Magnetic resonance imaging in the diagnosis of melanoma: *in vivo* preliminary studies with dynamic contrast-enhanced subtraction

G. M. Pennasilico*, **P. P. Arcuri, F. Laschena, C. Potenza, P. Ruatti, R. Bono, F. Sera and P. Falappa**

Department of Radiology (G. M. Pennasilico, P. P. Arcuri, F. Laschena, P. Falappa), Department of Plastic Surgery (C. Potenza), Department of Dermatological Oncology (P. Ruatti, R. Bono), Laboratory of Clinical Epidemiology (F. Sera), Istituto Dermopatico dell'Immacolata, IRCCS, Via Monti di Creta 104, 00167 Rome, Italy. Tel: (+39) 06 6646461; Fax: (+39) 06 66464678.

The aim of this study was to analyse the potential of fast dynamic subtraction magnetic resonance (MR) imaging in differentiating *in vivo* melanomas from benign melanocytic lesions. Dynamic MR imaging was performed after intravenous administration of gadopentetate dimeglumine (Gd-DTPA) in 18 patients with melanocytic skin lesions. Using a post-processing algorithm, time–signal intensity curves were obtained for the lesions and classified according to their shapes as type I (steady enhancement increase), type II (plateau of signal intensity) or type III (wash-out of signal intensity). Other parameters evaluated for their potential to differentiate melanomas from benign lesions were the enhancement rate (percentage of signal intensity increase) in the first minute after Gd-DTPA administration, the peak value of the enhancement rate, and the wash-out slope. The pigmented lesions were then surgically excised and the MR results compared with the histological assessment. In melanomas, the mean value of the enhancement rate in the first minute was 611%, whereas in benign lesions it was 131% ($P = 0.001$). The distribution of curve types was also different: seven of the nine naevi showed type I curves, while eight of the nine melanomas displayed a type III curve. In addition, distinctive wash-out dynamics were observed: the enhancement rate began to decrease between the first and third minutes for melanomas, but continued to increase until the sixth minute for naevi ($P = 0.000$). These findings, which are most likely related to the neoangiogenesis present in melanomas, indicate that dynamic MR imaging can be helpful in the differential diagnosis of pigmented skin lesions. © 2002 Lippincott Williams & Wilkins

Keywords: contrast medium, magnetic resonance dynamic imaging, melanoma, skin

---

*To whom correspondence should be addressed

Introduction

The use of unenhanced magnetic resonance (MR) imaging to characterize melanoma has yielded controversial results.[1-3] Various studies designed to differentiate benign from malignant skin lesions based on the evaluation of morphological parameters such as size, demarcation of margins, signal homogeneity, surrounding soft tissue oedema and measurement of relaxation times have shown that these parameters demonstrate low specificity and sensitivity.[4,5]

Recently, the development of MR software and the use of a gadolinium contrast agent in dynamic MR imaging have led to promising results in the differential diagnosis of benign and malignant breast lesions. The contrast enhancement obtained in breast cancer has been related to tumour neoangiogenesis.[6-11]

An increase in angiogenic factor production and vascularization is also present in malignant melanoma.[12,13] MR may therefore be able to distinguish *in vivo* the benign or malignant nature of pigmented skin lesions by evaluating contrast distribution. In the present study, the MR image technique used in breast diseases was applied to the analysis of pigmented skin lesions, in particular melanomas and melanocytic naevi. Despite specific problems related to skin examination, such as tissue thinness, movement artefacts and low enhancement values, our results show a significant difference in enhancement curves obtained in melanomas compared with naevi.

Materials and methods

Patients

The study design and protocol were reviewed and approved by the local Medical Ethical Committee; all patients gave informed consent to be examined after the nature of the procedure had been fully explained.

Among patients hospitalized in the Division of Plastic Surgery between September 1999 and March 2000 in order to undergo surgical excision of pigmented skin lesions, 29 agreed to participate in the study. Exclusion criteria were the presence of prostheses incompatible with MR, claustrophobia, and lesions located on a very concave or convex surface, which make use of the MR coil difficult. In addition, three patients were excluded from the study because they moved during the examination, invalidating the results. In total, 18 patients (age range 21–78 years, mean 41 years) completed the study.

