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Imaging in Bladder Cancer: Present Role and Future Perspectives

Key Words

Imaging · Bladder neoplasms · Tumor staging

Abstract

Advances in imaging have an increasingly significant role in the diagnosis, staging and restaging of patients with bladder cancer. This paper reviews the current use of imaging in bladder neoplasms, comparing the different radiologic investigations, and discusses the potential applications of novel imaging techniques in the management of patients with bladder cancer.

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Introduction

Bladder cancer is the 4th most common malignancy in men and the 9th most common malignancy in women [1]. Transitional cell carcinoma accounts for over 90% of cases and is by far the most common epithelial tumor of the bladder. A reliable screening test is not available. It is thought that patients at high risk for bladder cancer probably benefit from screening, although there are no conclusive data proving that screening reduces mortality from bladder cancer [2]. Treatment and prognosis of bladder cancer are based on the depth of primary tumor invasion and the presence of metastases [3]. Therefore,

accurate preoperative staging is critical to appropriately triage patient management. Staging with direct visualization through cystoscopy is most suited for non-muscle-invasive tumors, whereas non-invasive imaging is helpful in the detection of local extension of the tumor, lymph node involvement and distant metastases for invasive tumors. Because urothelial cancer is a panurothelial disease, extensive diagnostic workup is required for evaluation of the primary tumor and identification of possible extra tumors in addition to the primary tumor site [4]. Therefore, imaging of the bladder alone is not sufficient. Intravenous urography (IVU) supplemented by tomography has been largely replaced by newer imaging modalities such as computed tomography urography (CTU) and magnetic resonance imaging (MRI). New aspects have emerged from recent positron emission tomography (PET) studies, which have implications for the evaluation of lymph nodes in assessing tumor extent and for follow-up after radical cystectomy [5, 6].

Ultrasonography

Sonography is the mandatory exam in the clinical evaluation of hematuria for detection of bladder tumors because it is easy to perform and safe for the patient, but its success depends on size and location of the neoplasm [7]. Bladder tumors <0.5 cm in size and tumors localized

Fig. 1. Longitudinal US image of the bladder demonstrates a large intraluminal bladder mass. Biopsy of the mass revealed invasive high-grade urothelial carcinoma. **Fig. 2.** Intravenous urography demonstrates a discrete nodular filling defect (arrow) within the right bladder wall.

in the bladder neck or in dome areas are difficult to detect [7]. On the other hand, diagnostic accuracy may approach 95% for tumors >0.5 cm situated on the posterior or lateral walls of the bladder [7]. Bladder cancer on ultrasound (US) appears as an intraluminal still mass or focal area of bladder wall thickening (fig. 1). US examination is particularly useful for neoplasm in diverticula, sometimes difficult to evaluate by cystoscopy. Doppler flow should be employed to establish flow within the mass, differentiating the mass from sludge and clot. It is important to evaluate the bladder when it is fully distended [7, 8]. No statistical relationship between the characterization of vascularity at color Doppler US and tumor grade or stage has been demonstrated [8]. However, the extent of invasion of the bladder wall and extravesical extension cannot be assessed accurately by transabdominal US which does not allow evaluation of the entire genitourinary tract [8].

Hopefully, recent new developments such as 3-dimensional US may improve evaluation of bladder tumor. In a study of 42 patients presenting with hematuria, all cystoscopically proven tumors were detected with 3-dimensional US [9]. This technique is still undergoing active investigation.

Today, conventional cystoscopy remains the more sensitive and specific instrument for detection of bladder neoplasm and it is used to check patients with a high risk of bladder cancer. We need to use cystoscopy when ultrasonography misses a tumor mainly because tumors <1 cm are difficult to detect. Up to now, data by virtual cystoscopy are only investigative. Its indications are for

patients who firmly decline cystoscopy or in the case of hematuria [10]. It shows a better accuracy compared to ultrasonography for the detection of bladder neoplasm mainly <1 cm and for polypoid lesions but it is more expensive [10].

Ultrasonography is used as a first-line imaging modality in the case of hematuria, but patients who have suspicious findings suggestive of malignancy can be directed to CTU because it allows to study the whole urinary tract in a cost-effective manner [11]. If a bladder tumor has been clearly visualized by ultrasonography, the patient can directly undergo transurethral resection of the bladder (TURB).

