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Marco Cosentino, MD, FEBU

PhD Thesis

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DIRECTOR

Prof. Antoni Gelabert Mas (Catedràtic d'Urologia, UAB)

TUTOR

Dr Joan Palou Redorta (Professor Associat d'Urologia, Fundació Puigvert – UAB)

Barcelona, May 2013

ANTONI GELABERT MAS, Catedràtic del Àrea de Coneixement d'Urologia del Departament de Cirurgia de la Universitat Autònoma de Barcelona,

CERTIFICA:

Que el treball de recerca titulat

"Radical Cystectomy and urinary diversion, is there a role for bowel in the future?"

presentat per Marco Cosentino per a optar al grau de Doctor per la Universitat Autònoma de Barcelona, ha estat realitzat sota la meva direcció i està en condicions de ser presentat per a la seva lectura i defensa davant el tribunal corresponent.

I perquè consti i tingui els efectes que correspongui, signo el present document en Barcelona, a 2 de Maig del 2013.

Antoni Gelabert Mas

ABSTRACT

Urothelium, through its transitional epithelial cells, covers the luminal surface of the entire urinary tract extending from renal calyces to the proximal urethra. It represents the "core" of Urology and its functional alteration, oncological changes and substitution constitutes a relevant medical and social matter. Bladder cancer is the fourth most common malignancy in men and the eight in women; it represents the most common malignancy of the urinary tract with a peak incidence in the adult and elderly population. Although the majority of patients present with superficial bladder tumors, 20%–40% either present with or develop invasive disease. Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for organ-confined muscle-invasive disease and it is also a valid option for other selected patients. However, this curative procedure is complex and associated with a high rate of complications and morbidity. Such complications are considered to be primarily attributable to the use of bowel for urinary tract reconstruction; they have an effect on the patient's physical and psychological wellbeing and increase the total cost of the intervention. Since we are facing a rise in life expectancy, with increases in both the elderly and the bladder cancer population, treatment management for bladder cancer patients represents an important challenge for present and future Urology.

RESUM

La superfície luminal del tracte urinari des dels calzes fins a la uretra proximal està revestit d'un epiteli amb cèl·lules de transició, l'uroteli. Aquest estructura representa el nucli fonamental de la urologia i les seves alteracions, ja siguin per mal funcionament o oncològiques, constitueixen una qüestió mèdica i social rellevant. El càncer de bufeta és el quart càncer més comú en homes i el vuitè en dones; representa la neoplàsia maligna més freqüent del tracte urinari amb un pic d'incidència en població la adulta i gent gran. Tot i que la major part dels pacients presenten tumors vesicals superficials, un 20-40 % d'aquests desenvoluparan una malaltia invasiva. La cistectomia radical amb dissecció pèlvica dels ganglis limfàtics és el tractament 'gold standard' en el cas que sigui múscul-invasiva però és també el tractament d'elecció per la resta de pacients amb aquest càncer. Aquest procediment curatiu és complex i s'associa a una alta taxa de complicacions i morbiditat, atribuïbles principalment a l'ús d'intestí per a la reconstrucció del tracte urinari; aquest procediment té efectes sobre el benestar físic i psicològic del pacient amb un augment important del cost total del tractament. Atès que estem davant d'un progressiu augment de l'esperança de vida, això es traduirà en un augment de la seva incidència. La gestió i el tractament d'aquesta malaltia representa un repte important per a la urologia actual i futura.

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1. INTRODUCTION

In the Western world, bladder cancer is the fourth most common malignancy in men and the eight most common in women, with more than 330,000 new cases and more than 130,000 deaths per year. It represents the most common malignancy of the urinary tract, with a peak incidence in the adult and elderly population. Although the majority of patients present with superficial bladder tumors, 20%–40% either present with or develop invasive disease. Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for organ-confined muscle-invasive disease and it is also a valid option for selected patients with high-grade non-muscle-invasive bladder cancer, either as a primary treatment modality or for recurrent or refractory tumors after bladder-conserving regimens. However, this procedure, which is performed with a curative intent also in the elderly population, is complex, involving simultaneous surgery on the urinary and gastrointestinal tracts, and is associated with a high rate of complications (17%–66%) and morbidity, with prolonged hospital stay and potential readmission. The complications are generally considered to be primarily attributable to the urinary tract reconstruction (UTR), which relies on sampling of bowel to restore urinary bladder function. Such complications have an effect on the patient's physical and psychological wellbeing and increase significantly the total cost of the intervention. Since we are facing a rise in life expectancy, with increases in both the elderly and the bladder cancer population, our knowing on urothelium and treatment management for bladder cancer patients represents an important challenge for present and future urology.

Despite of the title, this Doctoral Thesis is presented as a “summary of publications” (“compendi de publicacions”) as permitted by the Universitat Autonoma de Barcelona.

The articles presented constitute a “conceptual unit” devoted to the Urothelial Carcinoma surrounding different aspects: diagnostic, therapeutic and the future.

In the first article (*Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma.* Worl J. Urol. DOI: 10.1007/s00345-012-0877-2. Epub 2012 May 3) on the timing of Upper Urinary Tract Urothelial Cell Carcinoma (UUC-UCC) and concomitant Urothelial Carcinoma of the Bladder (BC), the objective was to determine if exist any clinical factors that predict the presence of concomitant bladder cancer in patients with no previous history of bladder cancer who were diagnosed with primary UUT-UCC. So, a retrospective study of 673 patients diagnosed and treated for UUT-UCC was performed. Patients with history of BC were excluded. Authors investigated: age, sex, location of the upper tract tumour (calyx, renal pelvis, upper ureter, mid ureter, lower ureter), multifocality, clinical symptoms, tumor grade and pathological stage. Contingency tables and chi-square test were used for categorical variables and analysis of variance (ANOVA) for quantitative variables.

In the second article (*La re-resección transuretral puede no ser necesaria en todos los tumores vesicales no músculo-invasivos de alto grado.* Act. Urol Esp. Vol 36, Num 9, 2012. http://dx.doi.org/10.1016/j.acuro.2012.03.011), the authors propose, after reviewing the re-Trans Urethral Resection (re-TUR) of bladder tumors, to evaluate the persistency rate, understaging and peri-operative complications in patients with high grade non-muscle invasive bladder tumor that have undergone re-transurethral resection (re-TUR). This method of care is restricted to cases where the pathological sample, once performing TUR of, not offer the presence of bladder muscle, making it impossible to assess correctly the staging of tumor. Authors performed a

retrospective review, between January 2007 and December 2009, of 47 patients with high-grade non-muscle-invasive bladder tumor undergoing re-RTU at Fundaciò Puigvert evaluating the persistency of bladder tumor, the under-staging, surgical complications and the cost of re-RTU.

In the third article (*Alloplastic bladder substitution: are we making progress?* Int Urol Nephrol. Oct;44(5):1295-303. doi: 10.1007/s11255-012-0249-2. Epub 2012 Jul 21) the author carries out a meta-analysis on urinary bladder replacement with a "prosthesis" in cases of radical cystectomy and bladder substitution. While in most specialties the use of permanent implants is possible (e.g., articular or vascular prostheses), in urology this does not seem feasible as yet owing to infections and encrustations that result from the continual exposure to urine so, actually, bowel still represents and is used as the unique substitute of urothelium when the urinary tract removed. A comprehensive review of the literature was performed, various prostheses have been proposed for urinary bladder replacement being silicone the most frequently used material. Author analyzed data published on non-bowel, alloplastic bladder substitution, summarizing the evolution, the current situation, and the most relevant findings.

Key words: *urothelial cancer; upper urinary tract urothelial cell carcinoma; urothelial bladder carcinoma; trans urethral resection; bladder substitution; prosthetic bladder*.

2. RESULTS

Article 1 *Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma.* Worl J. Urol. DOI: 10.1007/s00345-012-0877-2. Epub 2012 May 3.

Between June 1950 and September 2008 673 patients, 551 men and 122 women (81.9% and 18.1%, respectively) underwent radical nephroureterectomy (RNU) with removal of bladder-cuff for Upper Urinary Tract Tumor (UUTT) or a conservative approach with endoscopic resection of tumor. UUTT were located in calyx and renal pelvis in 348 patients, upper ureter 156 patients, and lower ureter 40 patients. A total of 30 patients presented with concomitant tumors of calyx/pelvis and upper ureter: 12 with cancer in the upper and lower ureter, 16 with tumors of the calyx/pelvis and lower ureter, and 10 with tumors of the calyx/pelvis as well as the upper and lower ureter (61 missing data). The mean age of this cohort was 65 years (S.D. 10.82, range 27 - 91 years). A total of 223 (33%) patients were excluded from the study due to a previous history of bladder cancer; therefore, the review identified 450 patients suitable for the study. Of these patients, 76 (17%) were found to have concomitant primary UUT-UCC and bladder cancer and 374 (83%) were found to have solely UUT-UCC. In the group of patients with UUT-UCC and concomitant bladder cancer (76 patients), there were 64 males (84%) and 12 females (16%). The mean age was 66 +/-11 years. The location of the primary UUT-UCC was found to be in the calyx and/or renal pelvis in 25

patients (34%), in the upper ureter in 8 patients (11%) and in the lower ureter in 37 patients (49%). In 6 patients with concomitant bladder cancer (8%) the location of the tumor was not recorded. Both on univariate and on multivariate analysis, age, sex, clinical symptoms, multifocality, grade and pathological stage did not predict concomitant bladder tumor presence. In particular, regarding pathological stage, non-muscle-invasive tumor was present in 220 patients, while 195 patients presented with muscle-invasive UUT-UCC (35 patients missing data); tumor grade was G1 in 19 patients (4.2 %), G2 in 190 (42.2 %) patients and G3 in 184 (40.9 %) patients (57 patients no grade applicable). Data on radiological findings (both on IVU and on CT scan) like hydronephrosis, filling defect, non-functioning kidney and renal or pelvic mass were not significant for predicting the presence of concomitant BC.

On multivariate analysis the location of UUT-UCC in the ureter was the only predictive factor for the presence of a concomitant bladder tumour (OR 1,7 95% CI 1.007-2.906 p=0.047).

According to the study, location of the upper tract tumor was identified as the only predictive factor on univariate and multivariate analyses for simultaneous bladder cancer in patients with primary UUT-UCC. In these patients, the possibility of having a simultaneous urothelial bladder cancer is progressively higher as the ureteral tumor gets closer to the bladder. Tumors located in the renal pelvis/calices had a 10% possibility of diagnosis concomitant bladder cancer; however, tumors located in the lumbar and sacral ureter had a 18% and 33% possibility, respectively, of diagnosis concomitant bladder cancer ($p<0.001$).

Article 2 *La re-resección transuretral puede no ser necesaria en todos los tumores vesicales no músculo-invasivos de alto grado.* Act. Urol Esp. Vol 36, Num 9, 2012. http://dx.doi.org/10.1016/j.acuro.2012.03.011.

Between January 2007 and December 2009, 47 patients underwent to re-RTU, representing the 26.4% of the total of 178 patients that, in the same period, showed HG-NMIBC in the initial TUR. Male female incidence was of 83% Vs 17%, and with a median age of 62 years (44-81). 43% of patients were recurrent and 26% received prior intravesical treatment. In all cases the re-RTU was performed before the 8 weeks after the initial RTU, with a median of 43 days (18-55). 22 cases went to the re-RTU (46%) in absence of muscularis propria (cTx) in the initial TUR, the remaining cases by HG-NMIBC with incomplete resection of bladder tumor (3 CTA, 8 cT1, 2 cT1a, 5 cT1b, 7 cT1c). The most common finding at cystoscopy in the re-TUR was a scar area (61.7%) followed by slough (31.9%) and only in 3 cases (6.4%) suspected of residual tumor. There was no correlation between macroscopic findings and histopathology. In 21.2% of patients (10) the re-TUR showed residual disease in the bladder. In 8 cases (17.1%) was persistent BC (<cT2) and in 2 (4.2%) understaging (≥ cT2) . Median patient time in surgery (surgery + anesthesia) for the re-TUR was 74 min (48-115). The majority of patients were discharged within 48 hours after surgery without bladder catheter, with a median hospital stay after the re-TUR of 2,3 days (range 2-9). Hospital stay, surgical material used, the processing and the study sample and postoperative management were similar to the TUR, we can say that the economic cost of a re-TUR in our center is the same as that of a conventional TUR of bladder

tumor. Six patients (12.6%) had complications related to secondary or re-RTU: bleeding in 2 cases; 2 bladder perforation (one extraperitoneal, an intraperitoneal) conservatively managed; one febrile urinary tract infection requiring intravenous antibiotic treatment and prolonged hospital stay.

