitor the treatment response.[31,32,43] There have been increasing attempts to use this approach to assess spatial and temporal heterogeneity in tumor angiogenesis and to predict tumor biologic aggressiveness and treatment response in not only solid tumors,[44–47] but also in leukemia/lymphoma, multiple myeloma,[48] and myelodysplastic syndrome.[49]

2. Basis and methodology of DCE-MRI

DCE-MRI images are performed by using injecting low-molecular-weight gadolinium chelated contrast agent with a constant, stable rate.[50] The contrast agent is carried by blood flow into the tissue, causing increased signal intensity (SI) of the T1-weighted images due to the shortening of relaxation time of the tissue.[51] Within the tissue, the contrast agent passes from the arteries to the capillaries, and then permeates to the extravascular extracellular space (EES). The rate of contrast agent extravasation to EES in the tumor tissue is determined by vessel leaky and blood flow. Thus, the signal counted on DCE-MRI represents a combination of permeability and tissue perfusion. DCE-MRI is sensitive to alterations in vascular permeability, extracellular space, and blood flow. To ideally record the signal change in the supplying blood vessel and within the tumor, a regular injection rate of the contrast agent captured with proper temporal resolution according to the flow rate of the investigated tissue is recommended.[52]

This signal enhancement of bone marrow perfusion can be quantified either with a semi-quantitative or quantitative analysis. The semi-quantitative analysis is based on the calculation of heuristic parameters that can be easily extracted from SI curves. In contrast, the quantitative analysis needs model-based curve fitting algorithms using a bi-compartmental model as well as arterial input function. The parameters from both analysis methods have been shown to present correlation with bone marrow angiogenesis and MVD by immune-histochemical stain from biopsy tissue counting.[53] Our research protocols for the use of DCE-MRI of BM perfusion and angiogenesis measurement have been described previously.[54,55] In brief, DCE-MRI was performed at the midsection of vertebral bodies from T11 to sacrum, and the values of signal from L2 to L4 were measured by a radiologist and plotted as a time–SI curve. The time–SI curve was then fitted by the Mathematica (v 6.1) software (Wolfram Research, Champaign, IL) using a nonlinear curve-fitting function. The baseline SI (SI base) on a time–SI curve was defined as the mean SI for the first five images, and the maximum SI (SI max) was defined as the maximum value of the first rapidly rising part of the curve. We usually set the total duration of DCE-MRI examination at 600 s to track the uptake kinetics of contrast agents. The contrast enhancement rise time (T rise) was defined as the time between SI base and SI max. The two semi-quantitative parameters, Peak and Slope, were calculated as (SI max − SI base)/SI base and (SI max − SI base)/T rise, respectively.

On the other hand, the angiogenesis parameters based on DCE-MRI could be described by three model quantitative parameters, Amp, Kep, and Kel, calculated using the bi-compartmental model.[54,55] Data for each patient were represented as the average for the parameters of vertebral bodies from L2 to L4. Among these semi-quantitative and quantitative parameters, Peak indicates the contrast material in the intra- and extra-vascular interstitial spaces, representing tissue perfusion; Slope predominantly indicates the contrast agent in the intravascular space, which is determined by tissue vascularization and perfusion as well as capillary permeability; Amp is similar to Slope but provides better quantification of vascularity. The efflux rate constant is represented as Kep, which indicates the permeability. The Kep parameter is a rate transfer coefficient. More details about the measurement methods were listed as below:

3. Semi-quantitative analysis

Regarding the semi-quantitative analysis, different parameters that characterize the shape of the normalized SI time curve can be extracted: (1) area under curve (AUC): expresses the amount of enhancement over a defined period of time (usually from starting increment of the time intensity curve to 60 or 90 s); (2) maximum of SI or Peak enhancement ratio (SI maximum − SI baseline/SI baseline) of the enhancing curve; (3) wash-in Slope: determines the velocity of enhancement. It is calculated as the maximum change in enhancement per unit time, usually from 20% to 80% range of the slope of increment curve; and (4) mean transit time (MTT): represents the mean time for blood to perfuse a region of tissue and is affected by the blood volume and blood flow in the region under analysis.

The semi-quantitative analysis is widely used because it is easy to calculate without the need of modeling. However, these parameters are highly affected by the factor of the acquisition systems, contrast media volume and injection rate, because the true concentration of contrast agent in the tissues is not estimated. Thus, differences in temporal resolution and injection rates can easily change the shape and amplitude of SI curves, making comparison and quantification difficult.[56,57] Moreover, these descriptive parameters provide no physiologic meaning into the behavior of the tumor vessels.

4. Quantitative analysis

The quantitative analysis is based on modeling the concentration change of the contrast agent using pharmacokinetic modeling techniques.[58] An initial conversion of SI to concentration values is needed. Concentration *vs* time curves are then fitted using a bi-compartmental PK model (vessels and EES) with single vascular input (usually aorta or other). The following parameters can be derived from a mathematical model[59]: (1) Ktrans (volume transfer constant): determines the influx of the contrast agent from the intravascular space to the EES. It predominantly represents the vascular permeability in a permeability-limited (high flow) situation, but represents the blood flow into the tissue in a flow-limited (high permeability) situation; (2) Kep (reverse reflux rate constant): expresses the return process of the contrast agent from the EES to the intravascular space; and (3) Ve (volume fraction of EES): an indirect measure representing the cellular density of the tissue. In the micro-environment of bone marrow, the above mentioned parameters are more related to low flow status, because the blood perfusion rate of marrow is rather slow as compared with other organ/systems. Those data represents the blood flow into the tissue in a flow-limited situation.

