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Tumours of the bladder: What does the urologist expect from imaging?

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Abstract Cancer of the bladder is the seventh most common of all cancers observed in France, and is the second urological cancer after prostate cancer. It is mainly related to nicotine addiction. When doing the initial tests, ultrasound examination of the bladder can enable the clinician to diagnose a polypoid tumour and thus avoid his having to organise diagnostic fibroscopy. When the bladder tumour infiltrates the detrusor muscle, the situation becomes life-threatening for the patient and radical treatment is envisaged. Uro-CT is the standard examination to characterise the lesion and describe its relationship with neighbouring organs. It is essential, and must be performed before endoscopic resection of the tumour, to be correctly interpreted. It is imperative for imaging to look for a synchronous lesion in the upper urinary tract (ureters, renal pelvis), because the presence of such a lesion changes the prognosis of the disease and the sequence of therapy, which is decided by the urologist in a multidisciplinary consultation.

Each year, throughout the world, a bladder carcinoma is diagnosed or treated in 2.7 million people, and urothelial tumours appear in the majority of cases when an individual is in his or her 60s [1]. In France, this disease rates seventh, taking all cancers into account (INVS 2008), and is the second commonest urological cancer after prostate cancer. Carcinoma of the bladder is responsible for 3% of deaths from cancer; its incidence is increasing by approximately 1% per year, but mortality specifically from this disease seems to be reducing in men [2—4]. It is strongly recommended nowadays to use the designation non-muscle invasive bladder cancer (NMIBC) for superficial, non muscle-invasive tumours and muscle invasive bladder cancer (MIBC) where there is indeed tumour infiltration of the detrusor [5] (Table 1). At the time of initial diagnosis, 75 to 85% of tumours are NMIBC; 60 to 70%

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of lesions will recur in the first year and 10 to 20% will progress to become invasive and/or metastatic tumours [6]. Preventing superficial tumours is based on combating the main risk factors of smoking and exposure in the industrial workplace to chemical carcinogens [7]. In contrast, upper urinary tract urothelial carcinoma (UUT-UC) is much rarer, with an incidence of one to two cases per 100,000 inhabitants and per year [8,9]. The aim of this paper is to offer clarification concerning the place of imaging in the diagnostic process and in the management of urothelial tumours.

### Diagnosis of bladder tumours

#### Symptoms

Macroscopic, often terminal, haematuria is the most frequently encountered clinical symptom. Signs of bladder irritation (pollakiuria, imperative micturition, urinary burning) are observed in 20% of cases. As long as there is no urinary infection, these symptoms should lead one to suspect a bladder carcinoma in situ. Clinical examination is limited to pelvic palpation during which the extent of frozen pelvis can be assessed if there is an invasive tumour [1].

#### Paraclinical examinations for diagnosis

**Urinary cytology**

Urinary cytology:
- detects high grade tumour cells with very high specificity;
- its sensitivity is low for low grade tumours;
- its interpretation depends greatly on the doctor who performs it.

Positive urinary cytology can indicate the presence of a tumour anywhere in the urinary tract [1,9]. Cytology, along with cystoscopy, is still one of the standard examinations for detecting and monitoring NMIBC, particularly high grade ones.

**Imaging examinations**

**Ultrasound examination**

Suprapubic ultrasound is an indispensable examination, which can provide the clinician with certain items of information [10]:
- its sensitivity is 61% to 84% for polypoid tumours larger than 5 mm;
- for differential diagnosis, the presence of clots (which are mobile, with no Doppler vascularisation, and can be fragmented by pressure from the probe) is significant;
- indication for endorectal ultrasound: obese patient and empty bladder;
- a negative ultrasound examination does not mean cystoscopy can be avoided.

It is essential for the lesions to be mapped as accurately as possible. It will show the number of tumours, their topography relative to the prostatic urethra and to the urethral meatus, their size and their appearance (pedicled or sessile). When the patient is referred with an ultrasound image highly suggestive of a tumour of the bladder, the diagnostic cystoscopy stage before endoscopic resection is optional [1].