Article 3 *Alloplastic bladder substitution: are we making progress?* Int Urol Nephrol. Oct;44(5):1295-303. doi: 10.1007/s11255-012-0249-2. Epub 2012 Jul 21.

In the last 50 years, many different prostheses have been proposed for replacement of the urinary bladder, silicone being the most widely used material. The most common models described include: plastic reservoirs and mechanical valves with abdominal drainage of urine via a silicone tube, a silicone rubber prosthesis with transurethral drainage of urine, a bistable latex prosthesis, and a silicone rubber reservoir and artificial urethra equipped with a sphincter. A variety of other prostheses have been investigated during the past 53 years, with the most complex being those described by the Mayo Clinic group and Rohrmann et al in 1992 and 1996 respectively. All of the above prostheses were of silicone or silicone based; none was implanted in humans (all were implanted in dogs or sheep) and none presented acceptable durability as a precursor to human application. Since the very first model, with few exceptions, meticulous monitoring of prosthesis function was undertaken, including the performance of urography and cystography. All animals were sacrificed and the prosthesis and host tissue

were analyzed by a pathologist either at the end of the experiment or beforehand in the event of death or complications. None of the papers reviewed analyzed the cost of using the prosthesis for bladder replacement. An evaluation of costs of experimentation and the economic benefit that would derive from the ideal bladder prosthesis has, however, been undertaken relatively recently by McAteer et al.

3. DISCUSSION

Article 1

UUT-UCC is a rare disease with an estimated annual incidence in Western countries about one or two new cases per 100,000 inhabitants. Probably because of that reason and similarities with urothelial carcinoma of the bladder, we have been managing that pathology for many years as bladder cancer. In the recent years, we have realized the natural history of UUT-UUCs differs from that of bladder cancer: 60 % of UUT-UCCs are invasive at diagnosis though only 15–25 % of bladder tumors are invasive at presentation; furthermore, as compared to bladder cancer, the peak incidence is at a later age at 70–80 years. Although there is a lack of data in the current literature to provide strong recommendations, recent multicenter studies have motivated the European Association of Urology (EAU) Guideline Group on urothelial cell carcinoma of the upper urinary tract to publish new guides to aid clinicians in their daily practice; this document represents the first real Guidelines for UUT-UUC.

In accord with several previously published reports, this study revealed tumors within the renal pelvis are more common than ureteral lesions (pelvis/calyx 285 patients; 58 upper ureter; 114 lower ureter; populations of patients without previous BC) and also a similar percentage of multifocality, more than one lesion in UUT, around 10–20 %. The prognostic significance of UUT tumor location is controversial. However, several studies have suggested

that ureteral disease often confers a worse prognosis compared with renal pelvic tumors, with an associated higher risk of local recurrence and mortality. Recent multicenter studies have shown that there is no difference in outcomes between patients with renal pelvic tumors and those with ureteral tumors following nephroureterectomy. This finding confirms that only pT stage, grade and lymph node status were associated with disease recurrence and cancer-specific survival. The most common site of recurrence is the bladder representing about 30–51 % of all recurrences, whereas recurrence in the contralateral upper tract is observed in only 2–6 % of cases. Both upper urinary tract recurrence after treatment of bladder cancer and bladder recurrence after treatment of upper urinary tract TCC have been well documented but only a few studies have reported concurrence of UUT-UCC and BC; this is estimated to occur in 8–13 % of cases. Additionally, the analysis of risk factors and the incidence of primary UUT tumors and simultaneous bladder tumors in the absence of a previous history of bladder cancer have been poorly evaluated with no subsequent literature looking at this analysis depending on UUT tumor location.

In our series, location of the upper tract tumor was identified as the only predictive factor on univariate and multivariate analyses for simultaneous bladder cancer in patients with primary UUT-UCC. In these patients, the possibility of having a simultaneous urothelial bladder cancer is progressively higher as the ureteral tumor gets closer to the bladder. Tumors located in the renal pelvis/calices had a 10 % possibility of diagnosis concomitant bladder cancer; however, tumors located in the lumbar and sacral ureter had 18 and

33 % possibility, respectively, of diagnosis concomitant bladder cancer ($p<0.001$) (Table 1).

The evidence that the closer the location of the UUTUCC to the bladder, the higher the incidence of bladder cancer favors the seeding or cancer cell implantation theory. This theory had already been shown from the clinical point of view with a much higher incidence of tumors in the bladder after UUTT than UUTT after bladder cancer and with several basic research studies shoving monoclonality in this multifocal disease. The EAU guidelines recommend cystoscopy (Grade A) in all the patients diagnosed of UUT-UCC in order to rule out concomitant BC. Our article confirms a 10 % incidence of BC in patients with primary UUT-UCC localized in the upper urinary tract, and that one in 3 of patients diagnosed with UCC in the distal ureter will have concomitant BC. Following surgical treatment, it is also mandatory a closed bladder surveillance with cystoscopy and urinary cytology for at least 5 years because of the possibility to develop a BC in the follow-up. In our experience, in some cases in which we found concurrent bladder tumor with UTUC, a TURBT was performed in conjunction with UUT surgery (endoscopic resection, RNU, Ureterectomy), mostly in tumors that seemed to be non-muscle invasive during the TURB. The finding of concurrent BC has not changed the indication of UUT surgery but sometimes has changed the surgical approach in order to minimize the risk of tumor dissemination by providing, in case of concomitant bladder and upper tract tumor, bladder radical surgery if tumor is muscle invasive.

The main result of our study (location of primary UUT tumor is a predictive factor of concomitant bladder cancer) will not change the management of UUT tumors but may change future follow-up strategies for patients with primary UUT located in the lower urinary tract.

Bladder cancer	Localization UTT			Total
	Calyx/ pelvis	Upper ureter (lumbar)	Lower ureter (pelvic/sacral)	
Bladder and UUT-UCC (%)	25 (10 %)	8 (17.8 %)	37 (32.5 %)	70
UUT-UCC (%)	226 (90 %)	37 (82.2 %)	77 (67.5 %)	340

OR: 1.7; 95 % CI, 1.007–2.906, $p < 0.047$

Table 1: Localization of primary UUT-UCC and simultaneous bladder cancer.

Article 2

The HG-NMIBC has a high risk of recurrence and a moderate risk of progression to muscle-invasive disease. TUR + intravesical BCG maintenance therapy represent an effective conservative treatment. The most widespread attitude is a correct clinical staging, and a close cystoscopic and cytology monitoring each 3 months, especially in the first 2 years after from diagnosis, recommending starting radical surgery in selected cases. The initial TUR plays a key role in preventing recurrence, persistence and understaging. Brausi et al in their analysis from 7 EORTC studies observed substantial differences between early recurrence rates, ranging from 0 to 46%. Multivariate analysis

showed that these differences were not due to variations in the nature of the tumor, but to the quality of the TUR by individual surgeons being the absence of muscle specimen in the TUR the main risk factor understaging. The same author recently demonstrated in another study, improving the initial TUR with routine use of a camera, the presence of an adjunct to surgery and teaching sessions to reduce the rate of early recurrence from 28 to 16 % and increase the presence of muscularis propria in the samples from 50 to 80% in patients operated on by residents. Although the TUR for bladder tumor is a routine procedure, and that has not changed over the past decades, the quality criteria have never been clearly defined. Published series of re-TUR and early radical cystectomy in patients after resection of a HG-NMIBC have shown a high rate of persistence between 33-53% and 4-25% of understaging and, in some cases, until 40%. Grimm et al. found that in 81% of cases residual disease was at the site of the initial TUR. Because of this, guidelines recommend making a re-TUR in all cases of HG-NMIBC: HG or T1 or absence of muscular Tx (excluding tumors of LG). In our series, the rate of persistence was 17.1% and 4.2% understaging. Only in two cases where there was no muscle itself in the initial TUR, re-TUR revealed muscle-invasive disease, which means that none of the 22 T1 was down-staged. The 17.1% of persistence may seem to be high, but we resected a selected group with high risk of sub-staging and of residual disease. This pre-selection makes the excellent result which represents only 4.2% of understaging has even more value. It should be noted that none of the 7 or 5 T1b T1c presented under-staging (Table 2). In the current literature, between 30-50% of the samples that are submitted for study do not present muscular. The lack of muscle is

the major risk factor understaging and no doubt that in its absence in patients with high-grade tumor should always go to a re-TUR. There is more controversy about what to do with the HG-Ta and HG-T1 where the muscle is present and free of tumor. Regarding the HG-Ta, some authors have reported a low capacity of progression and understaging (less than 10%), which advise against re-TUR when the initial TUR was complete; others indicate a low incidence of Ta tumors, suggesting that all HG tumors should be considered as minimum T1 for their aggressive potential. To all this, must be added the lack of consensus among pathologists when tumors labeled as cTa or cT1. This difficulty can be increased by excessive in cauterizing in the tumor bed during the RTU. When analyzing HG-T1 tumors, the overall rate of progression is between 7 and 40%, which shows a great heterogeneity of behavior in this group. Since the description, in 1990 by Younes et al, of the sub-classification of T1 tumors using as a new reference the muscularis mucosae, different groups have published their results on HG-T1 tumors, confirming a trend towards greater progression and decreased survival at 5 years depending on the progressively deeper infiltration of the lamina propria. The re-RTU implies a new surgery that requires anesthesia and like any surgical procedure is not without complications. Furthermore, it is not technically easy because bladder thickness is lower due to recent TUR. One “advantage” of the re-TUR is that revising the bladder at 4-6 weeks it’s possible to find residual tumor, which could be misinterpreted at 3 months cystoscopy as an early relapse that, in case of high grade and persistent tumor, may indicate radical treatment. One limitation of our study is the fact that there have been no strict re-TUR criteria for all patients; we have been more selective choosing

mostly Tx and high risk residual disease patients. Another limitation of our study is the lack of monitoring of patients undergoing re-RTU order to know the rates of early recurrence and progression.

cT RTU inicial	cT re-RTU		
n (%)	cT0 n (%)	cT ≤ 2 n (%)	cT ≥ 2 n (%)
22 Tx (46,8)	20 (91)	0 (0)	2 (9)
3 Ta (6,3)	2 (66,6)	1 (33,3)	0 (0)
8 T1 (17,1)	2 (25)	6 (75)	0 (0)
2 T1a (4,3)	2 (100)	0 (0)	0 (0)
5 T1b (10,6)	5 (100)	0 (0)	0 (0)
7 T1c (14,9)	6 (85,8)	1 (14,2)	0 (0)
Total: 47 casos	37 cT0 (78,7)	8 persistencia-recurrencia (17,1)	2 infraestadificación (4,2)

Table 2: Pathological association between first TUR and re-TUR

Article 3

Many have already attempted to develop the ideal alloplastic neo-bladder, but without success (Table 3). The main causes of the failure were: deposition of connective tissue, encrustations, infections, hydroureteronephrosis, leakages of urine from urethral or ureteral anastomosis, and problems related to biocompatibility. Silicone has been the most widely used material but it has been shown that silicone is not the ideal material for bladder substitution because of its low resistance to infection and encrustation. Ideally, a well-functioning reservoir for urine should be totally biocompatible and impermeable, have the capacity to store a sufficient volume of urine, permit

filling and voluntary voiding without any pressure repercussions in the upper urinary tract, avoid any leakage of urine, resist encrustation and infection, be simple to implant and simple to remove/replace in the event of malfunction, and have an acceptable duration and cost.

Although some promising results have been obtained with the biologic and bioengineered biomaterials, no biomaterial is currently available to replace bowel tissue. Such biomaterials may play a role in the future of organ replacement but, unfortunately, results are still far from sufficiently compelling to warrant their daily use in urology.

