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Abbreviations:

SI = signal intensity
 SI% = percentage SI increase

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Solitary Pulmonary Nodules: Dynamic Contrast-enhanced MR Imaging—Perfusion Differences in Malignant and Benign Lesions¹

PURPOSE: To determine whether dynamic contrast material-enhanced magnetic resonance (MR) imaging with use of kinetic and morphologic parameters reveals statistically significant differences between malignant and benign solitary pulmonary nodules.

MATERIALS AND METHODS: Fifty-eight patients met the inclusion criteria of a solitary 5–40-mm pulmonary nodule without calcification or fat at computed tomography. Fifty-one patients were examined successfully; 46 received a histologic diagnosis, and five received a diagnosis by means of observation over 2 years. Dynamic MR images were acquired every 10 seconds for a total of 4 minutes. Diagnostic characteristics for differentiation were examined by using threshold values for maximum peak enhancement, slope of enhancement, and washout. Receiver operating characteristic curves were calculated to test the usefulness of these parameters. The diagnostic performance of a combination of curve profiles and morphologic contrast material distribution were tested by using a decision tree.

RESULTS: Frequency of malignancy was 53% (27 of 51 nodules). Malignant nodules showed stronger enhancement with a higher maximum peak and a faster slope ($P < .001$). Significant washout ($>0.1\%$ increase in signal intensity per second) was found only in malignant lesions (14 of 27 lesions). Sensitivity, specificity, and accuracy were 96%, 88%, and 92%, respectively, for maximum peak; 96%, 75%, and 86% for slope; and 52%, 100%, and 75% for washout. When curve profiles and morphologic enhancement patterns were combined, sensitivity increased to 100%.

CONCLUSION: Dynamic MR imaging delineates significant kinetic and morphologic differences in vascularity and perfusion between malignant and benign solitary pulmonary nodules. Washout seems to be highly specific for malignancy.

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The solitary pulmonary nodule is a common finding in chest radiology. The number of small nodules detected has increased since the introduction of multi-detector row computed tomography (CT) (1). Moreover, if lung cancer screening with low-dose CT becomes an accepted modality, even more small lesions (<10 mm) will be detected (2–5). Management of these nodules is uncertain because most of them are benign (6). A current acceptable approach is frequent CT follow-up to determine the growth rate through an increase in volume (4,7,8). Even when low-dose CT is used, however, radiation exposure in these patients is considerable, and most of them end up without a diagnosis of pulmonary malignancy (9,10). Nodules larger than 10 mm that are indicative of malignancy or indeterminate by means of morphologic analysis have to be defined by using invasive methods or surgical excision. The latter approach has shown benign lesions to make up 20%–50% of resected nodules (11–13).

Positron emission tomography (PET) with fluorodeoxyglucose, or FDG, and contrast material-enhanced dynamic CT are two major noninvasive functional methods used to

examine solitary pulmonary nodules. FDG PET, which is based on the metabolic uptake of FDG, distinguishes malignant from benign nodules with a relatively high accuracy of about 90% (14–16). Unfortunately, the sensitivity seems to decrease in nodules smaller than 20 mm (17).

CT allows detection of qualitative and quantitative differences in vascularity between malignant and benign neoplasms (18–23). Although a multicenter study has shown the detection rate of nodules 5–40 mm in diameter to be as high as 98%, there was an overlap in enhancement patterns between malignant and benign groups, with a resulting specificity of only 58% (22). Incremental acquisitions with an interval of 1 minute were used in these studies. However, a higher temporal resolution is necessary to assess tissue perfusion during first transit of the contrast material bolus. This is possible with CT but involves an increased level of radiation exposure (21,23).

The advantage of using dynamic contrast-enhanced magnetic resonance (MR) imaging in tumor characterization has been reported by several researchers (20,24,25). Sequences with short acquisition times enable the assessment of the first bolus transit in tumor perfusion (26–29). While the effect of iodinated contrast material in CT examinations is directly based on the concentration of contrast material in the blood, paramagnetic contrast material effects in MR imaging depend additionally on interactions of mobile water molecules in all tissue compartments, including interstitium and cytoplasm. Thus, enhancement measurements are not directly comparable.

In contrast to use in other organs, MR imaging of pulmonary nodules is not a standard examination because of known artifacts that result from tissue-air transitions and relatively low spatial resolution (30–32). Thus, few data are available on dynamic MR imaging of solitary pulmonary nodules (33–38). Preliminary results of these MR imaging investigations have shown sensitivities in the differentiation of malignant and benign solitary pulmonary nodules to be comparable to those obtained with dynamic CT, but with higher specificity. Investigators have explained the advantage of using MR imaging by measuring the slope enhancement during the first transit of contrast material. Complete signal intensity (SI) profiles have not been evaluated after the first bolus transit in benign and malignant lesions, to our knowledge. MR im-

aging protocols have been applied with high temporal resolution but low spatial resolution by using a turbo gradient-echo sequence (eg, turbo fast low-angle shot, or FLASH) with a body coil as the receiver and with a reduced in-plane matrix.

The purpose of our study was to determine whether dynamic contrast-enhanced MR imaging with use of kinetic and morphologic parameters reveals significant differences between malignant and benign solitary pulmonary nodules.

MATERIALS AND METHODS

Patients were selected from two departments of thoracic surgery according to the following criteria: (a) presence of a newly detected solitary pulmonary nodule at CT, which needed further evaluation; (b) absence of calcification or definite fat attenuation of the nodule at CT; (c) nodule diameter of 5–40 mm; (d) absence of recent history of pneumonia or immunodeficiency; (e) absence of contraindications to the administration of contrast material; and (f) probable ability to cooperate with the procedure. Lesion size was calculated by using the mean of the long- and short-axis diameter at the lung window settings in the transverse plane.

CT parameters were heterogeneous because the examinations were performed in different departments. Spiral CT scans existed for all patients except one. Section thickness ranged from 7 to 10 mm; in one patient, conventional incremental CT scans were obtained with a section thickness of 10 mm. From January to October 2000, 58 patients met the inclusion criteria and were referred for dynamic MR examination after giving informed consent. Study approval was obtained from the institutional committee on medical ethics.

