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RADICAL CYSTECTOMY AND URINARY DIVERSION: IS THERE A ROLE FOR BOWEL IN THE FUTURE?

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1. ABSTRACT

Transitional cell carcinoma (TCC) of the bladder is the most frequent malignancy of the urinary tract, and its incidence is rising. Depending on the stage of the tumor, the treatments for TCC of the bladder may vary from a conservative to a radical surgery. In case of invasive TCC of the bladder the gold standard treatment is represented by radical cystectomy with extended lymphadenectomy and configuration of a continent or non-continent pouch (conduit/pouch/neo-bladder). The reconstructive step of radical cystectomy is achieved with the use of bowel segments to restore bladder function. Unfortunately, the need for bowel has been universally considered to be the prime source of postoperative complications (i.e. fistulas, infections, metabolic disorders).

Since the 1960s urologists, scientists and the industry have been trying to obviate t he use of bowel with alternative synthetic and biologic materials to reconstruct the bladder. Despite the progress in technology and knowledge, the results have been quite discouraging. Since we are facing a rise in life expectancy with increase in both the elderly and bladder cancer population, treatment management in these patients represent an important challenge for present and future urology.

In this study we provide an analysis of problems deriving from using bowel for urinary bladder diversion, a comprehensive review of literature on pros and cons of previous alloplastic and biologic models and a critical analysis of possible benefits deriving from restoring urinary bladder function with an ideal synthetic prosthesis.

2. INTRODUCTION

The preservation or restitution of normal function, although not always is essential, is certainly the most desiderable goal to be obtained after any surgical procedure. In this respect, all operations for total removal of urinary bladder fail. This does not imply that the present's variety of urinary diversions after radical cystectomy (RC) are not satisfactory (for there is much evidence to the contrary), but that these operations do not attain the ideal of restoring the normal function of urinary bladder and urinary excretion.

More complex problems have always stimulated the creativity of surgeons. Urologist's "mission" to the preservation of the urinary tract, especially of the bladder, has guided the search for alternative methods of surgical reconstruction and physiological rehabilitation, using the intestine in many sophisticated surgical techniques and as the ideal alternative for substitute the urothelium.

During the last century, since 1851 exactly, urologic surgery has been advanced by the development of a great number of new surgical procedures, being the removal of urinary bladder and the reconstruction of this part of urinary tract, the urological challenge most studied, experimented and debated in literature. Facing the problem of a bladder which has lost his function owing to sclerosis of detrusor or in case of tuberculosis, or a bladder invaded by a tumor or any other problem which could not permit the partial resection of the organ, urologist were historically (and are) reduced to perform radical cystectomy always asking themselves with some distress "And now? Where can I place these 2 tubes?".

A simple question with about twenty different, valid and experimented answers. With the only exception of the vascular segment, every kind of intestinal segments was used as site of implant of ureters to reconstruct the urinary tract including stomach, ileum, cecum, colon, sigma, rectum and direct cutaneous diversion without the interpose of bowel [1].

Nowadays, the removal of the entire urinary bladder or the augmentation of his capacity is obtained exclusively with the use of bowel. While transitional cell carcinoma of the bladder represents the most frequent indication to the removal of the entire organ, pediatric pathologies and functional ones are the most frequent cause for augmentation or total substitution in no-oncological patients.

TCC of the bladder is the most common malignancy of the urinary tract, with a peak incidence in the adult and elderly population [2]. The gold standard treatment for muscle-invasive and any non-muscle invasive TCC of the bladder, even in the elderly population, is radical cystectomy, [3,4]. Nevertheless, radical cystectomy is a major surgical procedure performed with a curative intent and it is accompanied by a high rate of complications (17%–66%) [5-7]; its reconstructive part, which counts on sampling of bowel to restore urinary bladder function, is generally considered the main responsible for postoperative complications, prolonged hospital stay and readmission for complication's care. Such complications have an effect on patient's physical and psychological sphere and increase costs to the National Health system. Since we are facing a rise in life expectancy [8] with increase in both the elderly and bladder cancer population, treatment management in these patients represent 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 in absence of involuntary leakage of urine so, from a mechanical point of view, it can be considered as a sophisticated waterproof reservoir which fills and empties at low pressure [9].

