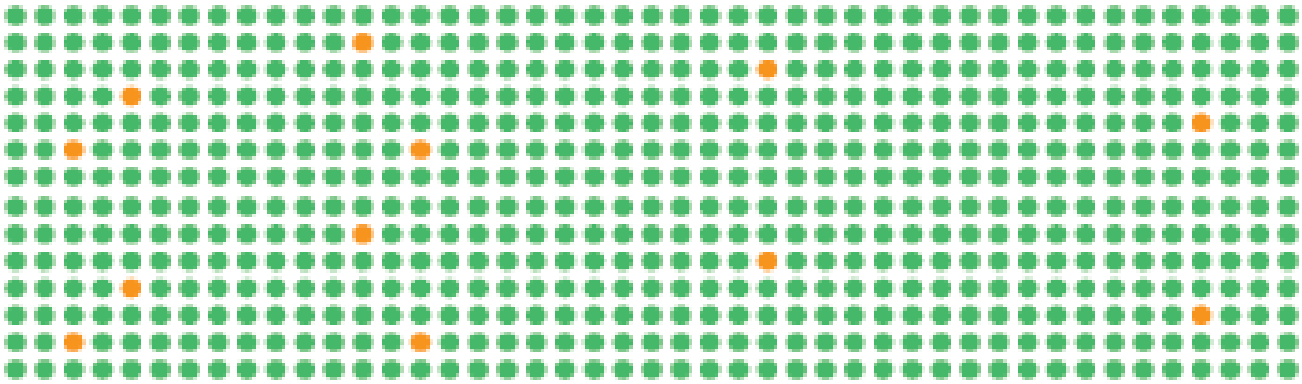
RARECAREnet

Rare cancers of prostate: information for patients



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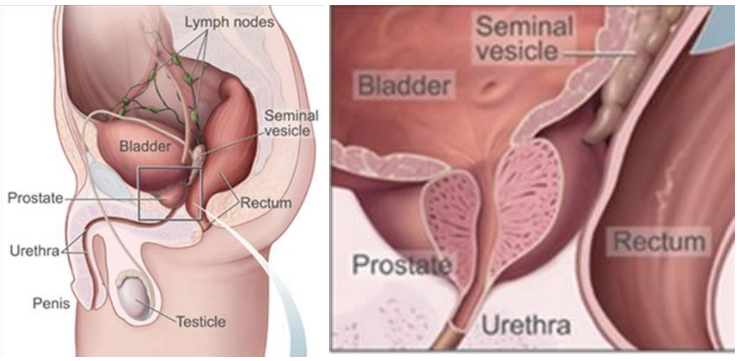
1. Rare cancer of prostate: definition

Prostate cancer is the development of cancer in the prostate, a gland in the male reproductive system. The function of the prostate is to secrete a slightly alkaline fluid, milky or white in appearance, that usually constitutes roughly 30% of the volume of the semen along with spermatozoa and seminal vesicle fluid. The prostate also contains some smooth muscles that help expel semen during ejaculation.



The adenocarcinomas are the typical prostate cancers. Among those, the acinar cell adenocarcinoma is the most common histological type. However, other types of adenocarcinoma might arise in the prostate such as mucinous adenocarcinoma, signet ring cell adenocarcinoma, lymphoepithelial carcinoma.

The rare cancers of the prostate with their incidence rate (IR), which express the number of new cases/year) follows:

- the squamous cell carcinoma with variants (IR=0.02/100,000);
- the infiltrating duct carcinoma (IR=0.5/100,000);
- the transitional cell carcinoma (IR=0.06/100,000) and,
- the salivary gland type tumours of prostate (IR=0.01/100,000).

In the following paragraphs we briefly report relevant information on prostate cancer highlighting differences and similarities between rare and common cancers of prostate.