Two patients were excluded from the analyses because of misregistration due to major patient movement during dynamic MR imaging and an incorrect selection of the section position. Additionally, two patients were excluded because no solitary pulmonary nodule was seen at the time of MR examination, which was confirmed by means of follow-up CT. Three patients were lost to follow-up.

Previous results (35) suggest that the distribution of contrast material first-pass slopes is skew, since the median is far from the middle of the range. A lognormal distribution was therefore assumed, and logarithms were used for planning. Medians were more than two logarithmic units apart, while ranges were 4.4 and 2.7

for 20 and eight observations, respectively. These ranges have to be divided by 2.6 and 1.5 (39), respectively, to obtain the SD, a value near 1.7. A *t* test on logarithms at the significance level of .01 and with a power of 0.9 then required 49 observations in groups of equal sizes so that our almost-balanced analysis set of 51 observations was large enough.

Fifty-one patients (11 women, 40 men; age range, 26–77 years; mean age, 61 years) with a solitary pulmonary nodule were included in the analysis. Median age was 63 years (range, 26–75 years) for women and 63.5 years (range, 41–77 years) for men (Kruskal-Wallis test, *P* = .88).

In 46 patients, a histologic diagnosis was reached by means of resection or biopsy. In five patients, follow-up CT was completed over a period of 2 years, which allowed a diagnosis to be assigned.

MR Imaging

MR imaging was performed with a 1.0-T MR imager (Magnetom Expert; Siemens, Erlangen, Germany) by using the phased-array coil as the receiver. For lesion detection, the thorax was examined from the apex to the base by using a transverse breath-hold electrocardiographically gated proton-density-weighted two-dimensional gradient-echo MR sequence (repetition time msec/echo time msec, 800–1,000/6; flip angle, 20°; voxel size, $1.3 \times 1.3 \times 6.0$ mm).

Dynamic contrast-enhanced MR images were acquired in the sagittal plane every 10 seconds over a total period of 4 minutes by using a T1-weighted in-phase two-dimensional gradient-echo MR sequence (20/4.8; flip angle, 70°; voxel size, $1.4 \times 1.4 \times 8.0$ mm). Sagittal dynamic imaging was performed across the maximal diameter of the nodule on transverse MR images. For every measurement, a short inspiratory breath-hold period of 4 seconds was required. Although expiratory breath holds are considered more reproducible, the images were acquired in inspiration because we assumed a better delineation of the lesion against enhanced vessels and inflated lung parenchyma, particularly in cases of small nodules. In contrast to transverse images, sagittal images can depict the nodule with all breath holds, even for slightly different inspiration levels, since the lateral to medial positional change of the nodules is minor.

Rapid bolus injection of a standard dose of 0.1 mmol per kilogram of body weight of gadopentetate dimeglumine

(Magnevist; Schering, Berlin, Germany), followed by 20 mL of 0.9% saline through a 21-gauge needle in an antecubital vein, was started at the time of acquisition of the second image (of a series of 24 images). All MR imaging examinations were completed within 25 minutes, including placement of the intravenous catheter. No adverse effects were observed.

Kinetic Parameters and Statistical Analysis

Mean SIs of the lesions were measured on the operator console by a chest radiologist with 5 years of experience (J.V.), who placed a freehand region of interest that encompassed all of the cross-sectional visible area of the lesion at the 24 designated time points. Regions with few pixels could have larger SDs over time. That was investigated by means of simple linear regression from individual unconditional SDs in nodule size (percentage increase in SI [SI%] per centimeter). Visible pulmonary vessels beneath the lesion were excluded from the region of interest, which was adapted to movement of the lesion caused by different inspiration levels. Additionally, a circular region of interest with a size of 30 mm was placed in the lung lobe that contained the nodule and was analyzed to assess the enhancement of parenchyma and pulmonary vessels. All measurements were obtained without prior knowledge of the histologic diagnosis. SI% of nodules was determined for each time point (t) with the following formula: $SI\%_t = ([SI_t - SI_{t_0}]/SI_{t_0}) \cdot 100\%$, where t_0 was the time point before the first detection of contrast material in the pulmonary artery. Time-intensity curves were plotted automatically for every lesion without any fitting.

The following parameters were evaluated. Early peak was determined as the highest SI% value in the first 30 seconds after t_0 . Maximum peak represented the maximum SI% value during the observation time. First transit slope represented the mean velocity SI increase per second from t_0 to the time of early peak (EP) enhancement and was calculated by using the following formula:

$$\text{slope} = \frac{\sum_{t_{EP}}^{t_0} (SI\%_t - SI\%_{t-1})}{(t_{EP} - t_0)}.$$

Washout phase was used to assess the changes in SI% per second for the 60-

second time interval after the early peak by using the following formula:

$$\text{washout} = \frac{\sum_{t_{EP+60\text{sec}}}^{t_{EP}} (SI\%_t - SI\%_{t-1})}{(t_{EP+60\text{sec}} - t_{EP})}.$$

Mean enhancement represented the mean value of all measurements of SI%.

After confirmation of lesion type by means of histologic examination or follow-up and classification of lesions as benign or malignant, medians and interquartile ranges were calculated for parameters of the time-intensity curves and nodule diameters. Medians of each time point of the time-intensity curves were calculated for both malignant and benign nodules to indicate location of values that were distributed abnormally. Locations of parameters were compared between the two groups by using the Kruskal-Wallis test because of non-Gaussian distribution of variables. A descriptive P value of less than .01 was used to indicate a statistically significant difference. The Spearman rank correlation coefficient (r_s) was used to measure the association between enhancement values at MR imaging and nodule diameters in both malignant and benign groups.

Receiver operating characteristic analyses were performed to test the usefulness of maximum peak, slope, and washout as indexes for differentiation of malignant versus benign lesions. Areas under the curves and asymptotic 95% CIs were calculated. Sensitivity, specificity, accuracy, and positive and negative predictive values were calculated for each level by varying the thresholds. For maximum peak and slope, sensitivity was defined as the percentage of patients with a malignant lesion who had levels greater than the threshold values. Specificity was defined as the percentage of patients with a benign nodule who had levels less than the thresholds. For the washout phase the calculation was vice versa, with negative values indicating malignancy. For sensitivity, 95% CIs were calculated. Feasible threshold values of the MR parameters were tested for potential to differentiate between malignant and benign nodules.