Since first cystectomy for bladder tumor, performed in late 1887 by Bardenheuer of Cologne, the surgical challenge moved to replace appropriately the function of this organ so, progressively, we have seen the developing of surgical techniques with reconstruction of the urinary tract aimed to maintain control on voluntary voiding and continence, preserve renal function, being aesthetically acceptable and providing a good quality of life.

One of the aspects that have attracted the attention of the industry in the past and the present is tissue engineering for organ replacement. The idea of replacing bladder with a synthetic scuffle obviating the need for bowel for reconstruction and, therefore, ideally diminishing complications during and after radical cystectomy has always been attractive and source of investigation.

Urinary bladder substitutes can be divided into two groups: *Biologic* and *Alloplastic*. Biologic ones are all urothelial substitutes synthesized or developed from living organism, while alloplastic can be simply defined as all non-biological materials.

During these last two decades, progress made in regenerative medicine, cell and stem-cell biology, material sciences and tissue engineering, enabled researchers to develop cutting-edge technology leading to the “construction” of different tissue (10-19). Urology in particular focused his interest in developing a substitute of urothelium for both urinary bladder replacement and treatment of urethral stricture. On urinary bladder replacement, object of this paper, many were experimenting cultures of regenerated multilayer urothelium, being the Group of Atala the first publishing on an "engineered bladder tissue created with autologous cells usable for a cystoplasty" [11].

While preliminary results on urothelial substitutes and firsts biologic neo-bladders seems to be promising, drawbacks as cell mutations, biodegradability of the scaffold, the lack of direct vascular supply, long-term outcomes of the "transplanted" new organ, the still elevated costs together with ethical and oncological considerations, were discouraging recommending further steps in this direction [13-19]. Not least, these promising tissues substitutes of urothelium are unable to carry out one of the main function of urinary bladder: that of fill (be distensible) and void (be contractile) (Fig.1).

On the other side, alloplastic materials joined progressively the daily clinical practice of every speciality. 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 [20], 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 is not feasible yet due to infections and encrustations that result from the continual exposure to urine.

Despite different alloplastic and biologic prosthesis investigated during these last 60 years, the aim of replacing this "simple" organ has still not been targeted. Technical designs have become more sophisticated and new biomaterials with high biocompatibility are now available, but we are still looking for an alternative to bowel sampling.

In this study we provide an analysis of problems deriving from using bowel for urinary bladder diversion, a comprehensive review of literature on pros and cons of previous alloplastic and biologic models and a critical analysis of possible benefits deriving from restoring urinary bladder function with an ideal synthetic prosthesis.

