Dynamic TurboFLASH Subtraction Technique for Contrast-enhanced MR Imaging of the Prostate: Correlation with Histopathologic Results

PURPOSE: To assess whether a TurboFLASH (fast low-angle shot) magnetic resonance (MR) sequence can improve the accuracy of fast spin-echo (SE) endorectal coil MR imaging in the staging and localization of prostate cancer.

MATERIALS AND METHODS: In 57 patients with prostate cancer, MR imaging was performed with the following sequences: T1-weighted SE, T2-weighted fast SE, single-section gadolinium-enhanced dynamic subtracted TurboFLASH (one image every 1.25 or 2.5 seconds), and late-phase gadolinium-enhanced T1-weighted SE. Retrospectively, two blinded independent readers graded tumor involvement and assessed tumor involvement and capsular penetration. MR findings were correlated with histopathologic results.

RESULTS: On TurboFLASH images, prostate cancer was characterized by early and rapidly accelerating enhancement compared with that of surrounding tissues. Average sensitivity, specificity, and accuracy for detection of tumor involvement for the two readers with TurboFLASH images were 73.5%, 81.0%, and 77.5%, respectively. These values with fast SE images were 57.5%, 80.5%, and 72.0%. Depiction of capsular penetration and delineation and staging of tumor were better when TurboFLASH images were included with fast SE images. Differences between the two sequences, however, were not statistically significant.

CONCLUSION: Because the TurboFLASH sequence did not statistically significantly improve tumor localization and staging results, routine use is not recommended. The technique may be useful for selected patients with equivocal evidence of capsular penetration.

MAGNETIC resonance (MR) imaging is considered an effective tool for staging prostate cancer (1). The information obtained with this modality, however, adds little to the information obtained by the traditional means of clinical staging and biopsy, such as tumor grade, number and length of cores containing malignancy, and involvement of seminal vesicles (2-4).

The use of a gadolinium chelate to increase the diagnostic information of MR imaging has been described in the literature (5-10). The results of these studies suggest that contrast material-enhanced T1-weighted MR imaging does not provide additional information compared with that obtained from T2-weighted imaging, but that the T1-weighted sequence may be useful in evaluating seminal vesicle invasion in equivocal cases (6,10). Therefore, the use of a gadolinium chelate is not warranted for routine staging of prostate cancer. Brown et al. (8) evaluated early-phase, T1-weighted, bolus-enhanced MR imaging for the evaluation of prostate cancer. They found that the information provided by T1-weighted images during the early phase of contrast enhancement enables the best delineation of tumor within the gland.

Experience with dynamic subtraction TurboFLASH (fast low-angle shot) Siemens, Erlangen, Germany) MR imaging in bladder and breast cancer indicates that malignant lesions demonstrate an earlier and faster enhancement compared with that of benign lesions (11,12). To our knowledge, the diagnostic value of fast dynamic contrast enhancement in prostate cancer has not been evaluated previously. The aim of the present study was to evaluate the complementary diagnostic value of single-section dynamic subtraction TurboFLASH MR imaging in patients with prostate cancer.

MATERIALS AND METHODS

The patient population comprised 57 men (age range, 48-73 years; mean age, 64 years) with clinically localized prostate cancer who underwent dynamic subtraction TurboFLASH MR imaging complementary to the routine staging MR examination of the prostate. The examinations were performed between August 1993 and February 1996. Only patients who underwent radical prostatectomy were included in this study. Patients who received hormonal treatment before surgery were excluded from this study. Biopsy procedures preceded MR imaging by an average of 3 weeks. Patients underwent radical prostatectomy within 3 weeks after imaging. All prostatectomy procedures were performed in patients in whom no lymph node metastases were found at laparoscopic lymph node dissection before the operation or at frozen section examination during the operation.

MR Technique

All images were obtained with a commercially available 1.5-T MR system (Magnetom SP; Siemens) by using an endorec-

Index terms: Gadolinium • Magnetic resonance (MR), pulse sequences, 844.121411, 844.121416, 844.12143 • Prostate, magnetic resonance (MR) imaging, 844.121411, 844.121416 • Prostate, neoplasms, 844.32 • Prostate, surgery, 844.451

Abbreviations: BPH = benign prostatic hyperplasia, FLASH = fast low-angle shot, SE = spin echo.