Threshold values were used retrospectively to define different types of time-intensity curves: curve type A, an intensive SI increase within the first 30 seconds and decrease after the first peak (slope > 1.5 SI%/sec and washout < -0.1 SI%/sec); curve type B, an intensive SI increase and no decrease afterward (slope > 1.5 SI%/sec and washout $\geq$ -0.1

SI%/sec); curve type C, moderate or low SI increase (slope < 1.5 SI%/sec); and curve type D, no significant SI increase over baseline (mean SI increase < 10%).

Morphologic Parameters and Statistical Analysis

Two radiologists experienced in chest radiology (J.V., 5 years of experience; J.F.S., 10 years of experience) performed a retrospective morphologic analysis of contrast enhancement by means of consensus. The readers had no knowledge of histologic findings. Images of the time series were displayed in cine mode on the operator console. The recall bias for J.V. was minimized by a time period of 6 months between the kinetic and morphologic analyses.

Five enhancement patterns were distinguishable: no enhancement, representing an absence of contrast material uptake in the lesion; homogeneous enhancement, representing uniform contrast material distribution; heterogeneous enhancement, representing irregular contrast enhancement with parts of no or low enhancement; nodular enhancement (hot spot-like), representing irregular enhancement with spotty high perfusion; and peripheral enhancement of capsular-like rim, representing smooth, thin, and uniform enhancement in the periphery of a round or ovoid lesion.

A generalized Fisher exact test was used to analyze any associations of time-intensity curves and enhancement patterns from morphologic analysis between the distributions of the different curve types (A-D). The Tukey-Kramer honestly significant difference test was used to compare means in nodule diameters for the various enhancement patterns.

To evaluate the usage of curve type and enhancement pattern combinations, we developed a decision tree. By using curve types in the first line and enhancement pattern in the second, a rule for differential diagnosis was proposed for further evaluation.

RESULTS

Of the 51 nodules, 27 were malignant, and 24 were benign (Table 1). Histologic examination was performed in 46 nodules after surgical resection (38 of 46 nodules) or biopsy (eight of 46 nodules). Primary lung carcinomas were diagnosed in 22 patients, the majority of which were adenocarcinoma, followed by squamous cell carcinoma, small cell carcinoma, and carcinoid. In five patients, a solitary lung

metastasis was identified. Nineteen of the 24 benign nodules had a histologic basis for diagnosis. In 12 cases, a hamartoma was diagnosed after surgical removal. Nonspecific inflammatory lesions were found in five cases. Additionally, one inactive tuberculoma and one intrapulmonary lymph node were resected. The remaining five nodules were considered to be granulomas because there was no increase in diameter during 2-year follow-up.

Kinetic Parameters

Nodule diameters ranged in size from 6 to 40 mm (median, 17 mm); 11 nodules were 10 mm or smaller. No significant difference in size was found between malignant and benign groups ($P = .07$) (Table 1). The correlation between nodule diameter and SI% was small ($r_s = 0.0009$ for malignant nodules, $r_s = 0.297$ for benign nodules). In the regression from SD on nodule size, slope was irrelevant and was not significant (95% CI: $-2.1, 5.8$ SI%/cm; $P = .34$).

Table 2 summarizes the parameters evaluated for time-intensity curves. Medians of early peak, maximum peak, slope, and mean enhancement were significantly higher in the malignant group than in the benign group ($P < .001$). The median washout was significantly lower in the malignant group than in the benign group ($P < .008$). A decrease in SI after the first bolus transit was found in 14 of 27 (52%) malignant nodules.

To differentiate malignant from benign lesions, threshold levels of 85% SI% for maximum peak, 1.5 SI%/sec for slope, and -0.1 SI%/sec for washout were found to be suitable (Fig 1). Areas under the receiver operating characteristic curves were 0.93 (95% CI: 0.85, 1.0) for maximum peak, 0.92 (95% CI: 0.84, 0.99) for slope, and 0.72 (95% CI: 0.57, 0.87) for washout. Table 3 summarizes the diagnostic characteristics according to threshold values. The sensitivity was 96% for both maximum peak and slope and 52% for washout. The specificity was 88% for maximum peak, 75% for slope, and 100% for washout. The highest positive predictive value of 100% was calculated for washout, and the highest negative predictive value of 95% was calculated for maximum peak and slope.

The medians at each time point for malignant lesions revealed a different profile than that for benign lesions (Fig 2). In the profile for malignant lesions, a fast SI increase was followed by a slight decrease, whereas the medians for the be-

TABLE 1
Nodule Diagnosis and Size

Diagnosis	No. of Nodules ($n = 51$)	Median Transverse Diameter (mm)
Malignant	27 (53)	18
Adenocarcinoma	10 (20)	18
Squamous cell carcinoma	7 (14)	22
Small cell carcinoma	3 (6)	23
Carcinoid	2 (4)	13
Metastasis	5 (10)	15
Benign	24 (47)	16
Hamartoma	12 (24)	18
Granuloma	5 (10)	12
Inflammatory lesion	5 (10)	19
Other*	2 (4)	7

Note.—Numbers in parentheses are percentages.

* One inactive tuberculoma and one intrapulmonary lymph node.

TABLE 2
Parameters of Time-Intensity Curves

Parameter	Malignant Nodules ($n = 27$)	Benign Nodules ($n = 24$)
Early peak (SI%)*		
Median	115	27
Interquartile range (25%–75%)	82 to 133	12 to 54
Maximum peak (SI%)*		
Median	126	42
Interquartile range (25%–75%)	105 to 144	26 to 79
Slope (SI%/sec)*		
Median	4.05	0.92
Interquartile range (25%–75%)	2.73 to 5.63	0.29 to 1.70
Washout (SI%/sec) [†]		
Median	-0.15	0.11
Interquartile range (25%–75%)	-0.62 to 0.18	0.03 to 0.30
Mean enhancement (SI%)*		
Median	91	27
Interquartile range (25%–75%)	73 to 104	12 to 60

* Significant difference between malignant and benign nodules (Kruskal-Wallis test, $P < .001$).

[†] Significant difference between malignant and benign nodules, ranging from negative to positive values in the malignant group (Kruskal-Wallis test, $P < .008$).

nign nodules showed a moderate SI increase followed by a second slight increase.