A new alloplastic reservoir that meets these requirements could have enormous clinical/practical, physical, psychological, and economic benefits. The need to restore bowel function is the principal reason why duration of surgery and inpatient recovery time are lengthy. Without the need for bowel surgery, the operation would entail simple reimplantation of ureters and urethra, easily halving the duration of surgery and the recovery time. Indirectly this would permit a reduction in drug administration during surgery and hospitalization, thereby saving money. The resultant quicker turnover of patients would also permit a reduction in the waiting list for surgery. Furthermore, absence of use of bowel segments to restore bladder function would potentially reduce readmission for potential attendant complications. In psychological terms, an orthotopic prosthesis would also have evident benefits as regards avoidance of an external stoma. The lack of a need for bowel surgery would permit more rapid restoration of physical activities and faster progression to adjuvant therapies on account of a better physical

condition. It would also reduce the enormous economic cost incurred by every national health system owing to (a) use of the instruments needed for bowel surgery (mechanical stapler, suture needles, etc.), (b) use of devices for the rest of the patient´s life, such as external stoma appliances/bags (in patients with external stoma) or pads (in incontinent patients with orthotopic reconstruction) and bladder catheters in patients performing self-catheterization, and (c) the need for subsequent interventions or readmission to hospital. Furthermore, the identification of a biomaterial which can be used as a surrogate for urothelium could be of value in the majority of pediatric pathologies which require the use of bowel (e.g., neurogenic bladder, bladder exstrophy). Such an ideal urothelial substitute could be easily tailored during surgery and used for bladder augmentation/substitution or as a graft for treatment of urethral strictures. Similarly, when the ureter is too short after ureterectomy, it could be replaced instead of doing a psoas bladder-hitch or a Boari bladder flap procedure with its inherent technical difficulties and postoperative hazards. Finally, the identification of biomaterials resistant to infection and encrustation and with reasonable durability when in contact with urine may provide a new "family" of urologic devices as urethral or ureteral catheters usable in daily clinical practice.

A critical analysis of urothelial substitutes reveals that, owing to the lack of knowledge on biology, cell cultures, and tissue engineering, the first ones were totally alloplastic and silicone based while more recently all attention has turned to the purely biologic materials. Perhaps this is one of the key factors in our failure to achieve bladder substitution. We tried purely alloplastic models without success and we are still experimenting with purely

biologic ones, again without significant success. Perhaps the solution is a "hybrid" model, both biologic and alloplastic, so that one biomaterial can help to solve the problems associated with the other. Although many different alloplastic and biologic prostheses have been investigated during the past 50 years and more, the challenge of replacing this "simple" organ remains. While technical designs have become more sophisticated and new biomaterials with higher biocompatibility are now available, we are still looking for a real alternative to bowel sampling. Maybe, collaboration between urologists, engineers, biologists, and biomaterialists, with the incorporation of recent developments and know-how in tissue engineering, will lead to technical and practical remedies to previous problems and the identification of all the features required for the ideal bladder prosthesis. Whether or when a biomaterial with the above-described properties will become available for commercial and medical use remains an open question given past disappointments.

Model (ref.)	Innovative features	Species	Main complications
Bogash [22]	1st model; silicone reservoir; external connection for drainage of urine	25 Dogs	Hydroureteronephrosis, renal failure, and UTIs due to external connection
Friedman [23]	Thin-walled collapsible reservoir	Dogs	Connective tissue deposition, alteration in dynamic properties, renal failure
Abbou, Auvert, Apoil and Vacant models [24–27]	Ovoid silicone reservoir, mechanical voiding system with urethral sphincter	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Stern [28]	Silicone reservoir with external strips (anchored system)	32 Dogs	Progressive renal failure due to papilloma formation
Kline and Belden models [29, 30]	Bistable prostheses (rigid base and flexible top)	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Gurpinar [34]	Bi layered prosthesis, interposition of ileal reservoir, external connection to drain urine	Dogs	Abundant residual volume, UTIs, encrustations
Mayo Clinic [35, 36]	Sophisticated reservoir with a mechanical system for filling and emptying	4 Dogs	Multiple technical failure
Aachen [37]	2 subcutaneous compressible reservoirs that drained into urethra through a "Y" form tube	Sheep	Urinary leakage from sites of anastomosis, not reproducible in humans

UTI urinary tract infection

Table 3: Main models of alloplastic neo-bladders.

4. CONCLUSIONS

The pool of patients affected by bladder cancer is increasing, at least in part because of the rise in life expectancy. Our contribution on the "diagnostic" of urothelial carcinoma is that tumor location in the upper urinary tract represents the only predictive factor for the presence of concomitant bladder cancer, becoming progressively higher as the upper tract tumor gets closer to the bladder. Our experience on the therapeutic approach and endoscopic management of the urothelial carcinoma of the bladder allow us to say that the inclusion of muscle layer on bladder sample during TUR is the main requirement for good results and that the lack of muscle is the only risk factor of down-staging. Radical cystectomy is the gold standard treatment for muscle-invasive bladder cancer, and bowel sampling for bladder substitution is still the only reconstructive alternative for such patients. Although artificial substitution of the bladder would be desirable owing to the physical, psychological, technical, and economic benefits, an alloplastic material usable as a surrogate of urothelium has yet to be discovered. Inter-professional collaboration, recent advances in technology, and innovations in tissue engineering may help in developing a suitable alloplastic or bio-artificial prosthesis. We still have to progress in the understanding and managing of this "endemic" tumor with one of the higher socio-economic impact.

5. ARTICLES

Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma. Worl J. Urol. DOI: 10.1007/s00345-012-0877-2. Epub 2012 May 3

La re-resección transuretral puede no ser necesaria en todos los tumores vesicales no músculo-invasivos de alto grado. Act. Urol Esp. Vol 36, Num 9, 2012.

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ORIGINAL ARTICLE

Upper urinary tract urothelial cell carcinoma: location as a predictive factor for concomitant bladder carcinoma

Marco Cosentino · Joan Palou · Josep M. Gaya · Alberto Breda · Oscar Rodriguez-Faba · Humberto Villavicencio-Mavrich

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Abstract
Objective To investigate the existence of predictive factors for concomitant, primary UUT-UCC and BC. Upper urinary tract urothelial cell carcinoma (UUT-UCC) is a pan-urothelial disease of the transitional epithelial cells. Although several studies have shown the association of bladder recurrence following UUT-UCC, little is known on the incidence of concomitant UUT-UCC and bladder cancer (BC) without previous BC.
Materials and methods A retrospective review of 673 patients diagnosed and treated for UUT-UCC was performed. Patients with history of BC were excluded. We investigated age, sex, location of the upper tract tumor (calyx, renal pelvis, upper ureter, mid-ureter, lower ureter), multifocality, clinical symptoms, tumor grade and pathological stage. Contingency tables and chi-square test were used for categorical variables and analysis of variance (ANOVA) for quantitative variables.
Results 450 patients eligible for inclusion were identified. Of these, 76 (17 %) presented concomitant primary UUT-UCC and BC. Location of primary UUT-UCC was in calyx and/or renal pelvis in 25 patients (34 %), upper ureter 8 (11 %) and lower ureter 37 (49 %). In 6 patients (8 %), data were missing. Concomitant BC was found in 10, 18, and 33 % of patients with primary caliceal/renal pelvis, upper ureter and lower ureter UUT-UCC, respectively. On multivariate analysis, location of UUT-UCC was the only predictive factor for concomitant bladder tumor (OR: 1.7; 95 % CI, 1.007–2.906 $p = 0.047$).
Conclusions Our findings suggest that the possibility of concomitant BC in primary diagnosed patient with UUT-UCC is as high as 33 % and mainly depends on upper tract tumor location.

Keywords Upper tract urothelial carcinoma · Bladder cancer · Cancer recurrence · Risk factors · Concomitant

Introduction

It is well known that UUT-UCC is a pan-urothelial disease of the urothelial cells, which covers the luminal surface of the entire urinary tract extending from renal calyces to the proximal urethra. Furthermore, many UCCs are multifocal and synchronous tumors that can be detected both in the bladder and in the upper tracts at primary diagnosis [1–7].

The possibility of developing synchronous, multifocal UCC in the urinary tract may be explained by two theories: The first is the "Field Cancerization theory" [3] in which the multifocal development of cancer is secondary to the continuous exposure of the urothelium to carcinogens in the urine and the second is the "seeding or cancer cell implantation of cancers cells theory" [4] in which multiple carcinomas are the result of intraluminal spread from a single lesion.

The urinary bladder is the most frequent site of recurrence following primary treatment of UTT, with rates that vary from 15 to 50 % [6, 8–12]. Up to 80–90 % of bladder recurrences occur within the first 2–3 years from primary treatment of UUT-UCC [6, 9, 10, 13–15]. Although UUT-UCC is an uncommon pathology after treatment of primary bladder tumors, it is known that its incidence is higher in

M. Cosentino · J. Palou (✉) · J. M. Gaya · A. Breda · O. Rodriguez-Faba · H. Villavicencio-Mavrich
Urology Department, Fundació Puigvert, Universitat Autònoma de Barcelona, c/Cartagena 340, 08025 Barcelona, Spain
e-mail: jpalou@fundacio-puigvert.es

M. Cosentino
e-mail: doccosentino@gmail.com

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patients with high-grade disease and those with urinary reflux [16, 17].

Very little is known on the simultaneous diagnosis of primary upper tract tumors and bladder carcinoma, although its incidence appears to be low. Only in 8–13 % of cases, concurrent bladder cancer is present [1, 5]. Specifically, to our knowledge, there are no studies that evaluate clinical factors that predict the simultaneous presence of UUT-UCC and bladder UUC.

Accordingly, the objective of this study was to determine whether exist any clinical factors that predict the presence of concomitant bladder cancer in patients with no previous history of bladder cancer who were diagnosed with primary UUT-UCC.

Materials and methods

Study design and data collection description

A retrospective analysis of 673 patients diagnosed and treated for UUT-UCC at our center from 1950 to 2008 was performed. Data collection and analysis were conducted in accordance with an Institutional Review Board (IRB) approved protocol. Patients were assessed and treated according to the Fundació Puigvert guidelines for the protection of human subjects recruited under institutional review board–approved protocols.

In order to evaluate preoperative predictive factors of concomitant bladder cancer and primary UUT-UCC, the study population was divided into two groups: (a) patients with primary UUT-UCC and simultaneous bladder cancer and (b) patients with primary UUT-UCC without bladder cancer.

Inclusion/exclusion criteria

Inclusion criteria were primary UUT-UCC treated either with radical or with conservative approach, and the presence of concomitant bladder cancer. Exclusion criteria were previous history of bladder cancer.

The following variables were investigated: age, sex, location of the tumor in the upper tract (calyx, renal pelvis, upper ureter, mid-ureter, lower ureter), multifocality (solitary/multiple), clinical symptoms (microscopic hematuria, gross hematuria, flank pain and urosepsis), radiological findings both on i.v. urography and on CT scan (normal, hydronephrosis, filling defect, non-functioning kidney, renal or pelvic mass), tumor grade and pathological stage. Location of primary upper tract tumor was confirmed by pathology specimen.

Tumors were staged according to the TNM classification 2002 and graded according the 1973 World Health Organization classification and then revisited according to last WHO and TNM classification.

Statistical analysis

Variables were described as mean and standard deviation for quantitative analysis, and as percentage and case load number for categorical analysis. Contingency tables and chi-square test were used for categorical variables analysis, and analysis of variance (ANOVA) was used for quantitative variables studies. Finally, a multivariate approach was performed using binary logistic regression and the forward stepwise method with the likelihood ratio (LR) for the choice of variables.

The final model was evaluated by the Hosmer–Lemenshow test.

The software used was SPSS (V18.0).

Results

Between June 1950 and September 2008, 673 patients, 551 men and 122 women (81.9 and 18.1 %, respectively), underwent radical nephroureterectomy (RNU) with removal of bladder-cuff for upper urinary tract tumor (UUTT) or a conservative approach with endoscopic resection of tumor. UUTT were located in calyx and renal pelvis in 348 patients, upper ureter 156 patients and lower ureter 40 patients. A total of 30 patients presented with concomitant tumors of calyx/pelvis and upper ureter: 12 with cancer in the upper and lower ureter, 16 with tumors of the calyx/pelvis and lower ureter and 10 with tumors of the calyx/pelvis as well as the upper and lower ureter (61 missing data). The mean age of this cohort was 65 years (SD: 10.82 and range: 27–91 years).