MR imaging

All patients were examined with a 1.5 T MR system (Magnetom Vision, Siemens, Erlangen, Germany) using a dedicated surface coil 3.5 cm in diameter. Before the examination an intravenous catheter was inserted into the patient's arm. Two-dimensional unenhanced T1-weighted spin-echo MR images with a short repetition time and a short echo time (repetition time in ms/echo time in ms = 400/17) and T2-weighted images with a long repetition time and a long echo time (4000/120) were performed in a plane perpendicular to the cutis. The slice thickness was 2 mm, the field of view was 250–320 mm, and the matrix used was 192 × 256 pixels.

The T2-weighted images were always combined with fat-selective presaturation. Three to four sections displaying the largest and most representative tumour dimensions were selected for a dynamic contrast-enhanced study.

An intravenous bolus of gadopentetate dimeglumine (Gd-DTPA) (0.1 mmol Gd-DTPA/kg body weight) was administered by an automatic injector at a rate of 3 ml/s (total injection time approximately 12 s) followed by 30 ml of saline solution flush immediately after contrast administration. At the same time dynamic MR imaging was started, consisting of a consecutive series of Flash-T1 sequences. The time resolution was 22 s and the duration of the dynamic studies was 6 min.

The enhancement rate was quantified by means of a region of interest-based determination of lesion signal intensity before and after contrast injection. At each time point, the enhancement rate (percentage of signal intensity increase) was calculated according to the formula

$$(SI_{post} - SI_{pre})/SI_{pre} \times 100$$

where SI_{post} is the signal intensity after contrast agent and SI_{pre} is the signal intensity before contrast agent (Figures 1 and 2). By plotting the enhancement rate over time, time–signal intensity curves were obtained to depict the lesion's enhancement behaviour in the early (first minute), intermediate (between the first and third minutes) and late (between the third and sixth minute) post-contrast period. The regions of interest (ROIs) were drawn to include as much of the lesion as possible in areas of homogeneous and strongest enhancement to minimize noise in the time–signal intensity data. Particular care was taken to identify any patient motion, which may lead to faulty time signal–intensity curves if the ROI includes different skin areas from one dynamic image to the other.

All the lesions were then excised surgically, and enhancement characteristics were related to histopathological findings.

Data and statistical analysis

On the basis of the preliminary experiences triggering this study and from data in the literature,[7] we distinguished three types of time–signal intensity curves (Figure 3): type I is a straight or curved line with a steady enhancement rate increase, where the signal intensity continues to augment over the entire dynamic period; type II is a plateau in which there is an initial upstroke followed by an enhancement plateau in the intermediate and late post-contrast periods; and type III is a wash-out in which there is an initial upstroke, followed by an abrupt cut-off of enhancement and a decrease in the signal intensity in the intermediate and late post-contrast periods.

The following outcome measures were considered: (i) enhancement rate at the first minute post-contrast; (ii) qualitative evaluation of the curve type; (iii) slope of the enhancement rate curves in the intermediate and late post-contrast periods; (iv) time taken to reach the maximum enhancement rate; and (v) maximum enhancement rate (peak value).