A significant difference of curve profiles (A–D) was calculated between malignant and benign lesions ($P < .001$) (Table 4, Fig 3). A type A curve was characterized by a fast SI increase and an obvious decrease after the first bolus transit. This profile was found only in malignant neoplasms ($n = 14$). The majority of adenocarcinomas (seven of 10) and the two carcinoids showed this curve type (Fig 4). A type B curve exhibited a rapid SI increase to the peak, followed by a second moderate SI increase or a plateau phase. For this profile, the largest overlap (2:1) between malignant ($n = 12$) and benign ($n = 6$) nodules was found, including malignant and benign neoplasms and inflammations. A type C curve was present

in 13 of 24 benign nodules but in only one carcinoma, showing a more continuous SI increase, followed by a plateau. A type D curve demonstrated no significant SI increase over the measured time period with a mean enhancement of less than 10%. This behavior was found in only five benign nodules.

Morphologic Parameters

Table 5 summarizes the results from the morphologic analysis of enhancement. A statistically significant difference between malignant and benign lesions was found (two-sided Fisher exact test, $P < .001$). Mean nodule diameters were not significantly different between enhancement patterns ($P > .5$), and no visible enhancement was found in five benign nodules. Both homogeneous and

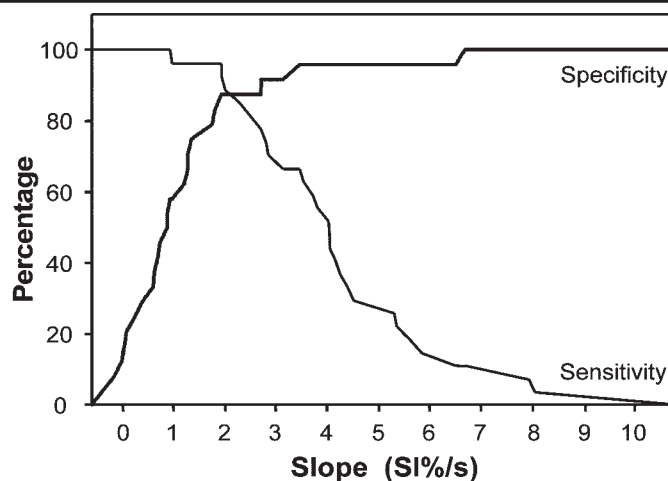
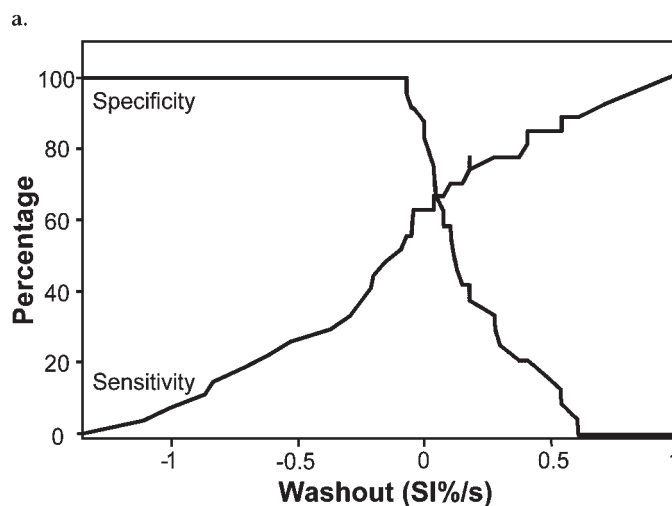
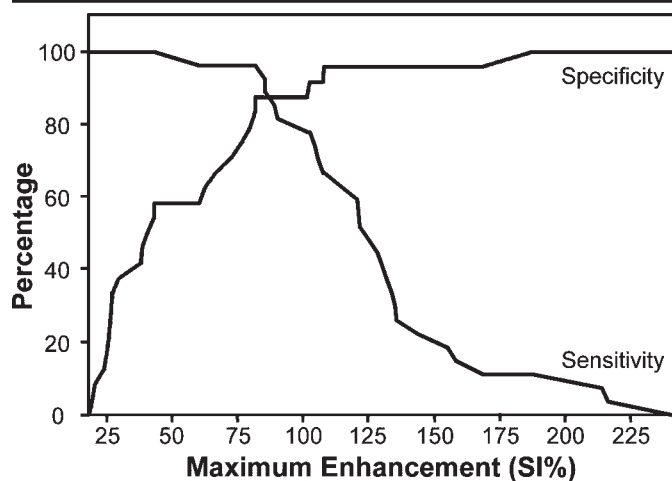


Figure 1. Graphs show sensitivity and specificity across levels of evaluated parameters from time-intensity curves. (a) Threshold for maximum peak enhancement was set at 85%. (b) Threshold for slope enhancement at first bolus transit was set at 1.5 SI%/sec. (c) Threshold for washout was set at 0.1 SI%/sec.

reached in 27 nodules. In these cases, the nodular hot-spot pattern was used as a strong sign for malignancy, and peripheral enhancement was used as strong sign for nonmalignancy. By summarizing the results from both the kinetic and morphologic evaluation, the sensitivity, specificity, and accuracy were 100% (27 of 27 nodules), 79% (19 of 24 nodules), and 90% (46 of 51 nodules), respectively.

DISCUSSION

Our study of dynamic MR imaging of solitary pulmonary nodules demonstrates that differentiation between benign and malignant nodules is feasible. For all evaluated kinetic and morphologic parameters, significant differences were found.

Rapid and strong contrast enhancement is related to high vascularity in tumors and interstitial accumulation of contrast material by means of increased permeability of tumor capillaries (40). These features are often present in malignant tumors (41–47). On the basis of these findings, enhancement in malignant solitary pulmonary nodules should have a strong initial increase after bolus application of contrast material with a higher enhancement than that in benign solitary pulmonary nodules. In another study (48), however, no parenchymal destruction or tumor-associated neovascularization was found in 16% of 500 stage I primary lung cancers. In addition, inflammatory conditions have been dem-

TABLE 3
Diagnostic Characteristics according to Threshold Values

Characteristic	Maximum Peak (85% SI% threshold)	Slope (1.5 SI%/sec threshold)	Washout (−0.1 SI%/sec threshold)
Sensitivity (%)*	96 (26/27)	96 (26/27)	52 (14/27)
Specificity (%)	88 (21/24)	75 (18/24)	100 (24/24)
Accuracy (%)	92 (47/51)	86 (44/51)	75 (38/51)
Positive predictive value (%)	90 (26/29)	81 (26/32)	100 (14/14)
Negative predictive value (%)	95 (21/22)	95 (18/19)	65 (24/37)

Note.—Prevalence of malignancy, 53% (27 of 51 nodules). Numbers in parentheses are raw data.