A total of 223 (33 %) patients were excluded from the study due to a previous history of bladder cancer; therefore, the review identified 450 patients suitable for the study. Of these patients, 76 (17 %) were found to have concomitant primary UUT-UCC and bladder cancer, and 374 (83 %) were found to have solely UUT-UCC. Demographic and radiological findings of the two groups are shown in Tables 1 and 2. Specifically, in the group of patients with UUT-UCC and concomitant bladder cancer (76 patients), there were 64 men (84 %) and 12 women (16 %). The mean age was 66 ± 11 years. The location of the primary UUT-UCC was found to be in the calyx and/or renal pelvis in 25 patients (34 %), in the upper ureter in 8 patients (11 %) and in the lower ureter in 37 patients (49 %). In 6 patients with concomitant bladder cancer (8 %), the location of the tumor was not recorded.

When looking at the overall population (450 patients), concomitant bladder cancer was found in 10, 18 and 33 %

Table 1 Clinical characteristics of the entire study population, including those without bladder cancer and those with simultaneous bladder

	Study population	UUT-UCC (%)	Bladder and UUT-UCC (%)	*p* value
N	450	374 (83.1)	76 (16.9)	–
Sex				
Male	355 (78.9)	291 (77.8)	64 (84.2)	0.28
Female	95 (21.1)	83 (22.2)	12 (15.8)	
Age (Mean)	64.2 ± 11	63.8 ± 11	65.9 ± 11	0.15
Multifocality				
Multifocal	263 (64)	216 (63.3)	47 (67.1)	0.58
Unifocal	148 (36)	125 (36.7)	23 (32.9)	
Clinical features				
Macrohematuria	349	51 (70.8)	298 (80.5)	0.07
Pain	121	11 (15.3)	110 (29.5)	0.016
Toxic syndrome	11	1 (1.3)	10 (2.7)	n.s.
Urography				
Hydronephrosis	344	57 (20)	15 (25.4)	n.s.
Filling defect		114 (40)	20 (33.9)	
Non-functioning kidney		68 (23.9)	15 (25.4)	
Normal		5 (1.8)	6 (10.2)	
Others		41 (14.3)	3 (5.1)	
CT SCAN				
Hydronephrosis	369	11 (3.4)	4 (8.7)	n.s.
Filling defect		74 (22.9)	13 (28.3)	
Renal or pelvic mass		187 (57.9)	25 (54.3)	
Others		49 (15.8)	4 (8.7)	

of patients with primary caliceal/renal pelvic, upper ureteral or lower ureteral UUT-UCC, respectively (Table 2). If we compare patients with or without concomitant bladder cancer, there were 52.8 % of tumors located in the lower ureter in patients with concomitant bladder cancer versus 22.6 % in those without.

Both on univariate and on multivariate analysis, age, sex, clinical symptoms, multifocality, grade and pathological stage did not predict concomitant bladder tumor presence. In particular, regarding pathological stage, non-muscle-invasive tumor was present in 220 patients, while 195 patients presented with muscle-invasive UUT-UCC (35 patients missing data); tumor grade was G1 in 19 patients (4.2 %), G2 in 190 (42.2 %) patients and G3 in 184 (40.9 %) patients (57 patients no grade applicable). Data on radiological findings (both on IVU and on CT scan) like hydronephrosis, filling defect, non-functioning kidney and renal or pelvic mass were not significant for predicting the presence of concomitant BC.

Table 2 Localization of primary UUT-UCC and simultaneous bladder cancers

Bladder cancer	Localization UTT			Total
	Calyx/ pelvis	Upper ureter (lumbar)	Lower ureter (pelvic/sacral)	
Bladder and UUT-UCC (%)	25 (10 %)	8 (17.8 %)	37 (32.5 %)	70
UUT-UCC (%)	226 (90 %)	37 (82.2 %)	77 (67.5 %)	340

OR: 1.7; 95 % CI, 1.007–2.906, $p < 0.047$

On multivariate analysis, the location of UUT-UCC in the distal ureter was the only predictive factor for the presence of a concomitant bladder tumor (OR: 1.7; 95 % CI, 1.007–2.906 $p = 0.047$) (Table 2).

Discussion

UUT-UCC is a rare disease with an estimated annual incidence in Western countries about one or two new cases per 100,000 inhabitants [18]. Probably because of that reason and similarities with urothelial carcinoma of the bladder, we have been managing that pathology for many years as bladder cancer. In the recent years, we have realized the natural history of UUT-UUCs differs from that of bladder cancer: 60 % of UUT-UCCs are invasive at diagnosis though only 15–25 % of bladder tumors are invasive at presentation; furthermore, as compared to bladder cancer, the peak incidence is at a later age at 70–80 years [1, 5, 19]. Although there is a lack of data in the current literature to provide strong recommendations, recent multicenter studies have motivated the European Association of Urology (EAU) Guideline Group on urothelial cell carcinoma of the upper urinary tract to publish new guides to aid clinicians in their daily practice [20]; this document represents the first real Guidelines for UUT-UUC.

In accord with several previously published reports [21, 22], this study revealed tumors within the renal pelvis are more common than ureteral lesions (pelvis/calyx 285 patients; 58 upper ureter; 114 lower ureter; populations of patients without previous BC) and also a similar percentage of multifocality, more than one lesion in UUT, around 10–20 % [23]. The prognostic significance of UUT tumor location is controversial. However, several studies have suggested that ureteral disease often confers a worse prognosis compared with renal pelvic tumors, with an associated higher risk of local recurrence and mortality [7, 24]. Recent multicenter studies have shown that there is no

difference in outcomes between patients with renal pelvic tumors and those with ureteral tumors following nephroureterectomy. This finding confirms that only pT stage, grade and lymph node status were associated with disease recurrence and cancer-specific survival [25].

The most common site of recurrence is the bladder representing about 30–51 % of all recurrences [25, 26], whereas recurrence in the contralateral upper tract is observed in only 2–6 % of cases [27, 28]. Both upper urinary tract recurrence after treatment of bladder cancer and bladder recurrence after treatment of upper urinary tract TCC have been well documented but only a few studies have reported concurrence of UUT-UCC and BC; this is estimated to occur in 8–13 % of cases [25, 26]. Additionally, the analysis of risk factors and the incidence of primary UUT tumors and simultaneous bladder tumors in the absence of a previous history of bladder cancer have been poorly evaluated with no subsequent literature looking at this analysis depending on UUT tumor location.

In our series, location of the upper tract tumor was identified as the only predictive factor on univariate and multivariate analyses for simultaneous bladder cancer in patients with primary UUT-UCC. In these patients, the possibility of having a simultaneous urothelial bladder cancer is progressively higher as the ureteral tumor gets closer to the bladder. Tumors located in the renal pelvis/calices had a 10 % possibility of diagnosis concomitant bladder cancer; however, tumors located in the lumbar and sacral ureter had 18 and 33 % possibility, respectively, of diagnosis concomitant bladder cancer ($p < 0.001$) (Table 2).

The evidence that the closer the location of the UUT-UCC to the bladder, the higher the incidence of bladder cancer favors the seeding or cancer cell implantation theory [4]. This theory had already been shown from the clinical point of view with a much higher incidence of tumors in the bladder after UUTT than UUTT after bladder cancer and with several basic research studies shoving monoclonality in this multifocal disease [29].

The EAU guidelines recommend cystoscopy (Grade A) in all the patients diagnosed of UUT-UCC in order to rule-out concomitant BC [20]. Our article confirms a 10 % incidence of BC in patients with primary UUT-UCC localized in the upper urinary tract, and that one in 3 of patients diagnosed with UCC in the distal ureter will have concomitant BC. Following surgical treatment, it is also mandatory a closed bladder surveillance with cystoscopy and urinary cytology for at least 5 years [20] because of the possibility to develop a BC in the follow-up.

In our experience, in some cases in which we found concurrent bladder tumor with UTUC, a TURBT was performed in conjunction with UUT surgery (endoscopic resection, RNU, Ureterectomy), mostly in tumors that seemed to be non-muscle invasive during the TURB. The finding of concurrent BC has not changed the indication of UUT surgery but sometimes has changed the surgical approach in order to minimize the risk of tumor dissemination by providing, in case of concomitant bladder and upper tract tumor, bladder radical surgery if tumor is muscle invasive.

The main result of our study (location of primary UUT tumor is a predictive factor of concomitant bladder cancer) will not change the management of UUT tumors but may change future follow-up strategies for patients with primary UUT located in the lower urinary tract.

A limitation of the study is that, even if we give a new predictive factor of concomitant BC, this will not going to change daily practise because cystoscopy has always to be done when we diagnose a primary UTT. We still do not know whether the locations of the UTT will influence bladder recurrence and/or change the follow-up schedule of the bladder.

Another limitation of the study involves the retrospective nature of this review with some data missing from the earlier proportion of this series (back to 1950).

Conclusions

We found that 17 % of patients with UUT-UCC and without a previous history of bladder cancer had a synchronous bladder tumor. In our data, tumor location in the upper urinary tract appears to be the only predictive factor for the presence of concomitant bladder cancer, becoming progressively higher as the upper tract tumor gets closer to the bladder.

We consider cystoscopy mandatory in the staging of UUT-UCC because the risk of a concurrent lesion in the bladder is not negligible. Early identification of a synchronous tumor may allow for more informed management options and better surgical planning.

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Conflict of interest The authors declare that they have no conflict of interest.

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ARTÍCULO ORIGINAL

La re-resección transuretral puede no ser necesaria en todos los tumores vesicales no músculo-invasivos de alto grado

J.M. Gaya*, J. Palou, M. Cosentino, D. Patiño, O. Rodríguez-Faba y H. Villavicencio

Unidad de Urología Oncológica, Servicio de Urología, Fundació Puigvert, Universitat Autónoma de Barcelona, España

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PALABRAS CLAVE
Tumor vesical no músculo-invasivo;
Alto grado;
Infraestadificación;
Recurrencia;
Re-resección transuretral;
Reestadificación

Resumen

Objetivo: Evaluar la tasa de persitencia, infraestadificación y complicaciones perioperatorias en pacientes con tumor no músculo-invasivo de alto grado que han sido sometidos a re-resección transuretral (re-RTU).

Material y métodos: Revisión retrospectiva de 47 pacientes con estadio clínico de tumor vesical de alto grado no músculo-invasivo sometidos a re-RTU entre enero de 2007 y diciembre de 2009 en nuestro centro. Evaluamos la tasa de tumor residual (persistencia) y de infraestadificación, así como las complicaciones quirúrgicas y el coste de la re-RTU.

Resultados: En 22 casos se indicó la re-RTU por ausencia de muscular propia en el espécimen (cTx). Observamos tumor residual en 8/47 pacientes (17%) e infraestadificación en 2 casos (4,2%), en los 2 únicos pacientes infraestadificados no se había observado muscular propia en el espécimen de la RTU inicial. Los 20 cTx restantes (90%), fueron cT0 en la re-RTU. No observamos ningún caso de cT1 en los que en la re-RTU apareciera infraestadiaje (≥ cT2). Seis pacientes (12,6%) presentaron complicaciones secundarias a la re-RTU (una estenosis uretral, 2 reintervenciones por sangrado, una infección urinaria febril y 2 perforaciones vesicales).

Conclusiones: En nuestro estudio la ausencia de muscular en el espécimen de la RTU es el único factor de riesgo de infraestadificación. Es por ello que en estos casos consideramos que la re-RTU es obligatoria. Por el contrario, en los casos donde la RTU ha sido completa y la muscular se encuentra libre de tumor (cTa-T1) creemos que la re-RTU sistemática es innecesaria, solo indicada en casos concretos y más no estando exenta de complicaciones.

* Autor para correspondencia.
Correo electrónico: 36178jgs@comb.cat (J.M. Gaya).

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KEYWORDS
Non-muscle-invasive bladder cancer;
High grade;
Understaging;
Recurrence;
Second transurethral resection;
Restaging

A Second Transurethral Resection Could Be not Necessary in All High Grade Non-muscle-invasive Bladder Tumors

Abstract

Objectives: Evaluate the rate of residual tumor, understaging and perioperative complications in patients with high grade non-muscle-invasive bladder cancer who underwent second transurethral resection (re-TUR).