Radiology 1997; 203:645-652

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MR Image Evaluation

The T2-weighted fast SE images, the T1-weighted postcontrast images, and the subtracted images were interpreted independently by two observers (G.J.J., J.O.B.) who were blinded to the clinical findings and laboratory and imaging results. The T2-weighted, postcontrast T1-weighted, and dynamic subtracted TurboFLASH images were interpreted for presence and location of tumor and capsular penetration by tumor. At the level of the dynamic subtracted TurboFLASH images, the prostate was divided into four areas: peripheral zone left and right and central zone left and right. The presence of tumor was scored on a five-point scale: 1 = definitely absent, 2 = probably absent, 3 =
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Figure 2. Case of a 63-year-old-man with tumor involvement on the right side. (a) T2-weighted fast SE image shows retraction of the capsule on the right side (arrow) that was not interpreted as capsular penetration. (b) Dynamic subtracted TurboFLASH image shows enhancement outside the contour of the prostate (arrow) interpreted as capsular perforation. Capsular perforation was present at final pathologic examination. (c) Histopathologic specimen at the level of the right neurovascular bundle shows that, at the dorsolateral side, tumor is present and growing outside the prostatic capsule (pT3a, in which p = pathologic classification and a = unilateral capsular extension) (arrows). (Hematoxylin-eosin stain; original magnification, ×20.)

The onset and slope of enhancement were assessed on hard-copy images made of the subtraction set. The onset of enhancement of prostatic tissue in relation to the onset of arterial enhancement was registered in seconds. The slope of enhancement was scored on a three-point scale: 1 = slow, 2 = normal, 3 = fast.

On the subtracted images, a lesion was considered to represent malignancy if the slope of enhancement was faster and the onset was earlier relative to the adjacent prostatic tissue. Enhancement outside the contour of the prostate was considered to represent capsular penetration (Fig 2).

With use of these criteria, the additional value of the TurboFLASH technique was assessed.

Pathologic Examination

The prostatectomy specimens were fixed in toto overnight in a solution of 10% neutral buffered formalin. Step sections were made at 4-mm intervals in a plane parallel to the base of the prostate, which corresponded to the sections used for axial MR imaging. After separating the step sections into right and left halves, all sections were routinely embedded in paraffin. Tissue sections of 4 µm were prepared and stained with hematoxylin-eosin. Regions representing cancer were outlined on the glass cover and retracted onto a diagram of the axial histologic sections that extended from the base to the apex of the prostate. The area of tumor involvement for each lesion was determined by using the ellipsoid formula, and the total area of cancer involvement was calculated as the sum of cancer areas on the selected section. Measurements were multiplied by a factor of 1.1 to correct for tissue shrinkage due to fixation.

Data Analysis

Analysis of the correlation of MR findings and histopathologic results was performed by two radiologists (G.J.J., J.O.B.) and one pathologist (E.T.G.R). The MR images were correlated with tumor maps on the basis of the histopathologic sections. The level of the dynamic subtracted TurboFLASH images was determined by its location between the apex and base of the prostate. The corresponding pathologic slice of the tumor map was then adjusted. Because of the difference between section thickness of the TurboFLASH images (10 mm) compared with that of the fast SE images (4 mm) and the gross specimen (4 mm), tumor maps of adjacent pathologic slices were also considered.

Penetration through the capsule was compared for each quadrant.

Statistical Analysis

The McNemar test (exact distribution) was used to evaluate the differences in assessing tumor presence and capsular penetration with both techniques. Cohen κ analysis was used to test for agreement between both readers with respect to the presence and absence of tumors and capsular penetration: κ < 0.40, poor agreement; κ = 0.4-0.75, good agreement; κ > 0.75, strong agreement.

When sensitivity and specificity values for tumor presence were calculated, scores 4 and 5 were considered “present.” When sensitivity and specificity values for capsular penetration were calculated, score 3 was considered “present.”

Additional Diagnostic Value

The overall additional diagnostic value of dynamic subtracted TurboFLASH images to routine MR imaging was determined as follows: Major improvement of the diagnostic performance was present when dynamic subtracted TurboFLASH images allowed correct overstaging (T2→T3) or understaging (T3→T2), minor improvement was present when the estimated area of tumor involvement as determined on the dynamic subtracted TurboFLASH images came within the 25% range of the actual tumor (Figs 3, 4). Diagnostic performance was defined as “worse staging” when over- or understaging was incorrect with dynamic subtracted TurboFLASH images and “worse (minor)” when the estimated
area of tumor involvement as determined on the dynamic subtracted TurboFLASH images exceeded the 25% range of the actual tumor area correlated with the corresponding step-section histologic slice (Fig 5). Additional information of dynamic subtracted TurboFLASH images that did not change the final staging result was called "minor." For example, dynamic subtracted TurboFLASH images depicted capsular penetration not depicted on fast SE images, but fast SE images had already depicted seminal vesicle invasion (T3c).