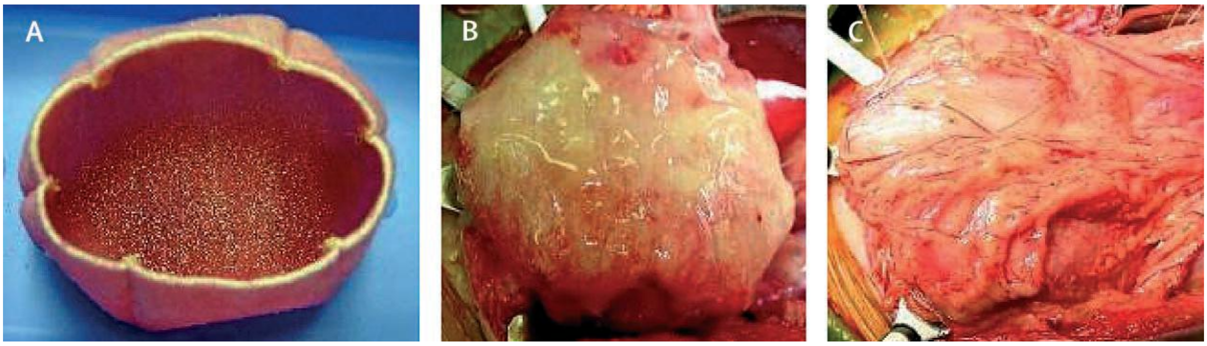

Figure 1: Construction of engineered bladder (From Reference 11)
Scaffold seeded with cells (A) and engineered bladder anastamosed to native bladder with 4–0 polyglycolic sutures (B); implant covered with fibrin glue and omentum (C).

3. MATERIAL AND METHODS

A comprehensive review of literature was performed using the Medline National Library of Medicine database and Google Scholar; key-words used were cystectomy and intestine/bowel, replacement, bladder substitution, urinary diversion, orthotopic neo-bladder, complications and cystectomy, uretero recto stomy, uretero sigma stomy, uretero cutaneous diversion, uretero bowel anastomosis, costs and cystectomy, organ replacement, artificial bladder, alloplastic material, biomaterial, tissue engineering. We considered suitable for our review all historical models of bladder substitute without the use of bowel, emphasizing alloplastic models. The review focused on articles between January 1st 1851 and September 1st 2010. Only articles in English were considered suitable for the study.

4. RESULTS

The first attempts of urinary diversion using a uretero-intestinal anastomosis were performed in bladder exstrophy. John Simon, in late 1851, was the first that suturing both ureters to the rectum caused a spontaneous fistula and subsequent uretero-recto-stomy [21]. Lloyd repeated this procedure the same year [22]. Both patients died for peritonitis after few days, so the interest in this derivation was diluted for many years.

From an anatomical standpoint three alternatives are presently used after cystectomy: 1) Abdominal diversion such us uretero-cutaneo-stomy, ileal or colonic conduit and various forms of a continent pouch; 2) Urethral diversion which includes various forms of gastrointestinal pouches attached to the urethra as a continent, orthotopic urinary diversion (neobladder, orthotopic bladder substitution); 3) Recto-sigmoid diversions, such as uretero-recto-stomy.

First's urinary bladder substitutions published included direct ureteral anastomosis with the bowel without the interruption of his continuity and with reconstructions such as uretero-recto or uretero-sigmoid or uretero-colon anastomosis, being uretero-sigmoid-stomy, perhaps, the oldest form of urinary diversion. It was realized primarily with a refluxive and then with an anti-reflux connection of ureters into the bowel [21,23]. Most of the indications for this procedure are now obsolete due to a high incidence of upper urinary tract infections and the long-term risk of developing colon cancer [24,25]. Bowel frequency and urge incontinence were additional side-effects of this type of urinary diversion; however, it may be possible to circumvent by interposing a segment of ileum between ureters and rectum or sigmoid in order to augment capacity and to avoid a direct interaction between urothelium and colonic mucosa together with faeces and urine [26]. The consideration on early and late complications, impose to consider different option in uretero-bowel technique opening of a new era in the surgery of urinary diversions: that of cutaneous diversion with an isolated segment of bowel. The first pioneer cited, Verhoogan M.D., performed in the late 1908, a "*Ureteral transplantation into an isolated segment of terminal ileum and ascending colon using an appendicostomy as a urethra*" [27]. All cutaneous diversions counts the separation of an isolated segment of bowel from intestinal continuity (with his vascular part) in which ureters are anastomized in his lower part while the upper is directly anastomized to the skin of the abdominal wall. Progressively, cutaneous diversions (non-orthotopic and non-continent) become, and maybe they actually are, the standard treatment for Bladder Cancer (BC) in many Centres of the World: a "rapid" technique with good functional and oncological long-term results.

