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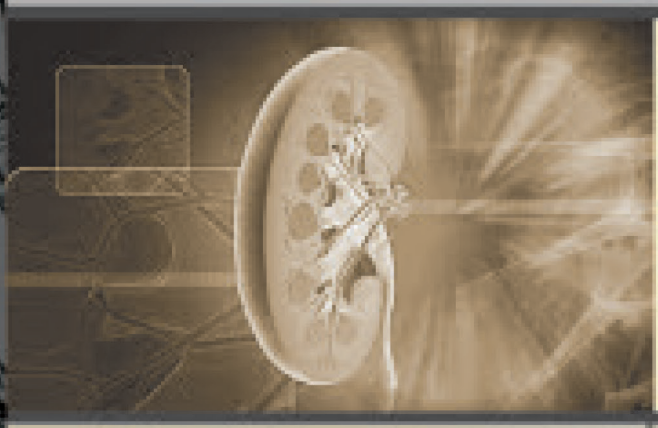

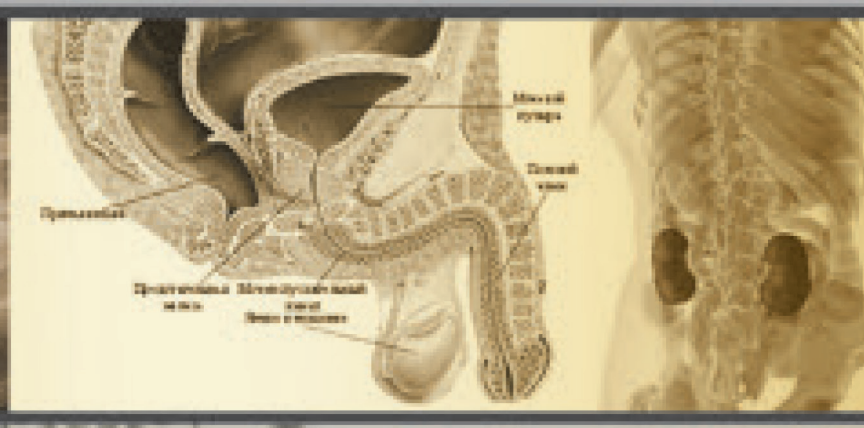

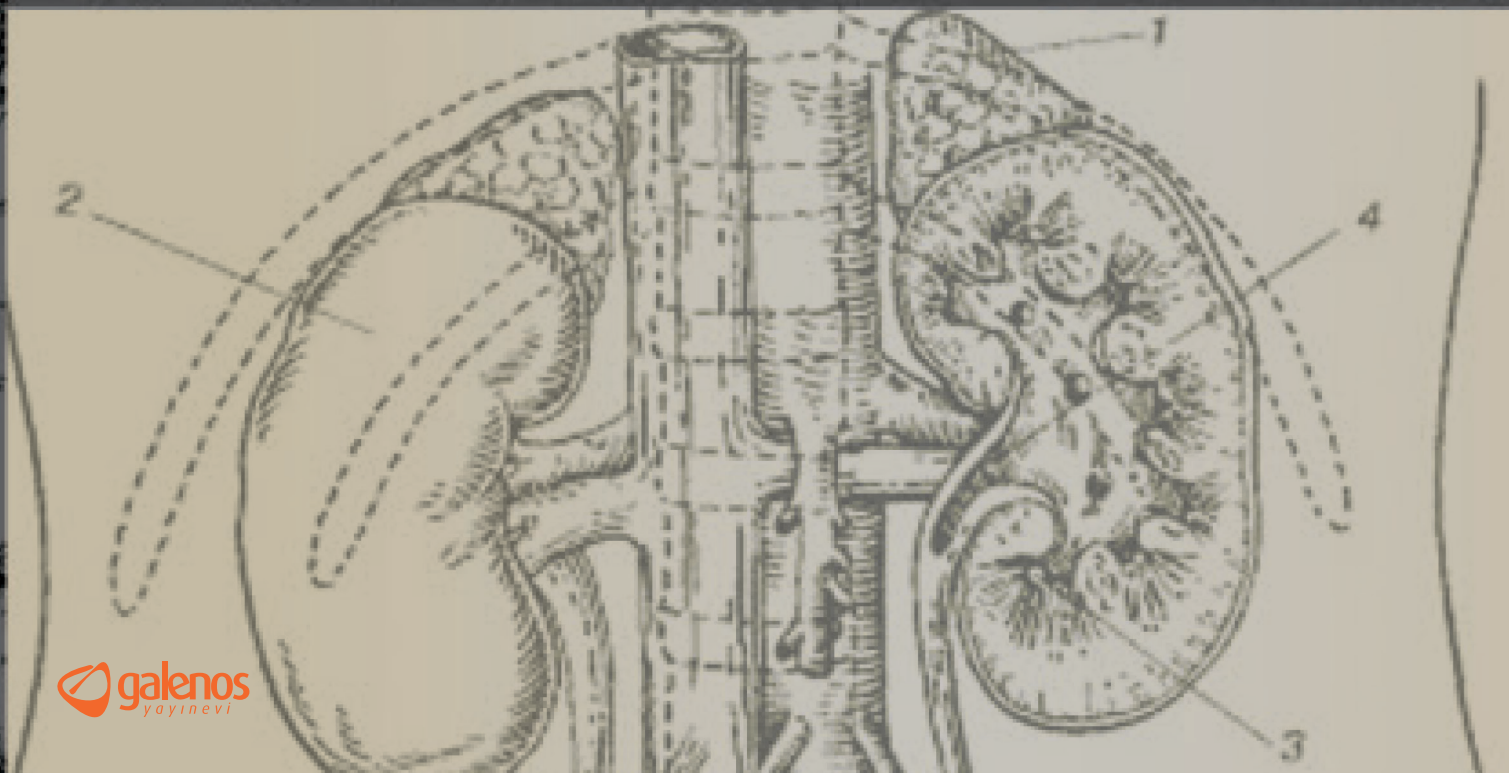

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2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

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Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

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CONTENTS

REVIEW

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The Clinical and Uropathological Aspects of Neuroendocrine Tumours of the Bladder: A Review

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What's known on the subject? and What does the study add?

Primary neuroendocrine tumors of the bladder are extremely rare tumors. Since metastatic tumors are seen more often, it is necessary to distinguish between primary and secondary tumors. Histopathological and immunohistochemical examination gains importance at this stage. With this review, it is aimed to improve the uropathological perspective and to guide the treatment to be given. At the same time, this review is emphasized that most neuroendocrine-like tumors do not have histological features compatible with neuroendocrine bladder tumors, but phenotypically resemble traditional urothelial carcinoma.

Abstract

Neuroendocrine tumours of the bladder are less common than other histologic types (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma), constituting 1% of malignant bladder cancers. Based on the "2016 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs", neuroendocrine tumours are classified into four subtypes: small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), well-differentiated neuroendocrine tumour (carcinoid tumour) and paraganglioma. SCNC is more common than other subtypes, and LCNC is exceedingly rare in the bladder. Although neuroendocrine tumours are not as common as neuroendocrine neoplasms of the lungs, the differential diagnosis of these tumours remains crucial and should be considered in uropathology. Neuroendocrine tumours of the bladder can present with distinctive morphology and grades, similar to their pulmonary counterparts. The knowledge of this diagnosis is critical to advance the uropathological field and accelerate drug development with inclusion, rather than exclusion, of patients with SCNC and other variants of neuroendocrine tumours of the bladder. Therefore, in this review, the bladder's clinical and uropathological aspects of neuroendocrine tumours are reviewed. This classification provides a useful platform to discuss the aetiology, pathogenesis, clinical and pathological characteristics and treatment of the neuroendocrine tumours of the urinary bladder. The overall prognosis of urinary bladder neuroendocrine tumours is worse than urothelial carcinoma. Various advances are expected in the clinical characterisation, prognostication and treatment of neuroendocrine tumours of the bladder with the technologies developed in genetic and cellular investigations.
Keywords: Bladder cancer, neuroendocrine tumours, small cell carcinoma, large cell neuroendocrine carcinoma

Introduction

Neuroendocrine tumours of the bladder are less common than the other histologic variants (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma) in the genitourinary system, constituting 1% of malign bladder cancers (1). Based on "2016 World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs", neuroendocrine tumours are classified into four subtypes: small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), well-differentiated neuroendocrine tumour (carcinoid tumour) and paraganglioma. LCNC is exceedingly rare in the bladder (2). Although the types of neuroendocrine tumours of the bladder are not as common as neuroendocrine neoplasms of the lungs, the differential diagnosis of these tumours is still crucial and should be considered in uropathology. The knowledge of this diagnosis is critical to advance the uropathological field and accelerate drug development with inclusion, rather than exclusion, of patients with SCNC and other variants of neuroendocrine tumours of the bladder. Therefore, in this review, the bladder's clinical and uropathological aspects of neuroendocrine tumours are reviewed.

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A. SCNC

SCNC, more commonly known as small cell carcinoma, is the most common malignant neuroendocrine neoplasia of the urothelium. It constitutes 0.5%-0.7% of all bladder carcinomas (3). Derived from the urothelium, SCNC has histologically similar features to those seen in the lung (4). However, it is a high-grade invasive disease. The overall 5-year survival rate is low, with reports ranging from 25% to as low as 8% (2,5-7). Patients are usually in the seventh or eighth decade of life. It is three times more common in men than in women (8).

1. Aetiology and Pathogenesis

SCNC has no known specific aetiology. Studies have shown that the neuroendocrine cells scattered in the normal bladder or metaplasia of the urothelium are derived from malignant transformation or multipotential urothelial stem cells (2,9,10).

Now, SCNC is believed to have a urothelial origin, determined by current molecular data. It has been demonstrated that it is frequently associated with other histological types of conventional urothelial carcinoma of the bladder. Since one of the same risk factors involved in urothelial carcinoma, mainly smoking, is also seen in SCNC, they are proposed to share the same origin (11,12).

Recently, routine standard-of-care DNA sequencing confirms and identifies SCNC as a distinct entity with a predictable mutation profile, similar to SCLC. RNA expression profiling differentiates pure SCNC from urothelial carcinoma (13). At the molecular level, bladder SCNC displays some chromosomal variations, such as inactivation of the tumour suppressor's p53 (encoded by the *TP53* gene) and retinoblastoma protein, pRb (encoded by the *RB1* gene), similar to that defined in lung SCNC (11,12). Besides this similarity, all SCNC of the bladder harbour promoter mutations of telomerase reverse transcriptase (TERT), which is frequently upregulated in many human cancers, but not identified in SCLC. Multiple studies have demonstrated that up to 70-80% of urothelial cancers carry the TERT promoter mutations regardless of grade, stage or location (14,15). Publications suggest that these promoters may be clinically measurable potential markers for the differential diagnosis of SCNC (11,14,16-18).

2. Clinical Characteristics

Macroscopic haematuria, dysuria and obstructive symptoms are the most common symptoms of SCNC. Metastases are frequently observed in the regional lymph nodes, and the bones, liver and lung (2,5,7). Brain metastases of SCNC are less common than those of the lung (6).

SCNC of the bladder generally arises in the lateral walls, the dome of the bladder (19-21).

3. Macroscopic and Microscopic Characteristics

SCNC usually appears as a single and sizeable polypoid mass. However, it can also be sessile, ulcerated and occasionally infiltrative. Most are invasive at least to the level of the muscularis propria. Histologically, SCNC tumours are arranged as sheets or islands of small to medium-sized cells with narrow cytoplasm, separated by the limited stroma. These cells have small, round to oval, overlapping nuclei with finely distributed chromatin, without prominent nucleoli (2) (Figure 1).

The Azzopardi effect, a histomorphologic phenomenon of incrustation of the blood vessel wall with basophilic nuclear material, indicates the tumour's high proliferative activity. Vascular invasion, mitosis and coagulative necrosis are common in SCNC (2,3).

For a tumour to be classified as SCNC histopathologically, small cell histology must be found in most of the tumour. Approximately 40-50% of cases have non-small cell carcinomas, such as carcinoma *in situ*, classical urothelial carcinoma, squamous cell carcinoma, adenocarcinoma and sarcomatoid carcinoma. The appearance of these morphologies does not exclude the diagnosis of SCNC (2,5,9,22).

Tumour cells immunohistochemically show both epithelial and neuroendocrine differentiation. Tumour cells are stained with synaptophysin, chromogranin and cytokeratin. Extensive staining is seen with Ki-67. Thyroid transcription factor-1 (TTF-1) staining occurs in half of the cases (23,24).

Metastases from other organs should be excluded to accept SCNC as a primary urinary bladder tumour. Differential diagnosis

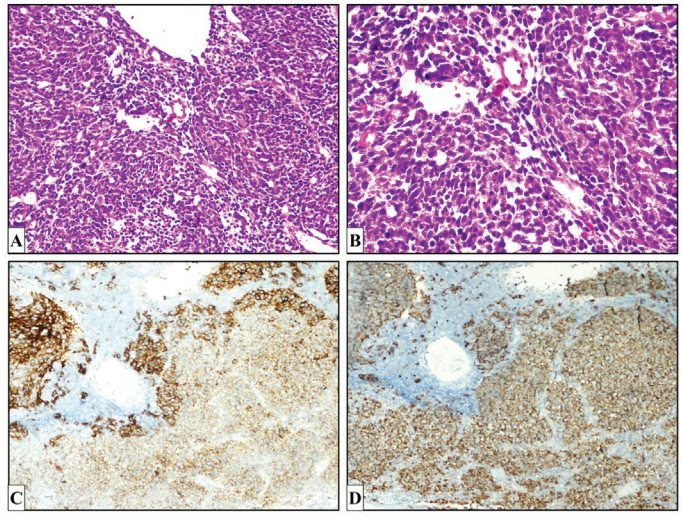

Figure 1. Small cells with ill-defined borders, scant cytoplasm, finely granular nuclear chromatin and absent nucleoli, H&E, (A) x100; malignant epithelial tumour- consisting with prominent nuclear moulding- are round and oval-shaped, H&E, (B) x200; micrographs of CD56 immunostainings, original magnification: (C) x100; micrographs of synaptophysin immunostainings, original magnification: (D) x100

should include lymphoma, lymphoepithelioma-like carcinoma, plasmacytoid carcinoma and poorly differentiated urothelial carcinoma. In these cases, immunostaining with TTF-1, GATA-3 and p63 would support the diagnosis of SCNC.

4. Treatment

Since SCNC is rare, the surgical or medical standard treatment strategies are not well established. Systemic chemotherapy, surgery and radiotherapy are the available treatment modalities. Some clinics perform radical cystectomy in non-metastatic cases. The chemotherapy applied is the same as that used in lung SCNC. In many clinics, adjuvant chemotherapy and radiotherapy or neoadjuvant chemotherapy and partial/radical cystectomy combinations are recommended. Due to its poor prognosis regardless of the treatment applied and low overall survival, research should be continued for new therapeutic agents specific for bladder SCNC (8).

B. LCNC

As a high-grade neuroendocrine tumour, the incidence of LCNC of the bladder is rare, with only a few case reports in the literature. Most cases have reported an aggressive clinical course, often with metastasis (25,26). The prognosis resembles that of SCNC.

1. Aetiology and Pathogenesis

The etiological factors for LCNC includes the personal or family history of cancer, possibly because of genetic predisposition, iatrogenic causes (chemotherapy- or radiotherapy-related factors e.g., postprostate-cancer external beam radiation therapy), or common environmental exposure (e.g., smoking) (27,28). As in SCNC pathogenesis, the most common hypothesis for LCNC include the origin of the multipotent urothelial stem cells that can differentiate into various cell types (29,30).

2. Clinical Characteristics

The clinical presentation of LCNC resembles conventional urothelial bladder carcinoma, with gross haematuria, which is a frequently observed symptom, and less frequently, dysuria and mucosuria, or no symptoms at presentation (29,31). Distant metastases have been reported mostly to the liver and lung (32-34). Both brain and skin metastases of the bladder LCNC have also been reported (29,33,35).

3. Macroscopic and Microscopic Characteristics

Macroscopically, LCNC presents in 4 cm diameter lesions, including nodular/polypoid, single, solid tumours, mostly located in the lateral bladder wall (2,8,29,36,37).

The tumour is a high-grade and poorly differentiated neoplasm exhibiting neuroendocrine features on H&E staining, high mitotic activity and necrosis, and immunohistochemical evidence of neuroendocrine differentiation.

Neoplastic cells are organised in sheet-like, trabecular palisading, or organoid nested growth patterns. Single cells are large, polygonal, with abundant cytoplasm and low nuclear to cytoplasmic ratio. Their nuclei are often large, polymorphic, oval, featuring coarse, granular or vesicular chromatin, often with prominent nucleoli (Figure 2). Occasional giant cells may be observed (38). Compared with SCNC, rosettes are often observed (2,26,29,39-41).

Some reported cases were associated with a component of conventional urothelial carcinoma. LCNCs may exist as either pure tumours or mixed forms with varying amounts of conventional urothelial and/or variant histology carcinomatous components (29).

4. Treatment

Although surgery alone is not recommended in LCNC cases, it plays an essential role in the accurate management of these cases. For radiotherapy, a bladder-sparing protocol seems to be less effective than radical surgery, but data remain contradictory (42). Since LCNC has potentially aggressive behaviour, early diagnosis and treatment with radical cystectomy and neoadjuvant or adjuvant chemotherapy may offer long-term control of a localised tumour. They may extend the overall survival of patients (34).