* Lower and upper 95% CI limits were 89% and 100% for the sensitivity of maximum enhancement and slope and 34% and 67% for the sensitivity of washout.

heterogeneous enhancement were detected in both groups at a ratio of six malignant to five benign nodules. Nodular enhancement was demonstrated in 15 malignant nodules, whereas only two benign lesions demonstrated this pattern (Fig 5). Rim enhancement was found in seven benign nodules but in no malignant nodules (Fig 6).

Combined Parameters

By using the curve profile in the first line of the decision tree, where type A indicates malignant nodules and type D indicates benign nodules, 19 nodules were classified correctly (Fig 7). In the remaining 32 lesions, which had type B or C curves, a correct differentiation was

onstrated to stimulate an increased blood flow in malignant lesions (21,34,38). Furthermore, the theoretical model of pulmonary tumor enhancement is complex because of dual circulation of blood in the lung. A variable mixed blood supply has been shown to exist for lung metastases and is dependent on the precise location (42). Thus, more information regarding tissue perfusion is essential for finding signs that can differentiate lesions and provide higher specificity.

In the present study, we observed an interesting behavior of time-intensity curves in malignant nodules: A significant SI decrease (>0.1 SI%/sec) was shown in 52% of nodules (14 of 27 nodules) after an initial strong SI increase. This washout phenomenon of contrast material has been seen in a variety of other tumor types with signs of hypervascularization (25,49,50). Quantitative evaluation of the washout phenomenon, by setting a decreased threshold level at 0.1 SI%/sec, revealed a specificity of 100% because no benign lesion had reached this level. Our study population contained no patients with acute infections that may have shown washout.

To our knowledge, no quantitative data have been published regarding washout in lung nodules and MR imaging. In two previous dynamic MR imaging studies (34,35), washout was implicated in one case of carcinoid and in inflammatory lesions. We believe that the present study presents a novel finding for washout in lung nodules, providing a new indicator of differentiation with high specificity.

By using dynamic CT in the standard manner, washout cannot be displayed adequately because of limited temporal resolution. The use of shorter scanning intervals (2 seconds), as used by Zhang and Kono (21) and Tateishi et al (23), was also not adequate in displaying this phenomenon. A plausible reason may be that CT measurements encompass only 70% of the nodule to avoid partial effects. Thus, in our study, complete nodules can be measured on MR images, enabling detection of washout in the peripheral area of the lesion.

In the present study, the sensitivity of dynamic MR imaging enhancement was 96% by using a threshold value for maximum peak and slope. This result is in accordance with that of previous studies of contrast-enhanced CT and MR imaging (18,19,22,34,35,38). The only false-negative observation was a squamous cell carcinoma that showed a slow SI increase and low maximum peak. Weak bolus

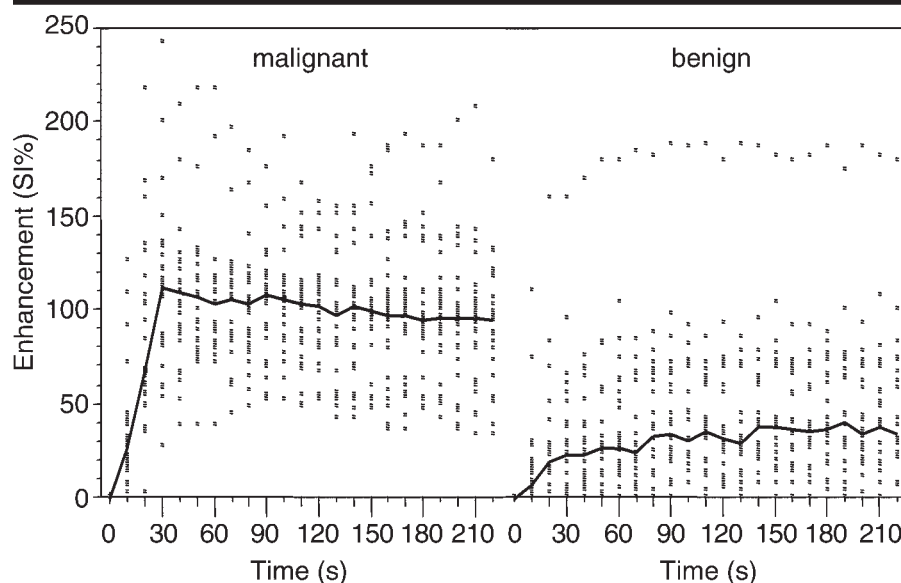


Figure 2. Graph shows SI% of nodules at each time point. Each dot represents a single measurement grouped according to benign and malignant lesions. Medians are connected for both groups. Resulting profile in malignant nodules differs from that in benign nodules, showing a faster SI increase in the first 30 seconds, followed by a slight decrease. No decrease is demonstrated in the benign group. Note that although many malignant nodules had values below the threshold value of 85% SI% in the time-intensity curve, in only one patient were all measurements of SI% less than 85%. In the benign group, one or more values were higher than 85% in three patients.

TABLE 4
Frequency of Curve Type according to Diagnosis

Diagnosis	Type A (n = 14)	Type B (n = 18)	Type C (n = 14)	Type D (n = 5)
Malignant	14 (100)	12 (67)	1 (7)	0 (0)
Adenocarcinoma	7	3	0	0
Squamous cell carcinoma	2	4	1	0
Small cell carcinoma	1	2	0	0
Carcinoid	2	0	0	0
Metastasis	2	3	0	0
Benign	0 (0)	6 (33)	13 (93)	5 (100)
Hamartoma	0	3	6	3
Granuloma	0	0	4	1
Inflammatory lesion	0	2	3	0
Other	0	1	0	1

Note.—Data are number of nodules. Numbers in parentheses are percentages.

preparation and reduced cardiac output could be ruled out in this case by calculating the enhancement of the lung parenchyma. The specificity was 88% and 75% for maximum peak enhancement and slope enhancement, respectively. These higher specificities, when compared with CT data, confirm the findings of other MR imaging investigators (35,38).