The statistical significance of differences between benign and malignant lesions was evaluated using the Mann–Whitney test.
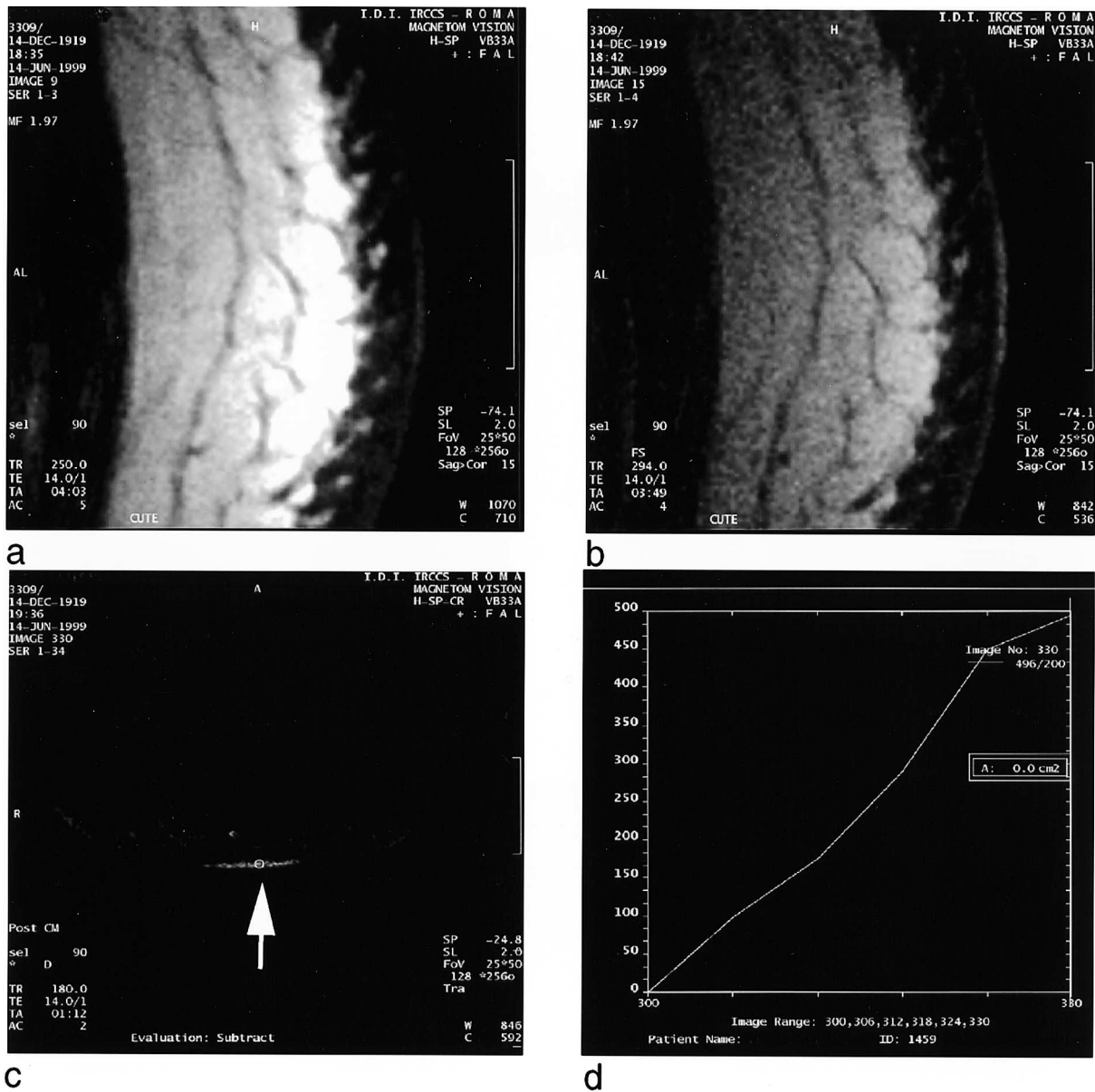
Figure 1. MR imaging and post-processing of a benign naevus. T1 and T2 fat suppression MR images show a thin hyperintense superficial area (**a**, **b**). In contrast imaging, a region of interest is chosen, depicted by a circle (**c**, arrow). The post-processing time–signal intensity curve is a straight line, with the signal intensity continuing to augment over the entire dynamic period (**d**).

Results

Out of the 18 lesions examined, nine were primary melanomas (Breslow's thickness < 0.75 mm in three cases, including one melanoma *in situ*, 0.75–3.00 mm in four cases, and > 4 mm in two cases) and nine were benign naevi (one congenital, two junctional and six composite).

The enhancement rate in the first post-contrast minute was significantly different ($P = 0.001$) in malignant lesions (mean ± SD = 611 ± 327%) compared with benign ones (131 ± 124%) (Figure 4). The shapes of the time–signal intensity curves of benign and malignant lesions also differed (Figure 5). In seven of the nine benign tumours a type I signal intensity–time curve was obtained, while eight of the nine melanomas showed a type III curve. A type II curve was identified in two of the nine naevi and in one of the nine melanomas.