RESULTS
Correlating MR and Histopathologic Findings

The correlation between MR images and the corresponding histopathologic section was difficult in most patients. The most caudal section of the MR images was 0.5-1.5 cm more distal than the most apical section of the prostatectomy specimen. Also, the angle by which the sections were cut in both techniques was never exactly the same for either technique (difference, 5°-15°). Furthermore, the shape of the prostate changed after surgery and fixation compared with the shape of the gland within the body at the time of imaging. Also making correlation difficult was the fact that prostate tumors are very irregular and often demonstrate fingerlike projections with ill-defined margins, which did not display on MR images of 4-, 5-, or 10-mm section thickness (whereas the histologic sections were only 4 μm thick). We tried to overcome these problems by using tumor maps, which gave a good three-dimensional picture of the prostate and were of help in assessing the corresponding level.
Figure 5. Case of a 52-year-old man with a very small focus of prostate cancer (0.4 cm³). (a) Time and (b) maximal signal intensity images show symmetrically rapid and early enhancement. (c) Gross specimen of the corresponding section shows BPH. No tumor was present at the corresponding level.

<table>
<thead>
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<th>Table 1</th>
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<tr>
<td><strong>Sensitivity and Specificity for Tumor Localization with Fast SE and Dynamic Subtracted TurboFLASH Imaging</strong></td>
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<tr>
<td><strong>Zone</strong></td>
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<td>Tumor present</td>
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<td>Peripheral (n = 72)</td>
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<td>Central (n = 30)</td>
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<td>Total (n = 102)</td>
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<tr>
<td>Tumor absent</td>
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<tr>
<td>Peripheral (n = 42)</td>
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<tr>
<td>Central (n = 84)</td>
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<td>Total (n = 126)</td>
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Note.—Numbers in parentheses are percentages.

**Characterization of Enhancement Patterns**

Differences in enhancement within the prostate were best depicted in the early phase of the first pass of contrast material. However, most glandular tissue of the prostate displayed early enhancement, and there was a considerable variation between the start of enhancement of the external iliac artery (t = 0) and the start of enhancement of prostatic tissue. Therefore, the onset of enhancement was judged relative to the adjacent prostatic tissue. We were also not able to characterize the time–signal intensity curve (slope of enhancement) for malignant or benign lesions. Therefore, relative differences in slope values in the selected section were used to differentiate between benign and malignant lesions.

**Interobserver Agreement**

Interobserver agreement for the interpretation of MR images with and without the dynamic subtracted TurboFLASH sequence was strong. The Cohen $\kappa$ values were 0.79 and 0.78, respectively.

Both observers agreed that nondynamic T1-weighted postcontrast images did not provide additional information compared with T2-weighted fast SE images.

**Detection of Tumor**

A total of 228 quadrants were identified, rated, and analyzed. Tumor was present in 102 quadrants. The results for predicting tumor presence with and without dynamic subtracted TurboFLASH images are presented in Table 1. For each reader, the sensitivity for detection of tumor with fast SE images was 57% and 58%, respectively, and with dynamic subtracted TurboFLASH images was 74% and 73%, respectively (the differences between sequences were not statistically significant). The specificity for fast SE images was 79% and 82% and for dynamic subtracted TurboFLASH images was 79% and 83%, per reader respectively (the differences between sequences were not statistically significant). The accuracy for fast SE images was 73% and 71% and for dynamic subtracted TurboFLASH images was 77% and 78% (the differences between sequences were not statistically significant).

**Tumor Volume**

In 17 (30%) and 18 (32%) of the 57 patients, the area of tumor involvement estimated with fast SE images was within the 25% range of the actual area of tumor involvement, per reader respectively. With dynamic subtracted TurboFLASH images, the estimated tumor volume was within the 25% range in 23 (40%) and 25 (44%) patients (the differences between sequences were not statistically significant).