Intravenous Urography

In a study by Hillman et al., only 60% of known bladder tumors could be detected on IVU. A bladder tumor may be recognized as a pedunculated, radiolucent filling defect projecting into the lumen or a focal irregularity of the bladder wall (fig. 2) [12]. Therefore, IVU remains a method for imaging the detailed anatomy of the pelvicaliceal system and ureters. It can be used to study the upper urinary tract in the case of hematuria or to study patients at high risk [4]. Its limitation is the evaluation of the full thickness of the bladder wall [13]. However, IVU gives useful information about the upper urinary tract and is of help in the assessment of synchronous lesions. In this case, IVU shows a sensitivity lower than CT.

Fig. 3. Early parenchymal phase CTU image demonstrates a bladder mass (arrow) with avid enhancement.

Fig. 4. Contrast-enhanced CT image demonstrates a large enhancing mass with invasion of the prostate (arrow).

IVU has recently been replaced by CT, especially CTU, in the workup for hematuria and suspected urothelial tumors despite a higher radiation dose. Thus, once the diagnosis of bladder cancer is made, CT or MRI is performed for staging and treatment planning, and routine IVU is generally not indicated [12, 13].

CT Imaging

In the presence of transitional cell carcinoma, the detailed evaluation of the entire urinary system provided by CTU is essential, because patients with urothelial tumor may have multifocal disease [14]. CT imaging is the more sensitive exam for the evaluation of bladder cancer, ranging from 79 to 89.7%, with a specificity of 91–94.7% [15]. Moreover, CT is more sensitive than ultrasonography or IVU in the identification of upper tract lesions [7]. A CT scan of the abdomen and pelvis may also provide some clinical information regarding the pelvic and retroperitoneal lymph node or the presence of any liver lesions [16, 17]. CT is useful for detecting metastases, but it may be inadequate for detecting and staging local urothelial lesions, if not correctly performed. The bladder should be adequately distended and the early enhancement of the tumor (approximately 60 s from injection) accurately searched [18]. A CT scan is usually made before the transurethral resection because it can provide information on liver lesions, pelvic and retroperitoneal lymph nodes that can change the surgical choice, but if

we have a single and small tumor that has been clearly visualized by ultrasonography, a TURB can be directly performed [11].

On CT examination, bladder cancer may manifest various patterns of tumor growth along the bladder wall, including papillary, sessile, infiltrating, mixed or flat intraepithelial growth [18]. T1 stage tumors appear as pedunculated lesions or asymmetrical thickening of the bladder (fig. 3). Hematoma and muscle trabeculations are potential mimics of these tumors. T2 stage lesions are characteristically sessile tumors. However, CT cannot determine the depth of bladder wall invasion, i.e. differentiating stage T2a from T2b disease; it can however distinguish T3a from T3b or higher stage tumors [19]. T3b tumors produce an irregular outer bladder wall or soft tissue infiltration or stranding into the perivesical fat in the region of the tumor. Adjacent organ invasion can be excluded if a clear plane of separation is preserved, although unfortunately, the presence or absence of the fat plane is not completely reliable for determination of microscopic invasion [20]. As the tumor grows, circumferential wall thickening may also be seen. The tumor tissue within the invaded organ enhances similar to the bladder tumor with associated enlargement of the invaded organ (fig. 4) [21]. A recent TURB frequently causes linear or focal enhancement along the bladder mucosa or bladder wall, and at times, bladder wall thickening, perivesical fat stranding or fibrosis [22], thus limiting the specificity of CT. The reported accuracy in local staging of bladder cancer varies widely. Overall accuracy for local bladder

cancer staging in the literature is near 60%, with a tendency to overstage [22]. Various techniques have been investigated to improve local staging. In a cohort of 65 patients with staging grouped at $\leq T1$, T2–T3a, T3b or T4 disease, an accuracy of 91% was achieved by distending the bladder with contrast, and an accuracy of approximately 95% was achieved when the bladder was insufflated with air [23]. More recently, sensitivity and specificity for perivesical invasion by CT, performed 7 or more days after TURB, were calculated at 92 and 98% respectively [24]. However, these decreased to 89 and 95%, respectively, in a larger number of patients without a delay between TURB and CT [24]. Kim et al. [25] showed an overall accuracy for CT in the diagnosis of perivesical invasion of 83%.

