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UPPER URINARY TRACT TUMORS: OUR EXPERIENCE

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Summary.- *OBJECTIVES: To study the clinical, diagnostic, and therapeutic features of upper urinary tract tumors.*

METHODS: We perform a retrospective study of upper urinary tract tumors treated in our Department at Clinica La Luz Madrid between 1995 and 2008.

RESULTS: We treated 42 tumors in 40 patients. Mean age was 64 years; there were 29 males and 11 females.

Macroscopic hematuria was the most frequent clinical presentation, in 45% of the cases, and the imaging diagnostic test most frequently used was intravenous urogram (62,5%).There were more tumors on the right side (20 cases) than the left side (18 cases), 2 cases were bilateral. Distal ureter was the most frequent site.27,5% of the patients presented associated bladder tumors.

The most frequently used therapy was laser endoscopic resection. 5 patients required a second operation due to recurrence and 2 more a programmed second procedure due to incomplete resection; 7 cases presented postoperative complications. 70% of the tumors were superficial. 40% of the cases underwent local chemotherapy with weekly bladder instillations of Mitomycin C for 8 weeks. Recurrence rate was 20% and mortality 10%.

CONCLUSIONS: Upper urinary tract tumors keep being a rare entity appearing in mid-advanced ages. Radical nephroureterectomy with excision of bladder cuff has been the treatment of choice for years, but in recent years endoscopic treatment is gaining more importance and is showing good results in selected cases.

Palabras clave: *Tumores del tracto urinario superior. Tratamiento endoscópico. Nefroureterectomia radical. Láser.*

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Resumen.- *OBJETIVO: Estudiar la clínica, el diagnostico y el tratamiento de los tumores de tracto urinario superior.*

MÉTODOS: Realizamos un estudio retrospectivo de los tumores de tracto urinario superior tratados en nuestro centro, Clínica La Luz Madrid, entre el 1995 y el 2008.

RESULTADOS: tratamos 42 tumores en 40 pacientes. La edad media fue de 64 años y encontramos 29 varones frente a 11 mujeres.

El debut clínico más frecuente fue la hematuria macroscópica en el 45% de los casos y el método diagnostico que más se utilizó fue la Urografía intravenosa (62,5%). El lado más afectado fue el derecho (20 casos frente a 18 del lado izquierdo) y en dos casos el tumor se presentó de forma bilateral. La región más afectada fue el uréter distal. El 27,5% de los pacientes presentaron asociado tumor vesical.

La terapia más utilizada fue la resecion laser endoscópico, 5 pacientes precisaron una segunda intervención por recidiva y dos programada por resecion incompleta, siete casos presentaron complicaciones post intervención. El 70% de los tumores fue superficial. El 40% de los casos fue sometido a quimioterapia local con instilaciones endovesicales con Mytomicina C a ritmo semanal por 8 semanas. La tasa de recidiva fue del 20% y la de mortalidad del 10%.

CONCLUSIONES: los tumores del tracto urinario superior siguen siendo una entidad poco frecuente que aparece en la edad media avanzada de la vida. Durante años el tratamiento de elección ha sido la nefroureterectomia radical con resecion de rodete vesical, en estos últimos años el tratamiento endoscópico está tomando cada vez más importancia y está dando buenos resultados en casos bien selecionados.

Keywords: *Upper Urinary Tract Tumours. Endoscopic treatment. Radical nephroureterectomy. Laser.*

INTRODUCTION

Tumours of the upper urinary tract account for approximately 5% of all urothelial tumours and, as in the bladder, they are characterised by multiple relapses over time and multifocality (1).

Pyelocalycial tumours represent 6-7% of primitive kidney tumours, except in endemic areas, such as the areas in which Balkan Nephropathy or Taiwan Blackfoot Disease are prevalent, where they account for up to 47-68% of primary renal tumours (1) and moreover, up to 5% of said tumours present synchronic bilateral affectation (2).

Although over recent years it has been observed that the incidence of renal pelvic tumours has remained steady, there has been an increase in the incidence of ureteral tumours; in general a higher incidence of urothelial tumours has been observed, sited in the pelvic region and final segment of the ureter (3).

In terms of men and women, the incidence of urothelial tumours shows a ratio of 3:2 for pelvic tumours and 2:1 for ureteral tumours (3), while the incidence of squamous tumours was found to be the same for men as for women.

The most frequent age at which said tumours appear is between the age of fifty and seventy years and only rarely are they to be found in people of under the age of forty (1).

