WHAT IS NEW IN BLADDER CANCER IMAGING

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Carcinoma of the urinary bladder, after prostate cancer, is the most common malignant tumor of the urinary tract in men and women and accounts for 2% of all malignancies. In 1993, in the United States 52,300 cases were registered. Although this number is still increasing because of aging of the population, smoking behavior (the most important single risk factor) is also an obvious influence. For example, bladder cancer mortality has decreased since 1990 because of changes in smoking behavior in the male Dutch population for successive birth cohorts after 1930 (Liemeney LALM, Witjes JA, unpublished data). The mortality in the United States in 1993 was 9900. Bladder cancer is seen predominantly in elderly men and the male to female ratio is 4:1.

About 90% to 95% of urinary bladder malignancies are transitional cell carcinomas, and the remaining 5% to 10% consist of squamous cell carcinomas and adenocarcinomas and a small number of sarcomas and metastases from other primary tumors. About two thirds of the tumors are superficial (< pT2) and are usually papillary. One third of the tumors show infiltration into or beyond the muscular layer of the bladder wall.

The initial treatment and prognosis largely are determined by the depth of tumor infiltration (tumor stage); the presence of positive lymph nodes and distant metastases; and the histologic tumor type. Therefore, exact staging is imperative. To describe local tumor extension (T), presence of lymph nodes (N), and distant metastases (M), the Union Internationale Contre le Cancer proposed a uniform clinical staging method (Fig. 1 and Table 1). Table 1 also presents the American classification, known as Jewett-Strong.

In superficial tumors, those without muscle invasion (stage Ta, T1, or carcinoma in situ), patients are treated with local endoscopic resection with or without adjuvant intravesical instillations. Patients with a tumor invading the muscle layer of the bladder wall or with only minimal perivesical extension (stage T2, T3a, or minimal T3b) are selected for radical lymphadenectomy and cystectomy or radiotherapy after neoadjuvant chemotherapy. If the local tumor is in an advanced stage (stage T3b, T4a, or T4b), or if nodal or distant metastases are present, the initial treatment is palliative chemotherapy or radiation therapy. If in such a patient adjuvant surgical therapy is considered, monitoring the response to chemotherapy or radiotherapy and determining the final outcome are important.

Because clinical staging is not reliable for determining tumor extension beyond the bladder wall, other methods are needed. In the field of imaging, rapid changes occur.
Figure 1. T stages of urinary bladder cancer extension.

After the development of CT scanning and ultrasonography, MR imaging has matured. Since the introduction of this technique, several reports in the late 1980s and early 1990s showed the superiority of this technique for staging urinary bladder carcinoma.\textsuperscript{2, 3, 7-9, 11-13, 15-18, 23, 25, 31} Even now, the end of rapid technologic improvements in MR imaging is not in sight, and visualization of the bladder and of bladder carcinoma is expected to improve still further. This article describes the appearance of MR images of the normal and abnormal urinary bladder. The role of MR imaging in staging this disease and in monitoring therapy is reviewed and illustrated. Finally, the authors present an overview of current and future applications of this technique.

**MR IMAGING ANATOMY**

The bladder wall consists of four layers: (1) the mucosa or epithelium, (2) the lamina propria or subepithelial connective tissue, (3) the muscle layer, and (4) the serosa. The muscle layer consists of bundles of smooth muscle tissue and has an intermediate-signal intensity, equal to that of skeletal muscle, on T1-weighted images and a low-signal intensity on T2-weighted images. According to Narumi et al.,\textsuperscript{20} the muscular wall consists of two different layers. The muscle fibers of the outer layer are looser and are interspersed with loose collagen fibers, blood vessels, and adi-

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**Table 1. COMPARISON BETWEEN TNM CLASSIFICATION AND JEWETT-STRONG STAGING SYSTEM**