Rare cancers of prostate

Squamous cell carcinoma

The incidence is less than 1% of all prostatic carcinomas (0.6-1%). It is assumed that the squamous differentiation could rise from the urothelial cells of the prostatic urethra, periurethral ducts as from a staminal cell. The squamous differentiation may be present in pure form or associated with acinar adenocarcinoma, urothelial carcinoma or sarcoma [Arva 2011].

Infiltrating duct carcinoma

The incidence of ductal adenocarcinoma is 3.2% of all prostatic carcinomas. The mixed variant (adenocarcinoma-ductal carcinoma) is more frequent than pure ductal carcinoma. The data available in the literature show as this variant occurs at an average age between 63 and 72 years [Lemberger 1984].

Transitional cell carcinoma

This histological type is frequently associated with a bladder, urethral or urothelial carcinoma. This association could be due to an intraprostatic extension of the tumour as well as to a multifocal disease which involves intraprostatic ducts epithelium (urothelium). It is often difficult to distinguish the origin of the disease. It is a rare histological type that represents only 1.1% of all prostatic carcinomas. The Gleason score is not useful to define histological grade in fact the WHO (world health organization) classification for urothelial cancer is used [Oliai 2001].

Salivary gland type tumour

It is a rare histological type described for the first time in 1974. It is frequently associated with the acinar variant. Only about 50 cases are described in the literature [Ahuja 2011].

Common cancers of prostate

The adenocarcinomas are the typical prostate cancers. The mucinous adenocarcinoma, the signet ring cell adenorcarcinoma and the lymphoepithelial carcinoma represent particular histological variants of the typical prostate adenocarcinoma. So far they are not rare tumours.

Mucinous adenocarcinoma

This histological type is characterised by the presence of extracellular mucin (glicoprotein), is defined as an adenocarcinoma with at least 25% of the tumour composed of "lakes" of extracellular mucin. It is a rare histological type, only 0.3% of all prostate cancers [Epstein 1985].

Signet ring cell adenocarcinoma

It is an extremely rare histological type with about 60 cases reported in the literature. To define this variant the required percentage of the tumour to be signet ring cells ranging from 5% to 50% [Segawa 1983].

Lymphoepithelial carcinoma

These very rare, poorly differentiated carcinomas histologically resemble lymphoepitheliomas of the nasopharynx, but do not appear to be related to Epstein–Barr virus infection. Histologically is characterised by a dense lymphocytic infiltrate is present, admixed with plasma cells and neutrophils [Adlakha 1994].

2. What cause prostate cancer?

The main risk factors for prostate cancer are age, race and familiarity.

Age. The risk of illness before the age of 50 years is very low, but increase significantly and rapidly with increasing age. About 81% of patients with prostate cancer are older than 65 years.

Familiarity. Those who have a blood relative (father, brother) with prostate cancer, have a double risk of getting prostate cancer compared to the general population. The risk increases with the number of relatives with cancer and is 4 times higher if the tumour arose in the family before the age of 60 [Castro 2012]. Such a risk is due more to genetics than to similar lifestyles. The presence of mutations in the genes BRCA1 and BRCA2 is associated with an increased risk of prostate cancer [Castro 2012].

Obesity and metabolic syndrome. The biological mechanisms behind prostate cancer, although not yet clarified, seem to be related to alterations in hormonal balances and other metabolites that regulate cell growth [Tewary 2012].

Diabetes. Studies of the last 10 years suggest an association between type 2 diabetes and a lower risk of prostate cancer [Jocelyn S. Kasper 2006]. The association is complex, but one possible explanation for the lower risk associated with diabetes may depend on the normo or hyperinsulinemia (a condition where the blood insulin level is higher than what is considered normal) that develops in diabetic patients many years after the diagnosis [Rëshu Tewari 2012].

Diet. No food is considered convincingly protective or risky for the prostate [WCR].

Environmental exposure. Literature data support a possible association between prostate cancer and exposure to pesticides, cadmium and Rubber Processing. Exposure to ultraviolet rays would, instead, have a protective effect mediated by increased serum levels of vitamin D [Mullins 2012].

The large geographical variability of prostate cancer also suggests the importance of risk factors related to **lifestyle and environmental exposure/employment**.