MATERIAL AND METHODS

Between 1985 and 2008 we treated a total of 42 tumours in 40 patients aged between 42 and 85, with a mean age of 64 years.

In terms of gender, the distribution was 29 (72.5%) men and 11 (27.5%) women.

Two were monorenal patients.

The personal backgrounds of the patients revealed several different risk factors: 20 (50%) smoked, 6 had a long history of lythiasic pathology, 2 had repeat urinary infections and one had congenital stenosis of the pyeloureteral junction on the side on which the tumour appeared.

In the cases of the patients with bilateral neoplasia, in one patient the tumours appeared synchronically while only one patient was affected by obstructive micturitional syndrome, not considered a risk factor for tumours of the upper urinary tract.

Fifteen of the patients had other diseases not considered pertinent from a urological point of view.

From the urological history of the patients we were also able to assess the fact that eleven (27.5%) of them had associated vesicular tumours appearing previously, synchronically or afterwards (Table I).

The most common initial symptoms were haematuria and pain in the lumbar region, similar to that caused by nephritic colic. In sixteen cases the diagnosis was incidental, deriving from tests for other conditions (Table II).

The diagnostic techniques employed were the following: in 25 cases intravenous urography was used, 5 cases abdominal-pelvic CT scan, 5 cases retrograde pyelography (of which 3 were also examined by ureterorenoscopy), 3 cases anterograde pyelography and 2 cases ultrasound scan (figures 1-2-3) (Table III).

TABLE I.

Concomitant vesical tumours	19 patients
Previous vesical tumours	8
Synchronic vesical tumours	3
Post-op vesical tumours	8

With respect to the location and site of the tumours, there were 20 cases in which the right side was affected, 18 in which it was the left side and 2 cases which were bilateral. The region most affected was the distal ureter followed by the kidney, mid-ureter and proximal ureter (Table IV).

The most commonly used procedure was endoscopic resection and, in fact, 23 patients were treated with endoscopic procedures, 18 of which were retrograde and 5 anterograde. Fourteen had a radical nephroureterectomy with resection of the cuff of the bladder.

TABLE III.

Diagnostic techniques	cases
Urography	25
Urography + CT scan	1
Abdominal-pelvic CT scan	4
Retrograde pyelography	2
Retrograde pyelography + URS	3
Anterograde pyelography	3
Ultrasound scan	2

TABLE II.

Clinical debut	Patients
Haematuria	18
Nephritic colic	8
Haematuria + Nephritic colic	7
Incidental diagnosis	16

Two underwent tumourectomy, one patient with orthotopic urinary derivation had a ureterectomy while another with bilateral affectation who had already had radical surgery on the right side, underwent the resection and re-anastomosis of the left ureter.

Palliative treatment (percutaneous nephrostomy) was given to one elderly patient (85 years) who presented multiple contraindications to anaesthesia (Table V).

Five recidivate patients required a second deferred operation.

TABLE IV.

Location of tumours	cases
Pelvis	9
Upper calyx	1
Lower calyx	1
Proximal ureter	4
Mid-ureter	10
Distal ureter	17

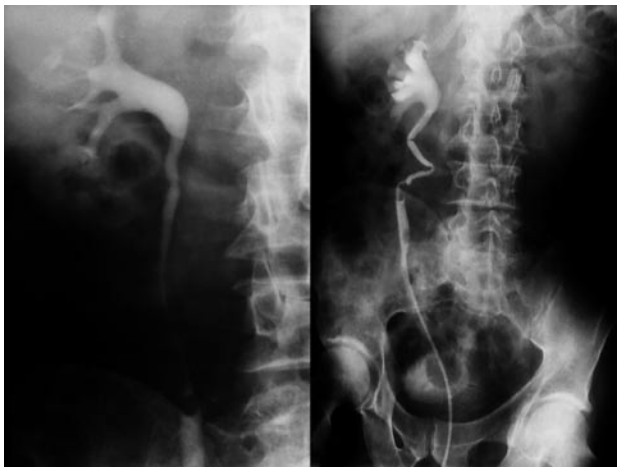

FIGURE 1. Diagnosis with intravenous urography and ascending pyelography.