C. Well-differentiated Neuroendocrine Tumour (Carcinoid Tumour)

Well-differentiated neuroendocrine tumour, formerly named as carcinoid tumour, is a neuroendocrine neoplasm resulting from

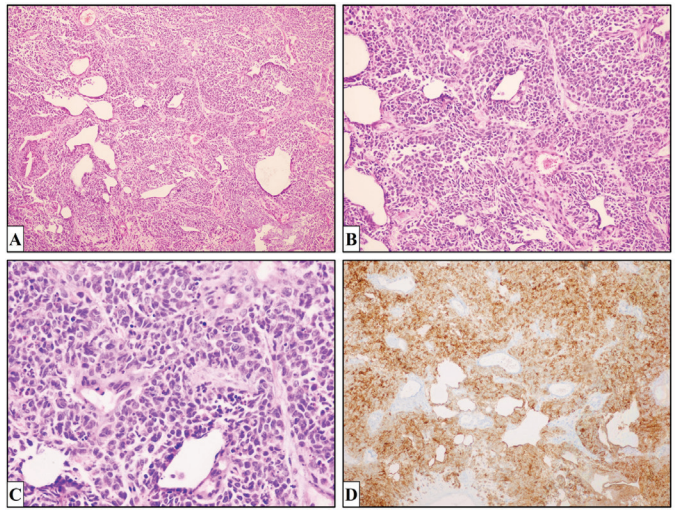

Figure 2. Histopathological section showing tumour tissue located inside the bladder, with neoplastic cells which are arranged in sheet-like, palisading, trabecular growth patterns, H&E, (A) x40; malignant cells with abundant cytoplasm are polygonal, large, and low nuclear to cytoplasmic ratio, H&E, (B) x100; nuclei with prominent nucleoli are polymorphic, oval, featuring coarse, vesicular chromatin, H&E, (C) x200; micrographs of chromogranin immunostainings, original magnification: (D) x100

isolated neuroendocrine cells located in the basal layer of the urothelium. These cells may become more abundant in reactive conditions. Well-differentiated neuroendocrine tumours have been rarely described in the true primary bladder (2,43). The patients were in the same age range associated with usual urothelial carcinoma.

The distinctive small well-differentiated neuroendocrine tumour is associated with a good prognosis. However, well-differentiated neuroendocrine tumours of the bladder may rarely present as muscle-invasive tumours, which must be distinguished from metastasis from other sites, such as the gastrointestinal tract (44).

1. Aetiology and Pathogenesis

Derived from the urothelium, well-differentiated neuroendocrine tumours are potentially malignant neuroendocrine tumours (45). These tumours' pathogenesis is believed to resemble SCNC of the bladder closely.

2. Clinical Characteristics

Haematuria is the most classical clinical presentation of well-differentiated neuroendocrine tumours, followed by irritative voiding symptoms. These tumours are generally observed in the bladder neck and trigone. Their relationship with Carcinoid syndrome has not been reported (2).

3. Macroscopic and Microscopic Characteristics

Well-differentiated neuroendocrine tumours characteristically present as small (mean diameter of 5 mm) polypoid masses restricted to the lamina propria. Histopathologically, these tumours exhibit the same typical features described at other sites, including uniform cells with round nuclei containing stippled chromatin, often with intracytoplasmic eosinophilic granules resembling Paneth cells. Hence, these lesions occasionally resemble adenocarcinoma. A distinctive feature of small well-differentiated neuroendocrine tumours is that the cells are arranged in a pseudoglandular pattern associated with cystitis cystica and cystitis glandularis, resulting in their misdiagnosis as a non-neoplastic condition. In rare cases, anastomosing trabeculae, nests and cords of cells without the prominent pseudoglandular morphology have been demonstrated in smaller superficial lesions. These well-differentiated neuroendocrine tumours are aggressive, express neuroendocrine markers immunohistochemically, and express prostate-specific acid phosphatase, but do not express other prostate markers (2,45).

4. Treatment

At present, there are no standard treatment guidelines for the management of well-differentiated neuroendocrine tumours. Metaiodobenzylguanidine therapy may offer some benefit in the adjuvant settings in specific cases, especially those considered not suitable for chemotherapy (2,45).

D. Paraganglioma

The primary paraganglioma is very rare among neuroendocrine tumours of the bladder, accounting for 0.05% of all bladder tumours. In contrast to SCNC and LCNC, paraganglioma is more common among females and whites (2,46).

1. Aetiology and Pathogenesis

Paraganglioma of the bladder derives from the paraganglion cells in the bladder wall. Although the exact aetiology is unknown, paraganglioma develops from the chromaffin tissue of the sympathetic nervous system (47).

2. Clinical Characteristics

Paraganglioma can locate in any part of the bladder and at any level of the bladder wall, preferring the detrusor muscle more. The most common sites of paraganglioma are the dome and trigone of the bladder (2). Paraganglioma patients may present with hypertension and hypertensive crisis during micturition and with headache, palpitation, blurred vision, and intermittent gross haematuria, based on the functional (i.e., secrete catecholamine) or non-functional features (48).

3. Macroscopic and Microscopic Characteristics

Cystoscopically, paragangliomas are well-circumscribed, dome-shaped/exophytic nodules smaller than 3.9-cm in size, covered with an intact mucosa but ulcerations can also exist. Unlike the extraadrenal ones found in other localisations, they exhibit malignant behaviour in a ratio of 20%. There is no definitive histopathological finding showing the distinction between malignant and benign disease. The presence of nuclear pleomorphism, mitosis and necrosis are unreliable findings in determining its clinical behaviour. The definitive malignancy criterion for these tumours is the presence of regional or distant metastases (2,49).

Histopathologically, paraganglioma consists of eosinophilic or granular cytoplasm and polygonal epithelioid or round cells. Nuclei are localised centrally, including vesicular and finely granular chromatin. Cells are present in an organoid/nest pattern called a Zellballen. These nests comprise the surrounding blood sinus and fibrous stroma (Figure 3). Immunohistochemically, cells are stained positive with chromogranin, synaptophysin and neuron-specific enolase. Sustentacular cells are stained with S100 (46,47).

4. Treatment

Complete resection is the most pivotal treatment of paraganglioma. However, there are other available strategies

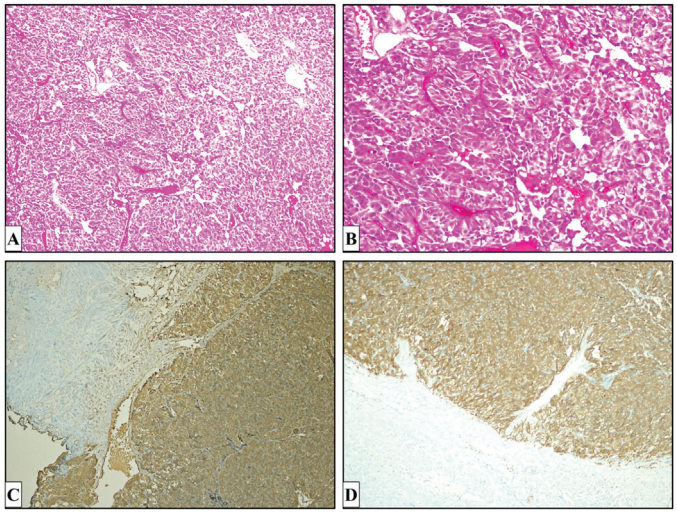

Figure 3. The trabecular pattern of neoplastic cells within a prominent vascular network, H&E, (A) x100; round cells with abundant eosinophilic finely granular cytoplasm, H&E, (B) x200; micrographs of chromogranin immunostainings, original magnification: (C) x100; micrographs of CD56 immunostainings, original magnification: (D) x100

depending on the disease stage, such as endourethral surgeries, including electrocision and laser resection, partial or radical cystectomy. Recently, minimally invasive surgery is increasingly replacing open surgery, which was generally performed in the past (47).

Conclusion

Neuroendocrine bladder tumours are rare variants, such as small cell or LCNC, well-differentiated neuroendocrine tumours, and paraganglioma varieties, based on 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organ classification system. This classification provides a useful platform to discuss the aetiology, pathogenesis, clinical and pathological characteristics of neuroendocrine tumours of the urinary bladder. The overall prognosis for urinary bladder neuroendocrine carcinomas is worse than the prognosis of urothelial carcinoma. In some cases, a small cell neuroendocrine-like subtype has been defined, having high expression of the neuronal marker and poor outcomes (50). Particularly, most neuroendocrine-like tumours did not have histological features consistent with neuroendocrine bladder tumours but were phenotypically similar to conventional urothelial carcinoma. Early and accurate differential diagnosis of neuroendocrine-like tumours may be possible by genomic analysis, which improves patient outcomes for the management of treatment, regardless of histological presentation (51).

Developing technologies in the genetic and cellular investigations, various advances are expected in the clinical characterisation, prognosis, and treatment of neuroendocrine tumours of the bladder. Based on the information reviewed on urology practice, diagnosis, treatment or follow-up, there is currently no recommended scientific guideline to use routinely. In summary, TUR-biopsy is the gold standard method in the differential diagnosis of neuroendocrine bladder tumours and immunohistochemical investigations.

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Bacillus Calmette-Guerin Increases Base Excision Repair in Bladder Cancer Cells

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What's known on the subject? and What does the study add?

Bacillus Calmette-Guerin (BCG) has been shown to increase reactive oxygen species and thus oxidative DNA damage in bladder cancer (BC) cells repaired by base excision repair (BER) pathway. Therefore, the BER capacity of BC cells could be an important factor in response to BCG therapy. We have demonstrated that BCG treatment increased the activities of uracil-initiated total BER and BER enzymes, uracil DNA glycosylase, 8-oxoguanine DNA glycosylase and DNA polymerase β, in the repair periods in BC transitional carcinoma cell line.

Abstract

Objective: Most patients with non-muscle-invasive bladder cancer (NMIBC) do not respond to intravesical Bacillus Calmette-Guerin (BCG) immunotherapy and have high risk of NMIBC recurrence and progression. In addition to its therapeutic effect which increases the local immune response, BCG also exerts an anti-tumour effect by increasing oxidative stress, and producing reactive oxygen species and oxidative DNA damage in bladder cancer (BC) cells. The oxidative DNA damage is repaired by base excision repair (BER) mechanism. Thus, BER capacity of BC cells could be an important factor in response to BCG therapy. Effects of BCG on the activity of BER in BC transitional carcinoma cell line, T24 have been investigated.
Materials and Methods: The uracil-initiated total BER and BER enzyme activities were measured in whole cell extracts with or without BCG treatment using a [γ-32P] adenosine triphosphate-labelled 51-mer DNA substrates.
Results: BCG treatment increased the activities of uracil-initiated total BER and BER enzymes, uracil DNA glycosylase and DNA polymerase β in 6 h and 24 h repair periods and increased the activity of 8-oxoguanine DNA glycosylase in 6 h repair in T24 BC cell line.
Conclusion: The enhanced BER activity in BC cells in response to BCG treatment could be an important factor in BCG resistance.
Keywords: Base excision repair, bladder cancer, Bacillus Calmette-Guerin

Introduction

Bladder cancer (BC) is the seventh most prevalent cancer in Turkiye and the ninth most common malignancy worldwide (1) (www.who.int). The majority of BC cases are non-muscle-invasive BC (NMIBC) and includes pathological stages Ta, T1 and carcinoma *in situ* (2). Approximately 30-80% of NMIBC will recur and approximately 10-20% will progress to muscle-invasive disease. Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy is the most efficient adjuvant therapy for intermediate and high risk NMIBC after transurethral resection of bladder tumour (3-5).

Approximately 50% of patients with NMIBC do not respond to intravesical BCG immunotherapy, making them at high risk of NMIBC recurrence and progression. The mechanism of action has not been fully understood; however, intravesical administration of BCG in NMIBC shows its effect through increasing the local immune response (6-8). It has also been demonstrated that BCG enhances oxidative stress in BC cells, which contributes to the anti-tumour efficacy of BCG (9,10). BCG increases the production of reactive oxygen species (ROS) such as hydrogen peroxide and superoxide radicals in BC cells (9,10), causing DNA damage repaired by base excision repair (BER) mechanism (9). BER protect the cells from cell death induced by DNA damaging

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agents, thus reducing the therapy efficacy. Therefore, the increased BER capacity is disadvantageous for cancer treatment. In addition, reduced BER activity and increased oxidatively induced DNA damage lead to genome instability and trigger the development of sporadic cancers (11), thus the BER capacity of BC cells could be an important factor in BCG therapy response.

The BER pathway is started with base excision by a DNA glycosylase enzyme, followed by the apurinic/apyrimidinic (AP) site cleavage by AP endonuclease 1 (APE1). Then, DNA polymerase β (Polβ) synthesises a single nucleotide to fill the gap, and DNA ligase seals the nick. DNA glycosylases are lesion-specific enzymes, for example, uracil DNA glycosylase (UDG), which is a major DNA glycosylase for uracil lesion and 8-oxoguanine DNA glycosylase (OGG1), which excises 8-hydroxy-7 and 8-dihydroguanine (8-oxoG) mainly (12). Several studies showed that changes in *BER* gene expression in BC tissues can affect the initiation and progression of BC (13-16). We have recently demonstrated that NMIBC tissues have increased BER activity compared to corresponding normal tissue from the same person, suggesting that enhanced BER activity may play a role in the aetiology and prognosis of NMIBC progression or response to genotoxic therapeutics (17). BCG increases oxidative stress and ROS production in BC cells (9,10) and causes DNA damage repaired by BER mechanism (9), thus effects of BCG on BER activity in T24 BC (transitional cell carcinoma) cell line has been investigated.

Materials and Methods

BCG Treatment to T24 BC Cell Line

T24 BC cell line was purchased from the American Type Culture Collection (ATCC HTB4; no ethical requirements for purchased cell lines). T24 cells are human urinary bladder transitional carcinoma epithelial cell line. T24 cell line were grown in Roswell Park Memorial Institute (RPMI) 1640 medium (Gibco-Life Technologies, USA) with 10% fetal bovine serum (FBS) (Gibco-Life Technologies, USA) and 1% Pen/Strep (Gibco-Life Technologies, USA). T24 cells were counted and plated in the RPMI growth medium at $3x10^5$ cells per plate and incubated overnight at 37 °C with 5% CO_2 incubator. The next day, T24 cells were treated with 3×10^6 CFU/mL BCG (OncoTICE contains live mycobacteria, USA) in RPMI medium containing 10% FBS and incubated 2 h at 37 °C with 5% CO_2 incubator (9,10). At the end of the incubation, BCG was removed and cultures were washed twice with 1X phosphate-buffered saline, and the new medium without BCG was replaced. Cells were incubated for 6 h and 24 h at 37 °C for repair. After the recovery (repair) period, cells were washed once with 1XPBS and were harvested for the whole cell lysates preparation.

Whole Cell Extracts Preparation

Whole cell extracts were prepared as previously described (17). Briefly, T24 cells were collected by centrifugation at 500 xg. Cell extracts were prepared using a Dounce glass-glass homogeniser in appropriate buffers. Protein concentration was determined with the Bio-Rad protein assay (Bio-Rad, USA).

Oligodeoxynucleotides

Oligodeoxynucleotide sequences are as follows: U = Uracil: 5′-GCTTAGCTTGGAATCGTATCATGTAUACTCGTGTGCCGTGTAGACCG TGCC-3′;OHG=8-oxoG:5′-GCTTAGCTTGGAATCGTATCATGTA OHGACTCGTGTGCCGTGTAGACCGTGCC3′;X=tetrahidrofuran: 5′-GCTTAGCTTGGAATCGTATCATGTAXACTCGTGTGCCGTGTAG ACCGTGCC-3′;1nt-gap:5′-GCTTAGCTTGGAATCGTATCATGTA ACTCGTGTGCCGTGTAGACCGTGCC-3′ and complementarystrand:3′-CGAATCGAACCT TAGCATAGTACATGTGAGCACACGGCACATCTGGCACGG-5′.

All oligodeoxynucleotides were purchased from DNA Technology, Denmark. Oligodeoxynucleotides were 5′-end-labelled using T4 polynucleotide kinase and [γ-^{32}P] adenosine triphosphate (Perkin Elmer, USA) as described before (17), and were annealed to the complementary strand by incubating at 90 °C for 5 min and slowly cooling to room temperature. Radiolabeled substrates were used in DNA glycosylase and APE1 activity assays.

Uracil-initiated Total BER Activity

The total BER reactions were performed as previously described (17). Briefly, reactions containing 2 µCi ^{32}P-dCTP (Perkin Elmer, USA), 100 fmol of uracil-containing double-stranded DNA substrate and BER buffer were initiated by 0.5 µg whole cell extracts and incubated at 37 °C for 1 h. Reactions were stopped by adding equal volume of formamide stop dye (90% formamide, 10 mM EDTA, 0.01% bromphenol blue and 0.01% xylene cyanol) and incubated at 37 °C for 10 min. Samples were then run on 20% denaturing polyacrylamide gel (PAGE-Urea) and visualised using a Typhoon FLA 9500 PhosphorImager. Results are presented as the mean ± standard deviation of three independent experiments.

Activities of DNA Glycosylases

Incision assays were performed as previously described (17). Briefly, uracil incision reactions containing uracil incision buffer and 100 fmol of ^{32}P-labelled uracil-containing DNA substrate were initiated by adding 0.25 µg whole cell extract and incubated at 37 °C for 30 min. The 8-oxoG incision reactions including 8-oxoG incision buffer and 50 fmol ^{32}P-labelled 8-oxoG-containing DNA substrate were initiated by adding 1 µg whole cell extracts and incubated at 37 °C for 30 min. Reactions were stopped by adding equal volume of formamide stop dye containing 100 mM NaOH and incubated at 75 °C for 15 min.

Samples were then run on 20% PAGE-Urea and visualised using a Typhoon FLA 9500 PhosphorImager. The percentage of incision was calculated as the amount of radioactivity present in the product band relative to the total radioactivity. Results were presented as the mean ± standard deviation of three independent experiments.