**Capsular Penetration**

Two hundred twenty-eight quadrants were evaluated. Capsular penetration was present at histopathologic examination in 19 different quadrants, in 14 patients. In the remaining 209 quadrants, capsular penetration was absent, including one site where capsular penetration could not be evaluated because the surgeon incised the capsule. With fast SE images, the readers correctly diagnosed capsular penetration in four and three quadrants, respectively. False-positive diagnoses were made at two sites. With dynamic subtracted TurboFLASH images, the readers correctly diagnosed capsular penetration in nine and 10 quadrants, respectively. With dynamic subtracted TurboFLASH images, false-positive diag-
noses were made in one and two quadrants, per reader respectively. When considering both sequences, capsular penetration was predicted more accurately with dynamic subtracted TurboFLASH images by both readers in six and nine quadrants in six (11%) and nine (16%) patients, respectively, but less accurately in zero and two quadrants in zero and two (4%) patients (the differences between sequences was not statistically significant). Three other patients, in whom the findings were true-negative for capsular penetration, had capsular penetration at a different level than that of the dynamic subtracted TurboFLASH images. Capsular penetration was depicted in one of these three on fast SE images.

**Additional Diagnostic Value**

The additional diagnostic value of dynamic subtracted TurboFLASH images to routine MR imaging is summarized in Table 2. We achieved overall major improvement in five and seven patients, per reader respectively, and overall minor improvement in eight and six patients, respectively.

**DISCUSSION**

The merit of MR imaging is in the local staging of prostate cancer. Although microscopic capsular penetration may not be demonstrated on T2-weighted images, MR imaging may be helpful in selecting patients with a potentially resectable disease (13,14). More accurate staging, however, is needed.

Several studies have addressed the use of contrast material in MR imaging of the prostate (5-10,15). In the normal prostate, the central zone enhances more than the peripheral zone. Both enhance homogeneously. In the presence of BPH, the enhancement pattern of the central gland is markedly inhomogeneous (6,8). BPH may occasionally arise within the peripheral zone of the prostate, leading to an inhomogeneous enhancement.

Prostate cancer is frequently reported to show increased enhancement compared with that of adjacent glandular tissue, especially in the peripheral zone; in the central zone, the difference is less obvious (8).

Reported studies suggest that contrast enhancement in prostate cancer is of limited value and may be only helpful in cases of seminal vesicle invasion (6,15).

Brown et al (8) evaluated bolus-enhanced MR imaging in prostate carcinoma. They showed that early-phase contrast-enhanced images best enabled the definition of tumor within the gland in 10 (50%) of 20 patients and demonstrated capsular spread more clearly in eight (80%) of the 10 patients. In that study, no pathologic correlation could be obtained.

Malignant breast, bladder, and bone tissues have demonstrated early and fast enhancement. The enhancement pattern can be characterized by the onset of enhancement (11,16) or by the slope of enhancement (17). We evaluated the enhancement of prostate cancer during the first pass of contrast material with fast dynamic imaging with a temporal resolution of one image per 1.2 or 2.24 seconds after bolus administration of intravenous contrast material. Our findings indicate that prostate cancer also enhances early and that differences in enhancement are visible in the early phase of the first pass. However, owing to a large variation in the onset and slope of enhancement among the patients in our study and minor differences between the onset of enhancement of carcinoma and benign tissue, which bring about a considerable overlap between benign and malignant lesions in quantitative measures, we were not able to define a cutoff time nor a slope value to differentiate benign from malignant prostatic tissue. Therefore, the onset and slope of enhancement were judged relative to adjacent prostatic tissue.

Because we used subjective signs, independent double reading was performed to test for interobserver variability. There appeared to be strong agreement between both readers for the interpretation of both fast SE and dynamic subtracted TurboFLASH images. This is contrary to other studies, which have reported high interobserver variation in estimating tumor location, tumor volume, and capsular penetration of the prostate (18,19).

The high agreement of our readers may be due to the study design. The section of the dynamic subtracted TurboFLASH images was chosen in a plane that was likely to contain both cancer and normal tissue on the T2-weighted fast SE image.

Reported data for detection of tumors with MR imaging are, in general, poor especially for central gland tumors (20,21). The sensitivity for localization of tumors with dynamic subtracted TurboFLASH imaging was consistently better than that with fast SE images. It was confirmed that tumors located ventrally and centrally in histopathologic specimens were easily missed on T2-weighted images.

With dynamic subtracted TurboFLASH imaging, there were 12 and 10 more true-positive centrally located tumors than with SE imaging but also six and eight more false-positive tumors.

Tumor volume is a predictor of pathologic stage (22). Except for one study performed with an external-array coil (23), studies performed with endorectal (13) and body coil MR imaging (24-27) reported a poor correlation between MR tumor volume and the volume as calculated from the pathologic specimen. Mirowitz et al (6) who studied postcontrast T1-weighted images also reported poor correlation between the estimated and calculated volume. Brown et al (8) found better correlation during the early phase of enhancement, but in that study pathologic confirmation was not obtained.