These parameters require additional calculations to generate parametric maps obtained after a pixel-by-pixel curve fitting process of the region under analysis. Thus, they are more computationally technical to obtain than the semi-quantitative ones. After generating parametric maps, the mean or median values within region of interests (ROI) are usually calculated to represent microvasculature, but histogram analysis[60] or heterogeneity in parametric maps[61–63] may also provide additional information. For optimum parameter quantification, a moderate temporal resolution is required to record initial rapid uprising of the SI curve immediately after the contrast agent administration.[64] The accuracy of these parameters is influenced by curve fitting algorithms[65,66] and magnitude of motion artifacts.[67] Luckily, the environment of BM would not count on motion artifact.

5. Model selection

Kety[68] first described the flow-limited tracer uptake in tissue, and since then several pharmacokinetic models have been proposed by Tofts et al.,[69] Brix et al.[70] All these models used single source of arterial input function. However, for BM parenchymal disease, which are supplied by small arteriole such as segmental artery directly arising from aorta, a single-input, bi-compartment PK model by Brix and Tofts is often used to obtain.

The choice of contrast agent molecular properties[71] and the temporal resolution of the acquisition have a clear influence on the parameters. To standardize calculations, the acquisition should have proper temporal resolution (about 5 s each image set, during at least 5 min or 300 s), and voxel-wise statistical analysis is suggested.

6. Clinical application of DCE-MRI

Increased bone marrow MVD was reported in patients with AML, but its association with patients' survival is unclear and inconclusive,[18,72,73] probably because the MVD detected by conventional immunocytochemical technique is unable to assess the global and dynamic angiogenesis of the bone marrow. Vascularity within a tumor can be spatially or temporally heterogeneous; and tumor vessels are much more permeable than are normal blood vessels. Thus, assessment of angiogenesis in the BM by traditional MVD poses special challenges.[74–76]

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can provide global and functional imaging of tumor angiogenesis. A previous research,[37] demonstrated that the rate of vertebral marrow perfusion decreased significantly in subjects older than 50 years, but it decreased in a relatively slow speed. However, the differences of BM perfusion between patients with AML and age- and sex-matched healthy subjects were drastic.[22] The patients with AML had much higher Peak values (as the key parameter) than did the age- and sex-matched controls (almost 4.8-fold difference), and the distribution had no overlap between these 2 groups. Thus, we can postulate that, although the age factor has influence on the Peak of the bone marrow, it is minor and can be overridden by the great effect of tumor angiogenesis.

Bone marrow DCE-MRI performed at diagnosis and complete remission of the acute myeloid leukemia (AML) patients, those multi-parametric data from DCE-MRI correlated significantly with treatment outcome. Three distinct parameters: peak enhancement ratio (Peak) to indicate tissue blood perfusion; amplitude (Amp) to reflect vascularity; and volume transfer constant (Ktrans) to indicate vascular permeability. The Peak and Amp decreased significantly at remission status after induction chemotherapy as compared to their initial status (Figs. 1 and 2). Patients with higher Peak or Amp at initial diagnosis (before any intervention) had shorter overall survival and disease-free survival than others. Cox multivariate analysis identified higher Peak value (hazard ratio, 9.181; 95% confidence interval, 1.740−48.437; $p = 0.009$) as an independent predictor for overall survival in addition to unfavorable karyotype and old age. These findings provide evidence that increased BM angiogenesis measured by DCE-MRI can predict adverse clinical outcome in AML patients and may help to select high-risk phenotype AML patients for tailored antiangiogenic therapy and to monitor treatment response.

DCE-MRI may be a better alternative method than MVD in bone marrow biopsy specimens because it is non-invasive and can evaluate much bigger bone volumes, thus better representing the overall disease burden. This has prompted novel antiangiogenic approaches in AML.[77–80] The current study's finding that DCE-MRI assessment of patients with AML with increased bone marrow angiogenesis can predict poor clinical outcome also indicates that anti-angiogenesis treatment may be beneficial for these patients.

More importantly, DCE-MRI can provide noninvasive, convenient, and reproducible serial evaluations of global bone marrow angiogenesis diagnostics with only 600 s of scanning time and preparation for whole scanning only less than 20 min. This is more practical than repeated bone marrow biopsies and MVD studies. In short, DCE-MRE play an important role to help physicians both identify the most appropriate patients for antiangiogenic therapies for the best treatment results and to monitor the response to treatment. Moreover, the finding that patients receiving bone marrow transplantation survive longer than those without in the group with higher Peak value implies that bone marrow transplantation may be a therapeutic option for those with higher bone marrow angiogenesis. Further studies in more patients are needed to clarify this point. According to the large-scale prospective study