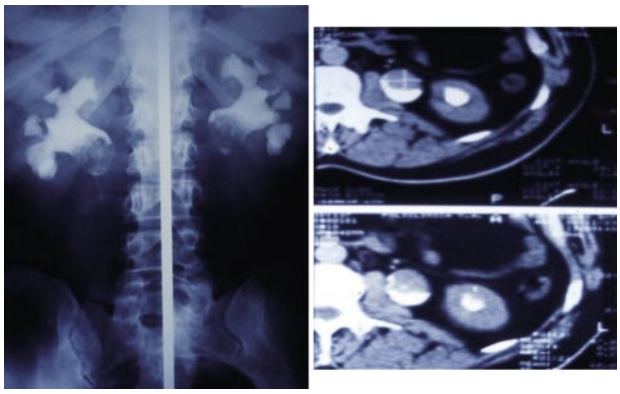

FIGURE 2. Diagnosis with intravenous urography and abdominal-pelvic CT scan.

Of these, the only patient who had had a partial ureterectomy had a secondary nephroureterectomy, due a relapse which occurred after two years.

Three patients who had already been endoscopically treated with retrograde access, afterwards required a nephroureterectomy with resection of the cuff of the bladder, likewise due to relapses (at 1, 2 and 5 years, respectively). One case, treated percutaneously, later required a secondary procedure consisting of the resection and re-anastomosis of the ureter in another hospital within the course of one year, due to tumoural stenosis.

Two patients required a programmed second look operation due to incomplete initial resection.

Post-operative complications were found in seven patients.

Three cases presented ureteral stenosis, secondary to endoscopic treatment, while in one case an iatrogenic ureteral lesion (rupture of the ureter) was provoked.

One patient required a transfusion for anaemia, occurring secondary to significant haematuria, and presented infection of the wound, secondary to an abscess in the renal cell with cutaneous fistulisation and the infiltration of neoplasic cells.

One patient died from significant post-operative gastric haemorrhaging.

The anatomopathological results show that all the tumours were urothelial, with the exception of six cases, which included one enteroid tumour, a diagnosis of fibroepithelial polyp, one case of pseudotumoural pyelitis, two cases with insufficient biopsy material and one undiagnosed case who was given a palliative nephrostomy.

70% of the tumours were superficial, limited to the mucous and sub-mucous tissue (Table VI).

40% of the patients received adjuvant therapy, with local chemotherapy comprising endovesical instillations of Mytomicin C once a week for eight weeks.

TABLE V.

Therapy	**cases**
Retrograde access endoscopy	18
Anterograde access endoscopy	5
Nephroureterectomy with cuff of bladder	14
Tumourectomy	2
Ureterectomy	1
Resection and ureteral re-anastomosis	1
Palliative nephrostomy	1

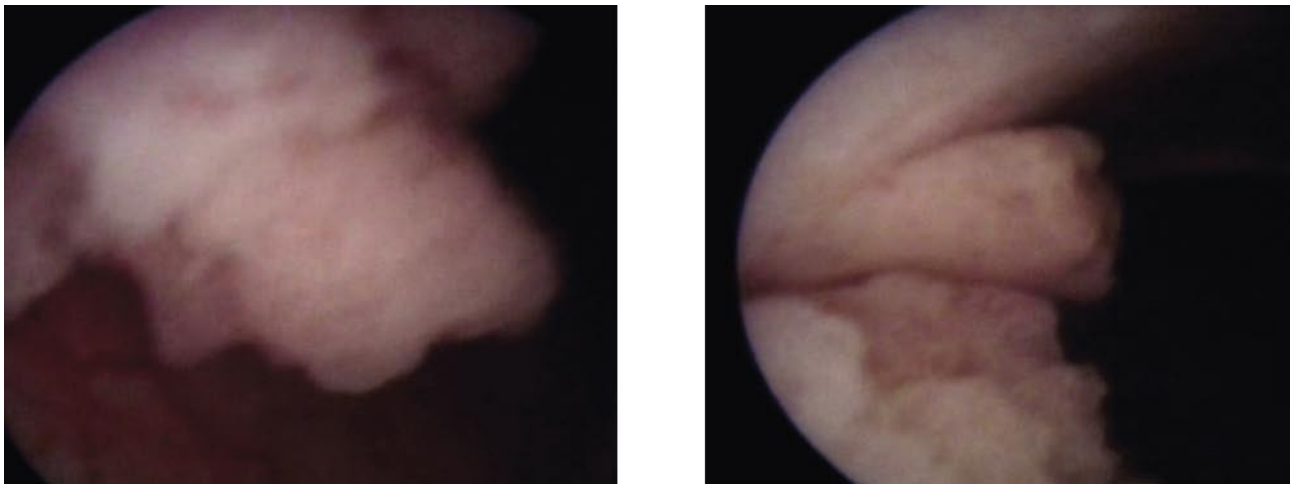

FIGURE 3. Diagnosis with ureteroscopy.