What about rare cancers of prostate?

There is not enough evidence to exclude that the risk factors associated with common prostatic adenocarcinoma do not have a role also in the rare cancers etiology except for squamous cell carcinoma. About half of squamous cell carcinomas arise after androgen deprivation therapy or radiation treatment for a conventional adenocarcinoma. However, some cases have been reported as "de novo" cancers in patients without previous prostate disease.

3. How is prostate cancer diagnosed?

Digital rectal examination is useful to assess the size and the characteristics of the prostate such as thickness and presence of nodules. The finding of an area of increased thickness raises the suspicion of prostate cancer.
PSA (prostate specific antigen) is a laboratory marker that was introduced into clinical practice at the beginning of 1990s. It is useful to calculate the risk of prostate cancer but it is not a disease specific marker, it is organ specific. In the case of suspicion of prostate cancer a biopsy is necessary to confirm it.
Some rare cancers are characterized by low PSA level as in ductal carcinoma. Furthermore squamous cells and urothelial cells do not produce PSA. In these cases PSA is not usable as a marker.

4. Symptoms

Men with early prostate cancer are unlikely to have any symptoms, as these only occur when the cancer is large enough to put pressure on the urethra (the tube that drains urine from the bladder). In men over the age of 50, the prostate gland often gets larger due to a non-cancerous condition called benign prostatic hyperplasia or hypertrophy (BPH).
The symptoms of both benign enlargement of the prostate gland and malignant tumours (cancer) are similar and can include any of the following:

- difficulty passing urine (which includes hesitancy, low flow, interrupted micturition-the discharge of urine from the bladder via the urethra)
- urine passing more frequently than usual, especially at night
- pain when urine passing
- Haematuria, i.e. blood in the urine (this is not common in conventional prostate cancer)

Rare cancers of prostate: symptoms

Squamous cell carcinoma

This histological type is frequently characterised by voiding symptoms (difficulty passing urine, reduced flow), locally advanced stage and typically low PSA levels (squamous cells do not secrete PSA) [Munoz 2007].

Infiltrating duct carcinoma

Usually this variant is more advanced at the moment of diagnosis than the conventional type. Voiding symptoms and haematuria could be present. Despite the fact that neoplastic cells secrete PSA, it is not uncommon that PSA levels are not high in all patients. Ductal prostate cancer is typically characterised by poorly differentiated cells (Gleason 4). The most common sites of metastases are bone, lung, liver and typically penis and testis [Ellis 2015; Seipel 2014].

Transitional cell carcinoma

It is typically characterised by haematuria and voiding symptoms. PSA levels are not high (urothelial cells do not secrete PSA) [Gakis 2013].

Salivary gland type tumour

The clinical presentation of this cancer does not differ from the conventional type [Ahuja 2011].

Rare cancers of prostate are generally diagnosed with a stage more advanced than the common one except for salivary gland type and mucinous adenocarcinoma.

Common cancers of prostate, some histological variants

Mucinous adenocarcinoma

It is clinically characterised by high PSA levels and organ-confined disease, similar to the conventional histology [Epstein 1985].

Signet ring cell adenocarcinoma

This variant is most frequent in patients older than those diagnosed with the conventional type and is typically locally advanced at the moment of diagnosis. Tumour's cells are poorly differentiated (Gleason 5) [Segawa 1993].

Lymphoepithelial carcinoma

The few cases reported in literature were diagnosed with locally advanced disease and elevated PSA levels. Sometimes haematuria was present [Lopez-Beltran 2009].

5. What are the treatment options?

Rare cancers of prostate

Squamous cells carcinoma

The local staging at diagnosis and the radio-hormones resistance often make necessary to perform a cystoprostatectomy and urinary diversion. About 50% of the cases arise in the settings of previous radiation or hormonal treatment for prostatic adenocarcinoma. Thus, it is not possible to repeat radiotherapy again, furthermore in naive patients the disease, as mentioned before, is usually radioresistant [Arva 2011].