<table>
<thead>
<tr>
<th>Jewett-Strong</th>
<th>TNM</th>
<th>Histopathologic Findings</th>
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<tbody>
<tr>
<td>O</td>
<td>T0</td>
<td>No tumor</td>
</tr>
<tr>
<td>O</td>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>O</td>
<td>Ta</td>
<td>Papillary tumor, confined to epithelium (≈ mucosa)</td>
</tr>
<tr>
<td>A</td>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue (≈ lamina propria)</td>
</tr>
<tr>
<td>B1</td>
<td>T2</td>
<td>Tumor invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>B2</td>
<td>T3a</td>
<td>Tumor invades deep muscle (outer half)</td>
</tr>
<tr>
<td>C</td>
<td>T3b</td>
<td>Tumor invades perivesical fat</td>
</tr>
<tr>
<td>D1</td>
<td>T4a</td>
<td>Tumor invades surrounding organs</td>
</tr>
<tr>
<td>D1</td>
<td>T4b</td>
<td>Tumor invades pelvic or abdominal wall</td>
</tr>
<tr>
<td>D1</td>
<td>N1-3</td>
<td>Pelvic lymph-node metastases</td>
</tr>
<tr>
<td>D2</td>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>D2</td>
<td>N4</td>
<td>Lymph-node metastases above the bifurcation</td>
</tr>
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</table>
pose tissue. Therefore, on T2-weighted in vitro MR images, the signal intensities of the outer bladder wall are higher. These findings, however, have been reported only on in vivo MR images in cases of bladder wall hypertrophy. At the site of the trigone, the wall consists of an extra triangular layer of muscle. Bundles from this layer link the ureteric ostia, forming the interureteric ridge. The serosa is not a bona fide layer but is merely a peritoneal covering, which, in fact, is in contact with the bladder only at the dome, which is just a small part of the entire bladder surface. The serosa is too thin to be recognized on MR images.

On T1-weighted images, urine has a low-signal intensity, whereas the perivesical fat has a high-signal intensity. Because urinary bladder carcinomas have an intermediate-signal intensity, equal to that of muscle, T1-weighted images are used to determine tumor infiltration into the perivesical fat (Fig. 2) and to show the endoluminal tumor component. T1-weighted images are also most suitable for imaging lymph nodes, the signal intensity of which is lower than that of the surrounding fatty tissue. Normal and abnormal lymph nodes, however, show no difference in signal intensity on these images. Therefore, a normal lymph node on MR images can be defined only by its size and shape. The signal intensity of bone marrow metastases is equal to that of the primary tumor; therefore, T1-weighted images, on which there is a good contrast between these metastases and the surrounding fatty bone marrow, are best for recognizing bone marrow metastases.

On T2-weighted images, the perivesical fat has a low- or a high-signal intensity, depending on the type of sequence used. Urine has a high-signal intensity. The tumor has an intermediate-signal intensity, higher than bladder wall or fibrosis and lower than urine. The zonal anatomy of prostate or uterus and vagina also can be well recognized on these images. These images are used for determining depth of tumor infiltration within the bladder wall (Figs. 3 and 4); for differentiating tumor from fibrosis; for assessment of invasion into the prostate, uterus, or vagina; and for confirming bone marrow metastases seen on T1-weighted images.

After intravenous administration of a gadolinium contrast agent urinary bladder cancer shows earlier and greater enhancement than does normal bladder wall or other nonmalignant tissues (Fig. 5). Enhancement occurs earlier in bladder cancer than in edema and granulation tissue.}

Figure 2. Axial T1-weighted three-dimensional MP-RAGE image in a patient with stage T3b urinary bladder cancer. Tumor infiltrates the perivesical fat (arrows) up to pelvic piriform muscle.
Figure 4: High-resolution axial T2-weighted TSE (1024 × 1024 matrix) in a patient with muscle wall infiltration of low-signal intensity bladder wall at site of tumor (black arrows) suggests infiltration in muscular wall.

Figure 3: Sagittal T2-weighted TSE image in a patient with two superficial (stage T1) urinary bladder cancers. Tumors have intermediate signal intensity and can be distinguished from low-signal bladder wall muscle. Because the low-signal intensity bladder wall muscle is not disrupted these probably are intermediate signal intensity bladders.
Figure 5. Same patient as in Figure 2 with infiltrative (stage T3b) urinary bladder cancer. A, Coronal T1-weighted unenhanced image shows tumor infiltration in perivesical fat (arrows). B, Enhanced T1-weighted image in same plane, and C, subtraction of A and B shows more enhancement of tumor (arrows) than of surrounding tissues; therefore, tumor is more visible. Central lack of enhancement is caused by necrosis (n).