In contrast to these observations, maximum peak was more specific than was slope in our study. Two main reasons for this discrepancy may be considered. First, the longer observation time with contin-

uous MR image acquisition during 4 minutes enabled us to register a further SI increase after the early peak. Second, the absence of patients with acute inflammatory lesions in our study reduces the overlap between malignant and benign lesions for maximum peak, whereas in previous studies, highest slope was found for active inflammations. In other studies (34,35,38), we found a similar overlap in slope in cases of more chronic inflammations.

To our knowledge, no quantitative data exist concerning correlation between the degree of inflammation and

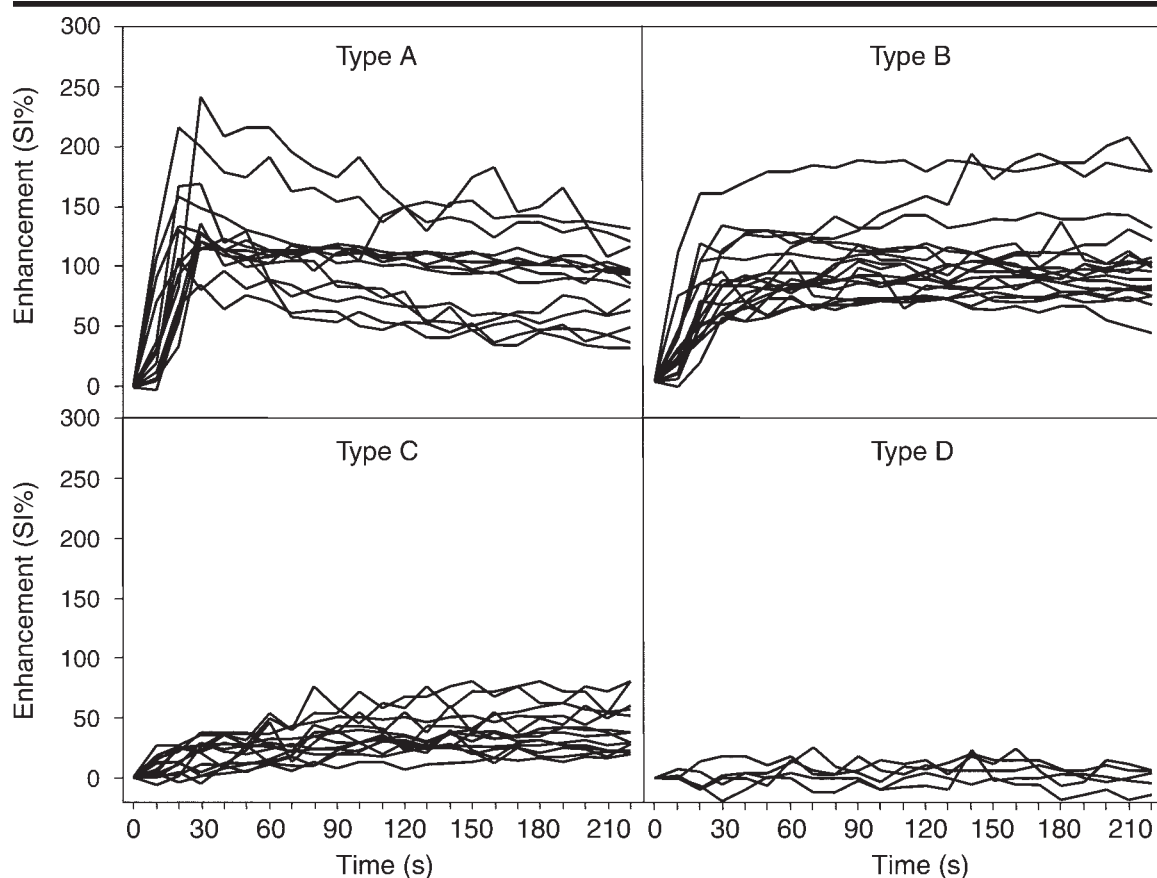


Figure 3. Time-intensity curves for all patients grouped according to curve types A–D. Fourteen malignant and no benign nodules demonstrated curve type A, demonstrating a fast initial SI increase and a marked decrease after 20 or 30 seconds. No SI decrease after the first bolus transit is present in curve type B, which was demonstrated by 18 nodules (12 malignant and six benign nodules). A more continuous SI increase without any sharp early peak after the first bolus transit demonstrates that curve type C was found in 14 nodules (one malignant and 13 benign nodules). Note that ultimately, the curves demonstrate a plateau. No relevant enhancement was calculated for the five benign nodules with curve type D.

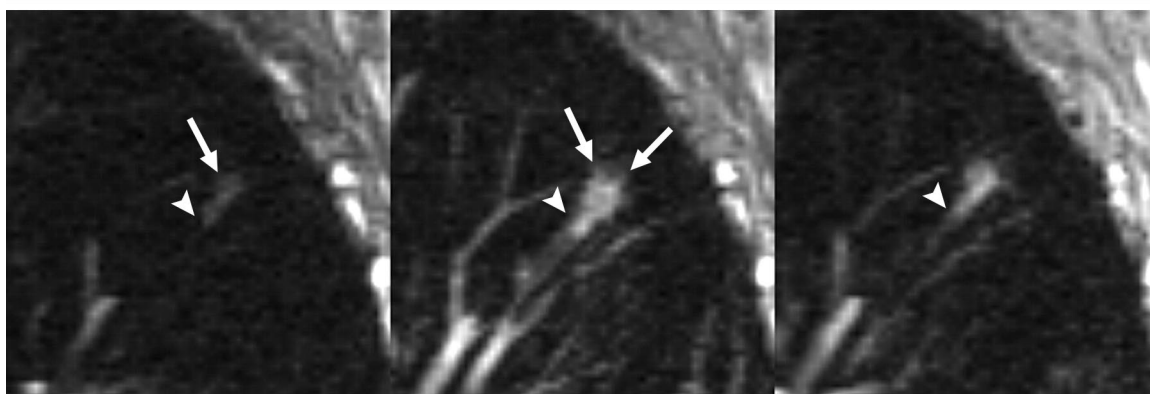


Figure 4. Sagittal dynamic two-dimensional gradient-echo MR images (voxel size, $1.4 \times 1.4 \times 8.0$ mm) in a 62-year-old man with a primary 8-mm adenocarcinoma in the left upper lobe. At 0 seconds (left image), a hypointense nodule (arrow) with indistinct margins is seen. At 30 seconds (middle image), the SI of the periphery of the lesion increased markedly, with visible spiculation (arrows). At 90 seconds (right image), the lesion appears smaller and less intense, which is explained by washout. An adjacent vessel is noted by the arrowhead on each image.