**CT examination**

CT is usually reserved for staging, in particular of MIBC before radical surgery. On the other hand, CT can be very useful for eliminating an associated lesion of the upper urinary tract. In this indication, the uro-scan is nowadays the reference examination (in hyperdiuresis in the excretory phase) and therefore replaces intravenous urography [11–15].

#### Diagnostic endoscopy

Diagnosis of bladder tumours depends mainly on the endoscopy examination and the histological examination of the entire resected lesion. Fibroscopy clarifies the number of foci, size, topography and appearance of the tumour and the appearance of the mucosa of the bladder, and is usually performed under local anaesthesia. However, when the patient is referred with an ultrasound that confirms the diagnosis of a bladder tumour, there is no need for the diagnostic cystoscopy stage before endoscopic resection, which the urologist can then immediately schedule for his patient in the operating theatre. As for virtual colonoscopy in gastroenterology, there are a certain number of imaging teams that are working on virtual cystoscopy and virtual ureteroscopy, but this work is still in the very early stages.

**Trans-urethral resection of the bladder**

Resection of NMIBC must be as deep and complete as possible. Histopathological analysis will determine the therapeutic sequence. It is not possible with CT to assess whether a urothelial tumour has infiltrated the bladder wall. Deep resection of a bladder lesion is still the best method for staging parietal infiltration in bladder cancer.

<table>
<thead>
<tr>
<th>T stage</th>
<th>Description</th>
<th>Name</th>
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<tbody>
<tr>
<td>pTa</td>
<td>Variable grade papillary tumour without infiltration of the subepithelial connective tissue</td>
<td>NMIBC</td>
</tr>
<tr>
<td>pTis</td>
<td>High grade flat tumour without infiltration of the subepithelial connective tissue</td>
<td></td>
</tr>
<tr>
<td>pT1</td>
<td>Variable grade papillary tumour with infiltration of the subepithelial tissue but without infiltration of the muscle</td>
<td></td>
</tr>
<tr>
<td>≥pT2</td>
<td>Tumour invading at least the muscle</td>
<td>MIBC</td>
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Paraclinical examinations for staging

CT examination
For NMIBC, staging using CT is not systematic, but is all the more justified when the tumour is high grade or of considerable volume, since there is a risk of under-staging.

For MIBC, CT is the standard examination [15–17] for staging, with which the urologist can:
- evaluate repercussions on the upper urinary tract and/or detect the presence of a synchronous urothelial lesion in this region;
- assess invasion of neighbouring organs and of the perivesical fat;
- look for adenopathy and/or metastases (the prime metastatic sites being the lymph nodes and lungs).

The sensitivity and specificity of diagnosis of infiltration of the perivesical or perilesional fat is 89% and 95% respectively, before resection. On the other hand, when CT is performed after trans-urethral resection of the bladder (TURB), staging can be over-estimated owing to inflammatory restructuring of the perivesical fat [15–17]. This examination is particularly important for guiding the urologist as he performs the surgical ablation, if this has been decided in a multidisciplinary consultation.

CT only detects massive invasion of the prostate or the seminal vesicles, but does allow assessment of possible invasion of the digestive structures and the existence of visceral (hepatic and pulmonary) metastasis. Invasion of digestive structures, in particular of the sigmoid colon or the loops of the small intestine, by a tumour of the dome is diagnosed by frontal, sagittal or oblique multiplanar reformations. Clinical signs and symptoms are an indication to look for locations in the brain.

MRI
MRI is only indicated if CT is contraindicated. In practice, pelvic MRI is only useful when extension is suspected to neighbouring organs (stage pT3b) and has diagnostic reliability of 94%. However, MRI with injection is contraindicated if there is severe renal impairment with less than 30 mL/min creatinine clearance, because there is a risk of nephrogenic fibrosis [18,19]. MRI without injection is possible, but its contribution amounts to less. MRI can also help diagnose invasion of the pelvic wall with bone lysis.