STAGING

MR imaging is unsuitable for diagnostic screening for bladder cancer because of its high cost, and cystoscopy remains the most appropriate method of detecting a bladder tumor. Once a bladder tumor is detected, staging is needed to plan therapy and prognosis. Most important in this regard is the distinction between superficial tumors and tumors invading the muscular bladder wall. Clinical staging, which includes transurethral resection and bimanual examination, is the best technique for separating superficial tumors (stage T1) from minimally invasive tumors (stage T2). Transurethral resection also offers information about tumor histology. Currently, with MR imaging, differentiation of stage T1 from stage T2 is difficult. Therefore, staging usually begins with transurethral resection.

Patients with superficial tumors are treated with local endoscopic resection followed by intravesical instillations of chemotherapeutic agents, BCG therapy, or both. In these patients, no additional staging procedures are
needed. An exception could be made for stage T1 tumors with a high malignancy grade (grade III), because these tumors have a high likelihood of progressing to an infiltrative tumor or of metastasizing.

Patients with muscle invasion, with perivesical infiltration, or with invasion into prostate, vagina, or uterus (stages T2–T4a) may undergo radical lymphadenectomy and cystectomy. When pelvic side wall infiltration or tumor extension into the abdominal wall (stage T4b) or metastases are present, alone or in combination, surgery usually is not the first choice. Instead, neoadjuvant chemotherapy or palliative radiation therapy is prescribed. Therefore, preoperative recognition of pelvic side wall infiltration or metastases is important. Because the accuracy of clinical staging in this matter is unreliable, other methods are required. CT scan seems to be a valuable addition in this setting. The overall primary staging accuracy ranges from 40% to 92% (mean, 74%).2, 3, 7–9, 13, 17, 18, 23, 25 The accuracy of MR imaging for primary tumor staging varies from 73% to 96% (mean, 85%). These values are 10% to 33% (mean, 19%) higher than those obtained with CT scan. Published data on the accuracy of MR imaging compared with that of CT scan for staging tumor and lymph node metastases are summarized in Table 2.

In staging lymph node metastases, MR imaging and CT scan are comparable when two-dimensional techniques are used; accuracy for CT scan is 83% to 97% (mean, 89%) versus 73% to 98% (mean, 89%) for MR imaging. With new three-dimensional techniques, however, MR imaging results are promising (accuracy, 90%) (Jager GF, Barentsz JO, Oosterhof GO, et al, unpublished data).4 Finally, MR imaging seems to have advantages over CT scan and nuclear bone scanning in the diagnosis of bone marrow metastases (Fig. 6).1, 3

Much interest has been generated by the possibility of using MR imaging to differentiate between superficial (stage T2) and deep invasion of the muscle layer of the bladder wall (stage T3a). With clinical staging, CT scan, and intravesical sonography, this distinction cannot be made reliably. Most published reports indicate that these stages can be differentiated on unenhanced T2-weighted images.3, 9, 11, 25, 31 More recently, Nicolas et al,24 Tachibana et al,29 and Sparenberg et al,28 showed that the extent of invasion in the bladder wall is better delineated on postcontrast T1-weighted images than on unenhanced T2-weighted images. From a clinical point of view, however, distinguishing between stage T2 and stage T3a tumors is rather unimportant.

For differentiation between muscular invasion (stage T3a) and invasion into the perivesical fat (stage T3b), results of MR imaging are equal to12, 13, 18 or slightly better than3, 8, 9, 11, 25

### Table 2. REPORTED STAGING RESULTS WITH MR IMAGING AND CT SCAN FOR TUMOR AND NODE STAGING

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients</th>
<th>Correct Staging of Tumors (%)</th>
<th>Correct Staging of Nodes (%)</th>
<th>Contrast Material</th>
<th>Number of Patients</th>
<th>Correct Staging of Tumor (%)</th>
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<td>—</td>
<td>61</td>
<td>84</td>
<td>93</td>
<td>IV</td>
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</tbody>
</table>

Dash indicates data not reported. IV = Intravenous.
those of CT scan. In most centers, however, patients with stage T3a and stage T3b tumors are treated with cystectomy.