Material and methods: A retrospective review of 47 patients with high grade non-muscle-invasive bladder cancer who underwent second TUR from January 2007 to December 2009 at our institution. We evaluated the rate of residual tumor and understaging detected by re-TUR, complications, and the cost of the surgery.

Results: Twenty-two patients underwent second TUR because of the absence of muscle in the initial resection specimen (cTx). We observed residual disease in 8/47 patients (17%) and understaging in 2 cases (4.2%), the only 2 patients understaged muscularis propria was not present in the sample of initial TUR. The other 20 cTx (90%) were cT0 in the re-TUR. We did not identify any case of cT1 understaged in the re-TUR (≥ cT2). Six patients (12.6%) reported complications related with the second TUR (one urethral stricture, two patients required reintervention because of bleeding, one febrile urinary infection and two bladder perforations).

Conclusions: Our findings show that the absence of muscle in the initial resection specimen is the only risk factor for understaging. Therefore, we consider re-TUR is mandatory in these cases. On the other hand, when complete TUR has been performed and the muscularis propria is present and tumor free (cTa-T1), we consider systematic re-TUR is not necessary and only indicated in selected patients, even more if we consider that re-TUR is not exempt from complications.

Introducción

En el 75-85% de los pacientes con tumor vesical la enfermedad está confinada en la mucosa (Ta, Tis) o en la submucosa (T1), es lo que llamamos enfermedad no músculo-invasiva[1]. En este extenso grupo tienen un especial interés los tumores vesicales no músculo-invasivos (TVNMI) de alto grado (TVNMI-AG), ya que se ha visto que tienen un elevado riesgo de recurrencia y lo que es más preocupante de progresión hacia tumor músculo-invasivo (TMI)[2].

La RTU inicial es el primer paso para un correcto tratamiento de estos tumores; de ella depende una buena obtención de la muestra para su estudio histológico y su estadificación clínica, a la vez que de ella se obtiene información adicional del tumor que puede influir en el tratamiento inicial y el pronóstico: el tamaño, la localización, la multiplicidad, el grado y la presencia de carcinoma in situ (CIS) asociado[3]. A pesar de que este es un procedimiento familiar para todos los urólogos, no siempre se realiza correctamente y a menudo no se obtienen los resultados esperados, hecho que influye negativamente en el pronóstico del paciente[4].

El inconveniente principal para el correcto manejo de estos tumores es la infraestadificación y la persistencia de enfermedad tras la resección transuretral (RTU)[5], siendo el factor de riesgo más importante de infraestadificación la ausencia de músculo en el espécimen de la RTU[6,7]. La infraestadificación en el tumor vesical conlleva desconocer la presencia de enfermedad músculo-invasiva y, por ello, un tratamiento inadecuado. Esta situación conlleva realizar, a menudo, la cirugía radical cuando la enfermedad ya no es órgano-confinada y una disminución de la supervivencia[8].

El elevado riesgo de progresión y la posibilidad de infraestadificación de los TVNMI-AG es el argumento sobre el que se basan algunos autores para indicar la cistectomía radical inmediata en estos pacientes, obteniendo excelentes tasas de supervivencias en pacientes no infraestadificados (80-90%), pero a expensas de una elevada tasa de sobretratamiento[9,10]. Por el contrario, la buena respuesta que han mostrado estos tumores a la BCG intravesical y la capacidad de las terapias de mantenimiento de reducir el riesgo de progresión ha hecho que la tendencia actual mayoritaria sea realizar un tratamiento conservador seguido de un estrecho seguimiento[11]. Por lo tanto, es básico una buena estadificación clínica de estos pacientes para no correr riesgos innecesarios. Con el fin de mejorar la estadificaión clínica y el tiempo libre de recurrencia[12,13], desde hace unos años la mayoría de las guías clínicas internacionales recomiendan en todos los tumores vesicales no músculo-invasivos de alto grado realizar una re-RTU antes de las 4-6 semanas[14].

Objetivo

El objetivo principal de nuestro estudio fue revisar la tasa de infraestadificación y tumor residual (persistencia) en los pacientes con TVNMI-AG que sometimos a re-RTU, para ver en qué casos es realmente necesaria esta segunda RTU. A su vez, también analizamos los costes y las complicaciones inmediatas y a corto plazo de esta RTU de reestadificación.

Material y métodos

Una vez el estudio fue aprobado por el comité ético de investigación clínica de nuestro centro, revisamos de forma retrospectiva las historias clínicas de los pacientes sometidos a una re-RTU entre enero de 2007 y diciembre de 2009

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en nuestra unidad de urología oncológica. En cada paciente valoramos las características antropométricas, el tiempo transcurrido entre la RTU inicial y la re-RTU, y la anatomía patológica de ambas cirugías. En el caso de la re-RTU analizamos también el tiempo quirúrgico, los hallazgos cistoscópicos, la técnica empleada, la estancia hospitalaria, el coste aproximado y las complicaciones perioperatorias.

En este periodo la re-RTU no se realizaba de forma sistemática en nuestro centro. Solo estaba indicada en TVNMI-AG con ausencia de muscular propia (cTx) y en casos muy concretos en los que, a pesar de una RTU aparentemente completa y presencia de muscular, por su tamaño-extensión, localización, multiplicidad, aspecto sólido o subestadificación se consideraba el tumor de alto riesgo de tener enfermedad residual.

Se definió RTU inicial como la cirugía que reportó la anatomía patológica que motivó la re-RTU, independientemente de si era un tumor primario o recidivante. En todos los casos la re-RTU se realizó antes de las 8 semanas tras la RTU inicial y antes de llevar a cabo ningún tipo de tratamiento intravesical, empleando en todos los casos la misma técnica. Tras colocar al paciente en posición de litotomía y bajo anestesia general o locorregional se realizó cistoscopia exploradora con óptica de 70° revisando de forma cuidadosa todas las paredes vesicales en busca de lesiones residuales y prestando especial atención a las áreas resecadas. Se describió en todos los casos las áreas resecadas previamente, utilizando 3 categorías (sospecha de tumor macroscópico, esfacelos o cicatriz). Una vez finalizada la cistoscopia, mediante un resector con simple (24 Fr) o doble vaina (26 Fr) se resecaron las áreas resecadas previamente y cualquier lesión residual o sospechosa. En los casos de tumor inicial múltiple en los que la información de la hoja quirúrgica de la RTU inicial no nos permitió identificar la ubicación del TMVNMI-AG que había justificado la re-RTU resecamos todas las cicatrices que se veían recientes. En todos los casos la resección fue con corriente monopolar y se realizó una resección amplia y profunda para asegurar márgenes y la obtención de muscular propia. En 17 casos (36%) se tomó tras la resección una muestra de la base del tumor con pinza fría. Tras el procedimiento se dejó sonda vesical Dufour 22 Fr (3 vías) con lavado vesical continuo. Se consideró complicación perioperatoria aquella relacionada directamente con la re-RTU y que sucedió desde la fecha del ingreso hasta 3 meses después.

Para el análisis de los datos se utilizó el programa estadístico SPSS versión 17.0. Se realizó un análisis descriptivo de las variables cualitativas del estudio y se calculó la media, mediana y desviación estándar en el caso de las variables cuantitativas.

Resultados

Epidemio-clínico-patológicos

Entre enero de 2007 y diciembre de 2009 sometimos a 47 pacientes a re-RTU, lo que supone el (26,4%) del total de 178 pacientes que en ese mismo periodo presentaron TVNMI-AG en la RTU inicial. Incidencia más alta de hombres que de mujeres (83 vs 17%) y con una mediana de edad de 62 años (44-81). Un 43% de los pacientes eran recurrentes y un 26% habían recibido tratamiento intravesical previo, ninguno de ellos entre la RTU inicial y la re-RTU. En todos los casos la re-RTU se realizó antes de las 8 semanas tras la RTU inicial, siendo la mediana de 43 días (18-55). En 22/47 casos (46%) se fue a la re-RTU por ausencia de muscular propia (cTx) en la RTU inicial, los casos restantes por TVNMI-AG (3 cTa, 8 cT1, 2 cT1a, 5 cT1b, 7 cT1c). En el 63,6% de los AGT1 el anatomopatólogo había conseguido una subestadificación según la afectación de la muscularis mucosae.

Tabla 1 Correlación entre los hallazgos en la cistoscopia exploradora durante la re-RTU y la anatomía patológica definitiva

Hallazgo macroscópico en la re-RTU aspecto/n/total/(porcentaje)	Anatomía patológica re-RTU (porcentaje enfermedad residual)
Esfacelos = 15/47 (31,9%)	13 T0/2 T1 (13,3%)
Cicatriz = 29/47 (61,7%)	22 T0/1 Ta/5 T1/1 T2 (24,3%)
Tumor macroscópico = 3/47 (6,4%)	2 T0/1 T2 (33,3%)

El hallazgo cistoscópico más frecuente en la re-RTU fue un área cicatricial (61,7%) seguido de esfacelos (31,9%) y solo en 3/47 casos (6,4%) sospecha de tumor macroscópico. No hubo correlación entre los hallazgos macroscópicos y el resultado anatomopatológico (tabla 1).

En el 21,2% de los pacientes (10/47) la re-RTU mostró enfermedad residual en la vejiga. En 8 casos (17,1%) fue persistencia (< cT2) y en 2 (4,2%) infraestadificación (≥ cT2). En 8/25 pacientes (32%) con muscular propia en la muestra de la RTU inicial encontramos enfermedad residual en la re-RTU, pero en ningún caso enfermedad músculo-invasiva. En los 2 únicos pacientes infraestadificados la indicación de re-RTU había sido por la ausencia de muscular propia en la muestra de la RTU inicial (cTx) (tabla 2).

En todas las muestras de re-RTU se obtuvo muscular propia y en algunos casos grasa, siendo mayor la incidencia de esta última en los casos en los que se tomó biopsia con pinza fría (23,3 vs 64,7%); $p < 0,05$ (tabla 3).

Costes y complicaciones de la re-resección transuretral

El tiempo medio del paciente en quirófano (anestesia + cirugía) para la re-RTU fue de 74 min (48-115). La mayoría de los pacientes fueron dados de alta a las 48 h de la cirugía sin sonda vesical, siendo la mediana de días de ingreso, tras la re-RTU, de 2,3 días con un rango (2-9). Teniendo en cuenta que la estancia hospitalaria, el material quirúrgico empleado, el procesamiento y el estudio de la muestra y el manejo postoperatorio son similares a una primera RTU, podemos afirmar que el coste económico de una re-RTU en nuestro centro es el mismo que el de una RTU convencional por tumor vesical.