The ileal-conduit is still an established option with well-known results however, up to 48% of the patients develop early complications including urinary tract infections, pyelonephritis, uretero-ileal leakage and stenosis [28]. The main complication in log-term follow-up studies are stoma complications in up to 24% of patients and functional and/or morphological changes of the upper urinary tract in up to 30% of cases [29-31]. An increase in complications was seen with increased follow up in one recent serie of 131 patients followed for a minimum of 5 years (median follow-up 98 months) [29]: the rate of complications increased from 45% at 5 years up to 94% in those surviving longer than 15 years. In this group, 50% and 38% of patients developed upper urinary tract changes and urolithiasis respectively.

Uretero-cutaneo-stomy is the simplest form of cutaneous diversion and it's considered as a safe procedure. This surgical technique is preferred in older and compromised patients who need cystectomy and a no longer staying in operating room [32,33]. Technically either one ureter to which the other shorter one is attached end-to-side is connected to the skin (transuretero-uretero-cutaneo-stomy) or both ureters are directly anastomosed to the skin. Due to the small diameter of the ureters, stoma stenosis has been observed more often than in intestinal stoma [32]. In a recent retrospective comparison with short or median follow-up of 16 months, the diversion-related complication rate was considerably lower for uretero-cutaneo-stomy compared to an ileal or colon conduit [34].

All this until last twenty years when, the psychological problems secondary to the distorted body image, to difficulties in having a ”normal” life because of the presence of the external urinary-stoma, and the need of the surgeon to propose something better functionally and, why not, aesthetically, lead urologists to the last step in urinary bladder reconstruction: that of the orthotopic neobladder reconstruction. This kind of reconstruction consist in the reconfiguration of an isolated segment of bowel (most often the terminal ileum) placed then orthotopically and directly anastomosed to ureters and urethra like in native bladder. In several large centres, this has become the diversion of choice in most patients undergoing cystectomy [35-37]. The empting of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis and sphincter relaxation. Early and late morbidity in up to 22% of the patients is reported [38-39]; long-term complications include diurnal (8-10%) and nocturnal incontinence (20-30%), uretero-intestinal stenosis (3-18%), urinary retention (4-12%), metabolic disorders and vitamin B12 deficiency in series with 1054 and more than 1,300 patients [36,40]. Urethral recurrence in neobladder patients seems rare (1.5-7% for both male and female patients) [36,41]. These results indicate that the choice of a neobladder both in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether a neobladder is better for quality of life compared to a non-continent urinary diversion [42-44].

Radical cystectomy (RC) with pelvic lymph node dissection represents the most complex and physically demanding (for both patient and surgeon) urological surgical procedure, provides the best cancer-specific survival for muscle-invasive urothelial cancer [45,46] and is the standard treatment, with 10 years recurrence-free survival rates of 50-59% and overall survival rates around 45% [45,47].

Unfortunately, the need for bowel use has been universally considered to be the prime source of postoperative complications with reported early complication (like wound infection, prolonged ileus, urinary tract infections, stoma necrosis, necrosis of diversion, rectal injury, fascial dehiscense, ureteroileal leakage, intestinal suture leakage, pelvic/abdominal abscess, bleeding, fistula, sepsis) rates of 16 % to 61 % ; late complications (urinary tract infections, herniation, diarrhea, dehidratation/metabolic disorders, uretero-ileal stricture, urethral stricture, fistula, stoma stenosis, lymphocele, ileus, vaginal prolapse, severe reflux) rates of 24 % to 66 % ; metabolic complications (hyperchloremic acidosis; hypochloremic acidosis; low vitamine B12, low folic acid); and perioperative mortality of 0.3 to 5.7 % [5-7, 28, 34, 48-52] (Tab. 1).

Table 1: Early postoperative complications reported in large series of radical cystectomy (2008–2009).