Cystoprostatectomy consists in the removal of the bladder, prostate and seminal vesicles followed by a reconstructive operation, done at the same time, that permits the urine to get out. Different techniques in urinary diversions are available and include external diversion (urine is collected in a bag applied to the abdominal skin) or a continent reconstruction (urine is collected in a pouch created with the bowel of the patient inside the body, and evacuated through the urethra (penis) or through a hole in the skin by a catheter). The type of diversion depends on the characteristics of the disease and the patient (extent of disease, age, body mass index, morbidity) .

Infiltrating duct carcinoma

Radical prostatectomy if the disease is organ-confined, radiotherapy if the disease is locally advanced.

Transitional cell carcinoma

The gold standard treatment of this cancer is represented by the cystoprostatectomy, urethrectomy and urinary diversion, however, selected cases with low volume and superficial disease (without invasion of stromal prostatic tissue) can be treated with transurethral resection and subsequent instillation of Bacillus Calmette-Guerin (BCG) [Gakis 2013]. The need to perform a cystoprostatectomy is due to the urothelial origin of the disease and the need to remove all the surrounding urothelial tissue.

Salivary gland type tumour

Radical prostatectomy if the disease is organ-confined, radiotherapy if the disease is locally advanced.

The treatment of the rare cancers does not basically differ from that of the common type and depends on the extension of the disease.

Organ-confined disease: tumour limited to the prostate

Locally advanced: extra-prostatic extension (seminal vesicles and/or bladder neck infiltration)

Advanced: nodes or distant metastasis

A different approach is used for transitional cell carcinoma and for squamous cells carcinoma. The different approach include the cystoprostatectomy.

Common cancers of prostate, some histological variants

Mucinous adenocarcinoma

Radical prostatectomy if the disease is organ-confined, radiotherapy if the disease is locally advanced.

Signet ring cell adenocarcinoma

Local radiotherapy is recommended because of the locally advanced stage at diagnosis. The majority of the cases in the literature are diagnosed as stage T4 (tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall) [Celik 2014]. Because of the advanced stage it is not possible to perform a surgery treatment.

Lymphoepithelial carcinoma

Radical prostatectomy if the disease is organ-confined, radiotherapy if the disease is locally advanced.

6. Prognosis

Rare cancers of prostate

Squamous cell carcinoma

It is an aggressive disease with poor prognosis. The mean survival reported in literature is between 1 and 24 months mainly due to the hormone refractory (which means that the cancer does not respond to treatment with hormones) [Munoz 2007].

Infiltrating duct carcinoma

The prognosis of this tumor is slightly worse than the common acinar adenocarcinoma of prostate [Seipel 2014].

Transitional cell carcinoma

The urothelial origin gives a worst prognosis than the common acinar adenocarcinoma of prostate with an average survival of 17–29 months [Gakis 2013].

Salivary gland type tumour

It is generally characterised by slow growth and, metastases are rare. Not many data about follow up are available in the literature.

Rare cancers of prostate are usually characterised by a worst prognosis than the common acinar adenocarcinoma of prostate and mainly because of the more advanced stage at diagnosis and some resistance to treatment particularly to the hormonal therapy. They usually occur in people older than those diagnosed with the acinar adenocarcinoma.