Gap-filling Assay

Single-nucleotide gap-filling reactions were performed as previously described (17). Reactions containing 100 fmol of 1nt gap duplex substrate and 2 µCi of 32P-dCTP (GE Healthcare, USA) were initiated by adding 0.5 µg whole cell extract and incubated at 37 °C for 1 h. Reactions were stopped by adding equal volume of formamide stop dye and incubated at 75 °C for 15 min. Samples were then run on 20% PAGE-Urea and visualised using a Typhoon FLA 9500 PhosphorImager. Results were presented as the mean ± standard deviation of three independent experiments. The incorporation of ^{32}P-dCTP was quantified as the increase in the signal intensity. Results were presented as the mean ± standard deviation of three independent experiments.

Results

A representative gel for activities of uracil-initiated total BER, uracil incision (UDG activity), 8-oxoG incision (OGG1 activity) and 1nt gap filling (Polβ activity) using T24 BC cell extracts with or without treatment of BCG is shown in Figures 1-4, respectively, and in Table 1. In uracil-initiated total BER assay, the efficiency of ^{32}P-dCMP incorporation in place of uracil within a 51-mer duplex substrate (Figure 1A-B, 26-mer band) and subsequent ligation (Figure 1A-B, 51-mer band) were determined. Quantitation of the total BER activity showed that incorporation in addition to ligation activities (Figure 1C) were increased at 6 h and 24 h repair periods compared to that of untreated cells (Figure 1C). UDG activity, which is the main enzyme for uracil incision, was increased at 6 h and 24 h repair periods compared to untreated cells (Figure 2A-B). OGG1 is the major DNA glycosylase for 8-oxoG incision. OGG1 activity was increased by 1.14-fold at 6 h repair period, whereas decreased by 1.53-fold at 24 h repair period (Figure 3A-B). One-nucleotide gap-filling activity of Polβ in T24 cells was measured. Polβ activities were increased at 6 h and 24 h repair periods compared to untreated cells (Figure 4A-B).

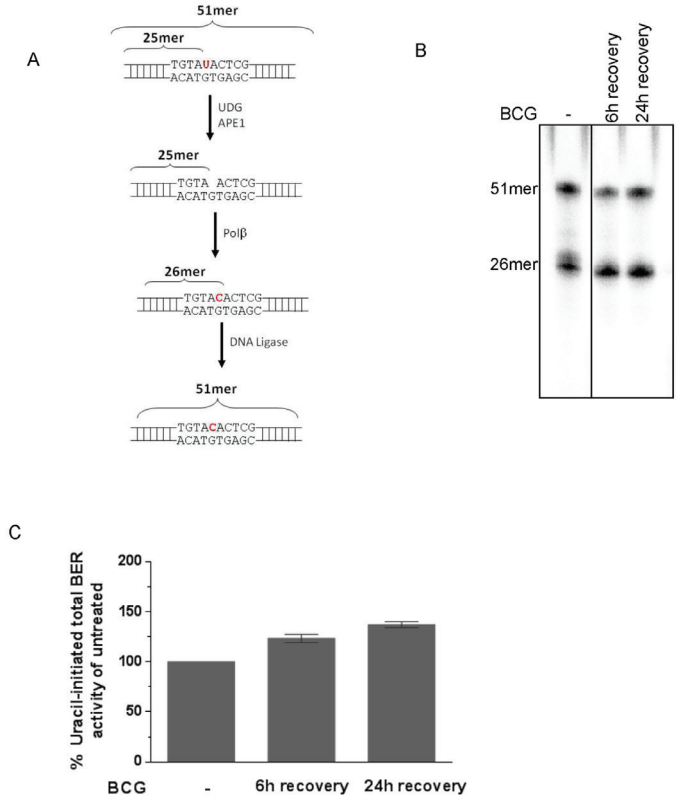

Figure 1. Effects of BCG treatment on the activities of uracil-initiated total BER in T24 BC cell line. A. Schematic of the uracil-initiated total BER assay. A 51mer DNA substrate containing a uracil at position 26; UDG removes the uracil base and APE1 incises the DNA strand 5' to the resulting AP site; Polβ synthesizes cytosine base and DNA ligase seals the DNA strand. B. A representative gel for uracil-initiated total BER activity showing products of 32P-dCTP incorporation (26mer) and ligation (51mer). The lower band represents 1-nt incorporation product (26mer) and the upper band represents the 51mer ligated product. C. Quantitation of the incorporaton plus ligation activities, percent of untreated. The data represent the average ± standard deviation of three independent experiments

BER: Base excision repair, BC: Bladder cancer, UDG: Uracil DNA glycosylase, BCG: Bacillus Calmette-Guerin, AP: Apurinic/apyrimidinic, APE1: AP endonuclease 1

Discussion

Several studies demonstrated that BCG causes bladder tumour cytotoxicity because of an immune response to BCG (7). However, BCG has also shown to increase oxidative stress including the generation of nitric oxide, lipid peroxidation, hydrogen peroxide and superoxide radicals in BC cells (9,10). Shah et al. (10) reported that oxidative stress generation in response to

Table 1. Percent BER activity of untreated cells

Recovery time after BCG treatment	Percent uracil-initiated total BER activity of untreated cells	Percent uracil incision of untreated cells	Percent 8-oxoG incision of untreated cells	Percent 1-nt incorporation of untreated cells
6 h recovery	123.36±4.15	121.49±0.76	114.26±0.09	146.63±6.13
24 h recovery	137.06±2.93	131.28±0.89	65.54±0.21	122.99±3.32

BER: Base excision repair, BCG: Bacillus Calmette-Guerin

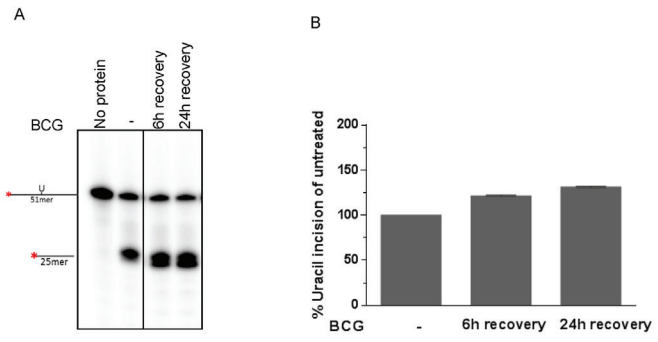

Figure 2. Effects of BCG treatment on the uracil incision in T24 BC cell line. A. Representative gel for uracil incision. Incision products are 25mer derived from cleaved 32P-labeled 51mer DNA substrate containing uracil at position 26. B. Quantitation of the uracil incision, percent of untreated. The data represent the average ± standard deviation of three independent experiments

BCG: Bacillus Calmette-Guerin, BC: Bladder cancer

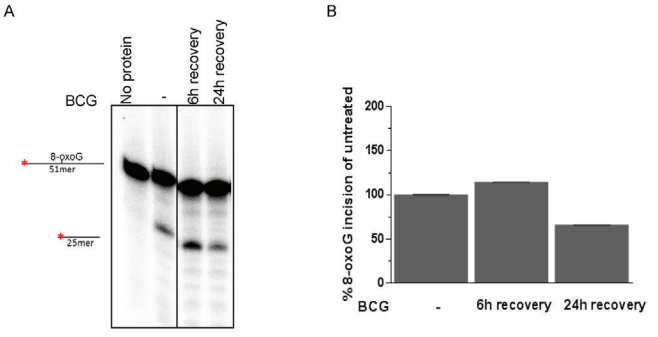

Figure 3. Effects of BCG treatment on the 8-oxoG incision in T24 BC cell line. A. Representative gel for 8-oxoG incision. Incision products are 25mer derived from cleaved 32P-labeled 51mer DNA substrate containing uracil 8-oxoG at position 26. B. Quantitation of the 8-oxoG incision, percent of untreated. The data represent the average ± standard deviation of three independent experiments

BCG: Bacillus Calmette-Guerin, BC: Bladder cancer

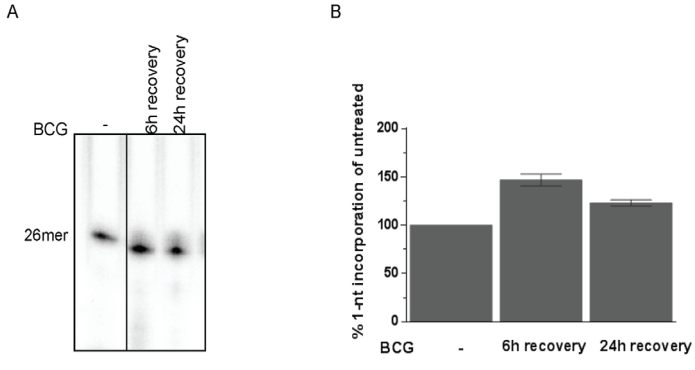

Figure 4. Effects of BCG treatment on single nucleotide gap-filling activity in T24 BC cell line. A. Representative gel for single nucleotide gap-filling activity showing products of 32P-dCTP incorporation. B. Quantitation of the single nucleotide gap-filling activity, percent of untreated. The data represent the average ± standard deviation of three independent experiments

BCG: Bacillus Calmette-Guerin, BC: Bladder cancer

BCG treatment in BC cells may contribute to BCG cytotoxicity. Patients with NMIBC who do not respond to intravesical BCG therapy are at high risk of NMIBC progression and recurrence (6-8). BCG causes oxidative DNA damage (9) repaired by BER mechanism and enhanced BER activity of cancer cells reduces the efficacy of the therapy (11); therefore, we have investigated whether BER activity in BC cells following BCG treatment is an important factor in BCG therapy resistance.

Our results demonstrated that activities of uracil-initiated total BER, UDG and Polβ in BC cells were increased in 6 h and 24 h repair periods. Consistent with this, Rahmat et al. (9) showed that the level of DNA damage is low in BC cells during BCG recovery. BCG increases the production of hydrogen peroxide and superoxide radicals in BC cells (9,10) that may induce the formation of 8-oxoG DNA lesions and cause an increase in the OGG1 activity at 6 h recovery. OGG1 activity has decreased at 24 h repair because of the possibility that 8-oxoG DNA lesions induced by BCG were repaired before the 24 h recovery period. These results indicate that increased total BER and BER enzymes activities in response to BCG treatment may contribute to BCG resistance.

Study Limitations

Limitation of the present study includes the cell-line based experiment. However, in order to determine the mechanisms of tumorigenesis, drug resistance/development and new biomarkers, the cell line-based experiments are useful. These experiments are necessary before retrospective and prospective studies.

Conclusion

The enhanced BER activity in BC cells following BCG treatment could be an important factor in BCG therapy resistance. In order to evaluate whether BER enzyme activities could be used as a biomarker for response to BCG, retrospective and prospective studies are still needed.

Ethics

Ethics Committee Approval: T24 BC cell line was purchased from the American Type Culture Collection (ATCC HTB4; no ethical requirements for purchased cell lines).

Informed Consent: T24 cells are human urinary bladder transitional carcinoma epithelial cell line.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.M., S.K., B.S., Design: M.M., S.K., B.S., Data Collection or Processing: M.M., S.K., B.S., Analysis or Interpretation: M.M.,

S.K., B.S., Literature Search: M.M., S.K., B.S., Writing: M.M., S.K., B.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Impact of Body Perception and Self-Esteem Status in Patients with Fournier's Gangrene

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What's known on the subject? and What does the study add?

No studies in literature have been reported about evaluating the psychological status of patients with Fournier's gangrene (FG). We evaluated the body perception and self-esteem status of patients, and determined that patients with FG have the tendency for low illness perception and high depression mood status.

Abstract

Objective: This study aimed to determine the body perception and self-esteem status of patients with Fournier's gangrene (FG) using the Body Cathexis scale (BCS) and Rosenberg's Depressed Mood subscale (RSES). Validity of the FG Severity index (FGSI), designed to determine disease severity in these patients, has also been evaluated.

Materials and Methods: A total of 44 men who underwent surgery for FG in authors' clinics between December 2009 and December 2018 were included in this study. Body perception and self-esteem status of patients with FG were measured by BCS and RSES in our study. The FGSI was evaluated and stratified by survival.

Results: The mean age of patients was 60±12 (range: 35-77) years. Out of 44 patients; 18.1% (n=8) died, whereas 81.9% (n=36) survived. The average BCS score of patients was 89±33 (range: 43-159). The mean BCS score of non-survivors was lower than that of survivors (59±25 and 94±31, respectively) (p=0.002). The average RSES score of patients was 2±1 (range: 0-5). No statistically significant difference noted between RSES scores of non-survivors and survivors (3±1 vs 2±1) (p=0.1). FGSI scores of non-survivor and survivor groups were similar (p=0.15).

Conclusion: Patients with FG have the tendency for low illness perception and high depression mood status. Also, FGSI score could not predict the disease severity and patients' survival. Follow-up of psychological status of these patients might yield higher treatment success and lower mortality rates.

Keywords: Fournier's gangrene, Rosenberg's Depressed Mood subscale, Body Cathexis scale

Introduction

Fournier's gangrene (FG), a life-threatening necrotising fasciitis of the genitourinary tract, which was first described by a French dermatologist Jean-Alfred Fournier in 1883 (1). Fournier reported the disease to be a pathology localised to the scrotum and penis, but FG is now known to have a potential to extend rapidly through the perineum, perianal tissues and even the anterior abdominal wall (1,2). The improving knowledge provided an algorithm through the aetiology and diagnosis to optimal medical and surgical treatment; however, mortality rates of FG still range between 10%-50% (3-6). The high mortality rate of FG has led to focus studies mainly on prognosis of the disease. However, none of studies in literature have aimed to release

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the psychological status of patients with FG. According to our observation, patients with FG are late in clinic admission, with perceptions problems about the disease.

This study aimed to determine the body perception and self-esteem status of patients with FG using the Body Cathexis scale (BCS) and Rosenberg's Depressed Mood subscale (RSES). The validity of the FG Severity index (FGSI), which was designed to determine disease severity in these patients, was also evaluated.

Materials and Methods

After the ethical committee approval (ANEAH: 2008-0044), a total of 44 men who underwent surgery for FG in authors' clinics between December 2009 and December 2018 were included in this study. All participants provided informed consent. The data enclosing medical history as well as biochemical and haematological laboratory study results were recorded upon admission. The timing and extent of surgical debridement were also indicated.

FG extension was calculated using nomogram, assessing the extent of burn injuries with the following: penis, scrotum and perineum 1% surface area each and each ischiorectal fossa is 2.5% (7). Preoperatively, all patients were administered with intravenous hydration and empirical antibiotherapy including 4 g/day of ceftriaxone and 1.5 g/day of metronidazole.

All patients underwent immediate debridement comprising resection of all necrotic skin, subcutaneous tissue, fascia and muscle until the viable tissue was revealed. Culture samples from necrotic tissues and abscess content were taken during debridement to determine the proper postoperative antibiotherapy. After the initial debridement, clean margined wounds of hemodynamically stable patients were debrided twice a day under local anaesthesia at the bedside. In case of a need for a broader debridement, patients were returned to the operation room after 24-48 hours from the first operation. Reconstruction and wound closure approaches (split thickness-skin grafting, rotational flaps and negative pressure wound therapy) were performed after obtaining the viable tissue beneath the granulation.

FGSI is a numerical scoring system utilised to determine the risk of mortality of patients with FG. FGSI consisted clinical (temperature, heart and respiratory rate) and laboratory (serum sodium, potassium, bicarbonate, creatinine level, haematocrit and leukocytic count) parameters. The degree of deviation from normal is graded from 0 to 4 for all parameters. FGSI score is obtained by the sum of all values (7). In this study, body perception and self to esteem status of patients with FG were measured by BCS and RSES. These forms were given to patients on the second postoperative day. BCS here is used to establish the association between the total score of the Dresden Body Image Questionnaire with body satisfaction, which was originally developed by Secord and Jourard (8) to assess the degree of satisfaction with parts and processes of the body. The original scale has 46 items, but most recent studies utilise a 40 to item version. Subjects evaluate body characteristics according to a 5 to point Likert scale, ranging from strongly negative to strongly positive, with higher scores reflecting greater body satisfaction. Orlandi et al. (9) stated that BCS is a useful instrument to address satisfaction with the body and judge the emphasis on bodily functions next to body parts to be an advantage. No cut off value is used. An overall score is achieved by summing the items. The highest total score is 200. RSES includes overall 63 items, with 12 sub to scales exploring aspects of self to esteem including self to confidence and self to liking. It contains positively worded items (e.g. "I feel that I have a number of good qualities") and negatively worded items Subscale of depression which includes 6 items. The highest total score is 6. A score between 0 and 2 is accepted as normal, with higher scores indicating a higher level of self-esteem. The depressive mood increases as the score gets higher (10). BCS and RSES were applied by one of the psychiatrist (C.K.).

Statistical Analysis

Statistical Package for Social Sciences for Windows (SPSS, Chicago, USA) version 13.0 was used for statistical analysis. Descriptive statistics were obtained as mean ± standard deviation. Data with normal distribution were compared with Student t-test, and data with abnormal distribution were compared with Mann-Whitney U test. Pearson correlation analysis was performed for the correlations. $P<0.05$ was considered statistically significant.

Results

The mean age of patients was 60±12 (range: 35-77) years. Out of 44 patients, 18.1% (n=8) died, whereas 81.9% (n=36) survived. Non-survivors were older than survivors (69±7 vs 58±11) (p=0.01).

Predisposing factors of patients were investigated. A total of 27 (61.3%) patients had uncontrolled diabetes mellitus (DM) (4 non-survivors and 23 survivors). Atherosclerotic coronary heart diseases were found in 10 patients (22%) (3 non-survivors and 7 survivors). Chronic renal failure was present in three patients (6.8%) (1 non-survivor and 2 survivors). Two patients (4.5%) (2 survivors) had anorectal fistula. Three patients (6.8%) (1 non-survivor and 2 survivors) had histories of hemorrhoidectomy operations. None of all patients had prior endourological interventions or indwelling urethral catheters upon admission.