In the setting of hematuria, CTU has been recently proposed as an examination to evaluate the entire urinary system and diagnose possible causes of hematuria, including lithiasis, other benign etiologies, renal parenchymal lesions and urothelial neoplasms, thus eliminating the need for additional imaging. In terms of cancer staging, CTU can detect direct perirenal, periureteral and extravesical tumor spread, as well as lymphadenopathy and distant metastases. Compared with traditional excretory urography, CTU requires a shorter examination time and has greater accuracy for detecting urothelial lesions [16]. CTU also allows more detailed evaluation of the renal parenchyma and perirenal tissues and permits better evaluation of obstructed collecting systems than excretory urography [17]. The advantages of CTU are made possible by multidetector helical CT with volumetric acquisition, which provides fast acquisition of high-resolution images and allows multiplanar reconstruction.

Numerous different image post-processing algorithms are available for CTU to provide 3-dimensional visualization of the urinary tract, or reconstruct intravenous pyelography-like projection images. The major role of post-processed images is to provide a general overview of the anatomy and accentuate the areas of abnormality. However, any abnormality visualized on the post-processed images needs to be confirmed on the axial source images. In addition, 3-dimensional reconstructions alone have been shown to have a suboptimal sensitivity in detecting upper tract lesions, even in retrospect [16]. Therefore, they are considered supplementary only and do not replace acquired axial source images for accurate interpretation. For example, in a study by Caoili et al. [16], 24 of 27 upper urinary tract neoplasms were detected with CTU. Of note, 21 of 27 lesions in this

study were missed using the 3-dimensional reconstructed images alone.

One important consideration in performing CTU is the high radiation exposure, which is increased because of multiphase, thin-section imaging. One recent study calculated the radiation risk for standard 3-phase CTU without adjustment of tube current factors and exposure technique for patient size to be approximately 1.5 times that of conventional excretory urography [16].

Virtual cystoscopy, obtained by manipulating CTU data acquired through the contrast-filled bladder during the excretory phase, allows navigation within a 3-dimensional model and has shown promise for detecting bladder mucosal lesions [26].

For lymph node evaluation, the accuracy of CT ranges from 73 to 92%, with a tendency to understage nodal involvement, particularly when based on criteria for short-axis nodal enlargement of near 1 cm [22]. Pelvic nodes are more difficult to recognize than para-aortic nodes, particularly in thin patients, although asymmetry can be a useful sign. Lymph nodes >8 mm in diameter in the obturator and internal iliac groups are now generally considered metastatic [19].

Normal pelvic structures such as unenhanced pelvic sidewall vessels, unspecified pelvic bowel wall loops and the normal ovary can be potentially mistaken for pelvic lymph nodes. Avidly enhancing lymph nodes not only occur in patients with bladder cancer but also in patients with concurrent inflammatory processes in the pelvis [27].

Distant metastases tend to occur late in the clinical course of bladder cancer and especially at the time of recurrence, with bones, lungs, brain and liver being the most common sites [3]. Both conventional abdominal/pelvic CT and CTU, which may be combined with chest CT if needed, can be performed to detect distant metastases. CT may also suggest adjacent visceral invasion, although MRI is superior because of better soft tissue contrast [28].

Retrograde Pyelography

Retrograde pyelography is used in the diagnosis of upper tract suspicion lesions when a well-defined IVU or CT is missing, because upper tract tumor occurs in 2–4% of patients with bladder cancer. But in our opinion, it is of no importance in the specific diagnosis for bladder cancer.

Fig. 5. **a** Axial T₂-weighted MRI demonstrates a bladder mass (arrow) with invasion of the anterior perivesical soft tissue. **b** In the same patient, at axial contrast-enhanced T₁-weighted MRI, an avid enhancement within the tumor is demonstrated and the perivesical soft tissue involvement is better shown. **c** Coronal T₂-weighted image in the same patient demonstrates the posterior extravesical invasion with involvement of the left ureter (arrow) and obstruction.

MRI

MRI has many advantages over other modalities for detecting and staging bladder neoplasm because of its intrinsic high soft tissue contrast and direct multiplanar imaging capabilities, so MRI has the potential to become the modality of choice in the staging of all pelvic malignancies. Although CT, especially CTU, is superior in the evaluation of upper urinary tract disease because of its higher spatial resolution, MRI is considered superior to CT scanning for local staging of bladder carcinoma. Dedicated multiplanar imaging and superior intrinsic tissue contrast allow better visualization of the bladder dome, trigone and adjacent structures such as the prostate and seminal vesicles. The reported accuracy of MRI in overall staging of bladder cancer varies from 60 to 85%, whereas that of local staging varies from 73 to 96% [29]. The reported overall accuracy of gadolinium-enhanced MRI for staging extravesical extension in bladder cancer is 73–100% [29].