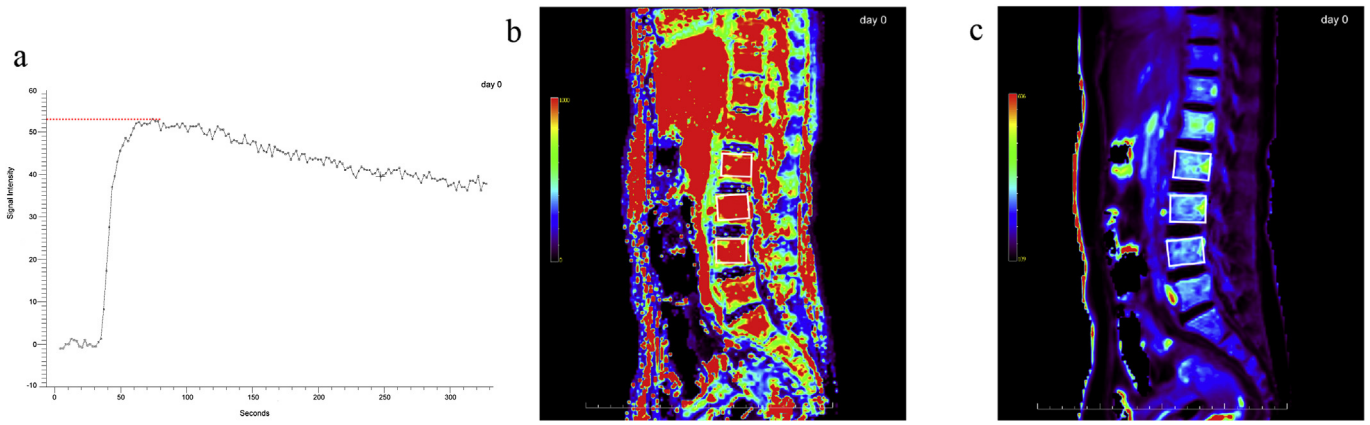

Fig. 1. a: Time–intensity curve of a 55 year-old female detected on day 0; the highest spot of the curve was noted as signal of 53. b: Peak derived color map for bone marrow of lumbar spine detected on day 0. The regions of interest (ROIs) were placed on 2nd, 3rd and 4th vertebrae. The average of the three vertebrae showed Peak value as 3.0. c: Kep derived color map for bone marrow of lumbar spine detected on day 0. The regions of interest (ROIs) were placed on 2nd, 3rd and 4th vertebrae. The average of the three vertebrae showed Kep value as 13.1.

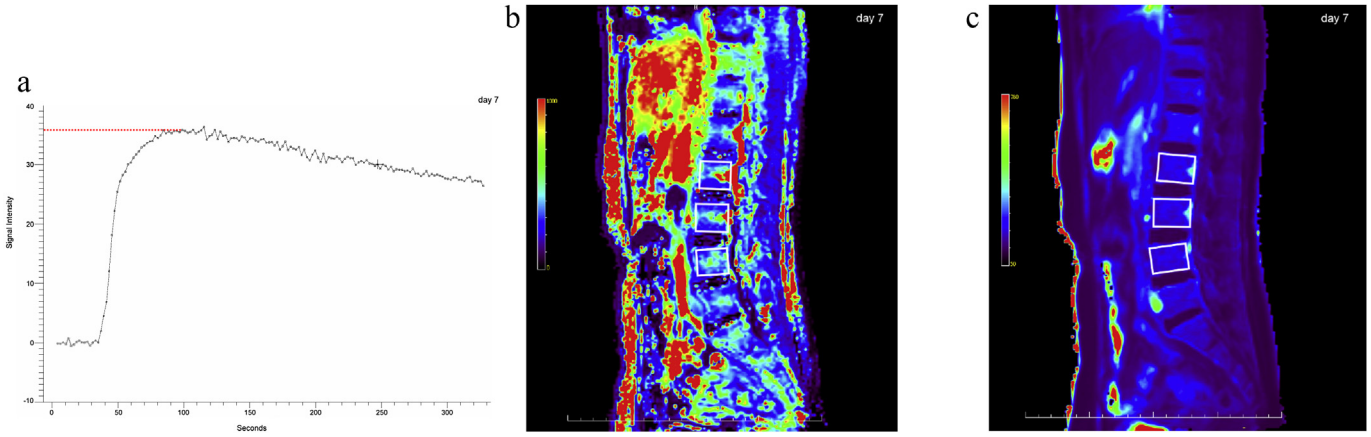

Fig. 2. a: Time–intensity curve of a 55 year-old female detected on day 7th; the highest spot of the curve was noted as signal of 36. b: Peak derived color map for bone marrow of lumbar spine detected on day 7th. The regions of interest (ROIs) were placed on 2nd, 3rd and 4th vertebrae. The average of the three vertebrae showed Peak value as 2.0. The Peak value had dramatic decrease on day 7 after induction chemotherapy. c: Kep derived color map for bone marrow of lumbar spine detected on day 7. The regions of interest (ROIs) were placed on 2nd, 3rd and 4th vertebrae. The average of the three vertebrae showed Kep value as 3.7. The Kep had dramatic decrease after induction chemotherapy.

that used DCE-MRI to evaluate the functional bone marrow angiogenesis in patients with AML is a possible and convenient method achievable. The pretreatment Peak, reflecting bone marrow perfusion, and Amp, reflecting vascularity, of functional bone marrow angiogenesis MRI can predict overall survival and disease free survival of patients with newly diagnosed AML. More intriguingly, higher Peak value was an independent predictor for poor overall survival. These findings suggest that functional MRI of BM angiogenesis is a useful biomarker to predict clinical outcome of patients with AML, and tumor angiogenesis may play an important role in the pathogenesis of AML.[19,77]

Another study also showed that a decreasing peak enhancement ratio after induction chemotherapy was associated with a higher chance of achieving complete remission (CR), better overall survival (OS), and also disease-free survival (DFS).[22] On the other way, the research has demonstrated that DCE-MR imaging parameters in AML patients with a CR status may be an indicator of survival and outcome and serve as an imaging biomarker for selecting risk-adapted treatment.[81] All DCE MR imaging parameters (peak, slope, amplitude, *K*ep, and *K*el) had a significant association with OS; however, only *K*ep was significantly related to RFS in the univariate analysis. Furthermore, *K*ep was an independent prognostic factor of OS and RFS in the multivariate.