Besides difficulties in distinguishing stage T1 tumors from stage T2 tumors, MR imaging has other limitations. Although differentiation between late fibrosis and granulation tissue and carcinoma is better with MR imaging than with CT scan and ultrasound, differentiation between acute edema or hyperemia, present during the first weeks after transurethral resection, and tumor is difficult. Therefore, staging after transurethral resection is somewhat inaccurate. This problem may be solved by using ultrafast dynamic sequences. An alternative is to perform MR imaging before transurethral resection. This strategy, however, results in unnecessary MR imaging examinations in all patients with superficial tumors, who make up two thirds of all patients with urinary bladder cancer. Taking into account the high cost and the limited availability of MR imaging time for abdominal studies, this approach does not seem acceptable for the health care system.

On the basis of published reports and the authors' own experience, Table 3 offers an overview of the value of the several staging techniques for urinary bladder cancer. MR imaging and clinical staging complement each other. MR imaging is the most accurate technique for differentiating between various stages of deeply infiltrating tumors (stages T2 and higher), whereas clinical staging is the best technique for differentiating between acute edema, early granulation tissue, and the various stages of superficial tumors (stages lower than T2). When MR imaging is available, CT scan is not needed.

**NEW DEVELOPMENTS**

Rapid improvements in hardware and software, innovations in contrast agents, and the use of MR imaging-guided biopsy make MR imaging an increasingly powerful tool for radiologists and urologists.

**Surface Coils**

With new phased-array surface coils, a series of T2-weighted high-resolution images can be made in 5 minutes (see Fig. 4). For evaluating the extent of muscle invasion, the combination of an external phased-array and an endorectal coil with these pulse sequences seems promising.

**Three-dimensional Sequences**

At the present, a three-dimensional data set can be obtained within a short time. With the help of fast postprocessing techniques, such as multiplanar reconstruction, images can be reconstructed in every desired plane. The use of multiplanar reconstruction improves local tumor staging. Local tumor growth, adhesions and bowel wall invasion, and bone marrow metastases can be visualized better than with conventional two-dimensional MR imaging techniques. In a series of 28 patients, accuracy of primary staging improved from

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**Table 3. ACCURACY OF DIFFERENT STAGING TECHNIQUES**

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Clinical Staging Including Transurethral Resection</th>
<th>Intravesical Sonography</th>
<th>CT Scan</th>
<th>MR Imaging</th>
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<tbody>
<tr>
<td>T0–T+</td>
<td>++</td>
<td>—</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Tis–Ta</td>
<td>++</td>
<td>++</td>
<td>—</td>
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</tr>
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<td>Ta–T1</td>
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<td>T3b–T4a</td>
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<td>—</td>
<td>—</td>
<td>0/+</td>
<td>+ +</td>
</tr>
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</table>

*Bone marrow infiltration.

T0 = no malignancy (e.g., scar, fibrosis, granulation tissue, hypertrophy); T+ = malignancy; ++ = highly accurate; + = accurate; 0 = not accurate; — = not possible.
Figure 6. Patient with infiltrative (stage T3a) urinary bladder cancer with bone marrow metastases. 

A, Semicoronal reconstructed spiral CT scan of lumbar spine (posterior view) does not show metastases. B, Bone scintigram of spine prospectively shows only minimally increased uptake in the lumbar region. C, On T1-weighted sagittal MR image, areas of low-signal intensity are present in the thoracic (arrow) and lumbar (open arrows) spine, which enhances on (D) postcontrast image and shows high signal intensity on (F) gradient echo T2-weighted image. Enhancement is more prominent on (E) subtraction of C and D. These findings are suggestive of metastases and were confirmed by clinical follow-up. Retrospectively, B shows lack of uptake at the site of the metastases in the thoracic spine (circle).