Analysis of the enhancement rate curve slope during the intermediate and late post-contrast periods confirmed the results of the qualitative evalua-
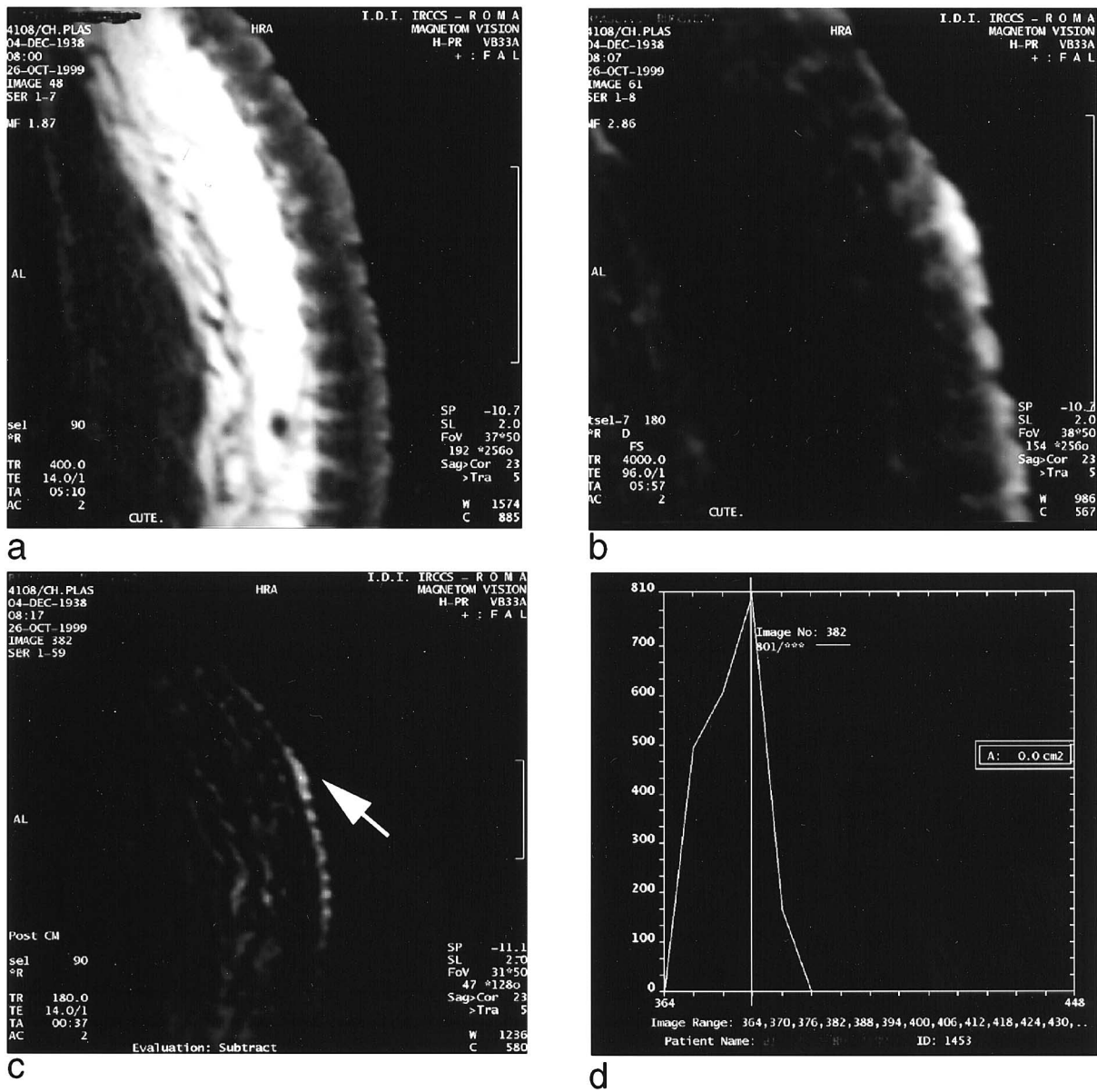
Figure 2. MR imaging and post-processing of melanoma. T1- and T2-weighted MR images show a superficially altered area (**a**, **b**). In contrast imaging, a region of interest is chosen (**c**, arrow) and the time–signal intensity curve obtained demonstrates a typical rapid increase in signal intensity followed by an abrupt cut-off (**d**).