Both T₁- and T₂-weighted images in multiple planes are required for staging bladder tumors. On T₁-weighted images, the tumor appears intermediate in signal intensity, similar to muscle precluding differentiation from the adjacent bladder wall. However, T₁-weighted images are valuable in the demonstration of the endoluminal component of the tumor and the assessment of infiltration of the perivesical fat. On T₂-weighted images, the bladder wall appears low in signal intensity and the perivesical fat ap-

pears high, if fat saturation is not used. Bladder cancers are intermediate to high in signal intensity on T₂-weighted images and, in respect to the normal muscularis, are greater in signal intensity on T₂-weighted images. The preservation of the low-signal bladder wall subjacent to the tumor on T₂-weighted images indicates a non-muscle-infiltrating tumor (stage T1) [30]. Late fibrosis appears low in signal intensity on both sequences, and therefore, can be distinguished from the tumor on T₂-weighted sequences. Invasion of the tumor into the adjacent organs such as the prostate, the uterus or the vagina is also better appreciated on T₂-weighted sequences. Conventional T₂-weighted images can be limited in assessing the extension of bladder wall involvement by the very strong signal from normal urine in the bladder lumen. Single-shot fluid-attenuated inversion recovery imaging may be applied for selectively suppressing the signal from urine for superior characterization of bladder tumors (fig. 5) [31].

Gadolinium-enhanced T₁-weighted imaging demonstrates intense and immediate enhancement of the tumor compared with the uninvolved bladder wall [32]. Imaging should be performed within 90 s after contrast injection to optimize tumor-bladder contrast [33]. Dynamic-enhanced imaging aids in the differentiation of bladder tumor from surrounding tissues because the tumor enhances earlier than the normal bladder wall, owing to neovascularization [34]. Fast dynamic MRI acquired at least once every 2 s helps in distinguishing tumor from postbiopsy tissue and enhances the accuracy of interpre-

tation by up to 10%, avoiding false positives [35]. However, overstaging is a common error in local bladder cancer evaluation because of the frequent presence of post-biopsy inflammation, fibrosis and granulation tissue mimicking perivesical invasion, especially soon after transurethral resection [25].

The accuracy of MRI in the staging of nodal metastases based on anatomic size criteria ranges from 73 to 90% and is comparable with that of CT [36]. A commonly used criterion to diagnose pathological adenopathy is a minimal axial diameter of 10 mm in oval-shaped nodes or 8 mm in round nodes [36]. However, microscopic metastatic deposits in normal-sized nodes can be missed when only size criteria are used for diagnosis [36], thus leading to false-negative diagnoses. Better results have been reported with intravenous administration of ferumoxtran-10, a type of ultrasmall iron particle that is taken up by macrophages and causes signal loss in normal, but not in metastatic, lymph nodes on T₂-weighted images [37].

MRI with ultrasmall super-paramagnetic iron oxide (USPIO) particles have shown that normal nodal tissue reveals uptake of this contrast material and a selective decrease in signal intensity on T₂-weighted MRIs, whereas nodal areas infiltrated with metastases lack uptake and retain their high signal intensity on USPIO-enhanced MRIs. This technique seems to improve MRI accuracy in the characterization of lymph nodes [37] even if Sinerem®, an USPIO, has been withdrawn from the market because its diagnostic effectiveness has not been statistically demonstrated.

Fast dynamic MRI sequences using dedicated liver protocols can detect metastases to the liver that usually show irregular rim enhancement. Bone marrow metastases have signal intensities equal to the primary tumor and are recognized best on T₁-weighted images where there is a good contrast between them and the higher signal of the surrounding fatty bone marrow. Peripheral enhancement can be appreciated following gadolinium administration. MRI can also detect tumor spread through the acetabulum, which requires palliative orthopedic surgery. Differentiation between radiation necrosis from tumor or infection is difficult, often requiring a biopsy for confirmation [19].

