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Genital-Sparing Cystectomy versus Standard Urethral-Sparing Cystectomy Followed with Orthotopic Neobladder in Women with Bladder Cancer: Incidence and Causes of Hypercontinence with an Ultrastructure Study of Urethral Smooth Muscles

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Abstract

BACKGROUND: Bladder cancer in women is an indication for radical cystectomy (RC) when the tumour is confined muscle-invasive bladder cancer (MIBC) of T2 N0M0, or high risk progressive non-muscle invasive bladder cancer (NMIBC). Radical cystectomy is either genital-sparing cystectomy (GSC) or standard urethra-sparing cystectomy (USC) that is followed with orthotopic ileal neobladder (ONB). Post-operative chronic retention "Hypercontinence" had been reported in different series following URS or GSC and ONB. In long-term follow-up, we evaluated the functional outcome of women who developed hypercontinence after USC or GSC and ONB.

AIM: An ultrastructure study of female urethral smooth muscle was done to elucidate the underlying causes of hypercontinence.

MATERIAL AND METHODS: Retrospective study was conducted on 71 women who underwent RC and ONB, 45women had undergone USC, and 26 women had GSC, follow-up ranged from 5 to 15 years. Ultrastructure studies were done on 5 urethral biopsy specimens from 5 women who had hypercontinence, and 4 biopsies were from a normal control.

RESULTS: Follow-up showed that women who had undergone USC and ONB, 28.88% developed hypercontinence, where in the series of GSC and ONB three women out of 26 developed hypercontinence (7.80%). Three women who had hypercontinence following USC and ONB, they developed stones in the ileal pouch. Ultrastructure study of urethral smooth muscles in women who had hypercontinence showed organized collagen fibrils, absent myelin sheath, and non-detected lymphatic vessels. Normal urethra showed collagen fibrils within the interstitial matrix, preserved myelin sheath of nerve fibres, the presence of lymphatic vessels in the matrix.

CONCLUSION: The present study shoes that GSC with ONB leads to the minimal incidence of hypercontinence (7.80%), while standard USC lead to higher incidence (28.88%). Ultrastructure changes of the female urethra who had hypercontinence were fibrotic changes, loss of myelin sheath and minimal vascularity, their findings explains the underlying cause of hypercontinence and support the technique of GSC rather than the standard USC.

Introduction

Urothelial carcinoma of the bladder manifest as MIBC or NMIBC, an early MIBC T_2 N_0 M_0 and NMIBC which is progressive and not responding to BCG therapy are an indication for RC [1], [2]. Orthotopic ileal neobladder reconstruction after RC became a standard technique in female patients; the 5 years survival was reported to be 62-83% with mean follow-up ranging from 29-103 months [3]. Functional outcome of RC and ONB in female patients showed that the incidence of hypercontinence were (24%), these women had an excellent disease-specific survival which indicated that ONB is a safe and effective urinary diversion in women [4]. An ideal functional result of ONB is achieved when the neobladder gained normal voiding pattern which is four to six micturition daily with 3 to 4 hours interval and voiding urine volume of 250 to 500 ml at a low pressure [5]. Chronic urinary retention in women after ONB is defined as hypercontinence which is the persistent inability to completely empty the neobladder that lead to high volume post-voiding of residual urine

greater than 150 ml urine, in that case, the patient is instructed to do regular clean intermittent catheterisation (CIC) four to five times daily. The incidence of hypercontinence had been observed in different series that ranged between 12% to 58%; Stenzel et al., (12%), [6], Lee et al., (21%) [7], Granberg et al., (35%) [8], Stein et al., (39%) [3], Anderson et al., (31%) [9], Jentzmik et al., (58%) [10]. The high incidence of hypercontinence had been suggested to be due to lax of support of pelvic structures similar to pelvic organ prolapsed; the procedure of sacrocolopexy was advocated after cystectomy by suturing the anterior vaginal wall and vaginal apex to the anterior longitudinal ligament of the sacrum [11]. Treatment of pelvic floor disorders was recommended in women who developed hypercontinence following USC and ONB [12]. Unadjusted analysis showed that hypercontinence was not associated with any variable [13]. During cystectomy, the preservation of the uterus and attempted unilateral or bilateral nerve sparing, resulted in better functional outcome post-operatively that was attributed to the preservation of the urethral innervations [14]. Urinary function and sexual function appeared to be better among those patients undergone GSC and ONB [15]. In GSC the uterus, ovaries, fallopian tubes and vagina are preserved, the ileal neobladder pouch was fixed to the anterior longitudinal sacral ligament, follow- up showed good quality of life, sexual function, with reported low incidence of hypercontinence 7.80% [16]. Standard USC without nerve sparing attempt had led to a higher incidence of hypercontinence of 62.5% [17]. Ultrastructue characteristics of urethral smooth muscle in women with urinary incontinence were the finding of a smaller dense portion of sarcolemma denoting intrinsic sphincter deficiency [18].

