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Newsletter

Onco-urology Update

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Urological cancers, *i.e. of the kidney, bladder and prostate, have an estimated incidence of about 100,000 new cases each year in France. They represent* ***more than a quarter of treated cancers*** *and about two thirds of cancers diagnosed in men. In recent years,* ***considerable progress*** *has been made with regard to the* ***treatment and diagnosis*** *of these cancers. Although recovery from localised forms is more frequent nowadays, the prognosis remains poor for patients with metastatic tumours.*

The TNM classification *(Tumour size, Node involvement , Metastasis[1]), which corresponds to local tumour size, regional lymph node involvement and metastatic spread of the tumour,* ***is a major prognostic factor*** *of these pathologies. The degree of cell differentiation, which indicates the aggressiveness of the cancer cells, also has significant prognostic value* ***(Gleason score for the prostate, Fuhrman grade for the kidney and WHO grade for the bladder).***

Prostate cancer: advances in diagnosis and treatment

This is the most common form of cancer in men over the age of 50 and the second most common cause of death by cancer for the male population. Its incidence increased between 2000 and 2006 owing to the development and generalisation of PSA tests in men over 50 years of age. ***A family history of prostate cancer is considered to be an important risk factor and should be routinely researched.***

Screening recommended from the age of 50

Although it is mostly asymptomatic, prostate cancer can manifest itself in the form of mictional disorders. Changes in general health, bone pain or the occurrence of a spontaneous fracture are other possible presentations at an advanced, metastatic stage. It can also be diagnosed on digital rectal examination (DRE) or by a PSA[2] blood test (risk of cancer with a level above 4ng/ml).

The recommendations are to undergo rectal examination and to have a PSA test every year from the age of 50, or from the age of 45 if there is a family history of prostate cancer. When DRE is abnormal or the PSA level is greater than 10ng/ml biopsies should be performed. If the PSA level is between 4 and 10ng/ml, the ratio of free PSA to total PSA should be calculated (biopsies should be performed if the ratio is lower than 18%).

(1) Tumor, lymph node, metastasis.

(2) Prostate Specific Antigen, normally secreted by the prostate into the semen.

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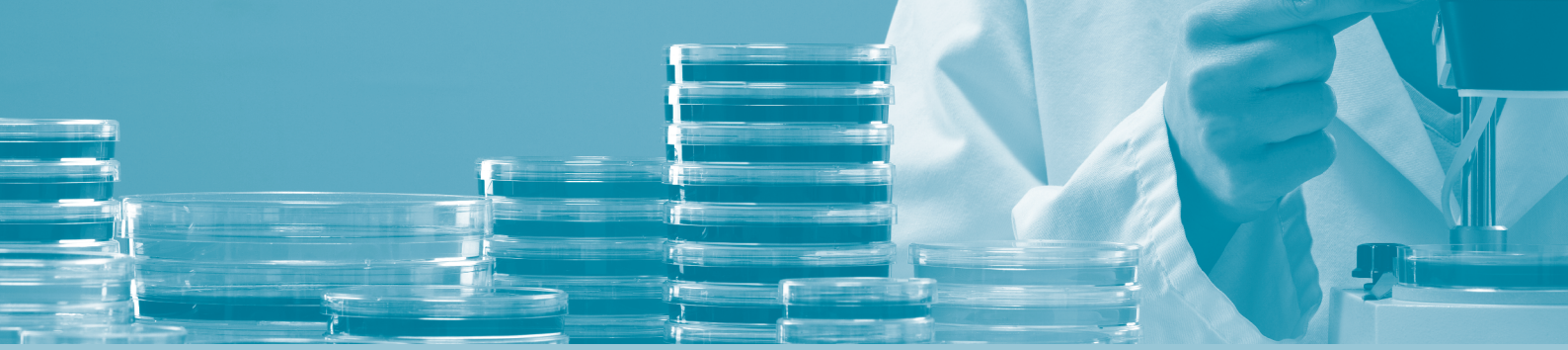


Diagnosis is based on the histological examination

A minimum of twelve prostate biopsies is recommended. **An adenocarcinoma is the commonest histological form of cancer and is found in 90% of cases.** Neuroendocrine cancer with a worse prognosis is found in the remaining 10% of positive biopsies. **The D'Amico criteria[3] (which are based on the stage, the Gleason score and the PSA level) make it possible to classify patients into three prognostic groups.**

At the time of initial diagnosis, 60% of tumours are localised and 30% of cases are locally advanced forms, with the remainder being metastatic cancers. The complementary investigations should include bone scintigraphy and a CT scan. Locally, certain factors should be determined: stage of tumour, PSA level and PSA doubling time (tumour growth kinetics), Gleason score and number of positive biopsies. It is thus possible to determine whether the patient has a localised tumour that will respond to a local curative treatment, or a locally advanced or metastatic cancer, which will require either a combined approach or medical treatment alone.