The mean extent of the body surface area involved in the necrotising process (BSAI) was 2.3% ±2. No statistically significant difference was noted between the mean BSAI of non-survivors and survivors (1% ±0.4 vs 2.5% ±2) (p=0.06).

The mean admission FGSI score was 3±3 (range: 0-13). The FGSI scores of non-survivor and survivor groups were similar (p=0.15).

The average BCS score of patients was 89±33 (range: 43-159). The mean BCS score of non-survivors was lower than survivors (59±25 and 94±31, respectively, with p=0.002). The average RSES score of patients was 2±1 (range: 0-5). No statistically significant difference was noted between RSES scores of non-survivors and survi-vors (3±1 vs 2±1, p=0.1). No influence of age on the BCS and RSES scores (p>0.05) was noted.

In the correlation analysis, no correlations were found between BCS and RSES scores of patients (RBCS-RSES =-0.15). BSAI correlations of BCS and RSES scores were significant (pBCS-BSAI =0.02 vs pRSES- BSAI =0.01). BCS scores of patients had a negative correlation with FGSI scores (RBCS-FGSI =-0.8). However, no correlation between RSES and FGSI scores was found (RRSES-FGSI =-0.01 respectively).

Discussion

FG is a rapidly progressing necrotising fasciitis of the scrotum, penis, perineum and perianal regions. This rapid progress is a result of endarteritis obliterans due to microorganism invasion into the subcutaneous tissue with local oedema, hypoxia and decreased local blood supply. The reduced oxygen in tissues extinguishes bacterial proliferation, necrosis and digestion of fascial layers (2-4). DM, chronic renal failure, urethral stricture, genitourinary infections, anorectal infections, trauma and malignancies were reported as etiological factors of FG in several studies (5-7). In light of literature, DM is a major predisposing factor with an incidence rate of 46-76.9% (2,3). In accordance to literature, 61.3% of patients had uncontrolled DM in our study. Out of 8 patients who died, 1 had two illnesses and 6 had one illness. Additionally, 61.1% of survivors and 50% of non-survivors had DM. Hence, DM is the most common predisposing factor in our study.

Historically, FG was described as a disease of youth (1). Recently, the mean age of patients with FG has increased rapidly (3). In our study, the mean age of patients was 60.4 years. The effect of age on survival is controversial according to literature. Some authors reported no significant difference between ages of survivors and non-survivors. However, a large group of studies reported non-survivors' poor prognosis to be significantly associated with their older ages (11). In our study, non-survivors were significantly older than the survivors.

The effect of the extent of the necrotising tissue was investigated in various studies. We previously reported BSAI as one the most prognostic factor in patients with FG (6). Antipathetically, our study showed that BSAI have no negative effect on the outcome in patients (4). In contrast to our previous studies, BSAI had no predictive contribution on mortality of patients in the current study.

Improving knowledge about the aetiology, predisposing factors, diagnosis, treatment options and intensive care techniques have provided awareness for FG; however, mortality rates are still high (2-6). The mortality rate was 18.1% in our study. High mortality rates have promoted investigations on stratifying risks of mortality in patients with FG. FGSI was described by Laor to predict the prognosis, severity and mortality of the disease (7). Laor et al. (7) also determined 9 as a cutoff value. Patients with FGSI scores above 9 were expected to have more severe and fatal clinical outcomes. However, Tuncel et al. (5), reported the median admission FGSI scores were 2.5 and 5 for survivors and non-survivors, respectively, but the difference was not significant, and they found no relation between FGSI and mortality. In our study, we found no significant correlation between FGSI and mortality either.

Majority of studies in literature have been focused on comparisons of results of surviving and non-surviving patients with FG due to the fatality of the disease. However, psychological status of patients with FG has never been a centre of interest in literature before. Medical and psychological literatures use Leventhal's Common-Sense Model for the evaluation and treatment of patients (12). In this model, cognitions based on past experiences and interpretations of symptoms are all referred to as illness perception (12,13). Illness perception is known to increase patient's self-control in diseases (14). Illness perception has been analysed in several organ pathologies such as cardiovascular disorders (15), respiratory disorders (16) and musculoskeletal disorders e.g. fibromyalgia (17), sports injuries (18), Chronic Fatigue syndrome and rheumatoid arthritis (13). The level of negative reactions and feelings related to the disease and treatment decreases as the level of illness perception increases (19). Richters et al. (20) investigated the effect of positive surgical margins (PSM) on illness perception after radical prostatectomy in patients with prostate cancer. In their study, patients with PSM were reported to have a higher illness perception rates than patients with negative surgical margins which yield an increase in treatment benefit. BCS is a stable and consistent method for evaluating body and illness perception (9,21). Body cathexis is the impact of bodily features on the individual's psychological status (22). BCS was first developed by Secord and Jourard (8) in 1953. BCS was designed to assess the degree of satisfaction or dissatisfaction felt about sundry parts and processes of the body. Cam and Gumus. (23) reported

patients with higher body perception scores in BCS give more importance to their health. In our study, patients with FG had a mean BCS score of 88.8 which stands for a low body and illness perception. Non-survivors had a significantly higher BCS scores than the survivors. This data was interpreted as a lower understanding of FG to lead an unawareness of the developing highly aggressive necrotising disease. This lack of awareness also makes the treatment process challenging.

Body perception is one of the most determinative characteristics of self-esteem which represents the individual's self-confidence. Self-esteem provides an individual to maintain a healthy life and take care of himself and concern with his health as a result (23). In this study, patients with FG had a mean RSES score of 2.4 which repre-sents a tendency towards depression and decreased self-esteem. Stein reported depression's negative alterations on immune system in 1989 (24). Depression and increased depressed mood would be considered to have unfavourable effects on the developmental process of the disease when majority of predisposing factors of FG are thought to be related with decreased immunoreactivity (2). In several studies depression was revealed as an etiological factor in various chronic diseases such as inflammatory bowel disease and ulcerative colitis (25-28). Low self-esteem was also shown to have a diminished adherence to treatment (29).

To our knowledge, this is the first study that evaluates the illness, body perception and self-esteem status of patients with FG in literature. Our results pointed out that low body perception and self-esteem status might result to a late notice of their own illness and postpone their admission to a doctor. Our data should be supported by other prospective studies.

Conclusion

Our results show that patients with FG have the tendency for low illness perception and high depression mood status. Also, FGSI score could not predict the disease severity and patients' survival. We believe that close follow-up of psychological status of these patients might yield higher treatment success and lower mortality rates. These results need to be confirmed with further studies.

Ethics

Ethics Committee Approval: The study was approved by Ankara Numune Training and Research Hospital Ethics Committee (approval number: ANEAH: 2008-0044).

Informed Consent: All participants provided informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Supervision: A.T., Concept: M.B., Design: M.B., Data Collection or Processing: U.O., T.K., K.E., C.A., B.E., Analysis or Interpretation: E.K., M.B., C.K., Literature Search: Ö.G., Writing: E.K., M.B.

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The Effect of Individual Stone Dimensions on Stone Passage Rates

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What's known on the subject? and What does the study add?

It is well known that the size of a ureteric stone affects the required for spontaneous stone passage. However, it is uncertain which of the three dimensions of a ureteric stone best correlates with the time required for spontaneous stone passage. Our pilot study investigated this clinical question. Although elongated stones required marginally less time to pass spontaneously, our results did not demonstrate a statistically significant correlation between the time required for ureteric stones to pass spontaneously with any particular stone dimension.

Abstract

Objective: The aim of this study is to determine the relationship between each of the three dimensions of a ureteric stone and the passage rate and to identify ureteric stones with an oval/elongated shape and determine whether the stone passage rate was most closely related to any of the three stone dimensions.

Materials and Methods: A retrospective study of all patients who had a computed tomography scan with renal colic protocol at our hospital between January 1, 2016 and June 30, 2017. The maximum axial diameter, axial width, maximum coronal length and location of all stones were recorded. Patients were followed up for at least six months to ensure that the stones had been expelled or surgically removed.

Results: Ninety patients spontaneously passed their ureteric calculus, and 80 patients received surgery in this study. If the patients who received surgery within three days of diagnosis were excluded, the spontaneous stone passage rate was 81.1%. Of the 90 patients with spontaneous stone passage, 38.9%, 15.6% and 6.7% patients had stones with at least a 1.0, 1.5 and 2.0 mm difference between the maximum axial and coronal dimensions, respectively. Within the subset of calculi that passed within 90 days, these elongated calculi required between 3 and 6 less median days to pass than the more rounded calculi, although this was not statistically significant.

Conclusion: This study showed that in isolation, the individual dimension of a ureteric calculus did not significantly affect the time required to pass the calculus spontaneously. Elongated-shaped calculi were not common in this study.

Keywords: Tomography, spiral computed, renal colic, ureterolithiasis, urinary calculi

Introduction

The ureteric stone passage rate with medical expulsive therapy is related to stones' size. However, radiological reporting of ureteric stone sizes is not standardised. It is not uncommon to see some reports based on either axial or coronal dimensions, or both. Published studies commonly reported the maximum diameter in any plane as the official stone size. However, some studies used the maximum axial diameter as the official stone size (1-3). Coll et al. (3) also proved that the maximum stone diameter in the axial plane, not just the maximum diameter in any plane, correlated with the chance of spontaneous stone passage. The presumed reasoning behind this is that the axial surface area is more relevant than the coronal/sagittal length as it passes through the cylinder-shaped ureter. This factor becomes more of a dilemma in cases of an oval-shaped/elongated stone with individual dimensions bordering the size limit that determines primary surgical intervention or medical expulsive therapy.

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No study was found in the current literature to show a relationship between the chance of spontaneous stone passage and all three individual stone dimensions in the same study or the same cohort of patients. Hence, this study's primary objective was to determine the relationship between the three ureteric stone dimensions and their passage rates. Our secondary objective was to identify ureteric stones with an oval/elongated shape that were expelled and determine whether the stone passage rate was preferentially related to any of the three stone dimensions.

Materials and Methods

We performed a retrospective study of all patients who had a computed tomography (CT) scan with a renal colic protocol at our hospital between January 1, 2016, to June 30, 2017, that diagnosed ureterolithiasis. No ethics committee approval was sought for this study because of its retrospective and observational (non-interventional) nature. Patients with renal calculus only (i.e. without ureteric calculus) were excluded. All CT examinations were performed with a Philips Brilliance 64 CT scanner (Koninklijke Philips N.V., Amsterdam, the Netherlands). Axial images were obtained from the top of the kidneys to the base of the bladder using a 3 and 1-1.5 mm thickness for thick and thin slices, respectively. A pitch of 0.891 or 1.173 was used for thick slices depending on the patient's body habitus as per our Radiology Department's protocol. Coronal and sagittal views were obtained with 3 and 5 mm-thick slices, respectively. These digital radiological images were displayed using the AGFA IMPAX version 6.5.3.1509 PACS (picture archiving and communication system) software (Agfa-Gevaert N.V., Mortsel, Belgium). Images and reports of all scans were reviewed to ascertain whether ureteric calculi were found. Axial measurements of each stone were taken from the thin axial slices, not the thick slices. The maximum axial diameter, axial width and maximum coronal length of each imaged stone was also measured to the nearest 0.5 mm under magnification for this study by an author (DC), irrespective of the reported measurements on the official radiology report. This is because most of the official radiology reports at our institution did not contain all three dimensions. Hospital identification number, date of birth, gender, date of initial and follow-up scan and all stones' dimensions and location were recorded. Follow-up scans or subsequent surgeries for each patient were recorded for up to six months after initial diagnosis to determine whether the calculus has been expelled or removed, and the number of days between scans. If there was no record of follow-up scans or surgery, each of these patients was contacted by phone to check if there was a follow-up scan or surgery done outside of the public hospital system, whether they have seen the calculus expelled and the estimated date this occurred. If they reported the stone passage in the urine (either by catching it or viewing it), they did not require a repeat imaging study. If they have not had any follow-up scan and have not seen the calculus expelled, they were advised to have a urinary tract imaging study to exclude a retained calculus regardless of whether they had any renal colic. Patients with incomplete records of follow-up imaging or surgical intervention were excluded from this study. The principles of the Declaration of Helsinki (2013) were followed when conducting this study.

Statistical Analysis

Descriptive summaries were based on frequencies and means for categorical and continuous data, respectively. Time to event data was summarised using means and medians with corresponding 95% confidence intervals. Days to pass stones were estimated using Kaplan-Meier survival probabilities, with log-rank tests to test statistical differences between survival curves for individual dimensions. Datasets were analysed using Stata 15.0 (StataCorp LLC, College Station, Texas) and IBM SPSS version 24.0 (Armonk, NY). P-values <0.05 were considered statistically significant.

Results

During the study period, 170 patients satisfied the inclusion and exclusion criteria of this study. In total, 90 patients had spontaneously passed their ureteric stones during this study, which included 61 men and 29 women with a mean age of 51.6 years. Among them, 76 patients passed their calculi within 90 days. One of them had bilateral vesicoureteric junction (VUJ) ureteric calculi. Eighty patients required surgical treatment for their ureteric stones, eight of which were bilateral stones or two stones in one ureter. The rate of spontaneous stone passage was 52.9% (90/170). Of these 80 operated patients, 59 were operated within three days of diagnosis. Retrospectively, this indicated that 111 patients were given at least four days for spontaneous stone passage, which was successful in 90 (81.1%) and failed in 21 (18.9%) patients who eventually required surgical calculi removal. The majority (44/91, with separate bilateral VUJ stones) passed stones that were located at the VUJ (48.4%) and the distal ureter (26.4%) at initial diagnosis. The median number of days required between the initial and follow-up scan or the date when the patient reportedly expelled the calculus was 38.0 days (range, 1-312 days). If only stones that passed within 90 days were analysed, the median number of days for stone passage was 32 days. The median size of expelled calculi in the maximum axial diameter, axial width and maximum coronal length were 4.1, 3.0 and 4.0 mm, respectively. On the other hand, all operated calculi's median size dimensions were 6.8, 5.0 and 7.0 mm, respectively.

In all patients who passed their calculi, there was no statistically significant difference in the time required to pass each calculus (Figure 1). Calculi with maximum axial, axial width and maximum

coronal diameters up to the median size required a similar number of days to pass spontaneously, with no statistically significant difference. This finding was also present for calculi with dimensions greater than the median size. A similar result was found for the subset of patients who passed their calculi within 90 days (Figure 2).

The stones of interest in this study were those with a more elongated or oval-shaped profile. These stones were identified by selecting stones with at least a 1.0, 1.5 and 2.0 mm difference between the maximum axial and coronal dimensions. Respectively, there were 35 (38.9%), 14 (15.6%) and 6 (6.7%) patients with such stones that passed spontaneously in the study. The log-rank test did not reveal a statistical correlation between the difference in maximum axial and coronal dimensions and the time required to pass these stones (Tables 1 and 2). Within the subset of calculi that passed within 90 days, these elongated calculi required between three and six less median days to pass than the more rounded calculi. However, this finding was not statistically significant across the calculi subset with a 1.0, 1.5 and 2.0 mm difference between the maximum axial and maximum coronal diameters (Tables 1 and 2).

Discussion

Radiological reporting of ureteric stone dimensions may not be standardised based on our literature search. Although it is sensible to assume that the oft-reported stone size in the medical literature reflects the largest diameter in any plane, some studies specifically reported stone size as the maximum axial diameter instead (1-3). This inconsistency may create confusion when interpreting research findings as oval-shaped/elongated stones are not uncommon. A literature search of studies published between 2007 and 2016 found only three non-case report studies that specifically measured the maximum axial and coronal dimensions of ureteric stones and these stones' passage rate (4-6). However, Nazim et al. (4) did not specifically study the effect of oval-shaped/elongated stones and whether their passage rate corresponds to the axial or coronal diameters. In contrast, both Furyk et al. (5) and Pickard et al. (6) used only the maximum dimension in any plane and did not separate the axial and coronal diameters for analysis. Only two studies were found that measured all three dimensions of ureteric calculi, but neither of these studies monitored the stone passage rate (7,8).