The objective of the present study was to find out in long term follow-up the incidence of hypercontinence in the standard USC and GSC and to define by transmission electron microscopy the changes and pattern of female urethral smooth muscle in women developed hypercontinence.

Material and Methods

Patients

Institutional Review Board approval was obtained in the course of approval of PhD thesis on orthotopic ileal neobladder in female patients with bladder cancer who are eligible for RC and ONB for the treatment of neoplastic disease. Eligibility was confined disease of MIBC and/or progressive NMIB or refractory to treatment with BCG. Standard USC was performed in 45 women, GSC was performed in 26 women, both procedures were followed with orthotopic detubularised U shaped ileal neobladder according to the procedure of CameyII [19]. Operative technique of GSC aimed at preserving the uterus, fallopian tubes, ovaries, vagina, broad lateral ligaments, and attempted unilateral or bilateral nerve-sparing [16]. Uretero-ileal anastomosis in the detubularised U-shaped ileal neobladder was done using a dipping technique [20]. The ONB following GSC was fixed on both lateral sides to the lateral pelvic wall and anterior, presacral ligament to prevent anterior angulations of the ileal-urethral junction. Patients were followed every 3 months in the first year, every 6 months for 2 years, and annually after that, follow-up was ranging from 5 to 15 years. Patients who had hypercontinence were defined as their need for daily catheterisation to evacuate the neobladder. Women who had hypercontinence undergone diagnostic urethrocystoscopy, a urethral biopsy was taken from 5 patients for ultrastructure study. Urethral biopsy of normally continent women was obtained from cystectomy specimen of 4 women who undergone RC and ileal conduit diversion; urethral biopsy was taken from the cystectomy specimens. The 9 urethral biopsy specimens were examined by transmission electron microscopy. Clinical and functional data with follow-up for 5-15 years were obtained and analysed.

Transmission electron microscopy

The urethral biopsy specimens were immersed fixed in phosphate buffer containing 4% paraformaldehyde and 3% glutaraldehyde, pH 7.4, 4°C for 2 h at 4°C and rinsed in phosphate buffer. Tissue was immersed in 1% osmium tetroxide for 2 h at 4°C, rinsed in distilled water and incubated with uranyl acetate overnight. Tissue was dehydrated in a graded series of ethanol and embedded in Epon epoxy resin. Ultrathin sections were cut with an ultra microtome and immersed in uranyl acetate and then in lead citrate. Specimens were observed with a transmission electron microscope (FEI/Philips EM208S Transmission Electron Microscope (FEI Electron Optics BV, Eindhoven, Netherlands) The Smooth muscle morphologic characteristics were assessed from a systematic random sample of electron micrographs of the 5 biopsies from women with hypercontinence. A further 4 urethral biopsy specimens from continent women were similarly analyzed to confirm the findings of the initial study.

Results

Patients

A total of 71 women with mean age 52 years (range 23-72) and follow-up for 5-15 years were included in the study. Forty-five women underwent USC, 26 women had undergone GSC, and both

procedures were followed with detubularised U-shaped ileal neobladder urinary diversion. Genital-sparing cystectomy was done as it was requested by women patients desiring future fertility and normal sexual life. The 45 women undergone USC thirteen of them 28.88% developed hypercontinence and were on regular CIC four times daily, 4 women had recurrent urinary tract infection, and 3 developed big stone in the ileal pouch, the stones were removed surgically (Figure 1). The 26 Women who had undergone genital-sparing cystectomy and ONB, three of them 7.80% developed hypercontinence and they were on daily CIC.

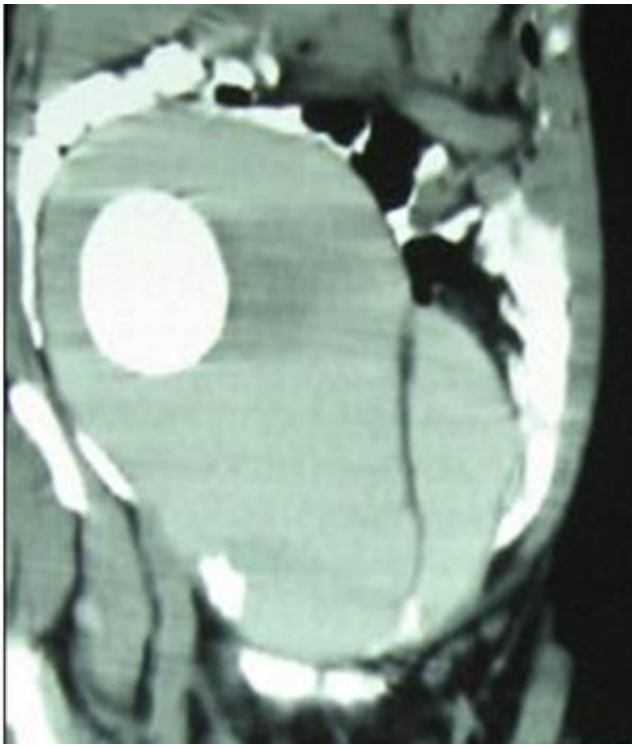

Figure 1: Image of computerised tomography of the urinary tract showing the stone in the ileal pouch in a woman having hypercontinence following standard urethral-sparing cystectomy and orthotopic neobladder

Transmission electron microscopy

Ultrastructural studies of the five urethral biopsy of women with hypercontinence following standard USC and ONB showed excess connective tissues with scattered myelinated nerve fibrils, few muscle fibrils where the scattered sarcolemma was smaller in comparison to normal control, the fibroblasts were characterized by lack of basal membrane (Figure 2d and 2e).