One case, staged at pT2aG1, received radiotherapy in addition to the instillations, while in another stage pTaG2 plus vesical pT2aG2 case, the patient received two sessions of high dose rate endoluminal brachitherapy.

Moreover, radiotherapy was used in two stage pT2G3 cases presenting associated infiltrating vesical neoplasia.

Systemic chemotherapy was administered to three patients who were staged, respectively, as follows: ureteral pTaG1 associated with vesical pT3G3N2, ureteral pT1G3 associated with vesical pT2G3 and one ureteral pT2G3.

The mean follow-up time was 47 months, with a minimum of four and maximum of 192 months.

The most commonly used techniques employed in the follow up were urography + cystoscopy (28 cases), two cases of uretherorenoscopy + cystoscopy and one single case of abdominal – pelvic CT scan + cystoscopy.

Check-ups were quarterly for the first three years, and every six months for the following two years.

There was no follow up on nine patients: five with negative diagnoses, one affected by an enteroid carcinoma and one who was given a nephrostomy.

In two cases follow up was in another hospital, while another was treated only two and a half months ago.

TABLE VI.

Pathological anatomy	**cases**
pTaG1	12
pTaG2	5
pT1G1	6
pT1G2	6
pT1G3	1
pT2aG1	2
PT2aG2	1
pT2G3	3
Unknown diagnosis	1
Insufficient material from biopsy	2
Enteroid tumour	1
Pseudotumoural pyelitis	1
Fibroepithelial polyp	1

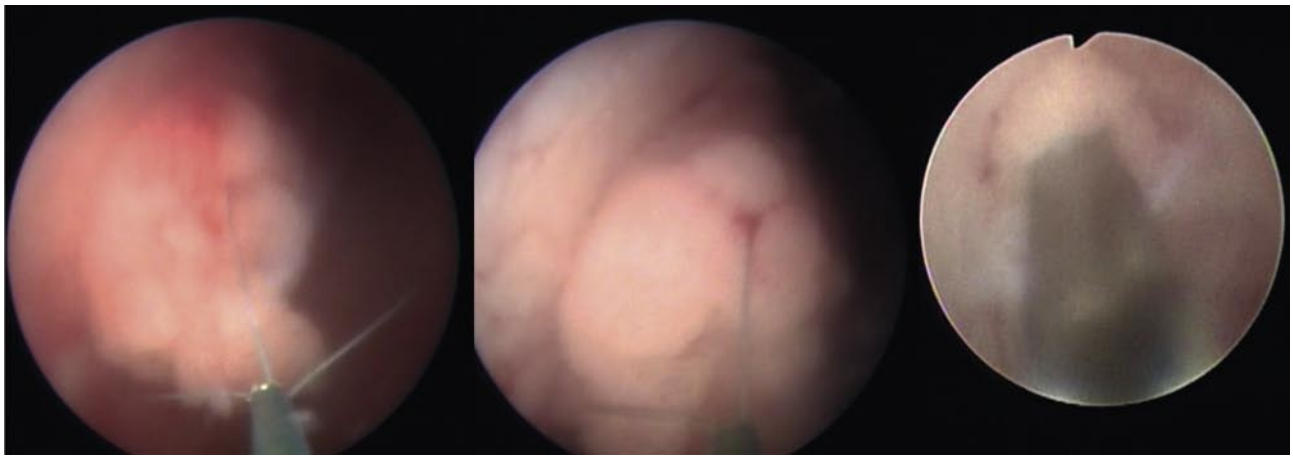

FIGURE 4. Basket and claw biopsy.

The present study has detected only 5 cases of relapse, three of which were in the renal pelvis, while in four cases the patients died from a urothelial tumour (patient with infiltrating stage tumour).

RESULTS

We found a greater incidence in men (72,5%) and the mean age at which the neoplasia appeared was 64 years, with six cases only in their forties.

Smoking was found to be the most significant factor of risk, followed by lythiasis and urinary infection.

A bilateral affectation was seen in two patients, and 42% of the patients had associated vesical neoplasia.

The main reasons for the subject's initial consultation were macroscopic haematuria in 62.5% of the cases, while nephritic colic was the second most common cause.

The majority of diagnoses were performed with intravenous urography (65%).

Laterality was similar (20 right side, 18 left side and 2 bilateral).

The most common location was the distal ureter, followed by the renal ureter (26%).