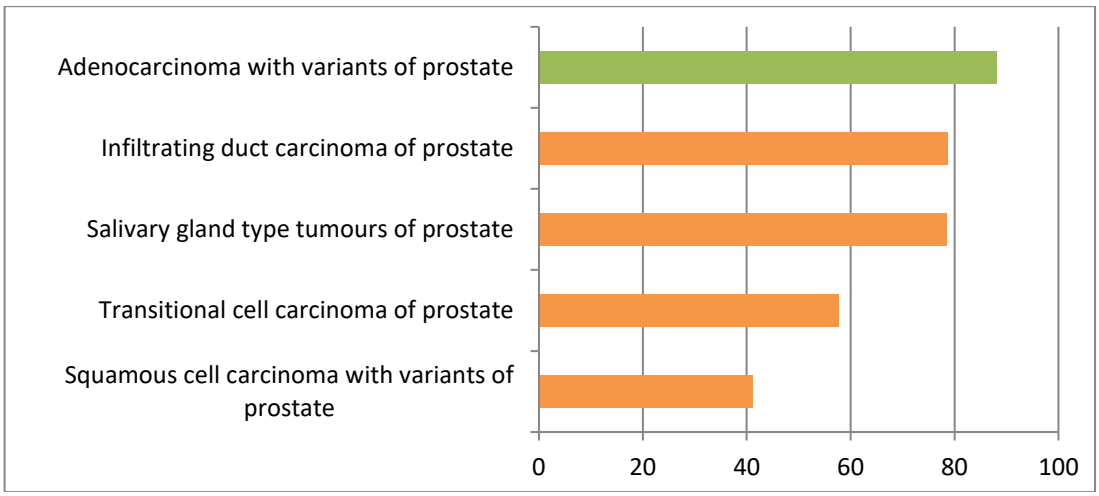


Figure 1. Five-year relative survival (%) of prostate cancers (*source*: RARECAREnet analyses www.rarecarenet.eu)

Common cancers of prostate, some histological variants

Mucinous adenocarcinoma

Some series available in literature reported a poorer prognosis of this variant compared to the acinar variant. This form is more likely to metastasize than the acinar one. Bone lesions are usually osteoaddensant as in the acinar type. Recent series reported that early surgical treatment for organ-confined disease provides good oncological control comparable to the control obtained in the acinar type [Lane 2006].

Signet ring cell adenocarcinoma

This variant is characterised by a poor prognosis mainly due to the staging at the moment of the diagnosis as to the hormone refractory. The mean survival reported in literature is about 28 months [Segawa 1983].

Lymphoepithelial carcinoma

It is an aggressive disease with poor prognosis. The mean survival reported in literature is between 8 and 26 months [Lopez-Beltran 2009].

7. Where should I go to get the appropriate treatment?

As surgery remains the mainstay treatment of the vast majority of these cancers, centres that treat many cases of prostate cancer cases with the surgery and that provide multidisciplinary teams in the decisional process for common prostatic cancer (e.g. centres where a Prostate Unit is provided), should be contacted for primary care or at least for second opinion prior to starting a treatment.

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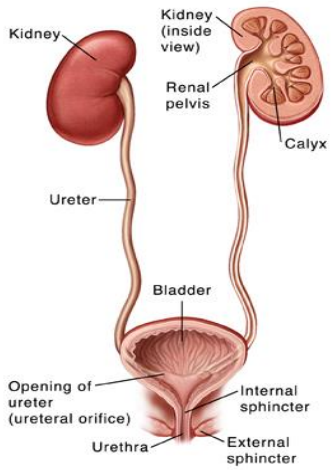
1. Epithelial tumours of the upper urinary tract

Epithelial tumours of the upper urinary tract include: urothelial cell carcinoma, squamous cell carcinoma and adenocarcinoma. The upper urinary tract includes: renal pelvis, calyx and ureter. All the epithelial tumours of the renal pelvis, calyx and ureter are rare cancers.



Urothelial cell carcinoma

Urothelial carcinomas originate from urothelium (layer of cells that lines the walls of the urinary tract: renal calices, renal pelvis, ureter, bladder, proximal urethra) and can be located either in the lower urinary tract (bladder, urethra) that in the upper urinary tract (renal calices, renal pelvis and ureter).

The urothelial tumours of the upper urinary tract are rare diseases that take up about 5% of all urothelial tumors that are localized mainly into the bladder [Munoz 2000]. According to RARECAREnet the incidence of urothelial carcinoma of renal pelvis, calyx and ureter is 1.4/100,000/year.