FDG PET-CT
There are insufficient data at the present time concerning the examination of urothelial tumours.

Evaluation of lymph node extension
The diagnostic criterion for pelvic metastatic adenopathy is identical in both CT and MRI, and based solely on size (8 mm in the short axis).

There is no significant difference between CT and MRI, with overall sensitivity of 36% and specificity between 80 and 97%. Conventional helical CT is the most commonly used method, and the most easily accessible, for detecting adenomegaly [20,21].

Looking for bone metastasis
Bone scintigraphy is not systematically indicated in MIBC, but is still the first-line examination if there is a clinical symptom. Suspect foci should be checked by conventional radiology, or better, by CT. If there is still any doubt, a CT-guided puncture biopsy should be envisaged as a last resort.

Histopathological diagnosis
Diagnosis of NMIBC implies analysing all the resected material. The cell grade and tumour stage are the two basic criteria for later management. The current reference system for grading urothelial tumours is the WHO classification 2004 (Boxed text 1) [1].

Diagnosing upper urinary tract urothelial carcinoma
UUT-UC are discovered either due to clinical symptoms or while staging a bladder tumour (Boxed text 2) [22]. In a third of cases, UUT-UC are multifocal, and in 2 to 8% of cases, bilateral. Less than 10% of UUT-UC have a synchronous bladder lesion, the most common site being around the meatus.


T Primary tumour
- Tx Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta Non-invasive papillae carcinoma
- Tis Carcinoma in situ: flat tumour
- T1 Tumour invades subepithelial connective tissue
- T2 Tumour invades muscularis propria
- pT2a Tumour invades superficial muscularis propria (inner half)
- pT2b Tumour invades deep muscularis propria (outer half)
- T3 Tumour invades perivesical tissue
- pT3a Microscopic invasion
- pT3b Macroscopic extravesical invasion
- T4 Tumour invades a neighbouring structure
- T4a Tumour invades prostatic stroma, vagina or uterus
- pT4b Tumour invades pelvic or abdominal wall

N Regional lymph nodes
- Nx Lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Single lymph node metastasis ≤ 2 cm and ≤ 5 cm or multiple lymph node metastases ≤ 5 cm
- N3 Lymph node metastasis > 5 cm

M Distant metastases
- Mx Metastases cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

T Primary tumour
Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma in situ
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades the muscularis propria
T3 Renal pelvis: Tumour invades beyond the muscularis propria into peripelvic fat or the renal parenchyma

Ureter: Tumour invades beyond muscularis propria into periureteric fat.
T4 Tumour invades adjacent organs, or through the kidney into the perinephric fat.

N Regional lymph nodes
Nx Lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node, ≤ 2 cm in greatest dimension
N2 Metastasis in a single lymph node, > 2 cm but not > 5 cm in greatest dimension or multiple lymph nodes, none > 5 cm in greatest dimension.
N3 Metastasis in a lymph node > 5 cm in greatest dimension.

M Distant metastases
Mx Metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Initial assessment

Urinary cytology
High-grade urinary cytology can strongly suggest a tumour of the upper urinary tract, when cystoscopy is normal, but is less sensitive, even for high-grade lesions, than it is for tumours in the bladder.

Uro-CT
Uro-CT is the standard examination for exploring the upper urinary tract and has now replaced intravenous urography [9,22]. Nevertheless, it is strictly defined and involves acquisition in the excretory phase:
• multiple protocols ranging from two to four spiral acquisitions, with slices of at least 1 mm, before and after injection of contrast agent;
• 2D multiplanar reformations in the excretory phase, essential for the upper urinary tract and the bladder;
• prior injection of a low dose of diuretic, essential for detecting a small lesion in the pyelocalyceal cavities and for seeing the ureter better;
• initially high rate of irradiation, but decidedly reduced on recent machines equipped with systems for modulating the dose appropriate to each patient.