It is noteworthy that, even with low tumor burden in these patients following CR, peak value at CR status is still a useful indicator for OS, both in the whole cohort, and more importantly, in the intermediate-risk subgroup. Slope is mainly determined by tissue vascularization and perfusion, but capillary permeability may also play an important role.[82–86] A previous study[40] showed that high values for amplitude at initial DCE MRI is a poor risk factor for disease-free and overall survival in AML patients. In addition, a high value for amplitude at DCE MRI in patients in CR is also associated with shorter OS. *K*ep, a rate transfer coefficient, represents contrast exchange between blood plasma and extravascular extracellular space.[55] It was strongly influenced by permeability and also positively correlated with the perfusion and plasma volume but negatively associated with the interstitial volume.[84] According to the hypothesis,[87] antiangiogenic agents can normalize abnormal tumor vasculature, resulting in more efficient delivery of drugs and oxygen to targeted cancer cells. Under this assumption, when patients achieve CR, bone marrow vessels and their endothelium should be normalized with reduced vessel wall permeability, and bone marrow cells should return to normal karyotype. Failure of this repair process would result in persistent high vascular permeability and a high value for *K*ep. Therefore, increased values for *K*ep in patients with CR status who undergo DCE MR imaging may indicate

a high risk of relapse and shorter OS and RFS. The high permeability of the bone marrow may also be associated with high vascular endothelial growth factor protein expression.[87,88] A high level of vascular endothelial growth factor expression in tumor cells is associated with neovascularization, tumor aggressiveness, and poor prognosis in AML patients.[24] The result implies that *K*ep at remission status, representing the interaction of capillary endothelial permeability, interstitial or intraosseous pressure, and diffusion of molecules between the capillary bed and the interstitial space,[89] may be a suitable marker for current angiogenesis.

In multiple myeloma (MM) patients, the angiogenesis parameters generated from DCE-MRI of vertebral BM reportedly also correlate strongly with histological grade of infiltration, osteolytic bone involvement, microvessel density (MVD), and serum markers of disease activity.[32,48] Extramedullary Disease (EMD) in patients with MM was defined as the presence of MCs outside BM, in one of the following forms: soft-tissue mass spreading from the bone (periosseous plasmacytoma), MCs arising in extraosseous organs (extraosseous plasmacytoma), malignant effusion, or plasma cell leukemia. The presence of EMD was diagnosed in most cases by MRI or computed tomography, which were conducted whenever EMD was suspected from clinical, laboratory, or radiographic findings. However, no data of prior study were available on the correlation between degree of BM angiogenesis and the development of EMD in MM patients. Huang et al. examined the correlation between angiogenesis parameters generated from DCE-MRI of vertebral bodies, together with MVD in BM (obtained from the posterior iliac crest), with the manifestation of EMD in patients with MM.[90] The mean MVD with significant differences being found for patients in different subgroups. Patients with extramedullary disease (EMD) had a higher mean MVD of 20.3 (95% confidence interval [CI: 15.3–25.2]), patients in the non-EMD group had a lower mean MVD of 3.2 (95% CI: 1.4–5.0); but patients with progression disease had a mean MVD of 15.7 (95% CI: 9.9–21.5). The time–signal intensity (SI) curve shown in DCE-MRI correlated strongly with tissue MVD, where a high peak and steep slope were associated with high MVD. By contrast, a lower peak and gentler slope were associated with lower MVD. Moderate correlations were found between MVD and the two semi-quantitative parameters Peak and Slope (both $p < 0.001$). The quantitative parameters, Amp and Kel, but not Kep, were also moderately correlated with MVD. Other salient characteristics significantly correlated with MVD were beta2-microglobulin, C-reactive protein, and percentage of MCs in BM. Further multiple linear regression analysis showed that only Amp and percentage of MCs in BM were independently correlated with MVD. In addition, multiple logistic regression model showed that Amp was the only significant factor associated with EMD (OR = 6.33). The accumulative incidence for development of EMD over time was significantly higher for patients with high Amp (>0.08) than for patients with low Amp (<0.08). Additional covariates were identified by univariate analysis as being significantly associated with the development of EMD, including light chain isotype, high Kel (>0.10), and high calcium (>2.4 mmol/l). However, multivariate analysis using the Cox regression model did not confirm that any of these factors was independently significant. This study demonstrates a possible correlation between the angiogenesis parameter Amp (generated from DCE-MRI of vertebral BM) and EMD in patients with MM. These results identified high Amp values (>0.08) as a possible risk factor associated with the development of EMD in MM patients; high Amp values indicate high tissue vascularity and permeability. This finding partly supports the hypothesis that BM angiogenesis may play role in the development of EMD in MM.[91] Thus, for MM patients, quantitative analysis is necessary using DCE-MRI data and angiogenesis and blood-vessel permeability based microcirculation variables. However, a fuller understanding of what these various measurements imply is necessary before such assessments can be incorporated into routine clinical practice.

Another recent study also concluded that presence of EMD at diagnosis, rather than any treatment modalities ever used, was the only significant predictor of extramedullary recurrence. This finding suggests that the development of EMD, even during treatment, may possibly reflect different tumor biology.[92] One issue raised about the MVD is the histological specimen was obtained usually from the posterior iliac crest and not the vertebral column. This is of some concern, because MM may grow in a patchy rather than diffuse pattern; therefore, the degree of infiltration of the BM by MCs cannot be expected to be equal throughout the skeleton.