The disease can also affect both upper urinary tracts (renal calyces/pelvis and/or ureters bilaterally). Patients with upper urinary tract tumours have higher risk (approximately 40%) to develop, at a later time, an urothelial cancer of the bladder as well as patients with urothelial bladder cancer have an increased risk of developing an upper urinary tract tumour (2-6%) [Novara 2009]. The disease occurs mainly as a sporadic form, however, can occur in the context of a familiar form (Lynch syndrome type 2) characterized by colon cancer, endometrial, ovarian and precisely urothelial.

Squamous cells carcinoma

The majority of cancers of the upper urinary tract are urothelial carcinomas. However, about 6-15% of cases are squamous cell carcinoma. Contrary to urothelial carcinomas seems to be a slight prevalence in female gender [Holmang 2007]. According to RARECAREnet the incidence of urothelial carcinoma of renal pelvis, calyx and ureter is 0.02/100,000/year.

Adenocarcinoma

The primary adenocarcinoma of the upper urinary tract is extremely rare (less than 1% of malignancy of the upper urinary tract) with prevalence in Asian populations. According to RARECAREnet the incidence of urothelial carcinoma of renal pelvis, calyx and ureter is 0.01/100,000/year. Adenocarcinomas of the upper urinary tract have some histological types: tubulovillous, papillary, mucinous and non-intestinal. Tubulovillous and mucinous variants are the most frequent and is up over 90% of cases [Raphael 2011].

2. What cause upper urinary tract cancer?

Urothelial cell carcinoma

Many environmental factors contribute to the development of upper urinary tract tumours. Some are similar to

those associated with bladder cancer, whereas others are more specific for upper urinary tract tumours. Tobacco and occupational exposure remain the principal exogenous risk factors for the development of these tumours [McLaughlin 1992].

Squamous cell carcinoma

Risk factors for this histological type are chronic inflammation and hydronephrosis frequently associated to stones [Holmang 2007].

Adenocarcinoma

Similar to squamous cell carcinoma, it seems to exist a close correlation between the development of adenocarcinoma and chronic inflammation.

A particular condition is represented by the degeneration of urinary tract endometriosis, a rare situation (1-3% of cases of endometriosis) in which endometrioid tissue (originating from endometrium, the epithelium that lines the inner cavity of the uterus) is localised out of the uterus. Few data are available in the literature [Jimenez 2000].

3. How is upper urinary tract cancer diagnosed?

Computed tomography urography is the imaging technique with the highest diagnostic accuracy for upper urinary tract tumours. Positive urine cytology is highly suggestive of upper urinary tract urothelial carcinoma when bladder cystoscopy is normal. Ureteroscopy can confirm the diagnosis [Roupret 2013].

4. Symptoms

Haematuria is the most frequent symptom, renal colic can be present in case of obstruction.

5. What are the treatment options?

Radical nephro-ureterectomy with excision of the bladder cuff (removal of kidney and all ureter until the bladder) is the gold standard treatment in patients with normal kidney function. Conservative treatments as segmental resection of the ureter or endoscopic ablation can be considered only in selected cases (low grade and low volume disease), but they may become imperative in patients with solitary kidney or renal insufficiency. Primary chemotherapy is the standard option in advanced disease (metastatic) [Roupret 2013]. No data are available about standard treatment for variants. They are generally treated with nephro-ureterectomy.

6. Prognosis in general but also compared to the common type if different

Urothelial carcinoma

The ten-year overall survival is about 50% in non metastatic patients treated with surgery [Abouassaly 2010].

Squamous cell carcinoma

It is an aggressive disease, with high risk of distant and poor five-years cancer specific survival [Holmang 2007].

Adenocarcinoma

It is generally an aggressive disease with high risk of local and distant recurrence. The data available in literature do not allow to a reliable prognosis in terms of cancer specific survival.