tions. Growth speed values were already negative between the first and third minutes for melanomas (mean $\pm$ SD $= -99 \pm 106$), while at this time they were positive for naevi (48 ± 41) ($P = 0.000$). Similarly, negative (-32 ± 30) and positive (30 ± 31) slope values were obtained between the third and sixth minutes for melanomas and naevi, respectively. The peak of maximum enhancement was reached on average after 81 s for melanomas and after 333 s for naevi ($P = 0.000$) (Figure 6). Finally, the average peak enhancement rate reached for melanomas was

$700 \pm 414\%$, while for naevi it was $316 \pm 214\%$ ($P = 0.038$) (Figure 7).

Discussion

The evaluation of melanoma is made nowadays through various instrumental examinations with the aim of improving the differentiation between benign and malignant lesions in the pre-surgery phase. The use of high frequency ultrasound has allowed the
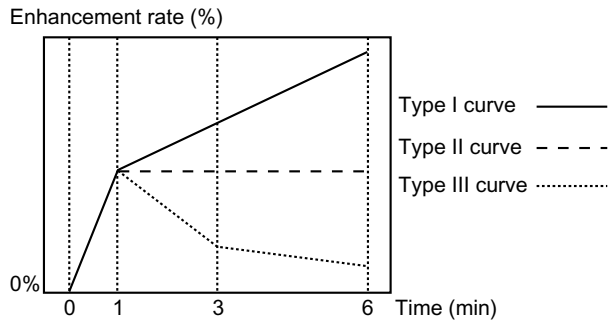
Figure 3. Schematic drawing of the time–signal intensity curve types.
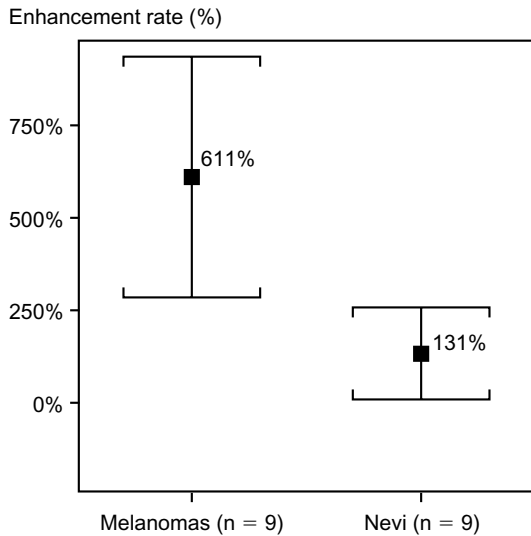
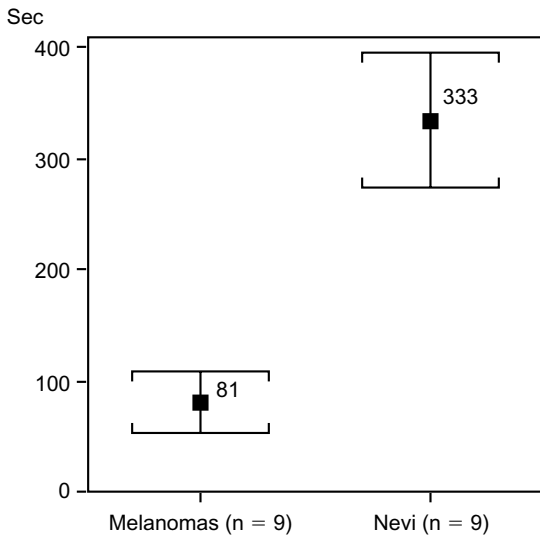**Figure 4.** Mean (± SD) enhancement rates in the first post-contrast minute for melanomas and naevi.
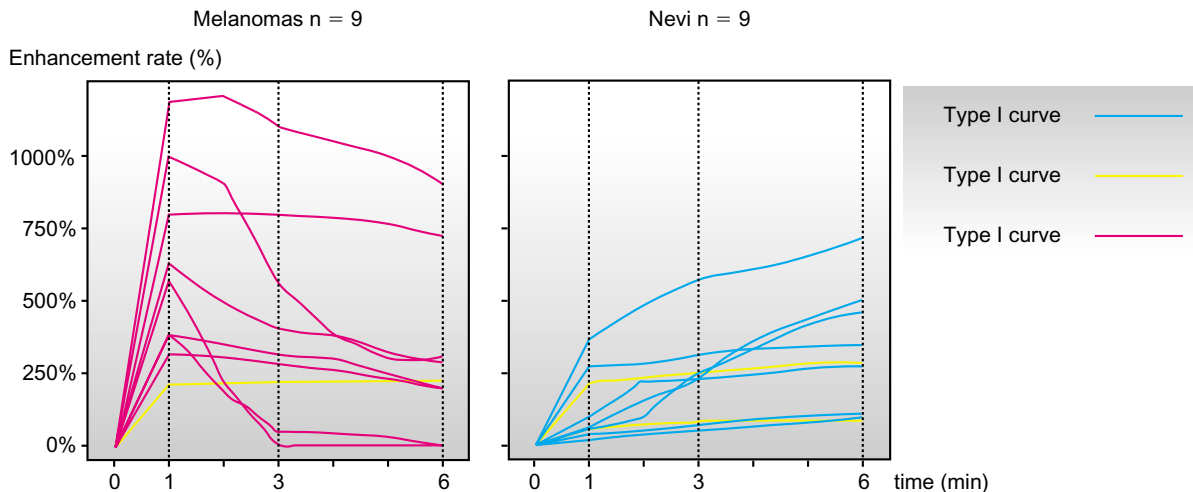
evaluation of tumour thickness, but has proven unhelpful in the differential diagnosis of pigmented lesions due to the similar ultrasound features of melanoma and melanocytic naevi.[14,15] The addition of colour Doppler has facilitated differentiation, although numerous false negative results are still obtained in small size melanomas due to lack of colour signal.[16]