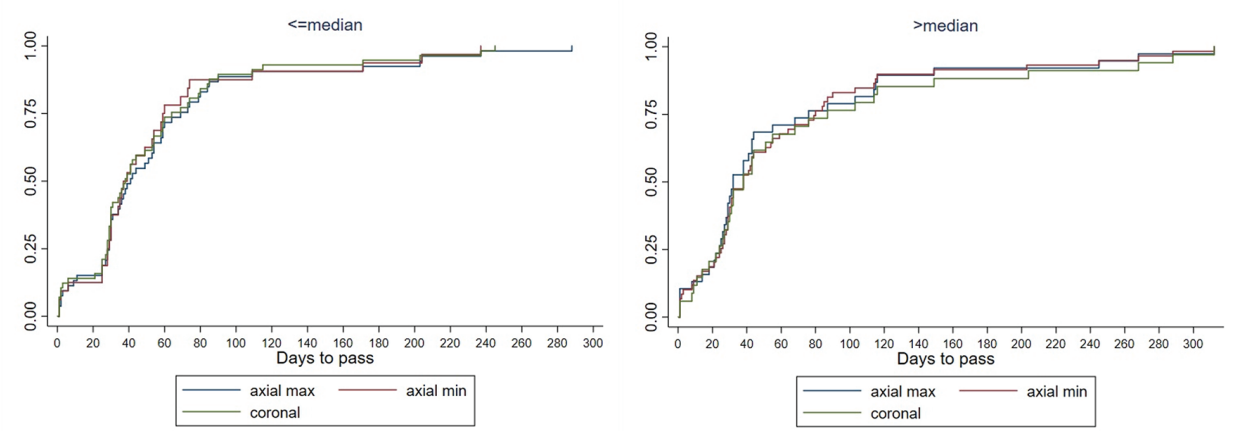

Figure 1. Kaplan-Meier inverted survival curve showing days to pass calculus (n=91) by dimension for calculi up to and exceeding median cut-off sizes

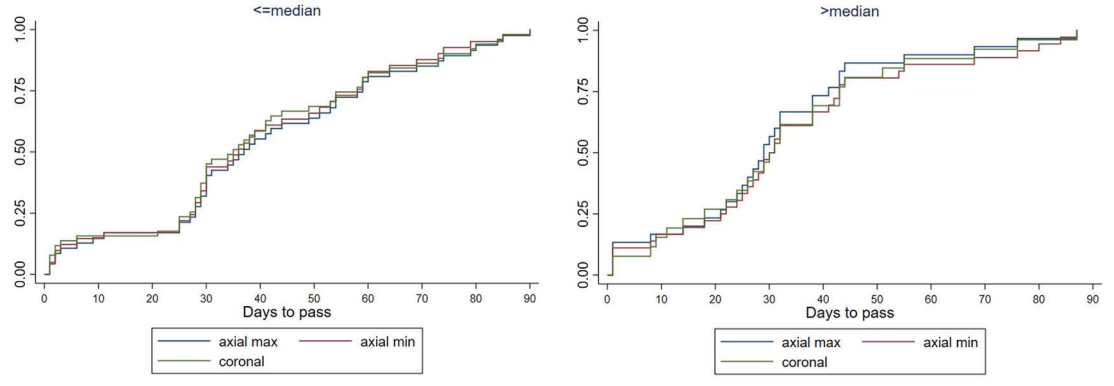

Figure 2: Kaplan-Meier inverted survival curve showing days to pass a stone (within 90 days, n=77) by dimension for calculi up to and exceeding median cut-off sizes (log-rank test: p=0.966)

Table 1. Log-rank testing of time taken to pass stones of elongated and non-elongated shapes for all stones

Classification	Difference in stone dimension*	Number of stones (Total n=91)**	Median (95% CI) number of days to pass all stones	p-value
Not elongated	<1 mm	56	38 (29.5-46.6)	0.869
Elongated	≥1 mm	35	31 (19.4-42.6)	
Not elongated	<1.5 mm	76	37 (29.5-44.5)	0.232
Elongated	≥1.5 mm	15	59 (12.3-105.7)	
Not elongated	<2 mm	85	38 (31.0-45.0)	0.575
Elongated	≥2 mm	6	29 (0.0-85.4)	

*Note: Difference in stone dimension is the difference between the maximal axial and coronal dimensions of a stone.
**Note: 90 patients were included, one of whom had a ureteric stone each on both sides thus 91 stones were included in the analysis
CI: Confidence interval

Table 2. Log-rank testing of time taken to pass stones of elongated and non-elongated shapes for stones that passed within 90 days of diagnosis

Classification	Difference in stone dimension*	Number of stones (Total n=77)**	Median (95% CI) number of days to pass all stones	p-value
Not elongated	<1 mm	49	35 (29.7-40.3)	0.398
Elongated	≥1 mm	28	29 (26.4-31.6)	
Not elongated	<1.5 mm	67	32 (26.9-37.1)	0.232
Elongated	≥1.5 mm	10	29 (0.0-69.3)	
Not elongated	<2 mm	72	32 (26.5-37.5)	0.250
Elongated	≥2 mm	5	29 (11.8-46.2)	

*Note: Difference in stone dimension is the difference between the maximal axial and coronal dimensions of a stone.
**Note: 76 patients were included, one of whom had a ureteric stone each on both sides thus 77 stones were included in the analysis
CI: Confidence interval

Our study attempted to determine which of the three dimensions of oval-shaped/elongated stones was the best predictive factor of stone passage time. Although a weak statistical correlation was found between each of the three dimensions of ureteric stones and the time required to expel them, we need to consider that a larger sample may be required to show any statistical significance considering the relatively small number of stones of particular interest in this study (stones with at least a 1.0-2.0 mm difference between maximum axial and coronal diameters). This can also explain the weak correlation between the individual dimensions of any passed stone and the time required for stone passage as logically there should be a strong correlation between these variables as shown in previous studies (3,9). Radiological reporting of stone size needs to be standardised towards the stone dimension with the strongest correlation to the chance of spontaneous passage, be it the maximum diameter in any or a specific plane. Although this study has attempted to identify which of these dimensions is the most important, the answer has not been scientifically proven.

Study Limitations

One of the limitations of this retrospective study was potential recall bias from reporting of the date that patients expelled their stone spontaneously. Another important note was that on CT, the axial views generally had thinner slices than the sagittal and coronal views; thus, the degree of precision in measurements may differ. We also assumed that urgent surgery would have occurred within three days of the diagnosis to differentiate patients allocated to spontaneous passage instead of urgent surgery from the outset. With a prospective design, one can more accurately record the exact number of patients allocated to passage or surgery from the outset and standardise the medical expulsive therapy regimen. Future studies may improve recall accuracy and data collection by prospectively employing more stringent and frequent follow-ups. This surveillance may address issues we encountered, such as uncompliant patients (ie, those who forgot about their stones, did not check their urine and missed follow-up scans and appointments). A prospective study design with weekly follow-up phone calls is one means of improving compliance and data collection. Conventionally, follow-up scans were requested to be done four weeks after the initial diagnosis. However, we found that patient non-compliance, availability of imaging services and non-standardised management by frontline doctors might have been a factor for the irregular periods between the initial and follow-up scans. An audit with our methodology is another tool to pick-up patients who are lost to follow-up. Standardisation of management protocols by frontline doctors

in future prospective-design studies might reduce the risk of this confounding variable.

Conclusion

This study showed that in isolation, any individual dimension of a ureteric calculus did not have a statistically significant effect on the time required to pass the calculus spontaneously over other calculus dimensions. Calculi of interest (elongated-shaped) were not common in this study. Although there was an inclination that these calculi pass earlier than the more rounded calculi, future prospective studies with a larger cohort might provide a more definitive answer. Although this study has not proved a preferential relationship for a particular stone dimension, this question remains unanswered because of the lack of studies specifically studying this topic in the current medical literature. If future studies prove an association, radiological reporting should include this particular stone dimension as a standard. This information is clinically relevant as it may improve the decision-making process for stones with borderline sizes and ensure that patients receive evidence-based treatment.

Ethics

Ethics Committee Approval: No ethics committee approval was sought for this study because of its retrospective and observational (non-interventional) nature.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.C., M.L., M.K., Design: D.C., M.L., M.K., Data Collection or Processing: D.C., Analysis or Interpretation: D.C., M.L., A.J., M.K., Literature Search: D.C., M.L., A.J., M.K., Writing: D.C., M.L., A.J., M.K.

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The Comparison of Flexible Ureterorenoscopy and mini-Percutaneous Nephrolithotomy in the Treatment of 10-25 mm Kidney Stones in Elderly Patients

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What's known on the subject? and What does the study add?

The surgery of elderly patients are mostly high risk due to the their comorbidities. Although the success rates are similar compared to flexible ureterorenoscopy (F-URS) and mini-percutaneous nephrolithotomy in the treatment of 10-25 mm kidney stones, F-URS is more safety treatment option due to the lower operation time and hemoglobin decrease.

Abstract

Objective: The elderly population has been increasing due to extension in lifespan. Chronic comorbid disorders and medications render a recheck of the treatment modalities of urinary stones for this population. This study aimed to analyse the results of mini-percutaneous nephrolithotomy (PNL) and flexible ureterorenoscopy (F-URS), which are minimally invasive techniques for the treatment of kidney stones in elderly patients.
Materials and Methods: Data of patients who are older than 65 years with 10-25-mm kidney stones and who underwent F-URS (n=51) and mini-PNL (n=33) between 2015 and 2019 were retrospectively studied. Demographic data, operative data and postoperative data were evaluated.
Results: The mean age of group 1 (F-URS) was 71.5±6.4 and of group 2 (mini-PNL) 70.2±5.6 and the mean stone size was 16.1±3.8 mm for group 1 and 19.7±3.5 mm for group 2. The complete stone-free rate was similar in groups 1 and 2 at 1 month postoperatively (78.4% and 72.7%, respectively; p=0.549). Haemoglobin decrease and operation and hospitalisation time were found to be higher in group 2 (p=0.000, 0.0001, 0.002). Complication rates (transfusion-required haemorrhage, fever and colon perforation) were not statistically different between the two groups (p=0.8).
Conclusion: In this study, although the stone-free rate in the F-URS and mini-PNL groups was similar, we believe that F-URS is a safer treatment method in elderly patients with 10-25-mm kidney stones than mini-PNL because of its shorter operation time and lower haemoglobin decrease.
Keywords: Flexible ureterorenoscopy, mini-PNL, urolithiasis

Introduction

Currently, the increase in the average life expectancy has led to an increase in the elderly population in Turkey and worldwide. According to the Turkish Statistical Institute data, the average life expectancy in our country was 78 years (1). This extension in lifespan is followed by an increase in comorbid diseases and the use of multiple drugs, particularly anticoagulants. Although stone diseases do not have an increased prevalence in this patient group, their treatment presents another problem. Therefore, the age and comorbidities of these patients require a review of our priorities in the treatment of kidney stones.

Treatments of kidney stones in elderly patients include shock-wave lithotripsy (SWL), flexible ureterorenoscopy (F-URS), percutaneous nephrolithotomy (standard, mini-, micro-PNL) and laparoscopic or open surgery, as in the normal population. With the recent advances in technology, the use of thinner ureterorenoscopes and nephroscopes has emerged and surgical interventions such as F-URS and mini-PNL have become alternatives to SWL for kidney stones. Studies that have compared mini-PNL and micro-PNL to standard PNL reported similar stone-free rates and similar or even lower complication rates than standard PNL (2,3). Concurrently, the diameters of flexible renoscopes gradually decreased and laser technology

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became stronger, and F-URS has become the forefront alternative surgical technique for kidney stones <2 cm. Several studies in the literature have reported F-URS to have lower complication rates than PNL and above 80% stone-free rates (3). Even though the European Urology Guidelines recommend PNL for stones over 2 cm and F-URS and SWL for stones under 2 cm, F-URS can be used frequently and safely for stones over 2 cm (4). Considering the current comorbidities in the elderly patient group, the use of F-URS is preferred primarily in stones over 2 cm, particularly by experienced clinicians.

This study retrospectively evaluated the minimally invasive techniques, mini-PNL and F-URS, in the treatment of elderly patients with kidney stones 10-25 mm in size and aimed to investigate the effectiveness and safety of two methods used in minimally invasive stone therapy in the elderly patients.

Materials and Methods

Patients and Grouping

Following the approval of the Koru Ankara Hospital local ethics committee (approval no: 07.05.2018/002-1), 174 patients over 65 years who underwent kidney stone treatment between February 2015 and January 2019 were retrospectively analysed. F-URS and mini-PNL surgeries for 10-25-mm kidney stones were included the study. The inclusion and exclusion criteria are presented in the patient flowchart (Figure 1). A total of 84 patients were included in the study, 51 for F-URS and 33 for mini-PNL. The patients who underwent F-URS were classified as group 1 and those who underwent mini-PNL as group 2. The patients' demographical data, comorbid diseases and chronic drug use were evaluated. Anaesthesia risk classification was evaluated using the American Society of Anesthesiologists (ASA) scores. The haemoglobin (Hb), creatinine, urinalysis, urine culture and bleeding parameters including prothrombin time/international normalised ratio were recorded for each patient in the preoperative period and analysed. Ultrasonography and computed tomography (CT) were the imaging methods used. For stone size imaging, the measurement of the longest diameter was used.

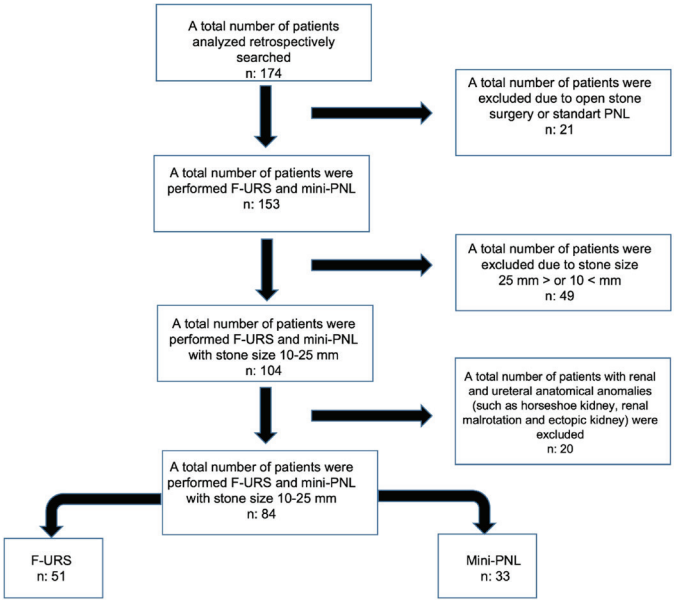

Figure 1. Patient flowchart

PNL: Percutaneous nephrolithotomy, F-URS: Flexible ureterorenoscopy

Hb measurements were performed in each patient in the postoperative period, and plain films of the kidney, ureter and bladder (KUB) were obtained to evaluate stone-free status in day 1. CT was performed to determine the final stone-free status at the first postoperative month. Stone-free status was defined as being completely stone-free in the follow-ups. The operative and postoperative data of the patients were recorded, and complication classification was evaluated using the modified Clavien-Dindo Classification (5).

Each patient was given a single dose of prophylactic antibiotic (third-generation cephalosporin or quinolone) intravenously in the operating room prior to the surgery. All surgeries were performed under general anaesthesia.

Surgical Technique

F-URS: Semi-rigid ureterorenoscopy (7.5 Fr, Richard Wolf GmbH, Knittlingen, Germany) was routinely performed in the lithotomy position for optic dilation and the simultaneous detection of ureteral stone. The ureteropelvic junction was accessed with a 0.035-inch-thick hydrophilic guidewire, which was left in the kidney, and the ureterorenoscope was removed. Then, as described previously (6), the ureter length was measured with a ureteroscope, and a 9.5/11.5-Fr (Cook Medical, USA) ureteral access sheath was placed in the ureter. In cases wherein the ureteral access sheath could not be inserted or no access could be created, the procedure was terminated by inserting a DJ stent in the ureter and postponed to a later time. These patients were excluded from the study. After creating ureteral access, the kidney was accessed using a 7.5-Fr F-URS (Flex X2, Karl Storz, Tuttlingen, Germany). The stone(s) was detected under endoscopic vision and was fragmented with holmium: YAG laser (270 mm fibre, 0.6 J and 6-8 Hz) until it decreased to a size that it could pass by itself. For stone samples, a fragment was taken where possible using a nitinol basket. At the end of surgery, DJ stents were routinely placed in each patient. The DJ stents were removed under sedation at postoperative days 15-21. Operation time was defined as the period starting from the beginning of general anaesthesia until the placement of the DJ stent.

mini-PNL: With the patient in lithotomy position, the open-ended ureteral catheter (5 Fr) was placed retrogradely with the use of a 22-Fr cystoscope in the ureter where the stone was

located. Then, a 16-Fr Foley ureteral catheter was placed in the bladder and determined with a ureteral probe. Afterwards, the patients were placed in the prone position by rotating them over silicone support pads corresponding the pressure points. An 18-gauge access needle was used to determine the appropriate calyx using a C-arm fluoroscopy device (SIEMENS Arcadis Varic C-arm), and entry was achieved. A 0.0035-inch-thick guidewire was sent through the needle and into the kidney (preferably to the upper calyx or the ureter). The nephrostomy tract was provided (14-16 Fr) with Teflon Amplatz dilators (Cook Medical®) through the guidewire. The fluids used had to be close to body temperature to avoid the risk of hypothermia. The stones were reached under endoscopic and fluoroscopic vision using a 10-Fr rigid nephroscope (Karl Storz, Berlin GmbH, Germany). After reaching the stone, ultrasonic, pneumatic (EMS Swiss Lithoclast®Master, Switzerland), or laser (Dornier© MedTech Laser GmbH, Medilas H, h20-1518, Germany) lithotripsy was applied. The fragmented pieces were removed with forceps or a nitinol basket. The operation was completed when no residual stone was seen endoscopically and fluoroscopically. An antegrade D-J ureteral stent and a 10-Fr percutaneous nephrostomy catheter were routinely placed in each patient at the end of the operation and removed at 18-48 hours postoperatively. The DJ stents were removed under sedation on postoperative days 14-21.

Postoperative Follow-up

On postoperative day 1, hemogram, routine biochemistry, and KUB tests were performed on each patient. Fever, urine output, haematuria status and nephrostomy colour were assessed during general examinations. In addition to general and routine examinations, CT was performed on each patient in the first postoperative month to evaluate stone-free status. Ultrasonography was not routinely performed. Ultrasonography was performed when needed. The patients were given a single dose of third-generation cephalosporin postoperatively for preventive purposes for 3-5 days. Paracetamol was preferred for analgesia. Meperidine hydrochloride was given in appropriate doses when needed and only within the hospital stay period. Those who discontinued anticoagulants were recommended to re-start taking their medications on postoperative day 7 if bleeding was not noted. During anticoagulant administration, low-dose enoxaparin sodium was applied subcutaneously. Enoxaparin sodium was started as of postoperative day 1.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 20.0 software (SPSS 20.0 for MAC). Descriptive statistics are presented as mean ± standard deviation, frequency and percentages. The Shapiro-Wilk test was used to determine whether the data showed normal distribution. It was observed that all the parameters we examined conformed to normal distribution. Student's t-test (t-test in independent groups) was used to compare normally distributed continuous variables, and the chi-squared test was used to compare stone-free rates. $p<0.05$ was considered statistically significant.