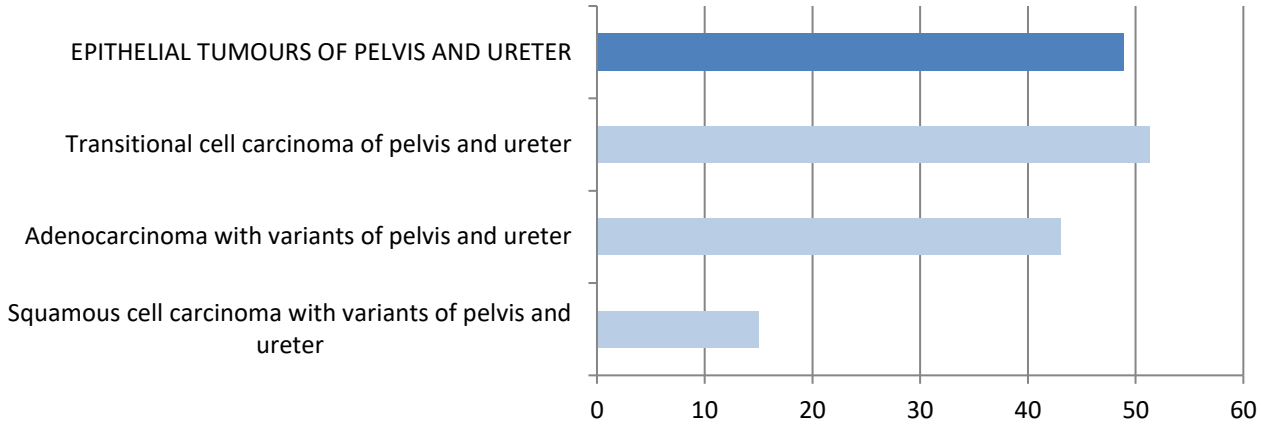


Figure 2. Five-year relative survival (%) of epithelial tumours of pelvis and ureter (*source*: RARECAREnet analyses www.rarecarenet.eu)

7. Where should I go to get the appropriate treatment?

As surgery remains the mainstay treatment of the vast majority of these entities, centres that display a high surgical volume of treatment for renal, ureteral and retroperitoneal tumours and that provide multisciplinary team in the decisional process, should be contacted for primary care or at least for second opinion prior to undergo a treatment.

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1. **Epithelial tumours of the urethra**

Primary urethral cancer is a rare cancer accounting for less than 1% of all malignancies. According to RARECAREnet the incidence of epithelial tumors of urethra is 0.13/100,00/year. The most frequent histological type is urothelial carcinoma (54-65%), than squamous cell carcinoma (16-22%) and adenocarcinoma (10-16%) [Visser 2012]. According to RARECAREnet the incidence rates are 0.09/100,000/year; 0.01 /100,000/year; and 0.01/100,000/year, respectively.

2. **What cause urethra cancer?**

Various predisposing factors have been reported, including urethral strictures, chronic irritation after intermittent catheterisation/urethroplasty, external beam irradiation therapy, radioactive seed implantation, and chronic urethral inflammation/urethritis following sexually transmitted diseases [Van der Voorde 1994; Medina-Perez 1999]. In female patients, urethral diverticula and recurrent urinary tract infections have been associated with primary carcinoma [Thomas 2008; Libby 2010].

3. **How is urethra cancer diagnosed?**

Urethrocystoscopy and biopsy are the gold standard to diagnose primary lesion. CT scan or magnetic resonance are utilised for the staging [Gakis 2013].

4. **Symptoms**

Urethral bleeding and initial haematuria (bleeding at the beginning of the micturition) are the main symptoms.

5. **What are the treatment options?**

In male urethral cancer the extension of the disease and the level (anterior *vs* posterior) are important parameter to define the treatment. An anterior lesion can be treated with an aggressive surgical excision of the primary lesion with a wide safety margin. For posterior disease the gold standard treatment is represented by radical cystoprostatectomy ad urinary diversion [Gakis 2013].
In women with localised urethral cancer (limited only to the urethra), to provide the highest chance of local cure, primary radical urethrectomy can be performed [Gakis 2013].
Several studies demonstrated as adjuvant chemotherapy provides good oncological results in local advanced disease [Cohen 2008].

