1 Introduction

Carcinomas of the urethra in both males and females are extremely rare, representing 0.02% of all malignant tumours. This disease is very serious because the diagnosis is frequently late, often with lymph node involvement. (6,11,15)

As in many lower-tract gynaecological tumours, HPV infection plays a role in the aetiology of cancer of the urethra. (3,6)

In men this cancer is more frequent between 50 to 60 years of age. The most common symptom is dysuria, sometimes associated with pain when passing urine, later with haematuria. (11)

In female patients comparable symptoms are noted and because of the anatomy they may be diagnosed very late. (2)

In advanced cases in both male and female patients, the first clinical sign may be an enlarged groin node. (3,6,11)

Prognostic factors are tumour size and tumour site, with better prognosis for distal locations. When the entire organ is involved, or when the tumour is fixed, infiltrating adjacent structures, or when there is lymph node metastasis, the prognosis is significantly worse. Recently Milosevic (12) studied the 7-year actuarial local relapse free rate in 34 women with primary urethral carcinoma. In a univariate analysis the prognostic factors were in increasing order of significance: tumour location, tumour extension TNM.

In locally extensive forms the best treatment may be surgery. For limited disease, according to the site of the tumour, brachytherapy has an important role, usually in combination with external beam irradiation or limited surgery, allowing a conservative approach. (6,12)

2 Anatomical Topography

2.1 Male

The urethra is anatomically and histologically divided into three parts: (2,3)
- prostatic urethra with transitional cell epithelium,
- membranous urethra with transitional cell urothelium,
- penile urethra with pseudostratified or stratified columnar epithelium.

2.2 Female

Divided into two parts, the female urethra consists of: (2,6)
- proximal urethra with transitional and stratified squamous epithelial cells,
- distal urethra with stratified squamous cells only.
2.3 Lymphatic drainage (3,6)

Tumours of the distal urethra, in both male and female patients, drain preferentially into the superficial inguinal lymph nodes, proceeding to the deep inguinal lymph nodes and to the iliac nodes. The posterior urethra in males and proximal urethra in females are directly drained into one or any combination of three pelvic lymphatic channels: presacral, obturator, external iliac.

3 Pathology

Four histological types have been recognised according to the tumour site in the urethra: squamous, transitional, glandular and undifferentiated. (9,11,13)

Macroscopically there is initially irregular superficial induration of the mucosa. When the lesion progresses, there is greater induration, ulceration and constriction. This annular constricting form is more frequent in the posterior male urethra and the proximal female urethra (Fig 22.1A female, Fig 22.1B male, 22.2 Female). (6,9,11)

4 Work Up

After clinical examination to determine if the tumour involves the urethral meatus (Fig 22.1A,B) and examination of the groin for palpable nodes, investigations are based on endoscopy and imaging. (3,6)

A careful urethrocystoscopy must be performed by an experienced urologist and biopsies taken to determine the pathological type. (14)

For primary lesions, the radiological examination of choice used to be retrograde and antegrade urethrography. Today, ultrasound, CT and MRI often replace classical urethrography. They allow precise definition of the tumour volume with associated local or locoregional extensions. (3,15)

While distant metastases are uncommon at the time of diagnosis, chest-radiograph is recommended. Lymph node involvement can be found in half of the patients. Inguinal lymph nodes are palpable and
ultrasound completes the clinical exam. (14) For pelvic nodes, CT scan or MRI are more commonly used today than lymphography. (15)

5 Indications

In order to be treated with brachytherapy, urethral carcinoma in male as well as in female patients must be anatomically accessible: for males the penile urethra, in females the whole urethra can be implanted. (6)

The thickness of the tumour does not constitute a definitive contraindication for brachytherapy because two types of brachytherapy, intraluminal and interstitial, can be combined. (6)

In case of very bulky infiltrating tumours, particularly in female patients with lymph node involvement, the treatment is a combination of external beam irradiation to the primary tumour, groin and pelvic nodes combined with a brachytherapy boost to the primary tumour. (6,11,12,15)

Surgical options include intraluminal or laser resection for superficial lesions. For locally extensive disease, radical surgery is indicated. (2,7,8,14,18)

6 Target Volume

Target volume is artificially divided into two parts: intraluminal and infiltrating. The topography and site of the tumour are established by an endoscopic examination. Modern imaging completes the clinical exam and evaluates more accurately the infiltration of the tumour. (6)

The target volume can be defined beginning with tumour volume determination (GTV). Many authors consider cancer of the urethra to be a disease of the entire organ and prefer to irradiate the entire length of the urethra, especially in female patients. This attitude is safe for superficial lesions, in which intraluminal irradiation alone is indicated; but in case of bulky infiltrating lesions, which would require a large target volume with interstitial brachytherapy, the risk of sequelae, particularly in penile urethra, seems too high. (3,15)

If brachytherapy is performed after a surgical endourethral resection, the target volume is reduced, facilitating brachytherapy to the residual disease (postoperative GTV) and reducing complication rates. If brachytherapy is indicated as a boost after external therapy, the evaluation of the target volume must take into consideration the initial volume, but this combination does not reduce complications. (6)

To summarise, the brachytherapy PTV includes the initial GTV if given with EBRT, and the postoperative GTV if combined with surgery. In all cases a safety margin of 10 mm is taken at each extremity of the tumour and a minimal safety margin of 5 mm according to the tumour infiltration (CTV).