The detection rate is satisfactory when this type of imaging is used: sensitivity is 96% and specificity 99% for a polypoid lesion of between 5 and 10 mm. In contrast, its sensitivity falls to 89% for a polypoid lesion smaller than 5 mm and 40% for one smaller than 3 mm. Flat undetectable lesions pose the main difficulty unless there is massive infiltration or they are simulating ureteritis.

MRI of the upper urinary tract
MRI is indicated if there is a contraindication to a CT examination: the rate of detection is 75% with injection of contrast agent for a tumour smaller than 2 cm. However, MRI with injection is contraindicated if there is severe renal impairment with less than 30 mL/min creatinine clearance, because there is a risk of nephrogenic fibrosis.

The contribution of imaging to treatment of bladder tumours

Using six main clinical and pathological parameters (grade, stage, tumour size, previous rate of recurrence, presence of concomitant carcinoma in situ [CIS] and number of tumours), it is possible to calculate the probability of recurrence and progression of a non muscle-invasive tumour according to the risk tables produced by the EORTC (http://www.eortc.be/tools/bladdercalculator).

Differentiation classically depends on the risk of recurrence and progression (Table 2).

Treatment for non-muscle invasive bladder cancer

Initial treatment: trans-urethral resection of the bladder
Apart from its importance for diagnosis and prognosis, as complete as possible, TURB constitutes the first stage of treatment. If the lesion is a high-grade, T1 stage tumour, a large volume tumour and/or is multifocal, or if resection was incomplete, it can be more precisely staged by endoscopic and histological re-evaluation within a period of four to six weeks, which will improve screening of patients (and therefore their response) to endovesical treatment, reduce

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Risk for recurrence and progression of bladder tumors without infiltration of the muscularis.</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>Ta: solitary, low grade or LMP (grade 1), diameter &lt; 3 cm, no tumour recurrence</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Ta: low grade or LMP (WHO 73), multifocal and/or recurrent</td>
</tr>
<tr>
<td>T1: low grade (grade 1–2)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Ta: high grade (grade 2/3 and 3)</td>
</tr>
<tr>
<td>T1: high grade (grade 2/3 and 3) or T1 recurring CIS (carcinoma in situ)</td>
<td></td>
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<tr>
<td>LMP: low malignancy potential.</td>
<td></td>
</tr>
</tbody>
</table>
the frequency of recurrence and may delay progression of the tumour.

Adjuvant treatment: endovesical instillation
In addition to TURB, treatment by endovesical instillation may be necessary depending on the risk of recurrence and progression, by either chemotherapy (mitomycin C [MMC]), or immunotherapy (Bacillus Calmette Guérin [BCG]).

Monitoring non-muscle invasive bladder cancer
Oncology monitoring
Because of the risk of a tumour recurring and progression of the bladder disease, the frequency of cystoscopy examinations must be adapted for appropriate surveillance depending on the risk group [7]. Indeed, delay in diagnosing and starting therapeutic management of high-grade tumour recurrence with a strong possibility of muscle infiltration is life-threatening for the patient. CT has a role particularly in looking for a metachronous UUT-UC.

Monitoring examinations are conducted according to the risk group of the bladder disease (Table 3).

Treatment for muscle invasive bladder cancer
T2 N0 M0 staging is basically clinical, because histology of resected material is insufficiently specific (minimum of T2) and neither local infiltration of the tumour (T) nor invasion of lymph nodes (N) can be reliably evaluated with a scan. The seriousness of invasive bladder tumours entails the patient receiving clear information about the risks of the disease progressing, the types of treatment that can be envisaged and the functional risks of radical surgery.