Results

The patients' demographic data and preoperative parameters are presented in Table 1. There was no statistically significant difference between the demographic data of the two groups. The mean stone size was calculated as 16.1±3.8 mm for group 1 and 19.7±3.5 mm for group 2 (p=0.687). The mean ages of the patients included in the study were 71.5±6.4 for group 1 and 70.2±5.6 for group 2.

When the groups were compared, the complete stone-free rates in the first postoperative month were similar (p=0.549). Hb decrease, operation time and duration of hospital stay were found to be higher in the mini-PNL group (p=0.0001, p=0.0001, p=0.002, respectively). Perioperative and postoperative parameters are presented in Table 2.

When preoperative anaesthesia risk classification was developed, group 1 had 1 ASA I patient, 26 ASA II patients, 22 ASA III patients and 3 ASA IV patients, whereas group 2 had 1 ASA I patient, 15 ASA II patients, 16 ASA III patients and 1 ASA IV patient (p=0.981).

When the patients were compared in terms of complications, no statistically significant difference was found between the two groups (p=0.08). No major complications were seen in group 1.

Table 1. Demographic data and preoperative parameters of patients

	F-URS (n=51)	mini-PNL (n=33)	p
Mean age ± SD	71.5±6.4	70.2±5.6	0.292
Mean stone size (mm)	16.1±3.8	19.7±3.5	0.687
Gender (male/female)	35/16	23/10	0.918
Surgical side (%)			
Right	21 (41.2%)	16 (48.5%)	0.122
Left	24 (47%)	17 (51.5%)	
Bilateral	6 (11.8%)	0	
Stone placement (%)			
Upper pole	4	2	0.346
Medium pole	5	4	
Lower pole	13	15	
Renal pelvis	19	7	
Multiple	10	5	

F-URS: Flexible ureterorenoscopy, mini-PNL: Mini-percutaneous nephrolithotomy, SD: Standard deviation

Non-persistent fever was recorded in two patients, and urinary tract infection was noted in one patient; both conditions were treated appropriately. In group 2, bleeding requiring transfusion was detected in one patient and colon perforation in another. The patient with colon perforation was explored intraoperatively and treated appropriately. The ASA scores and complications of the patients are presented in Table 3.

Table 2. Preoperative and postoperative parameters

	F-URS (group 1)	mini-PNL (group 2)	p
Fluoroscopy time (seconds)	0	183.1±33.1	0.0001
Operation time (minutes)	56.4±14.2	77.2±28.4	0.0001
Haemoglobin decrease (mg/dL)	0.21±0.2	1.96±0.9	0.0001
Complication rate (%)	3 (5.8)	2 (6.1)	0.08
DJ stent insertion (%)	46 (90.1)	29 (87.9)	0.856
Nephrostomy tube placement rate (%)	0	5 (15.15)	0.0001
Hospitalisation time (hours)	19.48±3.6	36.4±8.5	0.002
Stone-free rate (1st month) (%)	78.4	72.7	0.549

F-URS: Flexible ureterorenoscopy, Mini-PNL: mini-percutaneous nephrolithotomy

Table 3. ASA scores of patients and complications

Complication	F-URS (n)	mini-PNL (n)
Transfusion requiring haemorrhage (Clavien 2)	0	1 (ASA 2)
Fever (Clavien 1)	1 (ASA 2) 2 (ASA 3)	0
Colon perforation (Clavien 3)	0	1 (ASA 3)
TOTAL	3	2

F-URS: Flexible ureterorenoscopy, mini-PNL: Mini-percutaneous nephrolithotomy, ASA: American Society of Anesthesiologists

Discussion

Alternatives for surgical techniques for the treatment of kidney stone diseases have been gradually increasing with the advancement of technology. The surgical technique recommended for the normal patient population is generally clear, whereas it is not clearly defined for specific patients such as the elderly. Although the European and American guidelines have listed treatment options (4,7) according to parameters such as size, location, and type of the stone, the order of these options can vary in paediatric and elderly groups, patients with comorbidities, pregnant patients and groups with anatomical anomalies. Hence, we retrospectively screened patients who underwent F-URS and mini-PNL to determine the safest and most effective surgical treatment method for 10-25-mm kidney stones in elderly patients, which has increased in number with the extension of the average life span in our society.

Accompanying comorbid diseases, increased anaesthesia risks and multiple-drug use, particularly anticoagulant drugs, should be considered in urinary tract stone surgery in elderly patients. It is seen that the preoperative ASA scores of our patient group were concentrated at the second and third degrees. This comes with higher complication rates due to surgery compared to younger patients. In our study, the comorbid disease rate was found to be at 78%.

Currently, renal access diameters are known to be between 14 and 22 Fr for mini-PNL, 11 and 13 Fr for ultra-mini-PNL and 4.8 and 10 Fr for micro-PNL (8-10). Previous studies have stated that the reduction of renal access diameters have resulted in lesser haemorrhage incidence, analgesia and complication rate and shorter hospitalisation time. Moreover, stone-free rates have been reported to be the same as standard PNL (11-13). Stone-free rates appear to be at 87-90% for mini-PNL (14-18) in literature. In our study, the stone-free rate was found to be 72.7% in mini-PNL, which is not consistent with that of existing literature. We defined stone-free as no stone. However, the studies in the literature described stone-free as residual stones <3 mm. Thus, we believe that our stone-free rate seems to be low compared to that of the literature.

The most concerning complications that may occur during PNL operations in the elderly patient group are cardiac and pulmonary complications. No cardiac or pulmonary complications occurred in any of our patients. In a study by Okeke et al. (19), the results of PNL operations were compared between elderly and young patient groups, and it was found that stone-free rates did not change in PNL, while complication rates increased with age (20). In our study, the complication rate for mini-PNL was found to be at 6.1% in advanced age patients, similar to our complication rates after mini-PNL in the younger age group. The colon perforation that occurred in one patient was noticed during the operation, and a temporary ileostomy was opened in the patient with the help of the general surgery team. The patient was then discharged on postoperative day 4. One of our patients had an Hb decrease requiring transfusion in the postoperative period. Although our complication rates seem to be low in the mini-PNL group, we believe that more serious complications may be seen in elderly patients undergoing PNL. Causes such as bleeding diathesis due to intense use of anticoagulants and replacement of the colon and/or other organs to the back of the kidney in the retroperitoneum due to previous operations are some of the factors that increase the risk of complications.

In contrast, stone-free rates in endoscopic stone disease treatment with flexible renoscope have been reported to be between 75 and 85% in the literature, similar to mini-PNL (15,21,22). In our results, the stone-free rate after F-URS was found to be at 78.4%, consistent with that of the literature. In 2014, the Clinical Research Office of the Endourological Society

URS study group published the results of 1210 patients who underwent F-URS. The patients were divided into three groups according to stone size: under 10 mm, 10-20 mm and over 20 mm. In the study, stones larger than 1 mm were defined as residual kidney stones. According to this study, the stone-free rates were reported to be at 90.5% in the first group, 76.9% in the second group, and 31.4% in the third group. However, in this study, stones larger than 1 mm were considered as stone-free. Therefore, we hypothesised that the stone-free rates of F-URS are determined to be low for stones 10-20 mm and over 20 mm in size (23). In another study on 279 patients, stones larger than 3 mm were determined as residue stones, and the patients were similarly divided into three groups. In the study, the stone-free rates were reported as 84.4%, 76.5%, and 60%, respectively (24).

In studies comparing F-URS and mini-PNL, operation time and duration of hospital stay were reported to be higher in the mini-PNL groups. A study by Gao et al. (17) comparing the F-URS and mini-PNL groups reported that Hb decrease and hospitalisation time were significantly increased in the mini-PNL group; however, operation time and complication rate between the two groups showed no difference (19). Conversely, Pan et al. (25) compared operation times between two groups and reported them to be 73 minutes in the F-URS group and 62 minutes in the mini-PNL group. These studies were conducted on the young age group. In our patient group, the operation times were 56.4±14.2 and 77.2±28.4 minutes in groups 1 and 2, respectively, whereas hospitalisation times were 19.48±3.6 and 36.4±8.5 hours in groups 1 and 2, respectively. The mean Hb decrease was 0.21±0.1 mg/dL in group 1 and 1.96±0.9 mg/dL in group 2, including one patient in group 2 who had a Hb decrease requiring transfusion.

Study Limitations

Our study had two main limitations. The first was the low number of study patients. The other was that our study was conducted retrospectively. However, there are clear difficulties in carrying out a prospective study with a large population in this patient group, considering the conditions of our country.

Conclusion

Our results showed similar stone-free rates in the F-URS and mini-PNL groups. Additionally, both groups had extremely low complication rates. These results are consistent with those in existing literature. However, this study had a few negative outcomes such as longer operation times and higher Hg decrease in the mini-PNL group compared to the F-URS group. Thus, we suggest that F-URS is a more appropriate treatment option for renal stones 10-25 mm in size in elderly patients.

Ethics

Ethics Committee Approval: This study was approved by the Koru Ankara Hospital Local Ethics Committee (protocol no: 07.05.2018/002-1).

Informed Consent: All patients underwent the procedure after obtaining written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.E., B.K., M.K., Concept: G.E., M.K., Design: G.E., M.K., Data Collection or Processing: B.K., Analysis or Interpretation: G.E., B.K., Literature Search: G.E., B.K., M.K., Writing: G.E., B.K., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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Testicular Torsion: Experience in a Tertiary Urology Referral Centre

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What's known on the subject? and What does the study add?

In this study, the risk factors for orchiectomy in patients with testicular torsion were investigated.

Abstract

Objective: To evaluate the patients who presented to our department due to testicular torsion (TT) and investigate the risk factors affecting orchiectomy in patients with TT.

Materials and Methods: Between November 2005 and January 2018, the data of 46 male patients were analysed. The patients were divided into two groups: group 1, patients who underwent orchiectomy and group 2, patients who underwent detorsion and testicular fixation. The paternity rates between groups 1 and 2 were compared. Statistical analyses were performed to determine the risk factors for orchiectomy.

Results: The participants' mean age was 26.9 years. Of the cases, 35 (76.1%) were determined between November and March, when diurnal temperature changes were observed. Orchiectomy was performed in 31 patients (group 1) and testicular detorsion and fixation in 15 (group 2). The overall orchiectomy rate was 67.4%. The duration between the onset of complaints and the intervention was found to be the only risk factor for orchiectomy in TT. The paternity rate in groups 1 and 2 was 86.6% and 85.7%, respectively (p=1.0).

Conclusion: The prolongation between the onset of complaints and the application in TT is a risk factor for orchiectomy. Prompt diagnosis and intervention are required in treatment. Regarding paternity rates, groups 1 and 2 appear similar.

Keywords: Testicular torsion, orchiectomy, risk factor

Introduction

Testicular torsion (TT), which is typical in all age groups, is a common cause of urological emergencies (1). TT may cause necrosis due to the deterioration of the blood supply to the testicle as a result of spermatic cord twisting. It is a condition requiring urgent treatment as it can cause organ damage. In differential diagnosis, there may be similar acute conditions such as appendix testis and epididymis torsion, infectious diseases such as epididymitis and epididymoorchitis and scrotal masses such as hydrocele, spermatocele, tumour and acute scrotal oedema (2). TT could affect male fertility in adulthood and may be a critical cause of secondary male infertility (3). Laboratory analysis of semen samples has not shown adequate sperm count and sperm vitality in >50% of patients with TT (4).

This study aimed to retrospectively evaluate the patients who presented to our clinic due to TT and analyse the risk factors that affect orchiectomy in patients treated for TT.

Materials and Methods

We retrospectively reviewed the records of TT patients who underwent surgery between November 2005 and January 2018 in our clinic. A total of 46 male patients were included in the study. Clinical and demographic data such as age, the duration between the onset of complaints and intervention to the TT and body mass index and perioperative data were recorded. The patients were divided into two groups: group 1, patients who underwent orchiectomy and group 2, patients who had testicular detorsion and fixation.

The medical history and physical examination, laboratory and radiological findings of all patients admitted with suspected TT were evaluated. The presence of blood flow or ischaemia was evaluated by scrotal colour doppler ultrasonography. Surgical exploration was planned for patients suspected to have TT. After detorsion, circulation within the testis was observed by applying hot compress. If the testicle has returned to normal following

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detorsion, scrotal fixation was then performed (Figure 1). If necrosis was noted, an orchiectomy was conducted.

Patients in groups 1 and 2 were called by phone, and the paternity rates of their partners were determined. The inclusion criteria were being in a relationship with the intent to become pregnant for at least 1 year, age >18 years, and a normal contralateral testis. Conversely, patients with primary infertility, those who were unwilling to participate or unreachable, and those with a history of undescended testis and/or varicocele were excluded from the analysis.

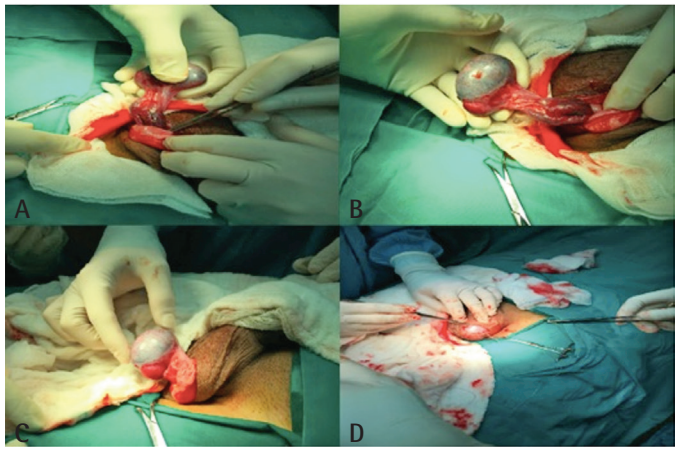

Figure 1. (A) Scrotal exploration of left TT. (B) Surgical detorsion performed in the operating room. (C) Blood circulation observed in the testis after warm gauze application. (D) Scrotal fixation performed

TT: Testicular torsion

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM SPSS Statistics for Windows, version 21.0. monk, NY: IBM Corp., Armonk, NY). Pearson's chi-square and Fisher's Exact tests were used to assess differences between the categorical variables, whereas the Kruskal-Wallis and Mann-Whitney U tests were used to identify differences between the median values. A p-value <0.05 was considered statistically significant. An ethics committee approval was not sought owing to the retrospective design of the study. The consent form was filled in by all the participants and their families.

Results

The mean age of the patients was 26.90±7.61. Of the patients, 31 were in group 1 and 15 in group 2. The demographic data is presented in Table 1. The mean follow-up time was 6.8 years (2-15). Among the patients, 27 had TT on the left testicle and 19 had it on the right. The average time between the onset of complaints and admission to the hospital was 28.3 (6-38) hours.

The patients presented with scrotal pain and swelling. Pre-diagnosis of all the patients was made by physical examination and verified with scrotal colour doppler US. Two patients could not be diagnosed using scrotal colour doppler ultrasonography. In 76% of cases (35 patients), the time of application was found to be at the time of diurnal temperature change (between November and March), and the orchiectomy rate was 67.4% (31 patients).

In group 1 patients, diffuse haemorrhage and infarction were observed during surgery. In these patients, orchiectomy was performed because no testicular blood supply was noted following hot compress application and circulation control after at least 15 minutes after surgical detorsion. The time from the onset of complaints to hospital admission period was 30.7 (10-36) hours for group 1 and 16.7 (6-20) hours for group 2 (p=0.001, Table 2).

A total of 22 patients were available for study inclusion criteria to compare paternity rate, including 15 and 7 in groups 1 and 2, respectively. The paternity rate in groups 1 and 2 was 86.6% and 85.7%, respectively (p=1.0).

Discussion

TT is an emergency medical condition that requires prompt and mandatory intervention. If therapeutic intervention is not provided immediately, testicular ischaemia and necrosis

Table 1. Characteristics of patients

Patient characteristics	**n**
No. of patients	46
Age (year)	
Mean (range)	26.9 (18-48)
Side	
Left	27 (58.7%)
Right	19 (41.3%)
The duration between the onset of complaints and application	
Mean (range)	28.3 (6-38)
Scrotal doppler US (ischaemia)	
Yes	44 (95.6%)
No	2 (4.4%)
Operation time (min)	
Mean (range)	32.4 (20-54)
Diurnal temperature change	
Yes	35 (76.1%)
No	11 (23.9%)
Hospitalisation time (days)	
Mean (range)	1.2 (1-2)

US: Ultrasonography

Table 2. The predictive factors for orchiectomy in patients with TT

	Group 1 (n=31)	Group 2 (n=15)	p-value
Age (year)			
Mean (+ SD)	27.1±8.9	26.2±6.6	0.412
Operation time (min)			
Mean (+ SD)	32.5±17.4	32.1±16.9	0.256
Body mass index			
Mean (+ SD)	22.27±4.8	22.82±4.6	0.785
The duration between the onset of complaints and the application			
Mean (± SD)	30.7±6.1	14.8±1.1	0.001
Hospitalisation time (days)			
Mean (± SD)	1.2±0.8	1.1±0.5	0.878
Side			
Left	18	9	
Right	14	5	>0.99
Diurnal temperature change			
Yes	25	10	
No	6	5	>0.99
Scrotal Doppler US finding (ischaemia)			
Yes	30	14	
No	1	1	>0.99

SD: Standard deviation, US: Ultrasonography, TT: Testicular torsion

can occur (3). The duration and severity of the rotation of the spermatic cord are determining factors of tissue loss in the testicle. Based on the results obtained in experimental studies, a 720-degree torsion is required for complete cessation of blood flow from the testicular artery and the formation of ischaemia (4). If this happens, testicular infarction occurs as a result of venous occlusion, congestion and arterial ischaemia. Studies have shown that testicles are affected within 4-6 hours in case of blood flow cessation and necrosis begins after 12-16 hours (5,6). In cases that were intervened within the first 6 hours, the testicle could be preserved close to 100%, whereas in cases intervened after 12 hours, preservation of the testicle was reported to decrease to 20% (7). In our study, the average time between the onset of complaints and admission to the hospital was found to be 28.3 (6-38) hours. This was found to be 30.7 (10-36) hours in group 1 and 16.7 (6-20) hours in group 2 (p=0.001). Thus, it was seen that the duration of hospital admission was a risk factor for orchiectomy. The incidence of TT was reported as 1/4000 before the age of 25; this rate decreases as the age increases (8). Depending on different etiological factors, TT commonly occurs in the neonatal period and adolescence, between the ages of 12 and 18 (8,9). The average age of patients in the study was found to be 26.90±7.61. The reason for the relatively high average age was that the patients who presented to our clinic were adults. Paediatric patients are brought to the paediatric surgery department in our hospital. Left TT was detected in 27 cases and right TT in 19 cases. Although the right/left ratio differs in the studies in literature, TT is believed to be more common on the left. In a study of paediatric patients in our country (Turkiye), it was reported that TT was seen more frequently in the left testicle than in the right (10).