Illustration continued on opposite page
Figure 6. See legend on opposite page
78% to 93%. Also with this technique, three-dimensional information concerning lymph nodes can be obtained. Normal nodes measuring 3 mm can be recognized, because the three-dimensional technique shows the size and shape of nodes. The maximal length and the axial size can be determined quantitatively, and round nodes can be distinguished from oval nodes by dividing the axial size by the length. Lymph nodes are considered to be enlarged pathologically when the index is more than 0.8 for a round node with a minimal axial size of 8 mm or more (Fig. 7), or when the index is less than 0.8 for an oval node with a minimal axial size of 10 mm or more (Fig. 8). An asymmetric cluster of small lymph nodes also is considered to be pathologic. When using these criteria in 134 patients with bladder (n = 71) or prostate cancer (n = 63), an accuracy of 90%, a specificity of 98%, a sensitivity of 75%, and a positive predictive value of 94% can be achieved (Jager GJ, Barentsz JO, Oosterhof GO, et al, unpublished data). Correct identification of pathologic nodes was possible in 33 cases; however, microscopic metastatic deposits in normal-sized nodes were not recognized in 11 patients. In only two patients with enlarged nodes without metastasis, a false-positive diagnosis was obtained. These results show that three-dimensional MR imaging can be used to select patients for MR imaging- or CT scan–guided biopsy or laparoscopic peritoneal lymph node dissection.

**Fast Dynamic Imaging**

Urinary bladder cancer shows more and faster enhancement than bladder after injection of MR imaging contrast agents, probably because of tumor neovascularity. Fast dynamic sequences (one image per second) allow evaluation of minimal differences in enhancement of bladder cancer and other structures. Urinary bladder cancer shows early enhancement beginning about 6 seconds after the initiation of arterial enhancement; the urinary bladder enhances about 4 seconds earlier than most other structures, including postbiopsy tissue. In a series of 61 patients, based on the beginning of enhancement, improved accuracy (from 79% to 90%) and specificity (from 33% to 92%) were obtained in differentiating postbiopsy tissue from malignancy. Overall accuracy of tumor staging improved significantly, from 67% to 84% (p<0.01).5

Metastases in enlarged or normal-sized lymph nodes may show early enhancement, equal to that of the primary bladder tumor (Fig. 9); therefore, recognition of metastases in normal-sized nodes may be possible. Current limitations of this technique, such as the inability to image at more than one level with
biopsy confirmed metastasis. Plane of C is represented by line in B.

MR-guided weightened MP-RAGE images show axial node of pathologic size (13 × 10 mm: circle). Sensitively and (O) semisagittal and (O) semialarial T1. Cancer prospectively no metastatic nodes were depicted. B, Semisagittal and (O) semialarial T1.

Figure 8. A, On contrast-enhanced CT scan in patient with initial bladder urinary bladder...
Figure 9. Patient with infiltrative (stage T3b) urinary bladder cancer (arrows) with metastatic node (circle). A, T1-weighted coronal MP-RAGE image shows enlarged node (23 × 16 mm). B, Subtracted maximal-signal-intensity image displays maximal enhancement in black. Node (circle) and tumor (arrows) show the most enhancement.

Illustration continued on opposite page
Figure 9 (Continued). C, On time image, start of enhancement in relation to onset of arterial enhancement is color coded. Color could not be printed so black-and-white scale is used. Every tone represents 1.25 seconds. White is $t = 0$ seconds; black is $t > 10$ seconds (for scale see Fig. 9). Node (circle) and tumor (arrows) start to enhance within 10 seconds after the artery, indicating malignancy. D, On slope image, maximal enhancement rate is color coded. Cranial part of node (open arrow) and central part of tumor (arrows) show high enhancement rate.

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Figure 9 (Continued). Three-dimensional reconstructions of MP-RAGE data parts E and F show vessels as dark, bladder lumen as speckled, and enlarged (circle) and normal-sized node (arrow) as darker speckled. Posterior view (E) and left posterior oblique view (F) (P = posterior; A = anterior; R = right; L = left).

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Figure 9 (Continued). Axial (G) and angulated (H) sagittal T1-weighted SE images during MR-guided biopsy. Needle is visible as black line. Needle tip is at site of node (arrow). The biopsy confirmed metastasis, and the patient had chemotherapy.

Illustration continued on following page
Figure 9 (Continued). I, Coronal MP-RAGE image after chemotherapy, identical to A, shows decrease of nodal (circle) and tumor size. J, Time image in same plane as A, C, and I after chemotherapy shows dark color of node and tumor, meaning late enhancement. Compared with C, enhancement is at least 18 seconds later; this difference is explained by decrease of tumor neovascularity because of response to chemotherapy.
this high speed, will be overcome in the future. Initial experiments already show that fast dynamic imaging is possible at four levels (Fig. 10).