MR has also been used in cutaneous tumours and particularly in melanoma detection.[17] However, attempts to differentiate benign from malignant lesions either through different signals in T1 and T2 sequences or on the basis of morphological features have been unsuccessful.[2] In addition, evaluation of the quantity and distribution of contrast in patients as well as in an animal model of melanoma did not provide univocal indications.[3,18]

The theoretical basis for the use of dynamic MR in cancer diagnosis is that malignant lesions are characterized by neoangiogenesis phenomena. MR is a potentially useful method for the measurement of the perfusion rate in human tumours. Following the intravenous administration of a contrast agent, dynamic imaging can record the kinetics of its distribution in the vascular and extracellular spaces of a tumour. Dynamic MR studies in human melanoma xenografts have shown that reliable estimates of tumour perfusion rates can be obtained by contrast agent kinetic evaluation.[19]

Various histological and immunohistochemical studies have demonstrated that the vertical growth phase of melanoma is accompanied by rich capillary growth occurring in response to endothelial growth factors produced by the tumour.[20–22] Highly invasive

Figure 5. Enhancement rate curves for the examined lesions.

Sec

Figure 6. Mean (± SD) time to reach the signal intensity peak for melanomas and naevi.
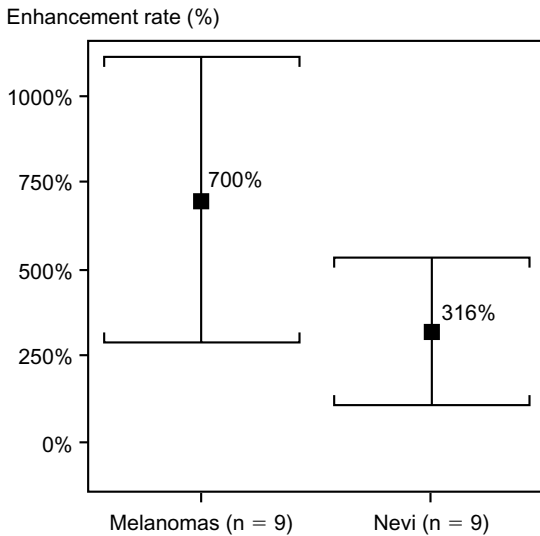
Enhancement rate (%)