slope of the first bolus transit. However, increased blood flow and capillary permeability are factors that should be con-

sidered in the inflammatory process as possibly affecting slope enhancement. In our series, symptoms of an acute pulmo-

nary infection and compromised immunity were definite exclusion criteria to avoid any bias in differentiating malig-

TABLE 5
Frequency of Enhancement Pattern according to Diagnosis

Nodule Type	Enhancement Not Visible (<i>n</i> = 5)	Homogeneous Enhancement (<i>n</i> = 11)	Heterogeneous Enhancement (<i>n</i> = 11)	Nodular Enhancement (<i>n</i> = 17)	Peripheral Rim Enhancement (<i>n</i> = 7)
Malignant (<i>n</i> = 27)	0 (0)	6 (55)	6 (55)	15 (88)	0 (0)
Benign (<i>n</i> = 24)	5 (100)	5 (45)	5 (45)	2 (12)	7 (100)

Note.—Data are number of nodules. Numbers in parentheses are percentages.

nant and benign nodules. Until now, however, only a small number of patients has been studied with comparable techniques.

Although better specificity has not yet been validated in larger cohorts with a higher proportion of benign solitary pulmonary nodules, MR imaging seems to have the potential to depict distinct differences in vascularity between benign and malignant nodules. High sensitivity for paramagnetic contrast material and high temporal resolution of dynamic MR imaging are both advantageous for this purpose.

Quantitative analysis of SI and the relative percentage SI increase in MR imaging depend on the chosen field strength, coil, sequence type, and parameter. Thus, in contrast to CT, MR imaging results are difficult to interpret in a standardized manner. A classification of SI curve profiles may be more appropriate and may also provide a means of visual evaluation.

In the present study, we saw four distinct SI profiles. The hyperperfusion of type A was found in malignant nodules with only a possible dependence on tumor subtype. Adenocarcinomas showed this hyperperfusion type in 70% of cases (seven of 10), but squamous cell carcinomas showed this type in less than one-third of cases (two of seven [28%]). These findings may be explained by the significant histologic differences in angiogenesis and microvessel density between these two tumor types (51,52). The type B curve encompassed both malignant and benign lesions. Factors to consider are that although vascularization showed less microvessel density than that shown for type A, the permeability of tumor capillaries and interstitial space was also increased. All tumor subtypes in our series were found in this curve, except for granulomas and carcinoids. The type C curve represents the benign pattern, showing continuous enhancement with one exception—namely, a squamous cell carcinoma that had a low vascularization. The type D curve seems to be strongly related to benign nodules. By using these

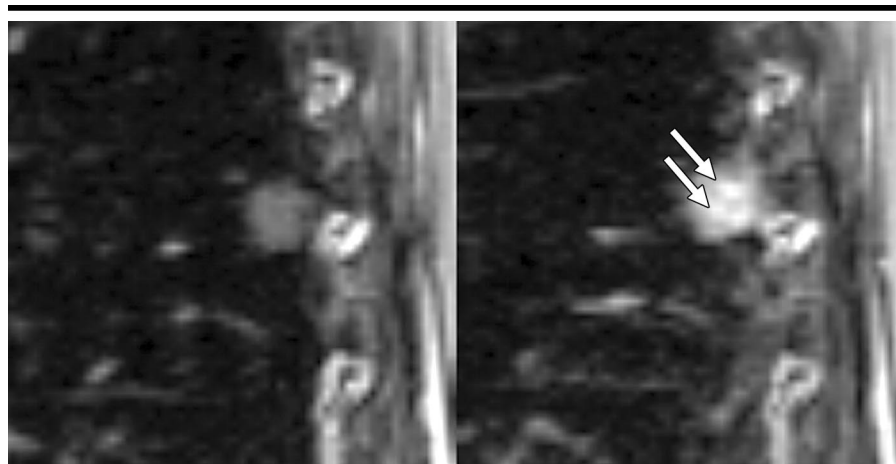


Figure 5. Sagittal dynamic two-dimensional gradient-echo MR images (voxel size, $1.4 \times 1.4 \times 8.0$ mm) in a 67-year-old man with a left lower lobe metastasis of a 15-mm adenocarcinoma of the colon. At 0 seconds (left image), a hypointense lesion with irregular margins is present. At 30 seconds (right image), a moderate SI increase of the entire lesion is visible. Arrows indicate centrally nodular hyperintensities after contrast material application.