Localised or locally advanced stage: well-codified treatments[4]

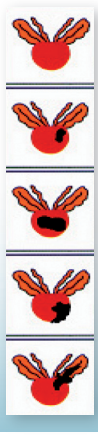
Watchful waiting is proposed for small, non-aggressive tumours which have a good prognosis. They are associated with a relatively low PSA level, few positive biopsies and a small degree of prostate invasion. This approach requires a DRE and a PSA assay every three to six months and annual biopsies. If the rectal examination shows any change or there is an acceleration of the PSA doubling time, an increase in the number of positive biopsies or an increase in the Gleason score, effective localised treatment should be proposed.

Radical prostatectomy is indicated for operable patients (without co-morbidities) under the age of 70. The first stage is lymph node dissection and then the prostate is removed by an open retropubic approach or by laparoscopic surgery. Although technical advances have reduced the number of complications, risks remain and the patient must be informed of these before undergoing the operation: erectile dysfunction, urinary incontinence and infertility. However, there are many advantages with radical prostatectomy: "one-off" treatment, psychological comfort, accurate histological analysis, and simple follow-up. **External beam radiotherapy** is suitable for patients who are older, inoperable or do not wish to undergo surgery. A more recent technique, **brachytherapy**, is only indicated if the tumour is not too large or aggressive, and if the PSA level and Gleason score are low. Lastly, **high-intensity focused ultrasound (HIFU)** is used electively for more frail patients aged over 70 with a life expectancy of at least seven years or for younger patients with associated comorbidities. The treatment decision requires discussion between the doctor and patient; medical information should be clear and the patient must be given sufficient time for reflection before starting the treatment.

In cases of **locally advanced prostate cancer,** the standard treatment combines **radiotherapy and hormone therapy, which are generally very effective and improve the overall prognosis for these patients.**

After curative treatment, PSA tests must be performed regularly.

TNM Classification 2002



TNM T stage

T1a: Normal DRE, tumour found in < 5% tissue resected
T1b: Normal DRE, tumour found in > 5% tissue resected
T1c: Normal DRE, elevated PSA

T2a: DRE reveals tumour in one lobe

T2b: DRE reveals tumour in both lobes

T3a: DRE reveals limited extraprostatic extension

T3b: DRE reveals extension to seminal vesicles

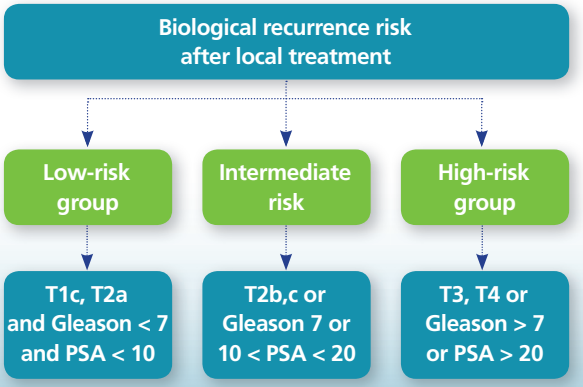
N stage

Nx: lymph nodes not assessed
N0: no regional lymph node metastasis
N1: regional lymph node metastasis present

M stage

Mx: distant metastases not assessed
M0: no distant metastases
M1: distant metastases present
- M1a: metastases in non-regional lymph nodes
- M1b: bone metastases
- M1c: visceral metastases

Prognostic categories: the D'Amico criteria



KATTAN MW et al, A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. JNCI, 1998; 90:766-771

(3) Classification taking into account the TNM stage, the Gleason Score and PSA level.

(4) Comité de cancérologie de l'Association française d'urologie (Oncology Committee of the French Association of Urology - AFU), 2010 recommendations in onco-urology, 2010 progress in urology.

Metastatic cancer: the anticipated benefits of new treatments

The aim of these treatments is to improve survival but also the quality of life. At the metastatic stage, the prognosis depends on the patient's hormone sensitivity or response to hormonal castration.

Standard treatments are LHRH agonists, prescribed over a long period. If there is a poor response (increase of PSA, appearance of metastases), "docetaxel"-type chemotherapy is initiated. This treatment of choice has been shown to be advantageous in terms of survival. A second option became available in 2010 with cabazitaxel, which also improves survival.

