Re: Tissue-Engineered Autologous Bladders for Patients Needing Cystoplasty
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Expert’s summary:
This paper reports the clinical results of augmentation cystoplasty undertaken with autologous tissue-engineered bladder substitutes in seven patients with poorly compliant neurogenic bladders due to congenital myelomeningocele.

Homologous bladder tissue was sampled from all patients by open biopsy 7–8 weeks before cystoplasty. Detrusor muscle cells were cultured and expanded in Dulbecco modified Eagle medium with 10% fetal bovine serum. Urothelial cells were expanded with keratinocyte growth medium. Cells required no more than five passages in each patient. The scaffolds used in the first four patients were made of homologous decellularised bladder submucosa; in the last three patients a biodegradable composite scaffold made of collagen and polyglycolic acid (PGA) was used. The total thickness of the scaffolds was 2.0 mm, and their size was fashioned according to volume calculations of the composite bladder according to the patient’s age and pelvic cavity dimensions. About 70 plates of each cell type (containing about $10^6$ cells per plate) were used to constitute one tissue-engineered bladder. Smooth muscle cells were seeded to the interior of the scaffold and urothelial cells were seeded to the exterior of the scaffold and urothelial cells were seeded to the interior at a concentration of $50 \times 10^6$ cells/cm$^2$. After several days of incubation and microscopic verification that cellular attachment to the scaffold had occurred, patients underwent augmentation cystoplasty. After bladder closure, fibrin glue was applied to the exterior of the bladder augmentate. Four patients received an additional omental wrap around the bladder to improve vascular support. Bladder cycling was started 3 weeks postoperatively. All patients were restarted on anticholinergic medication and continued to perform intermittent, clean self-catheterisation.

Follow-up ranged from 22–61 months and included urodynamic evaluations, protocol cystoscopies, and biopsies. In the early postoperative period, one patient had a fungal infection. There were no urinary leaks on cystography when the catheters were removed. Functionally, the average leak point pressure at capacity decreased by 12–56%. Postoperative bladder volume increased in the augmentations with an omental wrap, whereas it decreased in those without. Bladder compliance increased by 15–67%, with those with an omental wrap again having the better results. Renal function remained stable in all patients; two patients with preoperative reflux continued to be reflexive. No metabolic abnormalities were noted, and mucous production did not occur. Control cystoscopies and biopsies showed macroscopically normal bladder appearances as well as a three-layered bladder wall with urothelium, a submucosa, and a muscle layer at six to eight protocol investigations in each patient. One patient underwent standard intestinal augmentation cystoplasty for progressively increasing intravesical pressures on follow-up 4 years after the initial procedure.

Expert’s opinion:
This publication is the first-ever application of autologous tissue-engineered bladder substitution in humans and has rightly been heralded as a milestone in urologic tissue engineering [1]. It describes the first successful approach to a difficult concept successfully undertaken in humans and undoubtedly deserves considerable attention. The group of Atala and coworkers are well known for their successful experimental work in tissue-engineered bladder replacement in animals [2], and their pioneering clinical work was obviously well prepared. Different groups have for over 20 years worked on the problems of culturing and differentiating both urothelial and smooth muscle cells on various types of scaffolds to be used for tissue replacement in the lower urinary tract [3–5]. Atala’s group now present the first series of patients successfully operated on for whom some medium-term follow-up on clinical, functional, and histologic results is already available. The patient group chosen is a select group that safely allowed autologous cell culturing; the functional result to be achieved was an increase in bladder capacity only. Being a pilot study, the protocol used was changed several times, and the use of composite scaffolds as well as the addition of an omental wrap seems to have improved results, presumably because of better vascular support. However, whether the tissue-engineered bladder substitution will work in other patient groups, whether some innervation can ever be achieved, or whether whole bladder substitution will work is at present not foreseeable. It is also clear from this group’s work that, for a clinical routine, tissue-engineered cystoplasty is an extremely expensive technique, limiting its application to very few centres capable of financing such high-technology clinical research.
References


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Re: Radical Cystectomy after Bacillus Calmette-Guérin for High-Risk Ta, T1 and Carcinoma In Situ: Defining the Risk of Initial Bladder Preservation
Nieder AM, Simon MA, Kim SS, Nanoharan M, Soloway MS

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Expert’s summary:
The purpose of the authors of this paper is to evaluate the survival of a peculiar and homogeneous group of patients with high-risk noninvasive urothelial carcinoma. All patients had received intravesical bacillus Calmette-Guérin (BCG) and were later treated with radical cystectomy.

The paper deals with a retrospective study based on the survival of a series of 313 patients, 90 of whom underwent radical cystectomy after BCG treatment. The clinical and pathologic information of all cases that had been collected over the last 12 years is included.

The mean duration of follow-up from cystectomy was 32.1 mo, and the mean time from BCG to cystectomy was 27.9 mo. The disease-specific survival rate was similar according to early versus delayed cystectomy ($p = 0.9$), and the risk of progression related to more or less than 1 yr after BCG was 59% versus 36% ($p = 0.05$).

From these results the authors conclude that patients with high-grade tumours are at risk of dying, even if they undergo radical surgery. For this reason they claim that patients who receive BCG should know that they are at risk of disease progression and death. The proper time to indicate radical cystectomy in these patients remains difficult to establish.

Expert’s opinion:
The debate over the results of radical surgery in patients with high-risk noninvasive urothelial carcinomas is a topic of permanent argument [1,2].

The lack of biomolecular markers for a useful prognosis in daily clinical practice limits therapeutic decision-making and does not allow patients to be stratified in the best way. For this reason the risk of initial bladder preservation as a therapeutic option seems acceptable and should be adequately evaluated [1].

This worthwhile experience from the University of Miami tackles the problem using a homogeneous series of patients in whom cystectomy was performed by one surgeon, and BCG for Ta, T1, or CIS was given preoperatively to all 90 valuable patients. However, the number of courses of BCG was one of 6 wk in 54% of patients, and most of them were referred from elsewhere. The disease-specific survival at 5 yr was 65%, and carrying out of the cystectomy more or less than 1 yr after the first BCG course was not significantly related to survival. On the basis of the experience of this series, these patients carry a risk of death from bladder cancer, even after cystectomy.

The debate over early cystectomy as an initial bladder treatment in these particular patients remains open. Multiple factors will codetermine the final decision of the use of BCG and the timing for cystectomy. The results in the long-term survival with BCG range from 30–50% in these patients. On the other hand, disease-specific survival of 90% with early cystectomy has been reported [2]. With this retrospective analysis the authors were unable to ascertain the optimal time for cystectomy in patients who received BCG.

The adequate risk stratification for recurrence and progression in initially non-muscle-invasive lesions depends strongly on taking repeat transurethral resection (TUR) specimens. Repeat TUR is necessary for making the correct decision for our patients. In the particular case of patients with high-risk tumours, initial bladder preservation with conservative treatment can have a negative influence on the prognosis,