These fast dynamic sequences after administration of MR imaging contrast material are also useful in the evaluation of chemotherapy in patients with urinary bladder cancer. Initial results in 16 patients who received $3 \times 2$ MVAC chemotherapy treatments showed a reduction of tumor size on conventional unenhanced MR images in 10 patients (see Figs. 9A and 1). This correlated with a response in eight patients and no response in two. In six patients, no decrease in tumor size was visible on conventional MR images; however, two of these patients had complete response. In 10 patients, fast dynamic techniques showed delayed tumor enhancement after only two MVAC treatments. In these patients, tumor enhancement started later than 10 seconds after arterial enhancement, whereas before chemotherapy all tumors started to enhance within 6 seconds. In all 10 of these patients, response to the chemotherapy occurred (see Figs. 9C and 9F). In the remaining 6 patients, the enhancement persisted to be early, which correlated with no response.

Postprocessing

Progress in computer technology will result in innovations in the postprocessing of the acquired data. Fast multiplanar imaging allows evaluation of three-dimensional data sets in every plane. Three-dimensional segmentation techniques facilitate better visualization and understanding of the spatial relationship between normal and abnormal structures (see Figs. 9E and 9F). With the help of maximal intensity projections, vessels can be visualized without the use of contrast agents. Other techniques show quantitative information about time, slope, and washout of tumor enhancement in color, projected over the original images (see Figs. 9B, 9C, and 9D).

MR Imaging–guided Biopsy

The goal is to obtain a histologic diagnosis by as noninvasive a procedure as possible. This can be achieved by image-guided biopsies. At the present time, these biopsies are performed under the guidance of fluoroscopy, ultrasonography, or CT scan. Because of time constraints on MR imaging scanners, MR imaging guidance for biopsies is not used frequently. Nevertheless, MR imaging also has advantages over other imaging modalities in this respect. MR imaging is a three-dimensional imaging technique; therefore, multiple angulated biopsies can be performed best under MR imaging guidance. A good example in bladder cancer is the three-dimensional visualization of enlarged lymph nodes and subsequent MR imaging–guided biopsy (see Figs. 9G and 9H). In a preliminary study, the authors performed MR imaging–guided biopsies in 12 patients with slightly enlarged nodes; in 9 of the 12 patients, the biopsy yielded true positive results. These positive biopsy results obviated the need for lymph-node dissection. Another advantage of contrast-enhanced MR imaging is that its specificity and sensitivity in showing urinary bladder cancer and possible metastases are higher than those of ultrasonography and CT scanning. According to the enhancement pattern of the tumor, with MR imaging the part of the tumor that contains the greatest number of abnormal vessels, and therefore the most viable part of the tumor, can be localized and biopsied.

At present, specially designed MR imaging units are being developed to simplify localization under MR imaging guidance and to reduce biopsy time. With regular MR imaging machines, biopsies must be performed in the same way they are performed with CT scan. Special nonmagnetic needles are available; however, efforts must be made further to reduce susceptibility artifacts caused by these needles.

In the near future, fast, high-resolution, dynamic contrast-enhanced MR imaging of the urinary bladder will further improve diagnosis, staging, and follow-up in patients with urinary bladder cancer. Therefore, this technique will be used more and more frequently in these patients. MR imaging–guided biopsy will contribute to a less invasive diagnosis, thereby improving treatment planning.

CONCLUSION

At present, MR imaging is the modality of first choice for imaging the urinary bladder and urinary bladder cancer. Because of the limited resources of the health care system, however, this technique should be used only to obtain information that directly influences
Early enhancement of tumor (T) and metastatic nodes (circle) at multiple levels are visible. Every tone represents 1.5 seconds.

Figure 10. Patient with invasive (stage T3b) urinary bladder cancer and enlarged metastatic nodes. Multiphase fast dynamic imaging facilitated by.

Illustration continued on opposite page.
Figure 10. See legend on opposite page.
MR imaging and knowledge of radiologists obtain this goal knowledge of urologists of the therapeutic management and outcome. To attain these two specialties is a necessity. Continuous education and communication between these two specialties is needed. Therefore, references

**References**


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