In the near future, a large number of new molecules will come onto the market that will improve survival: a new generation of hormone therapy which is more specific in blocking androgen receptors (MDV3100) or enzymes involved in the synthesis of testosterone (abiraterone acetate); radioisotopes sterilising metastases (Alpharadin) and carbozantinib (anti-angiogenic and anti-cMet), are also being introduced.

In the metastatic stages of disease, follow-up comprises PSA testing, a CT scan and a bone scintigraphy.

Renal cancer: advances in diagnosis and surgical techniques

Renal cancer represents 2-3% of all malignant tumours in adults and is the third most common of urological cancers. The average age of onset is 62 years. Its incidence has increased 30% in ten years, whereas the survival rate after five years has increased from 30-40% to 50-60% in thirty years (1960-1990). It is estimated that smoking increases the risk of developing kidney cancer by 35%. ***There are also genetic factors (familial forms, Von Hippel-Lindau disease, etc.). Hence the value of individual screening in families at risk and the search for possible chromosomal anomalies in patients under 45 years of age.***

CT Scanning, the standard investigation for assessing the spread of the disease

This form of cancer is most frequently discovered during ultrasonography performed as a check-up for another disease. This often makes it possible to diagnose early stages, which are small and therefore have a better prognosis.
After the investigation of the extension of the disease, a CT scan usually enables the choice of management strategy. If a CT scan cannot be performed, it can be replaced by an MRI. The assessment should include a thoracic as well as an abdominal scan.

There are five main histological types which have prognostic value. **The prognosis also depends on the TNM staging** *(see flap TNM Classification)***: 80 to 100% survival at five years for tumours localised in the kidney**, 60 to 70% for locally advanced forms without regional node involvement or metastasis. **In addition to the general condition of the patient, the TNM staging and the Fuhrman grade are the essential prognosis factors.**

Which surgery, for which tumour and which patient?

The best treatment for kidney cancer is surgery. It has the biggest impact on the prognosis. Treatments for localised tumours are partial nephrectomy (conservative surgery) and total radical nephrectomy. A nephrectomy can be performed either by open surgery, a standard treatment for partial surgery, by minimally invasive laparoscopy, or by a robot-assisted laparoscopy technique. Partial nephrectomy is indicated for patients with two kidneys and a small tumour, but also for those who have a tumour in one kidney or bilateral tumours in order to avoid post-operative dialysis. Total radical nephrectomy is recommended when partial surgery is not feasible.

Ablative techniques in situ are also available, in particular cryotherapy and radiofrequency ablation. These are indicated for patients with a tumour size smaller than 4 cm who would not benefit from surgical treatment.

In more general terms if the tumour is smaller than 7 cm the question is: can conservative surgery be offered? The advantages are that the results are as good as total nephrectomy in oncological terms and it is possible to preserve good renal function, which means fewer cardiovascular problems and therefore reduced overall mortality. It is therefore necessary to perform it as soon as possible.

With regard to locally advanced cancers, the aim is to remove the entire tumour as well as the healthy margins regardless of the type of surgery performed. For more extensive tumours, it will probably be necessary to start medical treatment (anti-angiogenics) to reduce the size of the tumour and achieve healthy resection limits before surgery. At the metastatic stage, anti-angiogenics **(sunitinib) are the standard treatment but surgical** metastasectomy should be performed **if possible**.

What about monitoring? There is no marker for this disease and **regular CT scans remain the standard examination for postoperative follow-up. It should be pointed out that kidney cancer can recur more than 10 years after the end of treatment.**

Bladder cancer today

Cancer of the bladder represents 3-4% of cancers in adults and affects three to five men for every woman. The average age of onset is 69 years. Smoking is the main risk factor and probably accounts for 30-40% of cases, followed by industrial carcinogens. Although the incidence of this disease is increasing steadily, mortality is decreasing slowly in men and is stable in women. This development is probably related to improvements in diagnosis and treatment and better management of exposure to risk factors.

Endoscopic transurethral resection (TUR): the cornerstone of treatment

The presence of blood in the urine or haematuria is the most common presentation. A minimum investigation should routinely include a urine culture, urine cytology (search for neoplasic cells), a uro-CT (evaluation of the upper urinary tract) and a vesicourethral fibroscopy (elimination of the possible presence of polyps in the bladder). **If there are polyps, an endoscopic transurethral resection of the bladder is indicated. This surgical procedure makes it possible to diagnose cancer and to differentiate superficial tumours (80% of those treated) from infiltrating tumours, often very aggressive, with a different prognosis** (with regional lymph node spread or metastasis in half the cases). TUR also makes it possible to determine the stage of the cancer *(see flap TURBT)*.