Cystectomy is the standard curative treatment for MIBC but its indication should be discussed with a patient in his 80s. The length of time to performing the surgery should not be more than 12 weeks from the time of the diagnostic resection, or the prognosis could be worse (death specifically from the cancer and an overall greater risk of death). While it is still recommended to perform this procedure as open surgery, some teams are evaluating the advantage of mini-invasive surgery in this indication. This is nevertheless contraindicated if the tumour is voluminous, owing to the risk of disseminating cancer cells in a gaseous atmosphere [23]. The radiologist’s role in describing tumour volume and parietal infiltration is therefore crucial.

In men, total cystectomy removes the prostate and the seminal vesicles. If invasion is revealed on the supramontanal biopsy of the prostatic urethra and/or during extemporaneous examination of the urethral section, urethrectomy must be performed in addition. Urethral recurrence following cystectomy is a rare event (8% of cases), and is observed usually in the five years following the radical surgery, hence the need for constant monitoring (urinary cytology, cystoscopy, uro-CT). In women, cystectomy usually takes with it the complete uterus and urethra, producing an anterior pelvectomy.

In men, a neobladder must be systematically suggested as soon as the situation allows. The patient must be properly screened and prepared and in particular there must be monitoring every six months during the first three years, then annually thereafter. A low-pressure ileal or colonic neobladder is the standard treatment, allowing urinary continuity to be re-established.

A cutaneous diversion (Bricker procedure) is performed in the following situations:
- anatomical impossibility (a rare occurrence of which the patient will have been warned pre-operatively);
- tumoral invasion of the prostatic urethra and/or a positive extemporaneous biopsy of the urethral section, leading to urethrectomy;
- too great age or, above all, inappropriate mental state.

In women, a replacement bladder is possible, but specific criteria need to be met [1]. Replacement enterocystoplasty in women can mean that physical integrity and urinary function can be preserved, with better preservation of the possibility of sexual intercourse. If this is not possible, an external urinary diversion according to Bricker and continent pouches (Indiana pouch) are the urinary systems most often proposed.

Monitoring muscle invasive bladder cancer
For MIBC, monitoring for life is recommended. Uro-CT will be performed every six months for two years then annually following cystectomy [1].

Table 3 Monitoring examinations recommended for non-muscle invasive bladder cancer according to the risk for recurrence and progression.

| Low risk | Cystoscopy: at the 3rd, 6th, 12th month then annually for 10 years (for life, if nicotine addiction continues) |
| Intermediate risk | Cystoscopy: at the 3rd, 6th, 12th month then annually for 15 years (for life, if nicotine addiction continues) |
| | Urinary cytology: recommended, associated with cystoscopy |
| | Uro-CT: every 2 years and if cytology is positive or if any symptom indicates involvement of the upper tract |
| High risk | Cystoscopy at the 3rd, 6th, 9th, 12th month, then every 6 months in the 2nd year, then annually for life |
| | Urinary cytology at the 3rd, 6th, 9th, 12th month, then every 6 months in the 2nd year, then annually for life |
| | Uro-CT every 2 years or if cytology is positive or if any symptom indicates involvement of the upper tract |
Conclusion

The prognosis for tumours of the bladder is extremely poor once the tumour has started to invade the bladder muscle. At this crucial time in the disease, the radiologist must guide the clinician in the type of management he will offer the patient. Radical treatment has major consequences because it is mutilating and upsets an individual’s body image.

**TAKE-HOME MESSAGES**

Staging recommended for MIBC:
- Urinary cytology, ideally in situ.
- Uro-CT (acquisition in excretory phase).
- Ureteroscopy with biopsy samples.
- Cystoscopy to eliminate a synchronous bladder lesion.

Staging recommended for UUT-UC:
- Urinary cytology, ideally in situ.
- Uro-CT (acquisition in excretory phase).
- Ureteroscopy with biopsy samples.
- Cystoscopy to eliminate a synchronous bladder lesion.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References