Endoscopic treatment was employed in 57.5 % of the cases, 40 % had open surgery while in only one case (2-5%) was a nephrostomy performed as a palliative measure.

12.5 % of the patients required a deferred second surgical procedure for relapse while 5% had programmed second surgery after incomplete resection.

70% of the tumours were superficial, limited to the mucous and sub-mucous tissue.

40% were treated with local chemotherapy and 10% and 5 %, respectively, were treated with systemic chemotherapy and radiotherapy.

The mean time of follow up was 47 months, during which five cases relapsed (20%) and four died of urothelial neoplasia (10%).

DISCUSSION

In our study we encountered a similar level of incidence amongst men and women as is to be found in the literature, while the mean age of onset was also comparable; likewise the data concerning the most frequently encountered risk factors and previous manifestations of vesical neoplasia as a factor of risk were similar (1-2-3). In fact the literature reveals that the incidence of tumours in the upper urinary tract increases with a history of previous vesical neoplasia, indeed up to 15% if associated with vesicoureteral reflux and the possible migration and implantation of neoplasic cells (1-4).

Moreover, it was observed that 90% of those with synchronic upper urinary tract and vesical tumoural affectation are found to be at the same stage (1).

Our findings do not agree with the above, since our study revealed that of the patients affected

by the two neoplasia, 22% of the upper urinary tract tumours were at a more advanced stage, while in 39% of the patients the two tumours were staged evenly. On the other hand, 39% of vesical tumours were found to be at a higher stage.

The data we found regarding the side affected and bilaterality were also in line with those to be found in the literature (2-3).

However, with regard to location, our findings differed to those found in the literature as for us the incidence in the distal ureter was 1.5 times higher than in the pelvic ureter; according to the literature, there is a higher incidence of upper urinary tract tumours in the pelvic zone, in fact a pelvis/ureter ratio of 3:1 (3).

With regard to diagnosis, for many years our procedure of choice was urography while we only used retrograde pyelography when the patient first came in for recurrent analgesic resistant nephritic colic, since the technique permits both the diagnosis and resolution of the symptoms with the use of a ureteral catheter.

However, though over recent years our use of urography has continued to be high, there has been a growing tendency at our centre to start directly with retrograde pyelography, and ureterenoscopy as diagnostic tests, since they permit both the biopsy and the use of an exeretic approach, making the management of such tumours similar to the treatment of vesical tumours (Figure 4).

We have now almost completely abandoned the use of percutaneous anterograde pyelography, which was always somewhat controversial due to the risk of seeding tumour cells along the route of the needle (5), in favour of retrograde access which is less invasive and permits a flexible endoscope to fully explore all of the renal calices with ease.

We believe this approach swifter as it enables both diagnosis and treatment at the same time and, if the anatamopathological study shows superficial tumours, it can offer a definitive solution.

Initially, both at our centre and as evidenced in the literature, the only treatment of choice available for Upper Urinary Tract Tumours was, for many years, nephroureterectomy with resection of the cuff of the bladder, while endoscopic treatment was reserved for monorenal patients with kidney failure or for bilateral urothelial neoplasia in the upper urinary tract (3-6-10-11), or cases with small neoplasia (<1.5 cm) or with indications of superficial tumours not infiltrating the muscularis.

Over recent years, as was indeed predicted 20 years ago (12) with the advances made at the time with endoscopic instrumentation, laser and diagnostic techniques, we have increasingly tended to use endoscopic laser techniques as a first step, while ra-