Superficial or infiltrating tumours: a different treatment

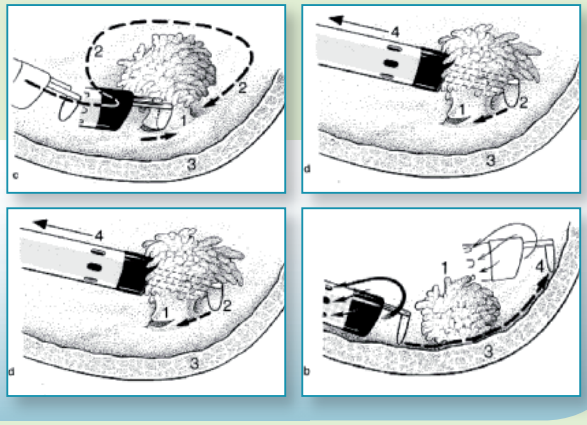
The treatment of superficial tumours which have a good prognosis is based on endoscopic transurethral resection. In patients with an intermediate risk *(see flap Risk groups)*, a complete resection is performed before proposing intravesical instillations of chemotherapy (ameticine). This chemotherapy is **performed within twenty four hours after the operation and the instillation of ameticine reduces the risk of recurrence by 50%.** In high risk cases, complete resection is followed by BCG instillations. If there is any residual tumour, long-term BCG treatment is started to avoid the risk of recurrence and infiltrating tumours. Superficial tumours require regular monitoring by urine cytology and urethrovesical endoscopy.

In infiltrating tumours, a prior assessment of the extension is vital with brain and thoracic-abdominal-pelvic CT scans and a bone scintigraphy. If there are no metastases, the **standard treatment is full surgical removal of the bladder (total cystectomy)** associated with extensive pelvic dissection. The case for neoadjuvant or adjuvant therapy – before or after surgery – is still under discussion. Radio-chemotherapy may be indicated if surgery is contraindicated and for small tumours that are sufficiently localised. If metastases are present, a poly-chemotherapy is started at dosages which respect cardiac and renal function. The follow-up consists of clinical, biological and radiological re-evaluation.

Three procedures are used for reconstruction after surgical excision: direct cutaneous ureterostomy (if the general condition of the patient prohibits other procedures), transileal ureterostomy or the *Bricker procedure* **(the most common procedure in France)** and an **orthoptic neobladder** (reconstructed from the small intestine). The latter requires strict selection of patients (respecting contraindications) but it is the **treatment of choice where possible.**

The risk of recurrence is greatest during the first two years after treatment and thorough monitoring is required. Whichever reconstruction method is chosen, follow-up is based on clinical examination and imaging (CT scan, echography or chest X-ray), every six months.

TURBT



Risk groups (superficial tumours)

Progressive risks	Progressive risks Superficial bladder tumour	Risk of progression at 5 years	Risk of death due to tumour at 5 years
Group 1 Low risk	single pTa G1 tumour pTa G1/G2 without recurrence at 3 months	7.1%	4.3%
Group 2 Intermediate risk	multiple pTa G2 tumours multiple recurrent pTa single pTa G3, pT1 G2	17.4%	12.8%
Group 3 High risk	pT1 G3 diffuse pTis multiple pT1 pT1 recurring in less than 6 months	41.6%	36.1%

TNM Classification

T	Primary tumour
Tx	Tumour is not assessed
T0	No evidence of a primary tumour
T1	Tumour limited to the kidney, 7 cm or smaller at its largest area
	T1a Tumour limited to the kidney, 4 cm or smaller at its largest area
	T1b Tumour limited to the kidney, between 4 cm and 7 cm at its largest area
T2	Tumour limited to the kidney, larger than 7 cm
T3	Tumour affects major veins or has grown directly into the adrenal gland or the perinephric fat tissue, but has not reached Gerota's fascia
	T3a Tumour has spread to the adrenal gland or the perinephric fat tissue of the renal sinus, but has not reached Gerota's fascia
	T3b Tumour extends macroscopically into the renal vein or its segmental branches or into the vena cava below the diaphragm
	T3c Tumour extends macroscopically into the vena cava above the diaphragm or its walls
T4	Tumour has spread to areas beyond Gerota's fascia
N	**Regional lymph nodes**
Nx	Not assessed
N0	No lymph node metastases
N1	Metastasis in only one lymph node
N2	Metastasis in several lymph nodes
M	**Distant metastasis**
Mx	Not assessed
M0	No distant metastasis
M1	Distant metastasis