Figure 7. Mean (± SD) maximum enhancement rate of signal intensity (peak value) for melanomas and naevi.

melanoma cells also appear to be able to mediate the formation of vascular channels not covered by endothelial cells, leading to a marked increase in the neoplasm's perfusion.[12] The increased vascularization is therefore also associated with augmented permeability. Indeed, in dynamic MR the signal intensity variations during intravenous infusion of the contrast medium are related first to its distribution in the capillary bed and then to its leakage into the extracellular matrix.[10]

The results of our study demonstrate that melano-

mas are characterized by an extremely rapid increase in the signal intensity, as revealed by the short time to the maximum enhancement rate (mean 81 s). In addition, the enhancement rate in the first post-contrast minute is significantly higher in melanomas compared with naevi. Therefore, MR sequences with an adequate temporal resolution must be used in order to show the different behaviour of malignant lesions compared with benign naevi and to achieve diagnostic efficacy.[23] Indeed, if the evaluation is limited to the maximum enhancement rate of skin pigmented lesions, a less evident but still significant difference is obtained between malignant and benign lesions.

In addition to the rapid increase in signal enhancement, melanomas are also characterized by a rapid decrease in the signal. In fact, the signal intensity–time curve in these tumours tends to wash-out (type III curve), while naevi display a longer enhancement (type I curve). A decrease in contrast medium intensity during a 6 min sequence, quantitatively expressed by the slope of the enhancement rate curves in the intermediate and late post-contrast time, is typical of melanomas and could be related to an increase in microcirculation permeability and tumour leakage space.

Some technical problems encountered during dynamic MR examination of pigmented skin lesions should be underlined. Since necrotic or haemorrhagic zones are frequently present in larger tumours, the ROI must be accurately selected in order to cover an area of significant and homogeneous enhancement. Another practical difficulty is related to patient movements during dynamic scans, possibly resulting in a modification of the area designated for the curve. This is particularly relevant for respiration movements when imaging melanomas on the thorax and abdomen. Automatic injection is useful in standardizing the injection time so as to produce a rapid and stable increase in plasma enhancement. On the other hand, different circulation times or kidney and heart conditions did not modify our evaluations.

Conclusion

Based on our findings, dynamic MR demonstrates a difference in behaviour between melanomas and melanocytic naevi. Lesions can be differentiated on the basis of signal variation in time after the administration of the paramagnetic contrast medium by analysis of intensity–time curves. These differ-

ences are most likely due to neoangiogenesis phenomena that characterize melanomas.

Despite these promising results that indicate the possibility of employing MR to differentiate melanomas from benign pigmented skin lesions, the cost and limited availability of MR machines represent major obstacles to the use of this technique in clinical practice. Future technical MR developments, such as coils that enable the examination of more lesions at one time or dedicated machines, might facilitate the use of dynamic MR in the differential diagnosis of pigmented skin lesions. Further studies on larger series of patients are required to assess the role of MR in combination with other non-invasive procedures, in particular epiluminescence microscopy, in increasing the diagnostic accuracy in melanoma and as a decision aid for the diagnosis of pigmented skin lesions.

References

1. Zemtsov A, Lorig MR, Bergfield WF, Bailin FPL, Thian F. Magnetic resonance imaging of cutaneous melanocytic lesions. *Oncology* 1989; **15**: 854–858.

2. Takahashi M, Kohda H. Diagnostic utility of magnetic resonance imaging in malignant melanoma. *J Am Acad Dermatol* 1992; **27**: 51–54.

3. Maurer J, Knollmann FD, Schlums D, Garbe C, Vogl TJ, Bier J, *et al*. Role of high-resolution magnetic resonance imaging for differentiating melanin-containing skin tumors. *Invest Radiol* 1995; **30**: 638–643.

4. Ono I, Kaneko F. Magnetic resonance imaging for diagnosing skin tumors. *Clin Dermatol* 1995; **13**: 393–399.

5. Gammal S, Hartwig R, Aygen S, Bauermann T, Gemmal C, Altmeyer P. Improved resolution of magnetic resonance microscopy in examination of skin tumors. *J Invest Dermatol* 1996; **106**: 1287–1292.