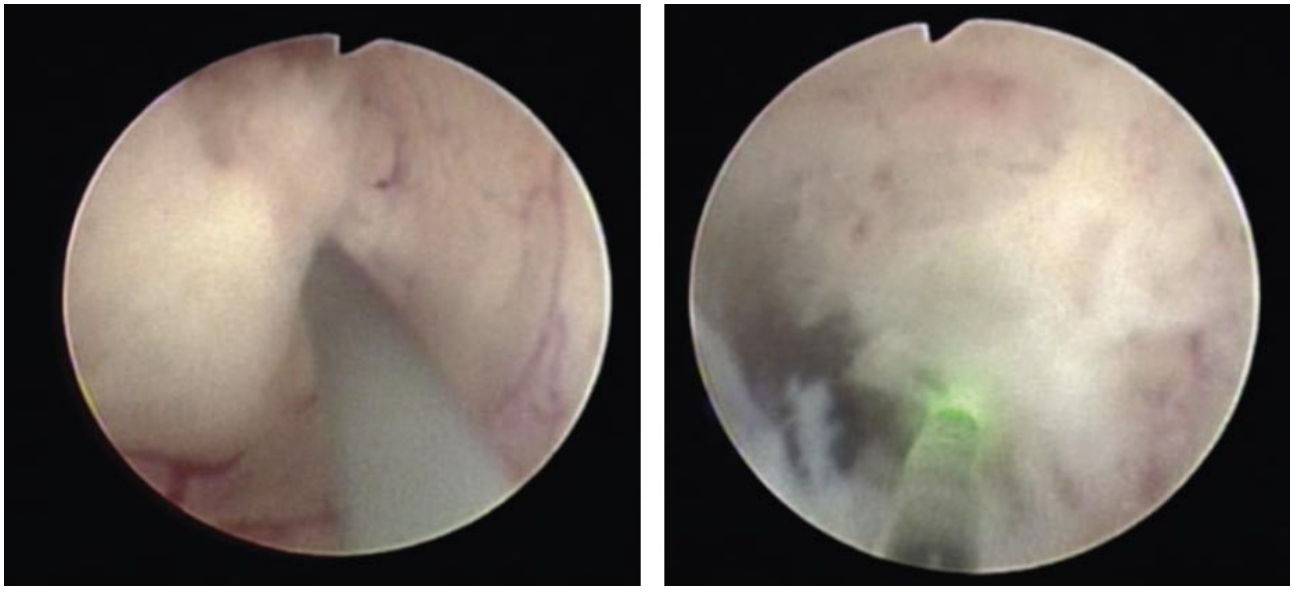

FIGURE 5. Ureteroscopy and resection with Holmium laser.

dical surgery is always the treatment of choice for infiltrating tumours.

Over the last five years we have treated most of the Upper Urinary Tract Tumours with indications of being superficial, including those sized over 1.5 cm, with retrograde endoscopy, thus again almost completely abandoning the percutaneous approach in favour of the use of a flexible endoscope.

Obviously, in the case of patients with large tumours we always perform a second look intervention one month after initial surgery, and check-ups will be scheduled more frequently for the whole of the follow-up period.

The treatment of such tumours basically became possible with the advent of the Holmium Laser (DORNIER), which replaced resectors and permitted increasingly precise resection with far better visibility since there is less bleeding, allowing most cases to be fully treated in one single session (Figure 5).

We treat superficial tumours with endovesical instillations of Mytomicin C, once a week for eight weeks.

Having seen in many studies a difference between patients treated with radical surgery alone and those also??? given adjuvant chemotherapy, above all for the greatly improved quality of life offered 9), together with an oncologist we now treat infiltrating tumours with systemic chemotherapy, radiotherapy and high dose rate intracavitary radiotherapy.

For many years our follow-up was performed in accordance with a protocol which associated intravenous urography and cystoscopy. Ureteroscopy was only used if there was a suspicion of relapse and the patients had suspicious symptoms, such as nephritic colic and haematuria. However, over recent years we have opted for cystoscopy associated with explorative ureterorenoscopy, with examinations every three months for the first two years and thereafter every six months for the three following years. After this the patient will have one ureteral endoscopic examination every year (9).

Said protocol affords us greater security and allows us to deal rapidly with any possible recidivism.

For many years the treatment we tended to use in the case of relapse was radical, regardless of the stage of the tumour. However, now for superficial relapse the treatment of choice preferred by our centre is to use an endoscope, backed up by Holmium laser (DORNIER).
The patients that died of urothelial tumours were all found to be in the infiltrating stage at the time of diagnosis, with the exception of one who had a pTaG1 stage tumour associated with an advanced vesical tumour.

CONCLUSIONS

Upper Urinary Tract Tumours remain infrequent and are, in most cases, superficial.

Urography is still the most widely used diagnostic technique at our centre, although ureterorenoscopy has been seen to be playing an increasingly important role, since it permits the patient to be both diagnosed and treated with one single procedure.

Over the last twenty years we have increasingly employed endoscopic treatment with Holmium laser (DORNIER) as a first step, and later as a method that permits a total control of the patient's evolution after non-aggressive treatment (12).

With respect to our results, we observed a rate of relapse of 20 % and a mortality rate of 10%, in line with the data to be found in the literature (7). To date we have observed no difference in the relapse and mortality rates between those patients treated with radical surgery and those treated with endoscopy.

Regrettably we do not have sufficient data to be able to draw any conclusions regarding the use of the endoscopic Holmium laser technique as the treatment of choice for urothelial tumours, given the small number of patients in our sample and the short period of follow.

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