SERIES (past decade, around 100 patients)	SUMMARY	SHABSIGH et al, 2009	NOVARA, 2009	BOSTRÖM et al, 2009	MEYER et al, 2009	NIEUWENHUIJZEN et al, 2008
Patients	96-6577	1142	358	258	104	281
Study period		1995-2005	2002-2006	1986-2005	1994-2003	1990-2005
Centres		Single	SIngle	Single	Multi (3)	Single
Mortality at 30d	0,3-3,9	1,5	3,0	3,9	1	2,8
Minor complications	18,6-58	58	36	26	-	19
Major complications	4,9-25,5	9	13	11	-	24
One postoperative complications ore more	19-57	64	49	34	24	44
Operating time, h	4,9-6,4	6,4	5	3,8	5	-
Estimated blood loss	600-1700	1000	600	1700	1500	-
Intraoperative transfusion rate (U) and perioperative	1-66	66	15	2,9	2 (in 82%)	-
MEDICAL						
Deep vein thrombosis	0-5,3	5,3	4	1,2	-	1,4
Pulmonary embolism	0-6	3,2	-	0,8	2	2,5
Septicaemia	0-9,6	6,6	-	1,2	-	9,6
Acute respiratory distress	0-3,8	3,5	1	-	-	1,1
Pneumonia	0-7,8	3,9	4	1,9	4	7,8
Failure to wean from ventilator/on ventilator>48h postop	0-2,6	-	-	-	-	-
Pulm emb; clinical evidence of PE	0-1,9	-	-	-	-	-
Reintubation	0-1,9	-	-	-	-	-
Cardiac (general)	0-13	2,3	4	-	-	-
Myocardial infarction	0-4	1,3	1,5	1,9	-	2,1
Dysrhythmia	0-7,2	7,2	2	1,9	-	-
Cardiac arrest	0-1,3	-	-	-	-	-
Enterocolitis	0-8	3,4	-	-	-	-
Acute renal failure	0-7	-	-	-	-	-
UTI	0-12,8	9,9	-	5	1	12,8
Pyelonephritis	0-7,4	2,5	1	3,5	-	-
Metabolic imbalance/delirium	0-4	2	0,3	0,8	-	0,7
Skin ulcer/pressure sore	0-0,6	0,4	-	-	-	0,4
PEG leakage	0-0,4	-	-	-	-	0,4
Stroke (neurologic)	0-1,4	0,5	0,5	-	1	--
SURGICAL						
Periop blood transfusion rate	0-2,3	-	-	-	-	-
Postop haemorrhage; transfusion >4U after operation	0-9	9	-	-	1	1,4
Subileus (paralytic)	0-22,7	16	-	4	-	2,8
Constipation	0-12	2,6	12	-	-	-
GI (emesis, gastritis ulcer)	0-16,1	1,4	3	-	-	-
Small bowel obstruction	0-7	7	-	0,8	4	-
Enteroanastomosis leak	0-8,7	0,9	2	0,4	-	0,7
Required TotalParentNutrition	0-9	100	-	-	-	-
GI bleed	0-1,3	1,3	-	-	-	-
Pyrexia of unknow origin	0-7,0	4,8	7	-	-	-
Pelvic lymphocoele with intervention	0-3,5	1,3				
Pelvic lymphocele (no intervent.)	0-5,4	-	-	-	-	-
Precutaneous draiange	0.2,7	-	-	-	-	-
Peritonitis	0-0,8					
Wound infection, including superf.	0-15	9,3	-	0,8	4	8
Deep (fascial/muscle) inf						
Wound dehiscense	0-9	4,6	5	-	3	5
Secondary healing	0-8	-	3	-	-	-
With revision	0-5	-	2	-	-	-
Pelvic haematoma	0-2	-	1	-	-	-
Pelvic/abd abscess	0-4,4	4,4	-	-	-	1,1
Without revision	0-0,4	0,4	-	-	-	-
With revision	0-0,4	-	-	-	-	-
Diversion related	0-16	-	-	-	-	-
Urine leak/pouch leak/other	0-7,7	2,6	1	-	3	-
Stomal necrosis/structure	0-1,7	0,4	-	-	-	0,7
Diversion necrosis	0-0,7	-	-	-	-	0,7
Rectal injury	0-1,7	-	-	-	-	0,7
Fistula	0-4	-	0,5	-	-	0,4
Reoperation rate	0-17	3	10	8	8	-
Other	0-14,5	4	8,3	5	1	-