Seis pacientes (12,6%) presentaron complicaciones secundarias o relacionadas con la re-RTU. Dos de ellos tuvieron que ser reintervenidos de forma endoscópica por sangrado, en otros 2 casos hubo perforación vesical (una

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Tabla 2 Correlación anatomopatológica entre la RTU inicial y la re-RTU

cT RTU inicial	cT re-RTU		
n (%)	cT0 n (%)	cT ≤ 2 n (%)	cT ≥ 2 n (%)
22 Tx (46,8)	20 (91)	0 (0)	2 (9)
3 Ta (6,3)	2 (66,6)	1 (33,3)	0 (0)
8 T1 (17,1)	2 (25)	6 (75)	0 (0)
2 T1a (4,3)	2 (100)	0 (0)	0 (0)
5 T1b (10,6)	5 (100)	0 (0)	0 (0)
7 T1c (14,9)	6 (85,8)	1 (14,2)	0 (0)
Total: 47 casos	37 cT0 (78,7)	8 persistencia-recurrencia (17,1)	2 infraestadificación (4,2)

Tabla 3 Obtención de muscular propia y grasa según técnica para obtención de muestra del lecho quirúrgico en la re-RTU

Técnica re-RTU n (%)	Muscular propia n (%)	Grasa n (%)
Solo RTU: 30 (63,8)	30 (100)	7 (23,3)
RTU + pinza fría: 17 (21,2)	17 (100)	11 (64,7)

Tabla 4 Complicaciones secundarias a la re-RTU según la clasificación de Clavien-Dindo revisada, 2004

1. Sangrado-hematuria	Grado III A
2. Sangrado-hematuria	Grado III A
3. Perforación vesical	Grado I
4. Perforación vesical	Grado I
5. Estenosis uretral	Grado III A
6. ITU febril	Grado II

ITU: infección del tracto urinario.

extraperitoneal, una intraperitoneal) que se manejaron de forma conservadora. Un paciente presentó una infección urinaria febril que requirió tratamiento antibiótico intravenoso y prolongó su estancia hospitalaria. Se objetivó un caso de estenosis a nivel de la uretra bulbar en el control cistoscópico a los 3 meses posterior a la re-RTU, que se trató mediante uretrotomía interna. Solo los 2 pacientes que presentaron perforación vesical fueron dados de alta con sonda vesical. En uno de ellos esta se retiró a los 7 días sin complicaciones y en el otro caso se tuvo que recolocar tras retirarla, por persistencia de la perforación, retirándose definitivamente a las 2 semanas bajo control radiológico. (tabla 4)

Discusión

Los TVNMI-AG tienen un elevado riesgo de recurrencia y un riesgo moderado de progresión hacia enfermedad músculo-invasiva[2]. La RTU + BCG intravesical con terapia de mantenimiento ha demostrado ser un tratamiento conservador efectivo[11]. La actitud más extendida, y la que se recomienda en la actualidad, es una correcta estadificación clínica, mediante una buena RTU y un estrecho seguimiento con controles cistoscópicos y citología cada 3 meses, sobre todo, en los primeros 2 años para el temprano diagnóstico de la recurrencia y, sobre todo, de la progresión, recomendándose la cirugía radical de inicio solo en casos muy seleccionados de TVNMI-AG que presentan factores de riesgo asociados[14].

La RTU inicial desempeña un papel primordial para evitar recurrencia-persistencia e infraestadificación. Brausi et al.[15] en su análisis de 2.410 pacientes pertenecientes a 7 estudios distintos de la EORTC observaron diferencias sustanciales entre las tasas de recurrencia precoz, variando desde el 0 al 46%. En el análisis multivariante demostraron que estas diferencias no se debían a las variaciones en la naturaleza del tumor, sino a la calidad de la RTU realizada por los distintos cirujanos incluidos en el estudio, siendo la ausencia de muscular propia en el espécimen de la RTU el principal factor de riesgo de infraestadificación, hecho ya demostrado en otros estudios[6,7]. El mismo autor demostró recientemente, en otro estudio[16], que mejorando la RTU inicial con el uso rutinario de una cámara, la presencia de un adjunto en quirófano y sesiones para enseñar a resecar se puede reducir la tasa de recurrencia precoz del 28 al 16% y aumentar la presencia de muscular propia en las muestras del 50 al 80%, en los pacientes operados por residentes. A pesar de que la RTU por tumor de vejiga es un procedimiento rutinario, y que no ha cambiado a lo largo de las últimas décadas, los criterios de calidad nunca han sido claramente definidos. Se deberá implementar en un futuro criterios validables para poder establecer los requerimientos mínimos y tener un control de calidad: tasa de muestras sin evidencia de muscular propia según grado del tumor, tasa de tumor residual e infraestadificación, recurrencia y progresión a 3 meses.

Las series publicadas, de re-RTU y cistectomía radical precoz en pacientes tras la resección de un TVNMI-AG, han demostrado una elevada tasa de persistencia de entre 33-53% y de infraestadificación de entre 4-25%[17–19], pudiendo llegar incluso en algún caso hasta el 40%[20]. A esto hay que añadirle que Grimm et al. observaron que en el 81% de los casos la enfermedad residual se encontraba en el sitio de la RTU inicial[13]. En estos elevados porcentajes de enfermedad residual son en los que se basan las guías y los expertos internacionales para recomendar realizar una re-RTU en todos los casos de TVNMI que sea: AG o T1 o en ausencia de muscular Tx (excluyéndose los tumores de bajo grado)[14].

En nuestra serie, la tasa de persistencia ha sido de un 17,1% y la de infraestadificación de un 4,2%. Solo en 2 casos donde no había muscular propia en la RTU inicial, la re-RTU reveló enfermedad músculo-invasiva, lo que significa que ninguno de los 22 T1 estaba infraestadificado. El 17,1% de persistencia puede parecer una cifra elevada, pero hay que recordar que no se trata de todos los TVNMI-AG resecados, sino de un grupo altamente seleccionado que por sus

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características de localización, extensión, aspecto o subestadificación consideramos de riesgo elevado de enfermedad residual. Esta previa selección hace que el excelente resultado que supone solo un 4,2% de infraestadificación tenga aun más valor. Hay que resaltar que ninguno de los 7 T1c ni 5 T1b presentaron infraestadificación. Esta baja tasa se valida de forma interna, al coincidir con nuestra tasa de progresión precoz en tumores vesicales T1 publicada hace unos años[21].

Esta baja incidencia de infraestadificación comparable a los mejores resultados publicados hasta el momento, la atribuimos a una RTU inicial meticulosa donde se obtienen márgenes amplios y muestras de profundidad por separado. La realización de una re-RTU a 22 casos por ausencia de músculo, supone solo un 12% del total de TMVNMI-AG resecados durante el mismo periodo en nuestro centro.

En la literatura actual, entre el 30-50% de las muestras que se remiten para estudio no tienen muscular propia[22,23], y son los casos que una vez realizada la re-RTU evidencian el mayor porcentaje de infraestadificación[7]. Es por ello que la ausencia de muscular es el principal factor de riesgo de infraestadificación y no hay duda de que en su ausencia en pacientes con tumor de alto grado se debe ir siempre a una re-RTU.

Pero existe mayor controversia sobre qué hacer con los AGTa y los AGT1 donde la muscular está presente y libre de tumor. Respecto a los AGTa, algunos autores han publicado una baja capacidad de infraestadificación y progresión de los AGTa menor del 10%[2], lo que desaconsejaría una re-RTU cuando la RTU inicial ha sido completa; otros indican una baja incidencia de tumores AGTa, sugiriendo que todos los tumores AG deberían considerarse como mínimo T1 por su potencial agresivo. A todo esto hay que añadir la falta de consenso y variabilidad entre anatomopatólogos, como han demostrado algunos estudios, a la hora de etiquetar los tumores como cTa o cT1[24,25]. Esta dificultad puede verse incrementada por el exceso de cauterización del tumor en el lecho tumoral en el momento de la RTU.

Al analizar los tumores AGT1, la tasa global de progresión está entre el 7 y el 40%, lo que demuestra una gran heterogeneidad de comportamiento en este grupo[2]. Desde que en 1990 Younes et al.[26] describieron una subclasificación de los T1, usando la muscularis mucosae como referencia, otros grupos han publicado sus resultados con tumores AGT1, confirmando una tendencia a la mayor progresión y menor supervivencia a los 5 años cuanto más profunda es la infiltración de la lámina propia, pudiéndose establecer un pronóstico en grupos de riesgo[27–29]. La subestadificación requiere un aprendizaje pero en algunos casos, por la naturaleza de la muestra (ausencia de muscularis mucosae en algunas zonas o artefacto), no es posible. Sin embargo, cuando se consigue se ha podido observar que influye en el pronóstico y también en la posibilidad de infraestadificación. Orsola et al.[28] observaron que la posibilidad de enfermedad residual en los cT1a era muy baja y en los cT1b dependía de otros factores de riesgo como el tamaño y la asociación con CIS, concluyendo que en todos estos casos posiblemente no es necesario realizar una re-RTU. En nuestra serie, ninguno de los 7 cT1c ni de los 5 cT1b presentaron infraestadificación, lo que reafirma la importancia de una correcta RTU inicial.

La re-RTU implica una nueva cirugía que requiere de una anestesia general o locorregional y como todo procedimiento quirúrgico no está exento de complicaciones. Además, no se trata de una técnica fácil,ya que se debe resecar una pared vesical de poco grosor debido a la RTU reciente y los hallazgos macroscópicos no suelen correlacionarse con los anatomopatológicos. Se han publicado artículos sobre las complicaciones de la RTU por tumor vesical, pero muy pocos han analizado,como en nuestro caso, las secundarias a la re-RTU. La incidencia de complicaciones en una RTU por tumor vesical varía entre el 5,7 y el 9,9%)[30], siendo el sangrado, la perforación vesical y las infecciones urinarias las más frecuentes. Nuestra tasa de complicaciones, en los pacientes sometidos a re-RTU, fue de un 12,6%. El someter al paciente a una nueva cirugía en poco tiempo, menor grosor de la pared vesical con mayor riesgo de perforación y ser portador reciente de sonda vesical son factores que creemos influyen en este aumento de complicaciones. A todo ello hay que añadirle el coste económico; la reestadificación supone un coste para el sistema sanitario y/o para el paciente. En un sistema sanitario universal como el nuestro, distinto al de muchos otros países, con recursos limitados, sobresaturar el sistema haciendo re-RTU a todos los TVNMI-AG significa aumentar las listas de espera.

Una de las ventajas de la re-RTU es que se revisa la vejiga a las 4-6 semanas, pudiendo encontrar tumor residual, que podría mal interpretarse en la cistoscopia de los 3 meses como una recidiva precoz, y si esta es de alto grado indicar un tratamiento radical[14], cuando en realidad debe considerarse como una persistencia de la enfermedad. Una de las limitaciones de nuestro estudio es el hecho de que no se han seguido los criterios estrictos de re-RTU que se indican en las guías europeasen todos los pacientes; hemos sido más selectivos, escogiendo mayoritariamente pacientes Tx y aquellos con riesgo elevado de enfermedad residual. Aunque son estos casos en los que se publican los peores resultados de infraestadificación.

Otra de las limitaciones de nuestro estudio es la falta de seguimiento de los pacientes sometidos a re-RTU para así conocer las tasas de recurrencia precoz y progresión. También lo es el hecho de que se hayan incluido pocos pacientes AGTa, lo que no permite evaluar la necesidad real de realizar la re-RTU en estos casos. No obstante, según los resultados obtenidos en los casos T1 de nuestra serie, con ningún caso de infraestadificación permite estimar que en Ta también sería mínima. La finalidad de nuestro estudio fue saber nuestra tasa de persistencia e infraestadificación y también, hecho raramente mencionado en otros artículos, revisar las complicaciones derivadas de una segunda RTU en estos pacientes.

Conclusiones

El principal requisito para unos buenos resultados (baja persistencia y baja infraestadificación) es una primera RTU meticulosa y sistemática que debe incluir muscular propia. En nuestra experiencia, la ausencia de muscular en el espécimen de la RTU es el único factor de riesgo de infraestadificación. En estos casos, la re-RTU es obligatoria y debe realizarse de forma sistematizada, con resección amplia del área cicatricial, para obtener muscular propia; y en caso de riesgo elevado de perforación se puede utilizar, tras un primer corte con asa, pinza fría para obtener la biopsia de la base del lecho quirúrgico.

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En los casos en que la RTU inicial ha sido completa y la muscular propia se encuentra libre de tumor (cTa, cT1) creemos que la re-RTU sistemática es más discutible, y más, ya que no está exenta de complicaciones, coste económico e implicaciones sociosanitarias. Por ello, solo la recomendaríamos en casos muy concretos donde por las características del tumor (tamaño-extensión, multiplicidad, localización) el riesgo de enfermedad residual es elevado.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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UROLOGY - REVIEW

Alloplastic bladder substitution: are we making progress?

Marco Cosentino · Josep M. Gaya · Alberto Breda · Joan Palou · Humberto Villavicencio

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Abstract Radical cystectomy with lymphadenectomy and urinary diversion is the gold standard treatment for bladder cancer in organ-confined muscle-invasive disease and selected patients who have high-grade non-muscle-invasive disease or are non-responders to BCG. The main and most morbid complications of this challenging surgery are related to the use of bowel for urinary tract reconstruction. For this reason, many past projects were devoted to finding an alternative to the use of bowel. The aim of this review is to provide a summary of the evolution of alloplastic bladder substitution. A comprehensive review of the literature was performed using the Medline National Library of Medicine database and Google Scholar. Keywords used were cystectomy and intestine/bowel, replacement, bladder substitution, organ replacement, artificial bladder, alloplastic material, biomaterial, and tissue engineering. Various prostheses have been proposed for replacement of the urinary bladder, silicone being the most frequently used material. The first published model of an alloplastic bladder was described by Bogash et al. in late 1959, while the last, in 1996, was suggested by Rohrmann. Interprofessional collaboration, recent advances in technology, and tissue engineering may help in developing suitable bladder prostheses. Urologists as well as engineers and the industry need to give this matter serious attention.