When compared with fast SE images, dynamic subtracted TurboFLASH images enabled better estimation of the area of tumor involvement in 10%-12% of the patients. However, in only 30%-32% of patients, the area of tumor involvement estimated with fast SE images was within the 25% range of the actual area of tumor involvement. One reason for overestimating tumor volume on dynamic subtracted TurboFLASH images was rapid enhancement of an area of BPH in the central zone (Fig 5). This error can be averted when symmetrically central enhancement is not considered as cancer.

In an overview, Schiebler et al (1) stated that body coil MR imaging gives unsatisfactory results in the detection of capsular penetration. The detection of capsular penetration improved with endorectal coil MR imaging (sensitivity, 67%) compared with body coil MR imaging (sensitivity, 44%) in the same patient cohort (28).
Results of recent studies with endorectal coil MR imaging, however, showed a limited accuracy to 33% for detection of capsular penetration (5,13,19,29,30). In the present study, the sensitivity for detection of capsular penetration was 21% and 16% with fast SE, and 47% and 53% with dynamic subtracted TurboFLASH, per reader respectively. These values appeared not to be statistically significant. The low sensitivity for detection of capsular penetration with fast SE is because, at least in part, we only studied one level, preferably in which capsular penetration was not obvious. False-positive results on dynamic subtracted TurboFLASH images may be due to enhancement of a capsular artery. The vessel may be differentiated from tumor by a different enhancement curve (Fig 1).

Better prediction of capsular penetration is of clinical relevance because pathologic stage is the most important prognostic factor. Staging results improved because of a more accurate assessment of the capsule with dynamic subtracted TurboFLASH (Table 2).

T2-weighted MR images do not provide information about tumor grade, another predictor of clinical outcome. A noteworthy finding of the present study was that dynamic subtracted TurboFLASH images depicted all poorly differentiated tumors and that five of them showed the earliest and fastest enhancement of all lesions. These numbers are, however, too small for statistical analysis, and our study was not designed to differentiate between low-grade and high-grade lesions. These preliminary findings seem to be in contradiction with the findings of Yoshizako et al (9), who reported that poorly differentiated tumors demonstrate less enhancement on contrast-enhanced T1-weighted images than that of moderately differentiated tumors. However, we also observed that rapidly enhancing tumors demonstrated relatively low signal intensity on late-phase postcontrast images (Fig 1d), which may be explained by the high washout of contrast material from the tumor (Fig 1c).

Our study shows that the results of MR imaging with the dynamic subtracted TurboFLASH sequence were consistently better than those of routine MR imaging, although routine use of single-section dynamic subtracted TurboFLASH images did not statistically significantly improve tumor localization and staging results. The results of dynamic subtracted TurboFLASH imaging may, however, be improved. First, there was a learning curve. Second, a number of examinations were carried out in patients in whom the clinical stage was obvious from fast SE images. In these cases, dynamic subtracted TurboFLASH images did not provide additional information.

More limitations were inherent to the TurboFLASH technique we used; the single-section imaging technique allows evaluation in only one plane. Capsular penetration may be present at another level. Better delineation of tumor and tumor volume may become possible when with echo-planar imaging a dynamic multisec tion technique can be performed with a time resolution of a minimum of 3 seconds. Also, the spatial resolution is considerably less than with fast SE images, and the section is twice as thick. Another limiting factor of our technique was the endorectal coil-dependent variation of signal intensity throughout the prostate gland. Especially, lesions located ventrally are difficult to recognize because they show relatively less enhancement. In addition, the rectum-prostate interface is full of enhancement-like artifacts. In our series, better staging occurred predominantly at the dorsolateral side. The assessment at the dorsal side was difficult. Easily applicable corrections for the coil profile may be helpful. These problems may be overcome with the introduction of a combined endorectal- phased array coil, which will provide a more homogeneous signal through the prostate, a higher signal-to-noise ratio, and a decreased reliance on filters. Another limitation of the dynamic subtracted TurboFLASH technique is that onset and slope of enhancement of benign and malignant tissue show some overlap; therefore, false-positive and false-negative results may occur.

In conclusion, we demonstrated that prostate cancer shows early and rapid enhancement and that with fast imaging and the use of a subtraction technique tumor assessment may be improved. However, routine use of the single-section method did not statistically significantly improve staging results. Further improvement of the technique may be achieved by application of a multissection sequence, by the introduction of a combined endorectal- phased array coil, and by correction for the sensitivity profile of the endorectal coil throughout the prostate gland.

Acknowledgment: The authors thank Howard M. Pollack, MD, for his review of the manuscript and helpful suggestions.

References