7 Technique

7.1 Male

Two types of brachytherapy may be indicated in the cancer of penile urethra.
1) **Intraluminal Implant**: This brachytherapy is performed either with a catheter (closed at the internal part) introduced into the urethra or with a Foley-catheter (Fig 22.2, male – see overleaf). Both are after-loaded with radioactive sources. With the former, suprapubic urinary diversion is necessary.

![Fig 22.2: Foley catheter which can be useful as an afterloading system for intraluminal brachytherapy.](image)

This kind of brachytherapy is reserved for very superficial lesions that measure no more than 5 mm in depth. (6,7)

2) **Interstitial Implant**: as for penile carcinoma, this kind of brachytherapy is more common. The technique of implantation is comparable to that used in the penis and reserved for the penile urethra. After introducing a Foley catheter, bevelled hypodermic needles with a length chosen according to the size of the penis are implanted perpendicular to the axis of the organ, equidistant to each other, usually in two planes, one above the urethra and the other one below. The different needles are maintained during the time of irradiation by two templates placed laterally to the penis (Fig 22.3,22.4,22.5).(6)

![Fig 22.3](image)  ![Fig 22.4](image)  ![Fig 22.5](image)

**Fig 22.3**: Interstitial brachytherapy with hypodermic needle and plastic template; equilateral triangular disposition which is “ideal” according to the Paris system.

**Fig 22.4**: Iridium insertion is achieved, the penis is maintained and the radioactive material is taken away from the testis by a perforated sponge.

**Fig 22.5**: Radiograph used for computerized dosimetry, showing the perfect parallelism and the equidistance between the needles.
The organ is kept as far as possible from the testis by an adapted sponge. Iridium wires are loaded according to the target volume.(6)

7.2 Female

For many authors, a combination of external beam therapy and brachytherapy constitute the treatment of choice. This conservative treatment is very often possible because the whole organ is accessible to brachytherapy. (11,12,15)

Both intracavitary and interstitial implants are used, the vagina is used to introduce sources with a vaginal applicator. As it is the case for cervical or vaginal tumours, different types of applicators can be used, but for LDR brachytherapy the use of a moulded vaginal applicator is recommended, which allows customized treatment (Fig 22.6,7).

Fig 22.6: Vaginal impression showing the extension to the anterior vagina wall (GTV)
Fig 22.7: According to the vaginal impression, an adapted mould is made. The projection of the tumour is drawn and the placement of the plastic tube will be decided.

After introducing a Foley catheter, which allows for evaluation of the position of the urethra, an interstitial implant is performed (“sandwich” Gerbaulet technique) (6,7). More often, two double guide gutters are implanted parallel to the axis of the urethra and laterally to it; the two anterior branches have a distance of 12 mm, the two posterior of 24 mm.

For optimal source distribution the radioactive position according to the Paris system, the moulded applicator (introduced after the interstitial implant before loading) will contain three anterior sources to irradiate the posterior part of the urethral carcinoma through the anterior wall of the vagina (Fig 22.8-11 female – see overleaf). (6)
Fig 22.8: Two guide gutters are implanted parallel to the axis of the urethra encompassing the Foley catheter; their length is chosen according to the PTV.

Fig 22.9: Insertion of the moulded applicator to complete the “sandwich technique” combining interstitial and intracavitary brachytherapy.

Fig 22.10: Follow-up radiograph, end of the brachytherapy procedure: the applicator with 2 iridium wires (plastic tubes), the two interstitial hairpins.

Fig 22.11: A second patient with an interstitial brachytherapy alone, without endocavitary applicator: radiograph (AP view) showing two iridium hairpins implanted in front and behind the urethra.

Another example of a “sandwich technique” combining intracavitary mould and interstitial implant with an Iridium hairpin can be see in Fig 22.12 (female). Blind plastic tubes can also be implanted around the urethra (Fig 22.13 female). With this technique, similar to the one used for the anterior wall of the vagina, the tumour is encompassed between interstitial and intracavitary sources. (6,7) For HDR brachytherapy, guide gutters should be replaced by plastic tubes or plastic needles but no data have been published as far as we know, about this procedure.
For an interstitial implant alone, the rules of the Paris system are used. For a combination of intracavitary and interstitial brachytherapy, ICRU 38 and 58 recommendations have to be taken into account (6) (see chapters on vagina and of interstitial brachytherapy in gynaecology).