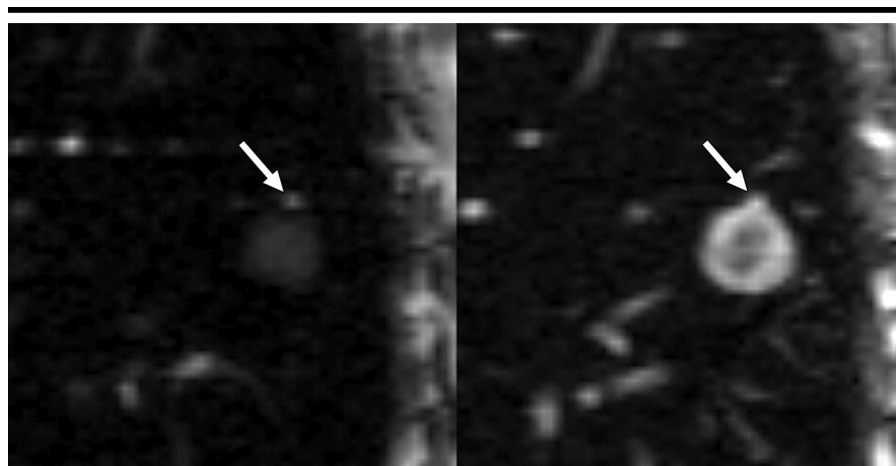


Figure 6. Sagittal dynamic two-dimensional gradient-echo MR images (voxel size, $1.4 \times 1.4 \times 8.0$ mm) in a 59-year-old woman with a 15-mm hamartoma of the left lower lobe with surrounding zone of inflammation. At 0 seconds (left image), a round hypointense nodule is present. Note the distance between the nodule and the neighboring vessel (arrow). At 30 seconds (right image), a strong SI increase in the periphery of the lesion is visible, demonstrating capsular-like enhancement. Note that the distance between the lesion and the vessel (arrow) is reduced after contrast material application.

four profiles, the complex processes in tissue perfusion could be simplified, and differentiation between malignancy or

nonmalignancy could become more independent from the MR imaging technique.

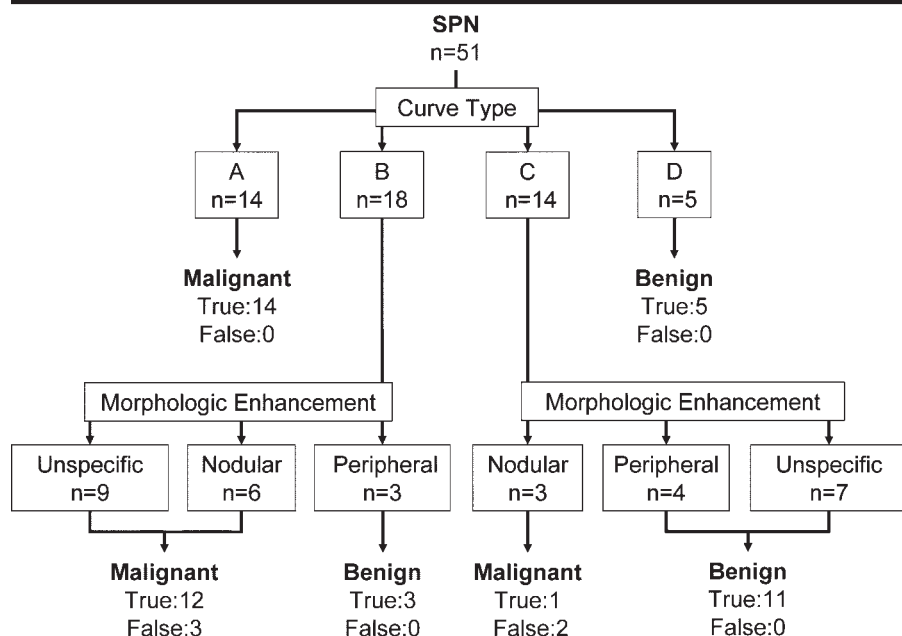


Figure 7. Decision tree contains numbers of lesions for each parameter evaluated. Lesions that fall through the kinetics mesh are sieved according to morphologic pattern of enhancement. Overall sensitivity, specificity, and accuracy were 100%, 79%, and 90%, respectively. The term *unspecific* includes nodules with homogeneous, heterogeneous, and no enhancement. SPN = solitary pulmonary nodule.

The local distribution of contrast material inside the lesions and enhancement patterns in the periphery of lesions are used routinely in diagnostic radiology. In accordance with the experiences of other investigators (20,35) who have performed contrast-enhanced studies of solitary pulmonary nodules, we found a strong relationship between thin capsular-like enhancement and benign nodules. More than one-third of the enhancing benign lesions had this pattern (ie, hamartomas and granulomas), representing an active zone in the periphery with chronic infiltration by macrophages found in surgically removed hamartochondromas. The nodular pattern with high-perfusion hot spot-like aspect has not been described in previous studies, to our knowledge.

Because of the higher spatial resolution used in our investigation, when compared with previous studies, this preliminary result could reflect areas of high perfusion with an increased vessel density. This finding was highly specific, occurring in 15 malignant nodules but in only two benign nodules. Necrotic areas or irregular partitions of fibrosis, which were present in both malignant and benign lesions, may explain the heterogeneous pattern, which seems to be unspecific.

Our data indicate that a combination

of kinetic and morphologic evaluation in dynamic contrast-enhanced MR imaging provides a promising method for differentiation of indeterminate lung nodules, reaching a sensitivity of 100% and specificity of 79%. Considering the wide variety of tumor subtypes in this study, we feel that confidence in differentiating between malignant and benign lesions is greatly improved.

In practice, use of quantitative parameters of enhancement kinetics alone leads to problems in differentiation because of these cases having values near the threshold levels or, as in our example, having curve types B and C. Thus, morphologic assessment as an additional parameter reduces these incomplete findings and prevents misclassification of malignant lesions as benign. This also reduces the need for further evaluation by means of histologic examination and, thus, unnecessary resections or biopsies of benign nodules. We believe that the combined use of kinetic and morphologic aspects of tissue perfusion is superior in the definitive diagnosis of indeterminate lung nodules. Furthermore, when considering the finding of numerous benign lesions in lung cancer screening, the use of a method that reduces radiation exposure has obvious benefits.

Our study has some limitations: (a) Although data acquisition was prospective,

kinetic and morphologic analyses were performed retrospectively and need further validation. (b) We characterized what we believe to be novel findings of enhancement pattern by means of consensus reading; thus, assessment of interobserver variability is not available. (c) A selection bias must be considered because of the referring departments of surgery that attend to a high percentage of hamartomas. (d) The evidence of the results in the subgroups is limited by the relatively small study population. (e) The marked specific washout in particular may be clinically helpful only if patients without symptoms of active pulmonary infections are examined. The cost-effectiveness of the presented approach has yet to be evaluated.

In conclusion, kinetic indexes of dynamic MR imaging provided accurate differentiation between malignant and benign lesions, where washout was a specific sign for malignancy. By combining SI profiles and morphologic enhancement patterns, the confidence in differentiation improved, which led to a sensitivity of 100% and a specificity of 79%.

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