However, controversy still surrounds the possible correlation between parameters of DCE-MRI and angiogenesis genes in MM patients.[30] Authors concluded that[90] among MM patients, the angiogenesis parameter Amp was strongly correlated with the tissue MVD of BM obtained from the posterior iliac crest. This finding possibly reflects not only the tissue-specific vascularity, but also the vascular permeability in a more sizable area than the MVD of BM. As a result, Amp rather than MVD may correlate with the development of EMD among MM patients. Thus, high Amp might be a risk factor that could help identify MM patients with the potential to develop EMD. When compared with patients without EMD, patients with EMD displayed significantly greater infiltration of MCs in BM and higher levels of angiogenesis parameter “Amp”. Multiple logistic regression model showed that Amp was the only significant factor associated with EMD.

7. Limitation and future direction

Dynamic contrast-enhanced MR imaging is a reproducible technique. According to many previous studies, the reproducibility of Peak, Amp, Kel and Ktrans is good. This suggests that in a well-conducted study, a change of Peak or Ktrans value is likely to indicate a significant biomarker of therapeutic prognosis. However, current DCE-MRI technique lacks standardization across multiple MR platforms and institutions, making it difficult to implement the technique in a multicenter setting. Besides, there is a need to establish clear thresholds for a significant response when using quantitative DCE-MR imaging parameters for assessment of therapy response.

8. Conclusions

Bone marrow angiogenesis can be measured by DCE-MRI. DCE-MRI may provide dynamic and functional tumor angiogenesis and may help identify high-risk patients for tailored anti-antigenic therapy and monitoring treatment response. Increased bone marrow perfusion as reflected by higher Peak value can independently predict adverse clinical outcome in patients with AML. All DCE-MR parameters were significantly associated with overall survival. In addition, DCE-MRI data of bone marrow in AML patients at remission status can provide useful information on clinical outcome of patients who achieve CR. High *K*ep is an independent factor of overall and relapse free survival in these patients in whom CR was achieved. Patients with a higher value for *K*ep at CR would have shorter relapse-free duration and may need to undergo additional therapy.

In multiple myeloma, DCE-MRI correlated strongly with tissue MVD, where a high peak and steep slope were associated with high MVD. Study identified high Amp values as a possible risk factor associated with the development of extra-medullary disease in MM patients; high Amp values indicate high tissue vascularity and permeability. This finding partly supports the hypothesis that BM

angiogenesis may play important role in the development of EMD in MM.

DCE-MRI is an imaging technique that appears to provide quantitative and biologically relevant information related to tumor vasculature and angiogenesis, which can inform novel drug efficacy, monitor treatment response and act as an imaging biomarker to predict treatment outcome and survival in hematological malignant patients. These parameters could serve as a guide for the selection of optimal management plans, thereby contributing to the development of "personalized medicine" for patient.

A 55 year old female was diagnosed as acute myeloid leukemia, M0, NPM1 (−), FLT3/ITD (−), RUNX1 (+), CEBPA (−). She suffered from intermittent fever and cough for about 1 week since middle of 2015 Feb. Mild dyspnea, rhinorrhea, chillness and abdominal discomfort were also noted few days later. She denied night sweating or weight loss. On Feb 20th, she went to emergency department, where blast cell in peripheral blood was noted with increased count (WBC: 19370, Blast: 71%). Bone marrow study on 2015/Feb 24th, which proved the diagnosis of AML(M0); Flow cytometry revealed: Acute myeloid leukemia, M0 (FAB); the blasts express CD34, CD38, partial CD33, dim CD13, but negative for PO staining or MPO. Cytogenetics: 47XX+11[5/6], 46XX [1/6]; Mutation: NPM1 (−), FLT3/ITD (−), RUNX1 (+), CEBPA (−). Based on the diagnosis confirmed, she received dynamic contrast magnetic resonance study (DCE-MRI) before induction chemotherapy (as day 0). After the MR study, induction chemotherapy started with I2A5 on 2015/March 10th. There was no specific discomfort. Grade IV neutropenia was noted on Day 4. Second DCE-MRI was performed at the end of induction chemotherapy (as day 7th).

Multi-parametric DCE-MR data was illustrated as below: Fig. 1a–c were the time intensity curve (a), peak (b) and Kep (c) acquired from patient before chemotherapy (day 0). Fig. 2a–c were the time intensity curve (a), peak (b) and Kep (c) were acquired from patient after complete the induction chemotherapy (as day 7). The difference was significant and well demonstrated.

Conflict of interest

Authors declare no conflict of interest for this article.