The most crucial radiological method used in the diagnosis of TT is scrotal colour doppler ultrasonography. However, higher sensitivity of scintigraphy has been overlooked due to the fact that it could not be applied easily in emergency conditions. It has been observed that arterial blood flow is lost in scrotal colour Doppler ultrasonography. Hypervascularization indicates inflammation. False-negative results can be detected in the early periods of TT, intermittent or incomplete torsions (11). Therefore, radiological evaluation should be considered together with clinical findings. In our study, false negativity was detected in scrotal colour doppler ultrasonography in two cases, one patient each in groups 1 and 2. These cases were found to be TT after surgical exploration.

In TT treatment, success is achieved by early diagnosis and detorsion in the fastest way, fixing both testicles to the scrotum. The most critical factor in determining testicular loss after TT is the degree of torsion and how many hours it lasts. In our study, 67.4% of patients in group 1 required orchiectomy. Mansbach et al. (1) reported that they performed orchiectomy in 34% of TT cases (762 of 2248), whereas Kandemir et al. (12) reported orchiectomy in 42.5% of TT cases. The rate in our study appears to be higher (67.4%) compared to the series in literature. We believe that the main reason for this is the delay of the application period. Additionally, it should be considered that our patient group did not include the neonatal and early childhood age group, contrary to the studies in literature. Therefore, new and further studies on this subject are warranted.

One of the secondary findings of our study; in 76% of TT cases, the application time was in the period when diurnal temperature change was detected (between November and March). Hence, as hypothesised, TT cases were found to commonly occur in winter and spring. When we look at the studies on this subject in the literature, Lu et al. (13) reported that the incidence of TT was higher (77.5%) when diurnal temperature changed, that is, in the winter and spring. Oxidative stress that develops in the presence of torsion causes necrosis in germinal cells and may cause infertility in the future (14). In studies, it has been reported that fertility is preserved in men who undergo detorsion in the early period (<13 hours), whereas fertility is negatively affected in men who undergo orchiectomy in the late period (15). Additionally, spermatogenic damage to the ipsilateral testis may affect the contralateral testis (16-18). In particular, the theory that the opposite testicle is affected by the immunological mechanism is at the forefront (16). Furthermore, there are

studies showing that fertility has not changed in patient groups with and without orchiectomy (19,20). A study investigated paternity rates among 63 couples where the men had been treated for TT. The study found no decrease in paternity rates among TT men when compared to the general population (21). To clearly determine the endocrine and exocrine function after TT, there is a need for larger prospective long-term follow-up studies using unselected control groups and reporting on future paternity rates. In our study, paternity rates between groups 1 and 2 were similar (86.6% vs 85.7%, respectively; p=1.0).

Study Limitations

The present study had limitations including its long period of data collection, non-randomisation, and the relatively small number of cases in the subgroups and the study being a retrospective study. Moreover, the patients in our study showed only the patient profile in the urology clinic, and the small number was seen as a limitation in this study.

Furthermore, maternal factors were not included in this study. Despite these limitations, our results suggest that the duration between the onset of complaints and application in TT is a risk factor for orchiectomy. Prompt diagnosis and intervention are required in treatment. However, we did not note significant differences regarding paternity rates between groups 1 and 2. Future studies should be prospectively designed to overcome existing limitations.

Conclusion

In this retrospective study, the duration between the onset of complaints and application in TT patients was found to be a risk factor for orchiectomy. Prompt recognition and treatment are necessary for testicular salvage.

Ethics

Ethics Committee Approval: An ethics committee approval was not sought owing to the retrospective design of the study.

Informed Consent: The consent form was filled in by all the participants and their families.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ç., Ç.D., B.Ö., Concept: S.Ç., Ç.D., B.Ö., Design: S.Ç., B.E., Ç.D., Data Collection or Processing: S.Ç., B.E., A.G., Analysis or Interpretation: U.A., A.G., Literature Search: S.Ç. Writing: S.Ç., B.E., Ç.D.

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Urodynamic Findings in Children with Cerebral Palsy Before Dorsal Rhizotomy Surgery

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What's known on the subject? and What does the study add?

It is well known that patients with upper motor neuron lesions may present with different urodynamic findings. To date, the number of published articles about urodynamic studies in patients with cerebral palsy is limited and of them, only half of them are about children. These present an important cross-section for assessing the need for urological follow-up which is not recommended by some authors. Our recent study provides an overview of those children, in terms of neurourological findings and symptoms.

Abstract

Objective: This study aims to investigate the neurourological and urodynamic findings of children with cerebral palsy (CP) that referred for dorsal rhizotomy surgery (DRS).

Materials and Methods: All children with CP who were scheduled for selective DRS were assessed with a detailed medical history, physical exam, urinalysis and urodynamic studies to assess bladder function and urinary problems. Urodynamic studies included filling and voiding cystometry, detrusor leak point pressure, external anal sphincter electromyography, flow rate and residual urine volume. All investigations and definitions relied on the standardisation of the International Continence Society.

Results: Overall, 24 boys and 10 girls were evaluated. The mean age of boys, and girls and the study group was 6.6 (1.7-9.8), 6.5 (3.5-11.4) and 6.6 (1.7-11.4) years, respectively. The most common complaints of the study group were urinary incontinence (58.8%), encopresis (32.4%) and constipation (17.6%) and 41.2% of patients needed diapers due to these problems. Twenty-five per cent (n=5) of male patients had an undescended testis. The most common clinical conditions at urodynamics, were low bladder compliance (85.3%), detrusor overactivity (67.6%), hyposensitive bladder (52.6%) and low bladder capacity (41.2%).

Conclusion: Upper motor neuron lesions, like CP, may present with various urodynamic findings. However, patients with CP are not routinely seen by urologists. Our findings revealed serious neurological problems in children referred for DRS. Therefore, every child with CP who has a DRS plan should undergo a detailed urological examination at least once before the procedure.

Keywords: Cerebral palsy, child, urology, urodynamics, rhizotomy

Introduction

Any damage to the developing brain can permanently lead to impaired control of movement and posture. These chronic palsies are broadly called "cerebral palsy" (CP) (1). This non-progressive brain disorder's spectrum of symptoms could change over time. It is the most common chronic disability in the childhood period (2). The underlying causes of CP are usually not known. However, predisposing factors, such as congenital abnormalities, genetic factors, infections, toxic factors, multiple gestations, vascular disease of pregnancy, preterm birth, postterm birth and maternal factors can lead to birth injuries and poor oxygen supply to the brain (3). The degree and location of brain damage finally shape the resulting motor and cognitive disabilities. CP has a broad spectrum of neurological findings that range from severe mental retardation and wheelchair-bound conditions to subtle

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neurological impairments, which can only be detected on full neurological examination. Likewise, urological findings of these patients may also vary widely. Lower urinary tract dysfunction is estimated in one-third of CP patients (4). We evaluated the urodynamic and neurourological findings of children with CP who were scheduled for dorsal rhizotomy surgery (DRS) for neurological findings.

Materials and Methods

In this retrospective study, a consecutive group of children with CP who were referred and scheduled for selective DRS (SDR) to a tertiary centre, Marmara University Neurosurgery Department, Istanbul, between January 2005 and January 2008 was included as the study group. All patients were evaluated with a detailed history, physical examination, a neurourological work-up of urinalysis, renal function test (creatinine), ultrasonography and urodynamic studies. Inclusion and exclusion criteria for selective DRS are provided in a supplementary file.

Criteria of Selective Dorsal Rhizotomy and Expected Outcomes

Children diagnosed with spastic CP and referred to our institution and operated with SDR at the lumbosacral level were included in the study. The standardised measures used for the selection process consisted of the modified Ashworth scale to assess spasticity (defined as a velocity-dependent increase in the tonic stretch response), the Medical Research Council scale to measure muscle strength, goniometry assessments to indicate contractures the Gross Motor Function Classification System (GMFCS) for gross motor function and gait inefficiency according to non-dimensional oxygen cost. No standardised measurements were provided for the SDR selection criteria. The preoperative assessment was performed by a single person (neurosurgeon OM). However, the SDR selection preoperative assessment was also in consultation with a multidisciplinary team, consisting of neurosurgeons, orthopaedic surgeons, developmental paediatricians, paediatric neurologists, paediatric physiatrists, physical therapists, occupational therapists, nurses and/or social workers. The goals of SDR intervention were to improve motor function (walking ability, sitting and standing), prevent contractures and hip dislocation, and reduce pain.

Inclusion Criteria for Selective Dorsal Rhizotomy

A. Body Structure and Function

The presence of bilateral spasticity in the lower extremities [lower limbs (diplegia or tetraplegia)], which negatively influence gross motor function and/or caregiver support, were selected to be operated on with SDR. Patients with periventricular leukomalacia on neuroimaging were operated.

B. Activity (Gross Motor Function)

1. Patients should be able to walk with or without assistive devices.

2. GMFCS levels were used to define gross motor performance. Patients classified as GMFCS levels I to III were chosen for selective DRS operations.

C. Personal and Environmental Factors

1. Spastic CP was mentioned most commonly.

2. A history of preterm birth.

3. The origin of the spasticity should be in the context of a brain lesion acquired before one month of age.

4. Diagnoses other than spastic CP-like spasticity due to anoxia, encephalitis or degenerative diseases non-progressive spasticity due to hydrocephalus, spinal lesions or human immunodeficiency virus encephalomyelitis and spasticity of unknown origin with normal brain magnetic resonance imaging findings as well as hereditary spastic paraplegia.

5. The child's age at the SDR multidisciplinary consultation.

6. The child's and caregivers' motivation and access to follow-up therapy.

Exclusion Criteria for Selective Dorsal Rhizotomy

A. Body Structure and Function

1. The absence of movement abnormalities other than spasticity (such as ataxia, dystonia or choreoathetosis).

2. The absence of good antigravity strength.

3. The absence of good motor control.

4. The presence of contractures.

5. The presence of spinal abnormalities or severe scoliosis.

6. The presence of hip (sub)luxation.

7. The presence of cognitive impairment.

8. Neuroimaging criteria suggesting any abnormalities in the basal ganglia.

B. Activity (Gross Motor Function)

1. Patients should be able to walk with or without assistive devices.

2. Patients classified as GMFCS levels >III.

C. Personal and Environmental Factors

1. As mentioned, a contraindication was previous orthopaedic surgery or treatment with botulinum toxin in the lower extremities within six months of SDR.

Urodynamic Evaluation

Urodynamic investigations included flow rate, residual urine, filling and voiding cystometry, detrusor leak point pressure (DLPP) and external anal sphincter electromyography. A computerised urodynamic system, Solar Silver Urodynamic System (Medical Measurement Systems International, Dover, NH, USA), was used to evaluate the lower urinary tract. Urodynamic studies were conducted in all patients after urine sterilisation. In urinary tract infection cases, appropriate antibiotic treatment was started with the guidance of urine cultures. Urine cultures were repeated after treatment to ensure sterile urine at the time of urodynamic studies. All patients suffering from constipation received enemas before the urodynamic investigation.

Initially, a non-invasive uroflow study was conducted with external urethral sphincteric electromyographic recordings. All urodynamic tests were performed in the supine position with the induction of a transurethral of a 6-F double lumen catheter and transrectal one-lumen catheter. Before the filling cystometry, residual urine volume was measured after the uroflowmetric. Later, the cystometric evaluation was started with a filling rate of 5 mL/min. Filling cystometry was limited to the sensation of a full bladder or total urine leakage. Total bladder capacity was taken as the total water volume infused until the end of filling the stage. All methods and definitions were based on the urodynamic standardisation of the International Continence Society (ICS) (5) and International Children's Continence Society (6). The expected bladder capacity is calculated using (age +1) × 30 (5). The observations were made by direct visualisation, and bladder compliance was measured considering the pressure change starting from zero volume of infusion at the empty bladder, ending at the infusion value where the leakage occurred (7). Children with bladder compliance of 15 mL/cm H_2O and higher were assigned to the normal compliance group, whereas those with bladder compliance less than 15 mL/cm H_2O were assigned to the low compliance group (8).

Namely, the ICS defines the DLPP as the lowest detrusor pressure value at which leakage occurs in the absence of abdominal pressure. The DLPP was measured by marking the lowest pressure when the urine seeped out from the urethral meatus. Continence was not assessed as a bothersome symptom under the age of three, as this is the age at which most children can postpone voiding and begin to achieve social daytime continence (9). In children younger than three years old and those with cognitive alterations, bladder sensation was not assessed. Constipation was considered as having fewer than three bowel movements per week (10).

Continuous data are given as median with the range in parentheses (the minimum and maximum values), and categorical data as the number of patients with the percentage of the total population in parentheses.

Statistical Analysis

Statistical analysis was done using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) Statistics for Windows (IBM Corp. Released 2017, Version 25.0. Armonk, NY: IBM Corp). The analysis was done as descriptive statistics. Shapiro-Wilk test was used to evaluate the distribution of variables and it was observed that the data did not show a normal distribution. Accordingly, continuous variables were expressed as median and minimum, maximum values and categorical variables as numbers and percentages.

Results

A total of 34 children [24 boys (70.6%) and 10 girls (29.4%)] were included in the present study. The mean age of boys, girls and the whole group at referral was 6.6 (1.7-9.8), 6.5 (3.5-11.4) and 6.6 (1.7-11.4) years, respectively. None of these children had prior urological evaluations or surgeries, and all were free of bladder medications. None of their parents was aware of a history of urinary tract infection. Serum creatinine levels were normal in all patients. A fifth of the male patients (20.8%) (n=5) had an undescended testis (UDT) on physical examination (Table 1). There was no abnormal sacral cutaneous finding in any of the patients. The most common bothersome urological symptoms expressed by the study group were urinary incontinence (58.8%), encopresis (32.4%), constipation (17.6%) and abnormal motor function of the lower extremity (91.3%). Motor dysfunction, the problem in micturition control and

Table 1. Findings of CP patients

	Female (n=10) N, (%)	Male (n=24) N, (%)	Total (n=34) N, (%)
Pathology on sacral examination	0 (0%)	0 (0%)	0 (0%)
Constipation	3 (30%)	3 (12.5%)	6 (17.6%)
Encopresis	1 (10%)	10 (41.7%)	11 (32.4%)
Daytime urinary incontinence	2 (20%)	1 (4.2%)	3 (8.8%)
Nocturnal enuresis	0	3 (12.5%)	3 (8.8%)
Day and night incontinence	4 (40%)	10 (41.7%)	14 (41.2%)
Normal function of lower extremity	1 (10%)	2 (8.3%)	3 (8.8%)
Wearing a diaper	2 (20%)	12 (50%)	14 (41.2%)
Patients without voiding symptoms	4 (40%)	10 (41.7%)	14 (41.2%)
Patients with daytime incontinence and encopresis	1 (10%)	1 (4.2%)	2 (5.9%)
Being circumcised	NA	8 (33.3%)	NA
Undescended testis	NA	5 (20.8%)	NA

NA: Not applicable, CP: Cerebral palsy

encopresis were the predominant symptoms that forced 41.2% of the group to use diapers (Table 1). Of all patients, 3 (8.8%) had only daytime, 3 (8.8%) had only nighttime, and 14 (41.2%) had diurnal incontinence episodes (Table 1). Renal ultrasonography did not reveal any abnormality, but mild hydronephrosis was present in the entire study group. None of the patients was previously on clean intermittent catheterisation (CIC). Some children had problems with co-operation during urodynamic studies, and because of this, inquiry about bladder sensation could not be performed and unfortunately, some could not void spontaneously. Therefore, 11 patients' (32.4%) information about bladder sensation and 9 patients' (26.4%) data about uroflowmetric studies are missing. All data about urodynamic studies are provided in Table 2. The most predominant urodynamic findings were low bladder compliance (85.3%), detrusor overactivity (67.6%), hyposensitive bladder (52.6%) and low bladder capacity (41.2%). Most children with CP seemed to have a normal bladder capacity (55.9%) and poor bladder compliance (85.3%) with urodynamic overactive detrusor (67.6%). Although half of these patients seemed to have a hyposensitive bladder, only a few patients (12.5%) with residual urine needed CIC. However, the rest of the children with CP had mean flow rates that were quite slow. In our series, detrusor dyssynergia was not a common finding (2.9%) in children with CP (Table 2).

Discussion

Previous studies had reported urological abnormalities and voiding dysfunction with urodynamic findings in CP patients. Patients with CP are an extremely heterogeneous group, ranging from simple impaired motor skills to requiring full-time nursing care with individualised therapy. Similarly, the location of lesions in the nervous system can change for all CP patients. Thus, only a few clinical studies reported various clinical findings and symptoms across the spectrum.