Keywords Urinary tract · Transplantation · Silicone · Scaffold · Bladder tissue engineering · Bladder

M. Cosentino (✉) · J. M. Gaya · A. Breda · J. Palou · H. Villavicencio
Department of Urology, Fundació Puigvert, Universitat Autonoma de Barcelona, c/Cartagena 340, 08025 Barcelona, Spain
e-mail: doccosentino@gmail.com

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Introduction

In the Western world, bladder cancer is the fourth most common malignancy in men and the eight most common in women, with more than 330,000 new cases and more than 130,000 deaths per year. It represents the most common malignancy of the urinary tract, with a peak incidence in the adult and elderly population, and at any point in time, 2.7 million people worldwide have a history of urinary bladder cancer [1–3]. Although the majority of patients present with superficial bladder tumors, 20–40 % either present with or develop invasive disease. Radical cystectomy with pelvic lymph node dissection is the gold standard treatment for organ-confined muscle-invasive disease, and it is also a valid option for selected patients with high-grade non-muscle-invasive bladder cancer, either as a primary treatment modality or for recurrent or refractory tumors after bladder-conserving regimens. However, this procedure, which

is performed with a curative intent also in the elderly population [4, 5], is complex, involving simultaneous surgery on the urinary and gastrointestinal tracts, and is associated with a high rate of complications (17–66 %) and morbidity [6–8], with prolonged hospital stay and potential readmission. The complications are generally considered to be primarily attributable to the urinary tract reconstruction (UTR), which relies on sampling of bowel to restore urinary bladder function. Such complications have an effect on the patient's physical and psychological well-being and increase significantly the total cost of the intervention. Since we are facing a rise in life expectancy [9], with increases in both the elderly and the bladder cancer population, treatment management in these patients represents an important challenge for present and future urology.

The function of urinary bladder is to store urine at low pressure and to permit voluntary voiding without involuntary leakage of urine; so, from a mechanical point of view, it can be considered a sophisticated waterproof reservoir which fills and empties at low pressure [10].

Since the first cystectomy for bladder tumor, performed in 1887 by Bardenheuer in Cologne, appropriate replacement of bladder function and reduction in the impact of cystectomy on the patient's quality of life (by maintaining control over voluntary voiding and continence, preserving renal function, and ensuring that UTR is esthetically acceptable) have become the main surgical challenges. Because of the impossibility of replacing the bladder with a transplanted one (allograft or xenograft), surgeons and researchers have sought alternative solutions for UTR that avoid the use of bowel tissue. The idea of replacing bladder with a synthetic prosthesis, thereby obviating the need for use of bowel and the associated numerous complications, has always been attractive and the source of investigation [11–37].

Recent initiatives in the development of biomaterials for organ replacement or functional reconstruction include alloplastic, biologic, and bioengineered biomaterials. Nowadays, urinary bladder substitutes can be divided into *biologic* and *alloplastic*. Biologic ones are all urothelial substitutes that originate from or have been synthesized or developed from living organisms, while alloplastic ones can be simply defined as all non-biologic materials.

Over the last two decades, advances in regenerative medicine, cell and stem cell biology, material sciences, and tissue engineering have enabled researchers to develop cutting-edge technology leading to the "construction" of different tissues [11–20]. Within urology, interest has in particular focused on development of a urothelium substitute for bladder, ureter, and urethra replacement. Regarding urinary bladder replacement, the subject of this paper, many groups have worked with cultures of regenerated multilayer urothelium, the group of Atala having been the first to publish on an "engineered bladder tissue created with autologous cells usable for a cystoplasty" [12]. However, while preliminary results on urothelial substitutes and the first biologic neo-bladders seemed promising, discouraging drawbacks emerged such as cell mutations, biodegradability of the scaffold, the lack of direct vascular supply, disappointing long-term outcomes of the "transplanted" new organ, and continuing high costs; taken in conjunction with ethical and oncologic considerations, these limitations illustrated the need for further advances [14–20].

Alloplastic materials, on the other hand, have progressively entered the daily clinical practice of every specialty. Urology, in particular, would not be the same without devices such as bladder and ureteral catheters. Since the Egyptians first used the stalk of papyrus to drain urine thousands of years ago [21], alloplastic materials have gradually become more useful, comfortable, and cheaper. However, while in most specialties the use of permanent implants is possible (e.g., articular or vascular prostheses), in urology this does not seem feasible as yet owing to infections and encrustations that result from the continual exposure to urine.

The main aim of this study is to analyze data published on non-bowel, alloplastic bladder substitution, summarizing the evolution, the current situation, and the most relevant findings.

Materials and methods

A comprehensive review of the literature was performed using the Medline National Library of Medicine database and Google Scholar. We considered suitable for our review all historical models of bladder substitution without the use of bowel, emphasizing the alloplastic models. The review included articles published between January 1, 1958, and September 1, 2011. Only articles in English were considered suitable for the study. Key words used were cystectomy

Table 1 Main models of alloplastic neo-bladders

Model (ref.)	Innovative features	Species	Main complications
Bogash [22]	1st model; silicone reservoir; external connection for drainage of urine	25 Dogs	Hydroureteronephrosis, renal failure, and UTIs due to external connection
Friedman [23]	Thin-walled collapsible reservoir	Dogs	Connective tissue deposition, alteration in dynamic properties, renal failure
Abbou, Auvert, Apoil and Vacant models [24–27]	Ovoid silicone reservoir, mechanical voiding system with urethral sphincter	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Stern [28]	Silicone reservoir with external strips (anchored system)	32 Dogs	Progressive renal failure due to papilloma formation
Kline and Belden models [29, 30]	Bistable prostheses (rigid base and flexible top)	Dogs	Connective tissue deposition, alteration in dynamic proprieties
Gurpinar [34]	Bi layered prosthesis, interposition of ileal reservoir, external connection to drain urine	Dogs	Abundant residual volume, UTIs, encrustations
Mayo Clinic [35, 36]	Sophisticated reservoir with a mechanical system for filling and emptying	4 Dogs	Multiple technical failure
Aachen [37]	2 subcutaneous compressible reservoirs that drained into urethra through a "Y" form tube	Sheep	Urinary leakage from sites of anastomosis, not reproducible in humans

UTI urinary tract infection

and intestine/bowel, replacement, bladder substitution, organ replacement, artificial bladder, alloplastic material, biomaterial, and tissue engineering. Research was directed at all forms of urinary bladder substitute, whether biologic or alloplastic. Aspects analyzed included the following: the kind(s) of material used for prosthesis; technical features of the prosthesis; the mechanism of urine storage and voiding; the system used to achieve continence; the type of anastomosis between the prosthesis, ureters, and urethra; the type of suture used for prosthesis implant; the system of prosthesis fixation; whether implantation was performed in humans or animals; the species of animal used for implantation; the number of prostheses implanted for each author/group; complications after prosthesis implantation; causes and effects of complications; time until presentation of complications; death after prosthesis implant; possibility of repair or substitution after implant; and durability of prosthesis.

In total, 73 articles published in 23 journals were included in the review and then further selected according to the author.

In the last 50 years, many different prostheses have been proposed for replacement of the urinary bladder, silicone being the most widely used material. The most common models described include the following: plastic reservoirs and mechanical valves with abdominal drainage of urine via a silicone tube [22, 23], a silicone rubber prosthesis with transurethral drainage of urine [24], a bistable latex prosthesis [25], and a silicone rubber reservoir and artificial urethra equipped with a sphincter [26]. A variety of other prostheses have been investigated during the past 53 years [27–37], with the most complex being those described by the Mayo Clinic group [36] and Rohrmann et al. [37] in 1992 and 1996, respectively (Table 1). Below we describe and analyze the most "popular" alloplastic implants.

Main alloplastic models

(1) The *Bogash model*: In this first model of artificial bladder, presented in the late 1960s by the pioneers in alloplastic substitution of the urinary bladder (M. Bogash, F.P. Kohler, and R.H. Scott), ureters drained into a silicone tube connected to the external abdominal wall. The prosthesis was implanted in 25 dogs divided into three groups according to the urinary diversion performed, the kind of ureteral reimplant, suture, and positioning of the bladder prosthesis.

Main issues: Hydroureteronephrosis due to retractile scarring occurred at sites of ureteral anastomosis, and urinary infections arose secondary to the external connection. The prosthesis lasted for 4 weeks [22].

(2) The *Friedman model* [23] was a prosthesis created to store an acceptable volume of urine without an increase in intravesical pressure; it consisted of a thin-walled collapsible neo-bladder with a storage volume of 250 ml. Ureters and urethra were directly anastomosed to the prosthesis. All animals developed hydroureteronephrosis within 2 weeks of implant.

Main issue: Deposition of connective tissue around the prosthesis interfered with the dynamic properties of the device, with subsequent hydroureteronephrosis and renal failure.

(3) The *Abbou model* [24] (Fig. 1) and contemporaneous French models [25–27] employed an ovoid reservoir originating from a basic silicone rubber prosthesis with a capacity of 200–600 ml and equipped with a mechanical voiding system. In these models, orthotopically placed ureters were connected with the posterior surface of the prosthesis and included antireflux valves; the urethra was equipped with a sphincter. Alloplastic ureters and urethra were anastomosed to the native ones, and the command mechanism and connecting tube were implanted near to the iliac crest. Tissue–prosthesis connections were achieved using a porous biomaterial or polyethylene glued to the silicone. Clinical research was performed on dogs; each dog was killed, and histologic analysis of the neo-bladder was performed to determine the "tolerance" to the prosthesis.

Main issues: A thick fibrous capsule was found to have progressively formed around the prosthesis, interfering with the dynamic properties of the devices (expansion and emptying); furthermore, progression to hydronephrosis and renal failure was documented in each dog.

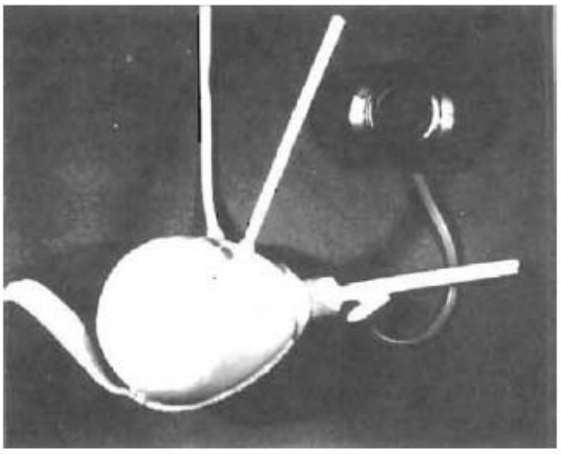

Fig. 1 One of the oldest alloplastic neo-bladders, the Abbou model: an ovoid prosthesis with its urethral sphincter (from reference [24])

(4) The *Stern model* [28] was a 200 ml total silicone prosthesis externally equipped with Dacron strips to anchor the reservoir to the retroperitoneal space. It was implanted in a total of 32 dogs.

Main issues: Hydroureteronephrosis and renal failure occurred due to urinary obstruction caused primarily by the intraluminal formation of papillomas at the ureteroprosthetic junction, probably as a result of the presence of pure silicone.

(5) The *Kline model* [29] (Fig. 2) was a bistable latex prosthesis with hydrogel lining the surface. It was implanted in the pelvic region, and emptying was provided by gravity, the weight of abdominal organs, and pressure caused by muscular tension in the abdominal wall. The *Belden* model [30] was a similar bistable prosthesis (with a rigid base and flexible top) tested in late 1990. The implanted prostheses were observed to void completely with a constant flow rate of 7–9 ml/s. The experiments were conducted on dogs, and functional results were achieved within quite a short time (9 days in the case of the Kline model), but no further analyses were done because problems similar to those mentioned above were foreseen in longer follow-up.