References

1. Langheier JM, Snyderman R. Prospective medicine: the role for genomics in personalized health planning. *Pharmacogenomics*. 2004;5:1–8.
2. Bell J. Predicting disease using genomics. *Nature*. 2004;429:453–456.
3. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature*. 2000;407:249–257.
4. Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med*. 1995;333:1757–1763.
5. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971;285:1182–1186.
6. Maniotis AJ, Folberg R, Hess A, et al. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. *Am J Pathol*. 1999;155:739–752.
7. Sharma N, Seftor RE, Seftor EA, et al. Prostatic tumor cell plasticity involves cooperative interactions of distinct phenotypic subpopulations: role in vasculogenic mimicry. *Prostate*. 2002;50:189–201.
8. Shirakawa K, Kobayashi H, Heike Y, et al. Hemodynamics in vasculogenic mimicry and angiogenesis of inflammatory breast cancer xenograft. *Cancer Res*. 2002;62:560–566.
9. Aguayo A, Kantarjian H, Manshouri T, et al. Angiogenesis in acute and chronic leukemias and myelodysplastic syndromes. *Blood*. 2000;96:2240–2245.
10. Bertolini F, Mancuso P, Gobbi A, et al. The thin red line: angiogenesis in normal and malignant hematopoiesis. *Exp Hematol*. 2000;28:993–1000.
11. Munshi NC, Wilson C. Increased bone marrow microvessel density in newly diagnosed multiple myeloma carries a poor prognosis. *Semin Oncol*. 2001;28:565–569.
12. Rajkumar SV, Leong T, Roche PC, et al. Prognostic value of bone marrow angiogenesis in multiple myeloma. *Clin Cancer Res*. 2000;6:3111–3116.
13. Vacca A, Ribatti D, Presta M, et al. Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. *Blood*. 1999;93:3064–3073.
14. Hillengass J, Wasser K, Delorme S, et al. Lumbar bone marrow microcirculation measurements from dynamic contrast-enhanced magnetic resonance imaging is a predictor of event-free survival in progressive multiple myeloma. *Clin Cancer Res*. 2007;13:475–481.
15. Rahmouni A, Montazel JL, Divine M, et al. Bone marrow with diffuse tumor infiltration in patients with lymphoproliferative diseases: dynamic gadolinium-enhanced MR imaging. *Radiology*. 2003;229:710–717.
16. Kini AR, Peterson LA, Tallman MS, et al. Angiogenesis in acute promyelocytic leukemia: induction by vascular endothelial growth factor and inhibition by all-trans retinoic acid. *Blood*. 2001;97:3919–3924.
17. Dickson DJ, Shami PJ. Angiogenesis in acute and chronic leukemias. *Leuk Lymphoma*. 2001;4:847–853.
18. Padro T, Ruiz S, Bieker R, et al. Increased angiogenesis in the bone marrow of patients with acute myeloid leukemia. *Blood*. 2000;95:2637–2644.
19. Hussong JW, Rodgers GM, Shami PJ. Evidence of increased angiogenesis in patients with acute myeloid leukemia. *Blood*. 2000;95:309–313.
20. Rowe JM, Kim HT, Cassileth PA, et al. Adult patients with acute myeloid leukemia who achieve complete remission after 1 or 2 cycles of induction have a similar prognosis: a report on 1980 patients registered to 6 studies conducted by the Eastern Cooperative Oncology Group. *Cancer*. 2010;116:5012–5021.
21. de Lima M, Strom SS, Keating M, et al. Implications of potential cure in acute myelogenous leukemia: development of subsequent cancer and return to work. *Blood*. 1997;90:4719–4724.
22. Hou HA, Shih TT, Liu CY, et al. Changes in magnetic resonance bone marrow angiogenesis on day 7 after induction chemotherapy can predict outcome of acute myeloid leukemia. *Haematologica*. 2010;95:1420–1424.
23. Yanada M, Borthakur G, Garcia-Manero G, et al. Blood counts at time of complete remission provide additional independent prognostic information in acute myeloid leukemia. *Leuk Res*. 2008;32:1505–1509.
24. Marcucci G, Mrózek K, Ruppert AS, et al. Abnormal cytogenetics at date of morphologic complete remission predicts short overall and disease-free survival, and higher relapse rate in adult acute myeloid leukemia: results from cancer and leukemia group B study 8461. *J Clin Oncol*. 2004;22:2410–2418.
25. Laubach J, Richardson P, Anderson K. Multiple myeloma. *Annu Rev Med*. 2011;62:249–264.
26. Vande Broek I, Vanderkerken K, Van Camp B, et al. Extravasation and homing mechanisms in multiple myeloma. *Clin Exp Metastasis*. 2008;25:325–334.
27. Blade J, de Larrea CF, Rosinol L, et al. Soft-tissue plasmacytomas in multiple myeloma: incidence, mechanisms of extramedullary spread, and treatment approach. *J Clin Oncol*. 2011;29:3805–3812.
28. Vacca A, Ribatti D. Bone marrow angiogenesis in multiple myeloma. *Leukemia*. 2006;20:193–199.
29. Gupta D, Treon SP, Shima Y, et al. Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications. *Leukemia*. 2001;15:1950–1961.
30. Hose D, Moreaux J, Meissner T, et al. Induction of angiogenesis by normal and malignant plasma cells. *Blood*. 2009;114:128–143.
31. Koh TS, Thng CH, Lee PS, et al. Hepatic metastases: in vivo assessment of perfusion parameters at dynamic contrast-enhanced MR imaging with dual-input two-compartment tracer kinetics model. *Radiology*. 2008;249:307–320.
32. Nosàs-Garcia S, Moehler T, Wasser K, et al. Dynamic contrast-enhanced MRI for assessing the disease activity of multiple myeloma: a comparative study with histology and clinical markers. *J Magn Reson Imaging*. 2005;22:154–162.
33. Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia: a report of the French-American-British Cooperative Group. *Ann Intern Med*. 1985;103:620–625.
34. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21:4642–4649 [Published correction appears in *J Clin Oncol* 2004;22(3):576].
35. Shih TT, Tien HF, Liu CY, et al. Functional MR imaging of tumor angiogenesis predicts outcome of patients with acute myeloid leukemia. *Leukemia*. 2006;20:357–362.
36. Shih TT, Chang CJ, Tseng WY, et al. Effect of calcium channel blockers on vertebral bone marrow perfusion of the lumbar spine. *Radiology*. 2004;231:24–30.
37. Chen WT, Shih TT, Chen RC, et al. Vertebral bone marrow perfusion evaluated with dynamic contrast-enhanced MR imaging: significance of aging and sex. *Radiology*. 2001;220:213–218.
38. Biffar A, Dietrich O, Sourbron S, et al. Diffusion and perfusion imaging of bone marrow. *Eur J Radiol*. 2010;76:323–328.
39. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. *J Clin Oncol*. 2006;24:3293–3298.
40. Shih TT, Hou HA, Liu CY, et al. Bone marrow angiogenesis magnetic resonance imaging in patients with acute myeloid leukemia: peak enhancement ratio is an independent predictor for overall survival. *Blood*. 2009;113:3161–3167.
41. Matuszewski L, Persigehl T, Wall A, et al. Assessment of bone marrow angiogenesis in patients with acute myeloid leukemia by using contrast-enhanced MR imaging with clinically approved iron oxides: initial experience. *Radiology*. 2007;242:217–224.
42. Hawighorst H, Libicher M, Knopp MV, et al. Evaluation of angiogenesis and perfusion of bone marrow lesions: role of semiquantitative and quantitative dynamic MRI. *J Magn Reson Imaging*. 1999;10:286–294.