Ultrastructure of four women who had normal urethra and normal voiding function showed abundant smooth muscles, organised fibrils within interstitium matrix, myelin sheath of nerve fibrils consists of many regular membrane layers, and the vessels were in good integrity (Figure 2a, 2b, and 2c).

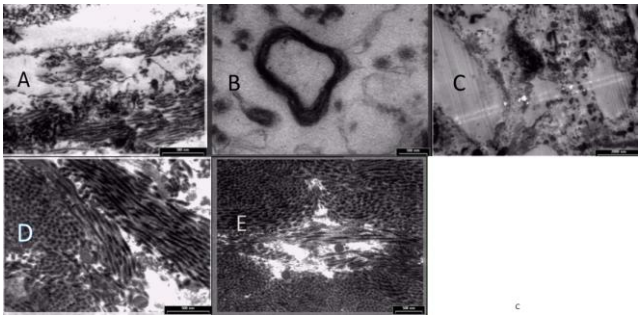

Figure 2: representative images of ultrastructure pattern of urethral smooth muscles in women with hypercontinence and normal urethra; A), B), and C) showing the pattern of normal urethral smooth muscles A) showing collagen fibrils within the interstitial matrix. B) Shows myelin sheath of nerve fibril that is consists of many regular membrane layers; C) Shows lymphatic like vessels in the matrix; D), and E) showing urethral ultra structure of women with hypercontinence, following standard urethral-sparing cystectomy and orthotopic neobladder showing areas of connective tissue with scattered myelinated nerve fibrils, and thin processes of fibroblasts that were characterized by lack of basal membrane

Discussion

Orthotopic ileal neobladder after RC in women has developed after many clinical series included standard cystectomy with urethral-sparing and genital-sparing cystectomy. Concerns remain about the problem of hypercontinence following RC and ONB. Here, we report difference incidences of hypercontinence following 2 operative techniques of RC, that was 28.88% among 45 whom undergone USC, this relatively low incidence is in accordance with results in other series that reported the incidence varied from12% to 24% [4], [6], [7], in other series they reported high incidence of 35% [8], 39% [3], and 31% [9], this wide variation in incidence of hypercontinence would be attributed to operative techniques, in our series the operative procedures were with intend of unilateral or bilateral preservation of neurovascular bundle. Fixation of neobladder to the lateral pelvic wall and anterior sacral ligament avoided angulations of the ileo-urethral angle to minimise the post-operative incidence of hypercontinence, that operative step is similar to the procedure of sacrocolopexy that had minimised the incidence of hypercontinence post operatively [11], [12]. Women whom underwent GSC the incidence of hypercontinence was 7.80%, these satisfactory results were due to the preservation of female genital organ, additionally preservation of ovaries maintained hormonal balance in premenopausal women and assessed in integrity of pelvic floor, the results of the present series of GSC with ONB are consistent with previous studies [15], [16]. Female urethral sphincter is located in the distal two-thirds of the urethra, branches from the pudendal nerve that supply the sphincter course deep to the endopelvic fascia and enter the urethra on lateral sides. During cystectomy,

careful dissection by avoiding distal dissection to bladder neck and preservation of endopelvic fascia would protect the urethral smooth muscles from neural and vascular denervation that will lead to post-operative incontinence or hypercontinencre. We studied by transmission electron microscopy the ultrastructural changed in smooth muscles of the urethra of women having hypercontinence following standard USC, we found that there were excess connective tissues with scattered myelinated nerve fibrils, few muscle fibrils where the scattered sarcolemma was smaller in comparison to normal control, the fibroblasts were characterized by a lack of basal membrane (Figure 2). Our finding indicated an insult during the dissection that leads to vascular and neural denervation of the smooth muscles and had lead to fibrosis, our results are in accordance with the findings in women with incontinence who had been studied by transmission electron microscopy and revealed that The electron-dense portion of the sarcolemma was smaller in urethral biopsy specimens taken from patients with intrinsic sphincter deficiency than in those from control subjects [18].

In conclusion, genital-sparing cystectomy in women with bladder cancer followed with orthotopic ileal neobladder provided good quality of life with a low incidence of post-operative chronic urinary retention, compared to the relatively higher incidence in standard technique; these findings are attributed to the preservation of neurovascular innervation to urethral smooth muscle in the GSC procedure. Ultrastructure analysis of urethral smooth muscles in women having hypercontinence following USC showed loss of myelin sheath, excess collagen fibrils, minimal muscle fibrils, which denoted affection of neurovascular supply. We recommended genital-sparing cystectomy when feasible.

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