Since the 1960s urologists, scientists and the industry have been trying to obviate the use of bowel with alternative synthetic materials to reconstruct the bladder. Despite the progress in technology and knowledge, the results have been full quite discouraging.

Various prostheses have been proposed for replacement of the urinary bladder being silicone the most widely used material: a plastic reservoir and mechanical valves with abdominal drainage of urine via a silicone tube; silicone rubber prosthesis with transurethral drainage of urine; a bistable latex prosthesis; a silicone rubber reservoir and an artificial urethra equipped with a sphincter.

A variety of other prostheses which may entail the use of Gore-tex, may or may not be orthotopic, and range from the simple to the sophisticated and from the rigid to the distensible. The most successful of the prostheses is that described by Rohrmann et al. and the last one derives from 1996, from the Mayo Clinic.

Here we report one of the representative models of alloplastic bladder published during this last 60 years.

Bogash model [53]: in this first model of artificial bladder, presented in late 1960 by the pioneer in alloplastic substitution of the urinary bladder (M. Bogash), ureters drained into a silicone tube connected to the external abdominal wall. Cons: Hydroureteronephrosis due to retractile scarring in ureteral anastomosis sites and urinary infection secondary to the external connection ensued, and none of the devices survived for more than 4 weeks.

One of the most sophisticated models was that known as the *Mayo Clinic model* presented by O'Sullivan et al [54] (Fig. 2): the model 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) 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 silicon tube inserted into the urethra. Watertight anastomosis was ensured by Dacron reinforcement in anastomosis sites. Cons: this too complex model failed inexorably within a few weeks because of infections and technical failure of components.

Another complex device, but with the longest known life (more than 18 months in two animals with no technical problems), was that known as the *Aachen model* described by Rohrmann et al [55]. 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.