43. Bhooshan N, Giger ML, Jansen SA, et al. Cancerous breast lesions on dynamic contrast-enhanced MR images: computerized characterization for image-based prognostic markers. *Radiology*. 2010;254:680–690.
44. Mayr NA, Yuh WT, Arnholt JC, et al. Pixel analysis of MR perfusion imaging in predicting radiation therapy outcome in cervical cancer. *J Magn Reson Imaging*. 2000;12:1027–1033.
45. Hawighorst H, Weikel W, Knapstein PG, et al. Angiogenic activity of cervical carcinoma: assessment by functional magnetic resonance imaging based parameters and a histomorphological approach in correlation with disease outcome. *Clin Cancer Res*. 1998;4:2305–2312.
46. Hawighorst H, Knapstein PG, Weikel W, et al. Angiogenesis of uterine cervical carcinoma: characterization by pharmacokinetic magnetic resonance parameters and histological microvessel density with correlation to lymphatic involvement. *Cancer Res*. 1997;57:4777–4786.
47. Hoffmann U, Brix G, Knopp MV, et al. Pharmacokinetic mapping of the breast: a new method for dynamic MR mammography. *Magn Reson Med*. 1995;33:506–514.
48. Moehler TM, Hawighorst H, Neben K, et al. Bone marrow microcirculation analysis in multiple myeloma by contrast-enhanced dynamic magnetic resonance imaging. *Int J Cancer*. 2001;93:862–868.
49. Scherer A, Strupp C, Wittsack HJ, et al. Dynamic MRI of the lumbar spine for the evaluation of microcirculation during anti-angiogenetic therapy in patients with myelodysplastic syndromes. *Rofo*. 2002;174:164–169 [in German].
50. Barrett T, Brechbiel M, Bernardo M, et al. MRI of tumor angiogenesis. *J Magn Reson Imaging*. 2007;26:235–249.
51. Ingrisch M, Sourbron S. Tracer-kinetic modeling of dynamic contrast-enhanced MRI and CT: a primer. *J Pharmacokinet Pharmacodyn*. 2013;40:281–300 [PMID: 23563847 DOI: 10.1007/s10928-013-9315-3].
52. Brix G, Griebel J, Kiessling F, et al. Tracer kinetic modelling of tumour angiogenesis based on dynamic contrast enhanced CT and MRI measurements. *Eur J Nucl Med Mol Imaging*. 2010;37:S30–S51.
53. Sourbron S. Technical aspects of MR perfusion. *Eur J Radiol*. 2010;76:304–313.
54. Türkbey B, Thomasson D, Pang Y, et al. The role of dynamic contrast-enhanced MRI in cancer diagnosis and treatment. *Diagn Interv Radiol*. 2010;16:186–192.
55. O'Connor JP, Jackson A, Parker GJ, et al. DCE-MRI biomarkers in the clinical evaluation of antiangiogenic and vascular disrupting agents. *Br J Cancer*. 2007;96:189–195.
56. Verma S, Turkbey B, Muradyan N, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. *AJR Am J Roentgenol*. 2012;198:1277–1288.
57. Essig M, Shiroishi MS, Nguyen TB, et al. Perfusion MRI: the five most frequently asked technical questions. *AJR Am J Roentgenol*. 2013;200:24–34.
58. Sourbron SP, Buckley DL. Tracer kinetic modelling in MRI: estimating perfusion and capillary permeability. *Phys Med Biol*. 2012;57:R1–R33.
59. Koh TS, Bisdas S, Koh DM, et al. Fundamentals of tracer kinetics for dynamic contrast-enhanced MRI. *J Magn Reson Imaging*. 2011;34:1262–1276.
60. Peng SL, Chen CF, Liu HL, et al. Analysis of parametric histogram from dynamic contrast-enhanced MRI: application in evaluating brain tumor response to radiotherapy. *NMR Biomed*. 2013;26(4):443–450.
61. Alic L, van Vliet M, van Dijke CF, et al. Heterogeneity in DCE-MRI parametric maps: a biomarker for treatment response? *Phys Med Biol*. 2011;56:1601–1616.
62. Rose CJ, Mills SJ, O'Connor JP, et al. Quantifying spatial heterogeneity in dynamic contrast enhanced MRI parameter maps. *Magn Reson Med*. 2009;62:488–499.
63. Rose CJ, Mills S, O'Connor JP, et al. Quantifying heterogeneity in dynamic contrast-enhanced MRI parameter maps. *Med Image Comput Comput Assist Interv*. 2007;10:376–384.
64. Ingrisch M, Dietrich O, Attenberger UI, et al. Quantitative pulmonary perfusion magnetic resonance imaging: influence of temporal resolution and signal-to-noise ratio. *Invest Radiol*. 2010;45:7–14.
65. Roberts C, Buckley DL, Parker GJ. Comparison of errors associated with single- and multi-bolus injection protocols in low-temporal-resolution dynamic contrast-enhanced tracer kinetic analysis. *Magn Reson Med*. 2006;56:611–619.