For intraluminal irradiation, the dose is expressed at a chosen distance according to the depth of the tumour and a safety margin and also to a fixed reference distance, e.g. 10 mm (see chapters on bronchus or oesophagus).

By definition, the first critical organ is the urethra, but in females the bladder, vagina and vulva, and in males the testes are also critical organs. The dose must be calculated at these different structures. For the testis, as in brachytherapy of the penis, some authors use a shielding system, but the protection is not complete and the patient may not tolerate it. (3)

In case of LDR brachytherapy alone, the total dose is 60 - 65 Gy delivered in 3 - 5 days. The total dose is 65 Gy for brachytherapy alone, 20 - 25 Gy for brachytherapy boost. (6)
For HDR brachytherapy, four sessions of 10 Gy each are given in 3 - 4 weeks, with no need for urinary diversion; one or two sessions if brachytherapy is a boost after EBRT, four to five sessions in case of brachytherapy alone. (10,17)
10 Monitoring

Intraluminal and intracavitary brachytherapy are generally well tolerated. In cases of interstitial implantation, the problems are similar to those observed in brachytherapy of vaginal and penile tumours (see chapters on vagina, interstitial brachytherapy in gynaecology, penis).

11 Results

11.1 Male

For the male urethra, the outcome in patients managed by local excision results in good local control, as reported in a study published by Zeidman et al. (18) Other multicentric studies carried out by the same author of 64 patients showed a disease free survival of 39%.

An overview of eleven different publications of 140 patients treated with radiotherapy alone for early stage urethral cancer yielded a survival rate of 67%. For advanced urethral cancer (157 patients) the survival rate was 34%. For localised cases (34 patients) combining radiotherapy and surgery, the survival rate was 55%. (3,6)

In an analysis of treatment outcome in 46 men with primary tumour of the bulbar and anterior urethra, Dalbagni (4) showed an overall survival rate of 42%, with a significant difference according to the tumour site, 26% for tumours of the bulbar urethra versus 69% for tumours of the anterior urethra.

11.2 Female

In the literature, studies of surgery alone (2,11,18) have relatively few patients: for local disease (10 patients), the survival was 80%, while for advanced disease (22 patients) it was 27%. For Micaily, (11) comparing results obtained by combined radiosurgical treatment or radiotherapy alone, the 5 year survival for female urethral carcinoma was very different from one series to another, ranging from 20 - 50%.

One of the largest series was recently reported by Milosevic. (12) Of the 34 patients, 10 presented T1-2 tumours, 15 T3 tumours and 9 patients T4 tumours. The different treatments were: 5 patients received brachytherapy, 14 EBRT only, 15 a combination of EBRT and brachytherapy. The brachytherapy used radium needles, caesium or iridium afterloading applicators. The median dose to the primary tumour delivered by EBRT was 50 Gy versus 65 Gy for EBRT and brachytherapy. One of the main interests of this study was “to demonstrate a significant improvement in local control attributable to the use of brachytherapy”. For patients treated with brachytherapy alone or combined with EBRT the local relapse free rate was 77% compared with 32% for patients treated with EBRT alone.

The 7-year actuarial overall survival reported in this series was 41%, in agreement with results of other literature series; so the overall survival rates were (Grigsby (8)) 42% in 44 patients, for and 32% in 72 patients (Dalbagni (5))

These results can be compared to those reported by Micaily (11) through a literature overview including 8 publications on 119 patients with low stage female urethral carcinoma, in which the mean 5-year survival rate was 62% versus 27% for 120 patients with an advanced tumour stage. In both groups radiation therapy represented 70% of the therapeutic management.
According to the experience of the Gustave Roussy Institute, (6,7,16) results for brachytherapy using various treatments are suboptimal, with 5-year survival rates ranging between 30 - 50%. The results vary according to the following parameters:

Tumour size:
- less than 20 mm: 5-year survival over 60%;
- between 20 - 50mm: 40%;
- more than 50mm: less than 20%.

Tumour site: survival rate is better for the anterior urethra (50 - 60%) than for the posterior urethra (20 - 30%).

11.3 Complications (in male and female)

One of the acute effects during brachytherapy is inflammation, which is usually painful. It can be complicated by local infection ± urinary infection, necessitating antibiotic treatment. These acute effects affect 20 - 30% of male and female patients. (6,11,12)

For urethral penile carcinoma treated with brachytherapy, complications are comparable to those observed in penis cancer treated with interstitial implant. But in cases of urethral tumours the risk of secondary strictures is higher. (1,3,6)

For females, different complications are encountered: local necrosis, cystitis, urinary incontinence and rarely vagina fistula. (5, 6,12)

In both cases, complications leading to permanent sequelae are observed in 25 - 30% of patients. (6,11,12)

12 References