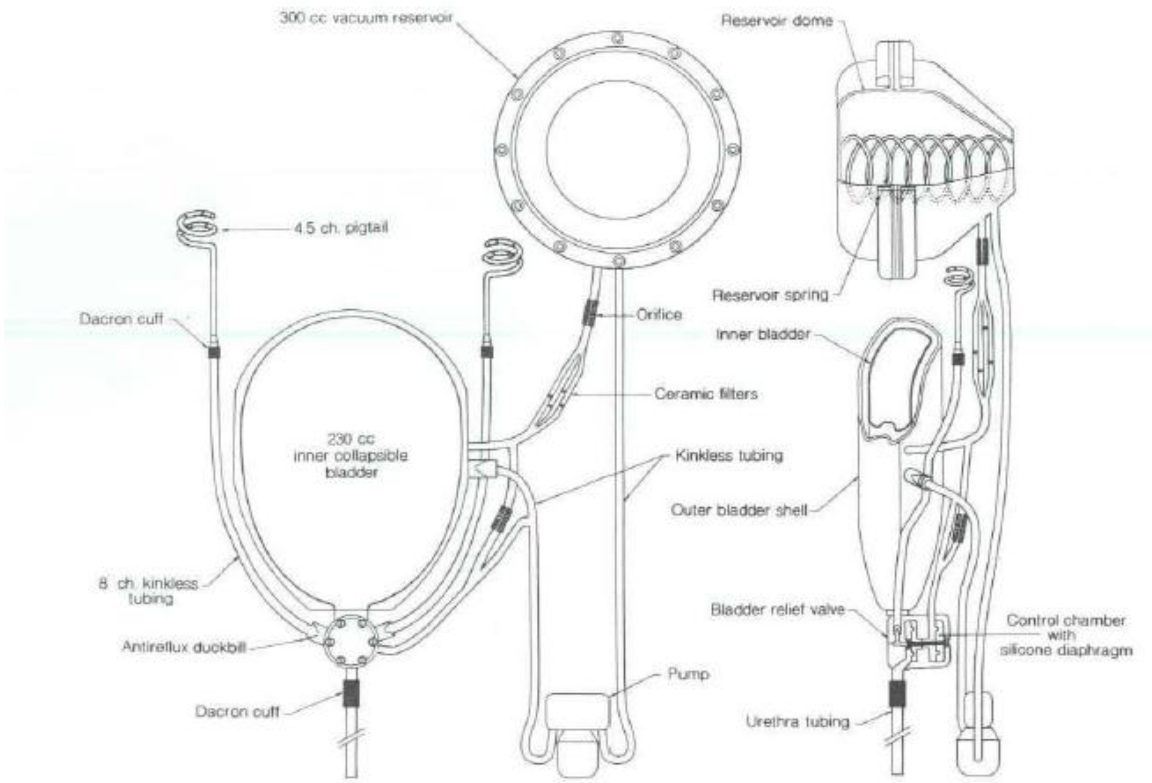

Figure 2: Anterior and lateral aspect of the Mayo clinic model (*From reference 54*)

5. DISCUSSION

As highlighted by the above results, many have already attempted to discover the ideal alloplastic neo-bladder however this result has yet to come. The main causes of failure of all these models were: deposition of connective tissue, encrustations, infections, hydroureteronephrosis, leakage of urine from urethral or ureteral anastomosis, and problems related to biocompatibility being silicone the most widely used material. Despite its biocompatibility, flexibility, and durability, 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 might permit extrapolation of fundamental data and development of guidelines for future models as listed by Desgrandchamps [56]. It is possible that scientific collaboration between engineers, biologists, and biomaterialists, with incorporation of recent developments and know-how in tissue engineering, would lead to technical and practical remedies to previous problems, and identification of all the features required for the ideal alloplastic bladder.

Ideally, a well-functioning reservoir for urine would be totally biocompatible and impermeable, 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 replace in case of malfunction, and have an acceptable duration.

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, orthotopic prosthesis would also have evident benefits respect to external stoma [57-60]. Avoiding bowel surgery physical activities would be more rapidly restored, with faster progression to adjuvant therapies on account of a better physical condition. The lack of need for bowel surgery would reduce too the enormous economic cost incurred by every National Health System owing to use of the instruments needed for bowel surgery (mechanical stapler, suture needles, etc.), use of devices such as external stoma appliances/bags (for patients with external stoma) or of pads (in incontinent patients with orthotopic reconstruction), and the need for subsequent interventions or readmission to the hospital. Secondary, the identification of a biomaterial which can be used as a surrogate for urothelium could be of value in the majority of the pediatric pathologies which require the use of bowel (e.g., neurogenic bladder, bladder exstrophy). Finally, the identification of such biomaterial resistant to infection, encrustation and with an acceptable duration in contact with urine, may provide a new “family” of urological devices.

The question remains as to whether and how a biomaterial with the above described properties will become available for commercial and medical use since up to now none is available.

6. CONCLUSIONS

The pool of patients affected by bladder cancer is increasing also 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 or biologic substitution of the bladder would be desirable due to the physical, psychological, technical, and economic benefits, an alloplastic or biologic material with compatible properties to the human body has yet to be discovered. So, the answer to the question proposed in the title (“is there a place for bowel in the future?”) must be unequivocal “no”, but not actually! 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. Inter-professional collaboration, recent advances in technology, and innovations in tissue engineering may help in developing suitable alloplastic prosthesis. Therefore both urologists, as well as engineers and the industry need to give this matter a serious attention.

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