Positron Emission Tomography/CT Imaging

One of the most promising new techniques to diagnose and stage bladder cancer is positron emission tomography (PET), which provides insight into the bio-

logical behavior of tumors rather than into their morphological appearance. PET allows to non-invasively determine various physiological and biochemical processes in vivo [38]. Currently, PET can target several biological features of tumors including glucose metabolism, cell proliferation, tissue perfusion and hypoxia [39]. Following malignant transformation, a range of tumors can be characterized by elevated glucose consumption and subsequent increased uptake of the radiolabeled glucose analogue [F-18]-fluoro-deoxyglucose (FDG) [40]. FDG-PET has been applied to tumor imaging for more than a decade. It is generally accepted that imaging of the metabolic activity of tumor tissue provides more sensitive and more specific information about the extent of disease than morphologic/anatomical imaging alone [38–41]. More recently, new PET tracers have been investigated in urological malignancies. These include [C-11]-acetate, [C-11]-methionine, [F-18]-fluorothymidine and radiolabeled choline [40].

The elimination of FDG via the efferent urinary tracts represents a significant limitation of FDG-PET for evaluation of primary bladder tumors, despite, for instance, continuous retrograde bladder irrigation. Nevertheless, initial studies using FDG-PET were promising, in fact 8 of 12 patients with localized bladder cancer were correctly identified [41]. In addition, 17 distant metastases were correctly identified with FDG-PET, including 2 of 3 lymph node metastases. In 2 cases, local recurrences were visualized within radiation-induced changes [41]. In a study of 55 patients, the addition of metabolic information from FDG to the anatomic information from CT yielded improved diagnostic accuracy in the preoperative staging of invasive bladder carcinoma [42]. Comparing imaging results with histopathology or clinical follow-up, the sensitivity, specificity and accuracy were 60, 88 and 78%, respectively. Similar results were found in 2 other studies indicating that FDG-PET was better than conventional staging [43, 44].

[C-11]-methionine uptake in tissue is an indication of amino acid transport and metabolism, which is often increased in malignant tumors [45]. An advantage of [C-11]-methionine is that it is not eliminated via the urinary tract. Twenty-three patients with biopsy-proven urinary bladder carcinoma underwent [C-11]-methionine-PET, which visualized 18 of 23 primary tumors [45]. The authors concluded that [C-11]-methionine could visualize urinary bladder tumors >1 cm in diameter, but its value for lesion staging is not superior to conventional methods.

The use of [C-11]-choline-PET/CT was evaluated in 18 patients with advanced transitional cell carcinomas [46].

All patients had negative CT scans of the chest, abdomen and pelvis. Increased [C-11]-choline uptake was found in all primary transitional cell carcinomas as well as in lymph nodes of 6 patients. Histopathology confirmed metastases in 3 of 4 cases who underwent surgery. No additional positive lymph nodes were found on histopathology. In 4 patients, [C-11]-choline-PET/CT also visualized bone metastases that were not seen on the initial CT imaging but that were later confirmed by follow-up CT [46].

Conclusions

US examination remains the first imaging modality employed if bladder cancer is suspected, but its accuracy in the detection of cancer lesion depends on the size and location of the neoplasm. When US identified the bladder cancer, CT is usually employed to detect liver lesions, pelvic, retroperitoneal lymphadenopathy and perirenal, periureteral and extravesical tumor spread. However, in the case of negative US examination, the causes of hematuria must be further investigated.

CTU has been proposed as an examination to evaluate the entire urinary system in the presence of hematuria, thus eliminating the need for additional imaging. How-

ever, although CT is widely accessible and has rapid advances in multidetector technology, the radiation dose should be considered. The triple bolus technique shows a higher radiation dose than IVU (11.6–35 vs. 2.5 mSv) while the double bolus technique, which shows a radiation dose comparable with the IVU, could hide the smallest lesions in the bladder as well as in the upper urinary tract.

Hematuria with negative US examination might be the only residual indication for IVU, because even the smallest lesions of the high urinary tract are generally identified.

MRI has a high accuracy for staging bladder cancer owing to its intrinsic tissue characterization. It is superior to CT in determining the depth of bladder wall invasion in spite of a lower spatial resolution.

CT as well as MRI are both useful in the detection of metastases to the lymph nodes, liver and bone.

Although PET imaging has been shown to be a clinically useful tool, its application in bladder cancer still needs to be fully determined by larger prospective trials. The introduction of novel PET radiopharmaceuticals along with the new technology of PET/CT will likely change the future role of molecular imaging in bladder neoplasms.

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