Urothelial carcinoma
It is very often localised in the posterior urethra thus it frequently requires a radical cystoprostatectomy.

Squamous cell carcinoma
It is mostly located in the anterior urethra thus it is generally treated with partial/total penectomy.

Adenocarcinoma
As the squamous cell form, it is frequently located in the anterior urethra thus a relatively conservative approach is possible. Usually the disease is metastatic at diagnosis and primary chemotherapy is required.

6. **Prognosis**

Generally anterior urethral tumours exhibit significantly better survival rates than the posterior ones. Cancer-specific survival at 5 and 10 years was 68% and 60%, respectively [Visser 2012].

Urothelial carcinoma

The five-year cancer specific survival is 43%.

Squamous cell carcinoma

The five-year cancer specific survival is about 50%.

Adenocarcinoma

The five-year cancer specific survival is about 50%.

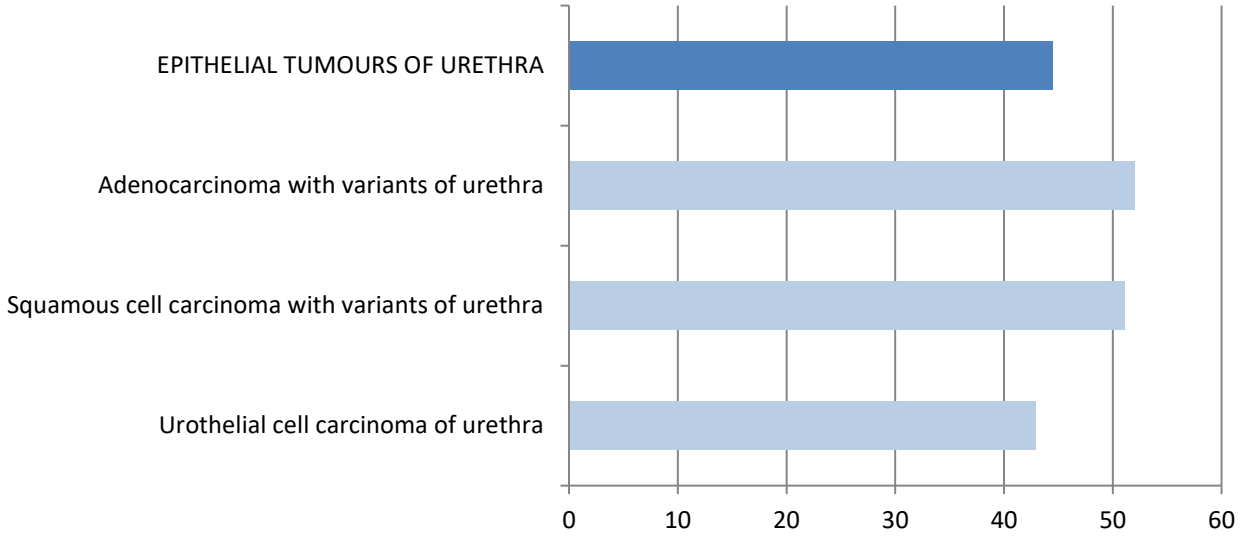

Figure 3. Five-year relative survival (%) of epithelial tumours of urethra (*source*: RARECAREnet analyses www.rarecarenet.eu)

7. Where should I go to get the appropriate treatment?

Surgery, very often in combination with other modalities (chemotherapy and/or radiation therapy) still remains crucial for a successful treatment of these entities. Conservative surgery of the urethra is technical demanding and, when indicated, requires high specialised surgeons. The whole decisional process should be delineated by a multidisciplinary team, but treatment delivery could involve different experts also from different centres in some cases (typically a surgeon specialised in urethral surgery when a conservative approach is recommended).
Centres that display a high surgical volume of treatment for renal, ureteral and retroperitoneal tumours and that provide multisciplinary team in the decisional process, should be contacted for primary care or at least for second opinion prior to undergo a treatment.

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