(6) The *Rigotti model* [31] and then the *Gleeson model* [32] were fixed-volume reservoirs designed to exceed, with their rigid scaffold, compressive forces resulting from connective deposition on the prosthesis and to reduce the risk of hydroureteronephrosis and renal failure. Emptying and voiding were allowed by an external air pump connected with the device.

Main issues: Infections occurred in association with the external connection, and cosmetic results were not good.

(7) The *Lutzeyer model* [33] was a single-chamber silicone prosthesis that rebounded to its original form after external compression. It was implanted in 17 sheep and worked well in approximately 50 % of them for about 7 months.

Main issue: The prosthesis was of limited use in humans because of the required subcutaneous implantation for compression.

(8) The *Gurpinar model* [34] was a fixed-volume reservoir anastomosed to native urethra and composed of two parts: an internal part made of silicone rubber

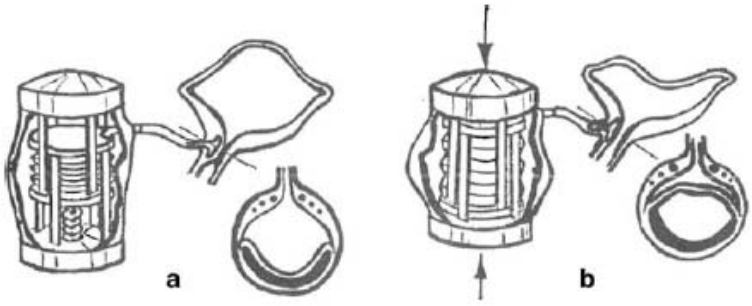

Fig. 2 The Kline model. Views of a urethral valve: **a** valve closed; **b** valve opened by manual pressure (from reference [29])

for urine and an external part made of a polytetrafluoroethylene polymer. It was hoped that this dual composition would avoid fibrous capsule formation that could be responsible for dynamic alteration in the device. Ureters were anastomosed to an ileal reservoir that was then connected to the prosthesis. This device needed an external connection to the abdominal wall to ensure anterograde drainage through the urethra.

Main issues: Infections due to the external connection, abundant residual volume of urine, ureteral dilatation due to chronic reflux, encrustation, and stone formation were the main causes of failure of this sophisticated device.

(9) The *Mayo Clinic model*, presented by O'Sullivan et al. [35, 36], was among the most sophisticated of the proposed models and was based on negative pressure drainage of urine from kidneys and active voiding. It consisted of two different shells: An inner one of silicone (230 ml) was surrounded by an external one of polysulfane (300 ml). Both were connected to the bladder neck with a 70-ml space between them. An internal spring mechanism generated negative pressure when compressed, facilitating filling, and a similar pressurized mechanism facilitated voiding. Ureters were intubated with an 8-Fr silicone catheter reinforced with a nylon spiral, and the prosthesis drained under positive pressure into a silicone tube inserted into the urethra. Watertight anastomosis was ensured by Dacron reinforcement at anastomosis sites. The prosthesis was implanted in four dogs.

Main issues: This overly complex model failed inexorably within a few weeks because of infections and the technical failure of various components.

(10) The so-called *Aachen model*, described by Rohrmann et al. [37], was another complex device and had the "longest" durability to date (>18 months in two sheep with no technical problems) (Fig. 3). It consisted of two separated subcutaneous and compressible elastic reservoirs, which drained urine from each kidney via a Dacron-covered silicone tube placed through the renal parenchyma like an "artificial ureter." Both reservoirs drained into the urethra through the interposition of a silicone tube with a "Y" form; external compression caused the positive pressure useful for voiding, with contemporaneous negative pressure within the reservoir to increase filling.

Main issue: Urinary leakage occurred owing to material failure (Dacron) at the anastomosis sites.

All of the above prostheses were of silicone or silicone based; none was implanted in humans (all were implanted in dogs or sheep), and none presented acceptable durability as a precursor to human application. Since the very first model, with few exceptions, meticulous monitoring of prosthesis function was undertaken, including the performance of urography and cystography. All animals were killed, and the prosthesis and host tissue were analyzed by a pathologist either at the end of the experiment or beforehand in the event of death or complications. None of the papers reviewed analyzed the cost of using the prosthesis for bladder replacement. An evaluation of costs of experimentation and the economic benefit that would derive from the ideal bladder prosthesis have, however, been undertaken relatively recently by McAteer et al. [38]. Conclusions of this interesting paper are that if the market sizes are deemed large (considering the number of patients treated per year), it could be worth proceeding with development of a new prosthesis.

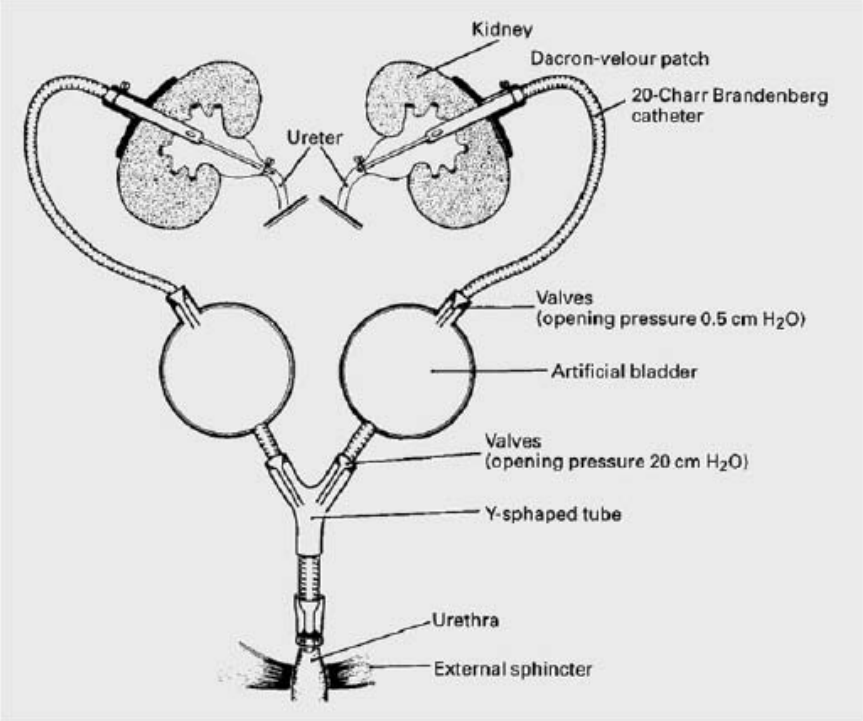

Fig. 3 The last alloplastic neo-bladder published: the Aachen (Rohrmann) model. Schematic view of two artificial bladders as they were implanted in sheep (from reference [37])

Discussion

As highlighted by the described results, many have already attempted to develop the ideal alloplastic neo-bladder, but without success. As mentioned above, the main causes of the failure of all these models were as follows: deposition of connective tissue, encrustations, infections, hydroureteronephrosis, leakages of urine from urethral or ureteral anastomosis, and problems related to biocompatibility. As regards the last mentioned, silicone has been the most widely used material, but it has been shown that silicone is not the ideal material for bladder substitution because of its low resistance to infection and encrustation. A critical and careful analysis of all the causes of failure as listed by Desgrandchamps and Griffith [39] might permit extrapolation of fundamental data and development of guidelines for future models. Ideally, a well-functioning reservoir for urine should be totally biocompatible and impermeable, have the capacity to store a sufficient volume of urine, permit filling and voluntary voiding without any pressure repercussions in the upper urinary tract, avoid any leakage of urine, resist encrustation and infection, be simple to implant and simple to remove/replace in the event of malfunction, and have an acceptable duration and cost.

Most of the results obtained with the biologic and bioengineered biomaterials are purely experimental. Although some promising results have been obtained, no biomaterial is currently available to replace bowel tissue. Such biomaterials may play a role in the future of organ replacement, but, unfortunately, results are still far from sufficiently compelling to warrant their daily use in urology. But why have so few clinical advances been made in this field of research over the last 60 years? Some of the reasons are inability to expand cells in vitro, inadequate vascularity of the implanted graft, and inadequacy of the currently available biomaterials.

A new alloplastic reservoir that meets these requirements could have enormous clinical/practical, physical, psychological, and economic benefits. The need to restore bowel function is the principal reason why duration of surgery and inpatient recovery time

are lengthy. Without the need for bowel surgery, the operation would entail simple reimplantation of ureters and urethra, easily halving the duration of surgery and the recovery time. Indirectly, this would permit a reduction in drug administration during surgery and hospitalization, thereby saving money. The resultant quicker turnover of patients would also permit a reduction in the waiting list for surgery. Furthermore, absence of use of bowel segments to restore bladder function would potentially reduce readmission for potential attendant complications. In psychological terms, an orthotopic prosthesis would also have evident benefits as regards avoidance of an external stoma [40–43]. The lack of a need for bowel surgery would permit more rapid restoration of physical activities and faster progression to adjuvant therapies on account of a better physical condition. It would also reduce the enormous economic cost incurred by every national health system owing to the following: (a) use of the instruments needed for bowel surgery (mechanical stapler, suture needles, etc.), (b) use of devices for the rest of the patient's life, such as external stoma appliances/bags (in patients with an external stoma), pads (in incontinent patients with orthotopic reconstruction), and bladder catheters (in patients performing self-catheterization), and (c) the need for subsequent interventions or readmission to hospital. Furthermore, the identification of a biomaterial that can be used as a surrogate for urothelium could be of value in the majority of pediatric pathologies that require the use of bowel (e.g., neurogenic bladder, bladder exstrophy). Such an ideal urothelial substitute could be easily tailored during surgery and used for bladder augmentation/substitution or as a graft for treatment of urethral strictures. Similarly, when the ureter is too short after ureterectomy, it could be replaced instead of doing a psoas bladder-hitch or a Boari bladder flap procedure with the attendant inherent technical difficulties and postoperative hazards. Finally, the identification of biomaterials that are resistant to infection and encrustation and have reasonable durability when in contact with urine may provide a new "family" of urologic devices, such as urethral or ureteral catheters usable in daily clinical practice.

Although the focus of this article is on complete bladder replacement with a prosthesis, it must be recognized that nowadays the functional results of urinary tract reconstructions, such as simple conduits, are acceptable and reasonably uniform. Bowel sampling for bladder substitution cannot represent the standard solution for future urology.

A critical analysis of urothelial substitutes reveals that owing to the lack of knowledge on biology, cell cultures, and tissue engineering, the first ones were totally alloplastic and silicone based, while more recently all attention has turned to the purely biologic materials. Perhaps, this is one of the key factors in our failure to achieve bladder substitution. Purely alloplastic models were tried without success, and we are still experimenting with purely biologic ones, again without significant success. Perhaps, the solution is a "hybrid" model, both biologic and alloplastic, so that one biomaterial can help to solve the problems associated with the other. Although many different alloplastic and biologic prostheses have been investigated during the past 50 years and more, the challenge of replacing this "simple" organ remains. While technical designs have become more sophisticated and new biomaterials with higher biocompatibility are now available, we are still looking for a real alternative to bowel sampling.

We hope that collaboration between urologists, engineers, biologists, and biomaterialists, with the incorporation of recent developments and know-how in tissue engineering, will lead to technical and practical remedies to previous problems and the identification of all the features required for the ideal bladder prosthesis. Whether or when a biomaterial with the above-described properties will become available for commercial and medical use remains an open question given past disappointments.

Conclusion

The pool of patients affected by bladder cancer is increasing, at least in part because of the rise in life expectancy. Radical cystectomy is the gold standard treatment for muscle-invasive bladder cancer, and bowel sampling for bladder substitution is still the only reconstructive alternative for such patients. Although artificial substitution of the bladder would be desirable owing to the physical, psychological, technical, and economic benefits, an alloplastic material with properties compatible to the human body has yet to be discovered. So, the answer to the question proposed in the title ("Are we making progress?")

must be either an unequivocal "no" or "insufficient." Indeed, the repeated failure of this therapeutic approach has been one of the factors prompting researchers to explore tissue engineering and other alternatives to conventional enterocystoplasty. Interprofessional collaboration, recent advances in technology, and innovations in tissue engineering may help in developing a suitable alloplastic or bioartificial prosthesis. Urologists, engineers, and industry all need to give this matter serious attention.

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