66. Luypaert R, Sourbron S, de Mey J. Validity of perfusion parameters obtained using the modified Tofts model: a simulation study. *Magn Reson Med*. 2011;65:1491–1497.
67. Melbourne A, Hipwell J, Modat M, et al. The effect of motion correction on pharmacokinetic parameter estimation in dynamic-contrast enhanced MRI. *Phys Med Biol*. 2011;56:7693–7708.
68. Kety SS. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev*. 1951;3:1–41.
69. Tofts PS, Wicks DA, Barker GJ. The MRI measurement of NMR and physiological parameters in tissue to study disease process. *Prog Clin Biol Res*. 1991;363:313–325 [PMID: 1988983].
70. Brix G, Semmler W, Port R, et al. Pharmacokinetic parameters in CNS Gd-DTPA enhanced MR imaging. *J Comput Assist Tomogr*. 1991;15:621–628.
71. Jaspers K, Aerts HJ, Leiner T, et al. Reliability of pharmacokinetic parameters: small vs. medium-sized contrast agents. *Magn Reson Med*. 2009;62:779–787.
72. Rabitsch W, Sperr WR, Lechner K, et al. Bone marrow microvessel density and its prognostic significance in AML. *Leuk Lymphoma*. 2004;45:1369–1373.
73. Kuzu I, Beksac M, Arat M, et al. Bone marrow microvessel density (MVD) in adult acute myeloid leukemia (AML): therapy induced changes and effects on survival. *Leuk Lymphoma*. 2004;45:1185–1190.
74. Hlatky L, Hahnfeldt P, Folkman J. Clinical application of antiangiogenic therapy: microvessel density, what it does and doesn't tell us. *J Natl Cancer Inst*. 2002;94:883–893.
75. Jain RK. Determinants of tumor blood flow: a review. *Cancer Res*. 1988;48:2641–2658.
76. McDonald DM, Choyke PL. Imaging of angiogenesis: from microscope to clinic. *Nat Med*. 2003;9:713–725.
77. Moehler TM, Ho AD, Goldschmidt H, et al. Angiogenesis in hematologic malignancies. *Crit Rev Oncol Hematol*. 2003;45:227–244.
78. Schuch G, Oliveira-Ferrer L, Loges S, et al. Antiangiogenic treatment with endostatin inhibits progression of AML in vivo. *Leukemia*. 2005;19:1312–1317.
79. Schuch G, Machluf M, Bartsch Jr G, et al. In vivo administration of vascular endothelial growth factor (VEGF) and its antagonist, soluble neuropilin-1, predicts a role of VEGF in the progression of acute myeloid leukemia in vivo. *Blood*. 2002;100:4622–4628.
80. Morgan MA, Reuter CW. Molecularly targeted therapies in myelodysplastic syndromes and acute myeloid leukemias. *Ann Hematol*. 2006;85:139–163.
81. Chen BB, Hsu CY, Yu CW, et al. Dynamic contrast-enhanced MR imaging measurement of vertebral bone marrow perfusion may be indicator of outcome of acute myeloid leukemia patients in remission. *Radiology*. 2011;258:821–831.
82. Verstraete KL, Van der Woude HJ, Hogendoorn PC, et al. Dynamic contrast-enhanced MR imaging of musculoskeletal tumors: basic principles and clinical applications. *J Magn Reson Imaging*. 1996;6:311–321.
83. Tofts PS. Modeling tracer kinetics in dynamic Gd-DTPA MR imaging. *J Magn Reson Imaging*. 1997;7:91–101.
84. Zwick S, Brix G, Tofts PS, et al. Simulation based comparison of two approaches frequently used for dynamic contrast-enhanced MRI. *Eur Radiol*. 2010;20:432–442.
85. Kiessling F, Krix M, Heilmann M, et al. Comparing dynamic parameters of tumor vascularization in nude mice revealed by magnetic resonance imaging and contrast-enhanced intermittent power Doppler sonography. *Invest Radiol*. 2003;38:516–524.
86. Oostendorp M, Post MJ, Backes WH. Vessel growth and function: depiction with contrast enhanced MR imaging. *Radiology*. 2009;251:317–335.
87. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005;307:58–62.
88. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005;23:1011–1027.
89. Ma HT, Griffith JF, Yeung DK, et al. Modified brix model analysis of bone perfusion in subjects of varying bone mineral density. *J Magn Reson Imaging*. 2010;31:1169–1175.
90. Huang SY, Chen BB, Lu HY, et al. Correlation among DCE-MRI measurements of bone marrow angiogenesis, microvessel density, and extramedullary disease in patients with multiple myeloma. *Am J Hematol*. 2012;87:837–839.
91. Padhani AR, Khan AA. Diffusion-weighted (DW) and dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) for monitoring anticancer therapy. *Targ Oncol*. 2010;5:39–52.
92. Varettoni M, Corso A, Pica G, et al. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. *Ann Oncol*. 2010;21:325–330.