6. Daniel BL, Yen YF, Glover GH, Ikeda DM, Birdwell RL, Sawyer-Glover AM, *et al*. Breast disease: dynamic spiral MR imaging. *Radiology* 1998; **209**: 499–509.

7. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gleseke J, *et al*. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiology* 1999; **211**: 101–110.

8. Buadu LD, Murakami J, Murayama S, Hashiguchi N, Sakai S, Masuda K, *et al*. Breast lesions: correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis. *Radiology* 1996; **200**: 639–649.

9. Parker GJ, Suckling J, Tanner SF, Padhani AR, Husband JE, Leach MO. MRIW: parametric analysis software for contrast-enhanced dynamic MR imaging in cancer. *Radiographics* 1998; **18**: 497–506.

10. Schorn C, Fisher U, Luftner-Nagel S, Grabbe E. Diagnostic potential of ultrafast contrast-enhanced MRI of the breast in hypervascularized lesions: are there advantages in comparison with standard dynamic MRI? *J Comput Assist Tomogr* 1999; **23**: 118–122.

11. Tofts PS, Berkowitz B, Schnall MD. Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model. *Magn Reson Med* 1995; **33**: 564–568.

12. Denijn M, Ruiter DJ. The possible role of angiogenesis in the metastatic potential of human melanoma. Clinicopathological aspects. *Melanoma Res* 1993; **3**: 5–14.

13. Maniotis AJ, Folberg R, Hess A, Seftor EA, Gardner LM, Pe'er J, *et al*. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. *Am J Pathol* 1999; **1555**: 739–752.

14. Pennasilico G, Santini A, Bono R, Cacciaguerra G, Puddu P, Falappa P. Preoperative melanoma thickness measurement with very high frequency (20 MHz) ultrasonography. *Radiol Med* 1994; **88**: 388–391.

15. Solivetti FM, Thorel MF, Di Luca Sidozzi A, Bucher S, Donati P, Panichelli V. Role of high-definition and high frequency ultrasonography in determining tumor thickness in cutaneous malignant melanoma. *Radiol Med* 1998; **96**: 558–561.

16. Lassau N, Paturel-Asselin C, Guinebretiere JM, Leclere J, Koscielny S, Roche A, *et al*. New hemodynamic approach to angiogenesis: color and pulsed Doppler ultrasonography. *Invest Radiol* 1999; **34**: 194–198.

17. Enochs WS, Petherick P, Bogdanova A, Mohr U, Weissleder R. Paramagnetic metal scavenging by melanin: MR imaging. *Radiology* 1997; **204**: 417–423.

18. Maurer J, Strauss A, Ebert W, Bauer H, Felix R. Contrast-enhanced high resolution magnetic resonance imaging of pigmented malignant melanoma using Mn-TPPS and Gd-DTPA: experimental results. *Melanoma Res* 2000; **10**: 40–46.

19. Lyng H, Dahle GA, Kaalhus O, Skretting A, Rofstad EK. Measurement of perfusion rate in human melanoma xenografts by contrast-enhanced magnetic resonance imaging. *Magn Reson Med* 1998; **40**: 89–98.

20. Vlaykova T, Laurila P, Muhonen T, Hahka M. Prognostic value of tumor vascularity in metastatic melanoma and association of blood vessel density with vascular endothelial growth factor expression. *Melanoma Res* 1999; **9**: 59–68.

21. Erhard H, Rietveld FJR, Van Altena MC, Brocker EB, Ruiter DJ, De Waal RM. Transition of horizontal to vertical growth phase melanoma is accompanied by induction of vascular endothelial growth factor expression and angiogenesis. *Melanoma Res* 1997; **7**: S19–26.

22. Birck A, Kirkin AF, Zeuthen J, Hou-Jensen K. Expression of basic fibroblast growth factor and vascular endothelial growth factor in primary and metastatic melanoma from the same patient. *Melanoma Res* 1999; **9**: 375–381.

23. Buckley DL, Mussurakis S, Horsman A. Effect of temporal resolution on the diagnostic efficacy of contrast-enhanced MRI in the conservatively treated breast. *J Comput Assist Tomogr* 1998; **22**: 47–51.