Lower urinary tract symptoms could be expected in about one- to two-thirds of CP patients (11). Urinary incontinence was reported to be the most common presenting symptom (47%-74%), followed by difficulty urinating (44%) (11,12). Urge incontinence was reported to be the most common type of incontinence in children with CP (76%) (11). Our patient population had a higher incidence of diurnal incontinence episodes. Concerning symptoms of micturition, only Bernuy and Lacert (13) reported dysuria as a common urological symptom in CP, and none of our patients had a complaint like dysuria. As patients got older, difficulty in voiding became a more prominent symptom; however, urinary incontinence frequency did not change (14).

The most extensive epidemiological study of lower urinary tract symptoms in 459 children with CP was conducted by Roijen et al. (15). This heterogeneous group consisted of patients with low

Table 2. Urodynamic findings in children with CP

	N	(%)		Median, (Min-Max)
Bladder capacity (n=34)*			Maximum bladder Capacity (n=34) (mm)	156 (52-355)
Low	14	(41.2)		
Normal	19	(55.9)		
High	1	(2.9)		
Detrusor activity (n=34)			Maximum Detrusor Pressure (n=34) (cm H_2O)	51 (10-105)
Normoactive	11	(32.4)		
Overactive	23	(67.6)		
Bladder compliance (n=34)*			Bladder compliance (n=34) (mL/cm H_2O)	5.5 (1.1-22.6)
Poor	29	(85.3)		
Normal	5	(14.7)		
Bladder sensation (n=19)			Detrusor Leak Point Pressure (n=9) (cm H_2O)	56 (37-78)
Hyposensitive	10	(52.6)		
Normosensitive	7	(36.8)		
Urinary retention (n=34)	4	(11.8)	Uroflowmetry (n=21)	
			Maximum flow rate (mL/sec)	8.5 (3-26)
Detrusor dyssynergia (n=34)	1	(2.9)	Mean flow rate (mL/sec)	6 (2-14)
			Voided volume (mL)	130.5 (49-292)
			Median PVR (mL) (n=30)	15 (0-97)

*Low bladder capacity = Less than 65 per cent of expected bladder capacity; high bladder capacity = More than 130 per cent of expected bladder capacity; poor bladder compliance is compliance less than 15 mL/cm H_2O; normal bladder compliance is compliance greater than 15 mL/cm H_2O, PVR: Post-void residual, CP: Cerebral palsy, Min: Minimum, Max: Maximum

(30.1%) and high (68.4%) intellectual capacity, mainly spastic hemiplegia (30%), diplegia (19.2%) and spastic tetraplegia (46.2%). The primary urinary incontinence prevalence of 23.5% (108 of 459) was reported for the whole study population, and all types of incontinence prevalence increased with age. The most important factors that influenced urinary incontinence in this group were tetraplegia and low intellectual capacity (15). Unfortunately, we cannot comment on our cohort's intellectual capacity as we did not assess it with a validated tool. We could not inquire about the information on bladder sensation because of co-operation problems (32.4%). Children with mental retardation due to chromosomal aberrations, single-gene disorders, peri-/post-natal injuries and particularly those diagnosed with CP had a high UDT prevalence of (16). Confirming this, our patient group had a high incidence of UDT (20.8%). A most probable mechanism for this high incidence is postulated by Smith et al. (17) with an increase in the cremaster muscle spasticity leading to the testis' pathologic retraction out of the scrotum.

Most studies inspected urological findings of CP patients when they were referred for urological problems, as did Decter et al. (18). They evaluated 57 CP patients with urodynamic studies and reported pure upper motor neuron lesions and incomplete lower motor neuron injury in 86% and 11%, respectively. The most common abnormalities detected in urodynamic studies were neurogenic detrusor overactivity (70%), and detrusor sphincter dyssynergia (DSD) (12%). Mayo studied urodynamics in 33 CP patients with lower urinary tract symptoms. The main complaints of their patients were difficulty in voiding and urge incontinence. The least DSD percentage reported in the English literature was noted by Mayo (3%) (19). Reid and Borzyskowski (12) studied urodynamics in 27 CP patients and found abnormal findings in 85%. The authors noted that hyper-reflexic detrusor contractions with reduced bladder capacity were the most common finding in 20 patients (74.1%) and 18.5% (n=5) of all patients had DSD. Karaman et al. (11) studied urodynamics in 36 CP patients with lower urinary tract symptoms. They reported neurogenic detrusor overactivity with reduced bladder capacity as the most common finding (47.2%), and DSD (11%). Concerning the problems in bladder function, some authors elaborated on the urological care and assessment and suggested urodynamics for every child with infantile CP, free of decision making, clinical findings and symptoms (20). This might be correct, since at least two-thirds of children with CP have clinically silent bladder dysfunction (21).

The present study suggested that one-third of the patients had normal bladder sensation, whereas 52.6% had a hyposensitive bladder. Neurogenic detrusor overactivity (93.8%) with reduced bladder capacity (90.6%) and low compliance (90.6%) was cystometric evaluation's most common finding. As previously demonstrated by other studies, DSD was not a common feature for our population and only observed in one patient (2.9%). Our patients' flow rate studies showed somewhat of a slow rate. Of all patients, 13 (38.2%) could not void spontaneously, and 4 (11.8%) got urinary retention following urodynamic assessment. The difficulty voiding might result from a hypertonic pelvic floor and a lack of voluntary control over the pelvic floor (19). However, it could also be due to a co-operation problem, which is not mentioned in any publications.

Mayo suggests that patients with urge incontinence seem to remain stable and respond to anticholinergics (19). This reason seems unlikely according to Reid and Borzyskowski (12). They explained that incontinence results from impaired mobility as there is a delay in reaching the toilet with a sudden urge to pass urine. Nevertheless, the mainstay of treatment in CP patients with dysfunctional voiding is anticholinergic drugs with or without CIC. Almost all patients seemed to improve or get symptomatic relief (12). Since none of our patients had previously visited urology clinics before, they were not on any incontinence medications. However, almost 40% of them were wearing diapers for various problems. Another treatment option for these children is corrective surgery of the underlying pathology. Some studies reported improved spasticity and the bladder storage capacity following SDR (21,22).

Any problem in bladder functions can lead to upper urinary tract deterioration. Gundogdu et al. (23) reported that 12.1% of upper urinary tract deterioration occurred in 33 children with CP. They concluded that other symptoms of bladder dysfunction and culture-proven true febrile urinary tract infection episodes were valuable indicators of upper urinary tract anomalies in children with CP. Unlikely, abnormal imaging findings were quite rare in our study. The utility of ultrasound was assessed by Silva et al. (24) to differentiate lower urinary tract dysfunction in patients with CP. However, bladder wall thickness did not correlate with the presence of bladder dysfunction in children with CP.

Constipation is another issue in CP. Gundogdu et al. (23) reported that over half the children (57.5%) had persistent constipation problems (fewer than three bowel movements in a week) for at least six months. Bladder dysfunction, elimination problems, constipation and decreased hygiene conditions cause bacteriuria or cystitis in CP children. So, it is also essential to ask about bowel problems. Mobilisation skills and nutritional status could contribute to bowel movements of children with CP. In healthy children, faecal load affects bladder functions, especially functional bladder capacity. Constipation may contribute to decreased bladder volumes in children with CP. The present study found that 17.6% of CP patients had constipation, and 32.4% had faecal soiling, affecting bladder functions.

Children with CP are prone to urinary tract infections, and circumcision is advised in such cases. However, only 33.3% of the children with CP were circumcised in our study group. This is unusual, as circumcision is also expected as a cultural element in Turkish society.

It is well known that patients with upper motor neuron lesions may present with different urodynamic findings. We cannot advise all CP patients to visit a urologist. However, the children who apply for SDR are a select group, which usually do not receive any prior evaluation and treatment by a urologist. Although these patients do not have upper urinary tract deterioration, they usually have pathologic bladder functions and need further treatment. A detailed urological evaluation should be suggested to every child. This assessment is important as lower urinary tract dysfunction, and UDT are common pathologies that require further treatment with anticholinergic therapy, CIC, voiding and storage biofeedback, surgery, or follow-up before SDR.

Knowledge of urodynamic features and clinical problems in patients with CP is insufficient. Interestingly, there is limited data about neurourological findings of children with CP, especially before DRS. At present, only 27 articles are published about urodynamic findings in children with CP; however, only three of them address the findings in children before DRS (21,22,25). The current study is providing the second-largest patient group about this topic.

Study Limitations

The present study is a non-randomised study with retrospective data analysis. No validated questionnaires were used to assess dysfunctional voiding patterns and constipation patterns. However, it is very challenging to complete these questionnaires in this patient population. Ultrasound was not utilised to measure bladder wall thickness. No urodynamic evaluation was present following DRS. Our patient group was a selected group limited to children with CP referred for DRS. Thus, two major limitations of the present study were the selection of cases and initial data collection. Another limitation is the utility of urodynamics studies without simultaneous videofluoroscopy. Patients with a neurogenic bladder can have secondary reflux. Therefore, the best practice is to perform videourodynamics to evaluate neurogenic patients. However, we lack this capability at our institution, and our patients did not have hydronephrosis in the ultrasonography. So, we did not ask for voiding cystourethrography study. A current study reported that the incidence of vesicoureteral reflux (VUR) in patients with CP was between 12.5% and 20%. Also, the authors suggested that DSD was a risk factor as 89% of the children with CP and VUR had DSD (26).

Conclusion

Lower urinary tract dysfunction and abnormal physical findings on the urologic examination are not rare in children with CP referred for DRS. These patients should be assessed by a urologist before surgical intervention.

Ethics

Ethics Committee Approval: This study was approved by the local ethical committee of Marmara University School of Medicine (Application ID: 2021-168) and followed the Research Guidelines for the Institutional Review Board (IRB) of Human Subjects.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.T., M.Ö., Concept: T.T., M.Ö., Y.T., M.B.Ö., Design: T.T., M.Ö., Y.T., M.B.Ö., Data Collection or Processing: Y.T., M.B.Ö., M.Ö., T.T., Analysis or Interpretation: Y.T., M.B.Ö., M.Ö., T.T., Literature Search: Y.T., M.B.Ö., M.Ö., T.T., Writing: Y.T., M.B.Ö., M.Ö., T.T.

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ORIGINAL RESEARCH
Transplant

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Comparative Study of Outcomes Following Laparoscopic Versus Open Peritoneal Dialysis Catheter Insertion at a Tertiary Care Centre

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What's known on the subject? and What does the study add?

Currently, different surgical techniques are in practice for peritoneal dialysis catheter placement with varied success and complication rate. Literature describes a failure rate of 10-35% when catheters are placed via open technique and 2.8-13% via laparoscopic technique. Despite open technique being most frequently used, laparoscopic procedures have shown superiority by reducing morbidity, length of hospital stay, postoperative pain and shorter convalescence. In the existing literature, there is no consensus about the preferred operative technique for peritoneal dialysis catheter insertion. The study sheds further light on the advantages and drawbacks of laparoscopic peritoneal dialysis catheter insertion and compares it to the conventional technique of open continuous ambulatory peritoneal dialysis catheter insertion.

Abstract

Objective: Continuous ambulatory peritoneal dialysis is a common treatment mode in patients with end-stage renal disease. Various insertion techniques of continuous ambulatory peritoneal dialysis catheters have been described in the literature, including percutaneous, open and laparoscopic techniques, with no consensus about the preferred operative technique.

Materials and Methods: Between August 2016 and March 2018, 50 patients undergoing catheter insertion were randomised to insertion by either the open technique or laparoscopy. The demographic, preoperative and postoperative profiles of these patients were recorded and patients were followed up for six weeks postoperatively. The Pearson chi-square test was used to compare the results with historical controls. Fisher's Exact test was used to assess the incidence of surgical complications. The significance level was set at 0.05.

Results: A comparison between the two groups indicated that the only significant difference was in postoperative pain on postoperative evening, lower in the laparoscopic group and statistically significant ($p<0.05$). There was no statistically significant difference in catheter tip migration, catheter exit-site infection, catheter-associated peritonitis or catheter functional status between the two techniques.

Conclusion: The laparoscopic technique does not provide any additional advantage than the open technique in patients undergoing continuous ambulatory peritoneal dialysis catheter placement.

Keywords: Continuous ambulatory peritoneal dialysis catheter, comparison, open surgery, laparoscopic

Introduction

Peritoneal dialysis (PD) is an effective treatment for end-stage renal disease (ESRD). The key to successful PD is the presence of a well-functioning dialysis catheter, defined as one that facilitates free dialysis solution inflow and outflow. However, several complications, such as inflow and outflow obstruction, peritonitis, exit-site infections, leakage and catheter tip migration, can lead to loss of peritoneal access.

Currently, different surgical techniques are used for catheter placement with varied success and complication rates. The literature describes a failure rate of 10% - 35% when catheters are placed via open the technique and 2.8%-13% via the laparoscopic technique. Although the open technique is most frequently used, laparoscopic procedures have shown superiority by reducing morbidity, length of hospital stay, postoperative pain and shorter convalescence (1). In the existing literature, there is no consensus about the preferred operative technique

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for PD catheter insertion. The hypothesis of this study was that the laparoscopic PD catheter insertion procedure leads to a lower incidence of catheter malfunctioning at six weeks postoperatively.

Materials and Methods

We conducted a randomised controlled study at our hospital between August 2016 and March 2018. After obtaining institutional ethical committee approval (Institutional Ethics Committee, Army Hospital (R & R), Delhi Cantt, IEC Regn no: 93/2016), all patients for PD were included in this trial after obtaining written informed consent. Random numbers were generated using the RAND function of MS Excel. Patients were divided into two equal groups. The results were kept in serially numbered, sealed opaque envelopes. These envelopes were kept with a third person (Head Clerk) at the hospital. Once the patient was enrolled, a call was made to the third person to ascertain the group. Both surgeon and patient were informed about the technique only on the morning of the surgery. All procedures were performed by consultants having a similar experience with vancomycin injection as antibiotic prophylaxis under general anaesthesia.

Patient's with a body mass index (BMI) >35 kg/m^2, age <18 years and those unfit for general anaesthesia were excluded.

The primary objective was to determine a better surgical placement procedure to minimise the incidence of catheter malfunction at six weeks postoperatively.

We also wanted to assess if the use of the laparoscopic insertion technique reduces the rate of surgical complications, surgical mortality, leakage, catheter tip migration, catheter-related readmissions, exit-site infections, peritonitis and postoperative pain.

Surgical Interventions

Laparoscopic Technique

Preoperatively, the catheter's exit-site was jointly marked by the surgeon and patient and was sited well above the belt. General anaesthesia and antibiotic prophylaxis (vancomycin, 1000 mg IV) were administered. After cleaning (chlorhexidine disinfection) and draping, the patient was put in the Trendelenburg position. A 10-12 mm port was placed supraumbilically using the open technique and pneumoperitoneum was created.

Using a 30 degrees camera, the peritoneal cavity was inspected. Adhesiolysis was performed wherever necessary. A double-cuffed Swan Neck Tenckhoff dialysis catheter was placed on the patient's abdomen, to determine the best entry and exit points. Subsequently, a small incision was made at the entry point. Using an 8 mm trocar, a subcutaneous tunnel was created. The trocar was then introduced into the peritoneal cavity. A catheter was then introduced with a stylet, without twisting the catheter around. If necessary, an additional 5 mm trocar was inserted to enable securing the catheter in the correct position and the catheter tip was placed in the pouch of Douglas. The stylet and 8 mm trocar were subsequently removed. The distal cuff of the catheter remained just outside the peritoneum. The peritoneal cavity was desufflated. The free inflow and outflow were tested with at least 500 cc of saline with the patient in the neutral position. Then, the balloon trocar was removed. The subumbilical fascia was closed with vicryl round body 3-0 and the skin was closed using Monocryl.

Open Technique

The preoperative measures were the same. A 4-5 cm transverse incision was made two finger breadths below the umbilicus. Then, the anterior rectus fascia was opened, the muscles were split and the dorsal rectus fascia was opened. The surgeon ensured that the surrounding peritoneum was free of adhesions with his finger. Preferably, the os pubis was felt. The catheter was then introduced as described above and the tip was placed in the pouch of Douglas/rectovesical pouch. Inflow and outflow testing were done as described above. The peritoneum and fascia were closed with a purse-string suture using PDS 3-0. The catheter's proximal end was brought out from a point along the catheter's natural curve, ensuring that the proximal cuff was far enough from the exit point.

In the immediate postoperative period, patients had a plain abdominal X-ray abdomen after 24 to 48 hours of catheter placement (after the passage of stools) to document the catheter tip's correct position. Postoperatively, patients were also asked to complete different standardised questionnaires to evaluate pain [visual analogue scale (VAS) score]. The patients were reviewed on postop evening (D+0), D+1, D+2, D+3 and D+7 to assess pain scores as per VAS. PD training was started in both groups after 14 days postoperatively. They were followed till six weeks postoperatively to assess the catheter's functional status and document any complications.

Statistical Analysis

Categorical variables were presented as numbers (percentages). Continuous variables were presented as medians (ranges). Categorical variables were compared using the chi-square test. Continuous variables were compared using the Mann-Whitney U test. All analyses were conducted using SPSS (version 17.0, SPSS Inc., Chicago, USA). A p-value <0.05 was considered significant.

Results

Total of 50 patients who underwent continuous ambulatory peritoneal dialysis (CAPD) catheter placement at our institute

between August 2016 and March 2018 were recruited. They were randomised equally, with 25 patients undergoing laparoscopic catheter placement (group 1) and 25 undergoing open catheter insertion (group 2). Patients were reviewed on D+0, D+1, D+3, D+7 and D+6 weeks to respond to various study parameters and check the catheter's functional status (Table 1).

Group 1 comprised 18 (72%) males and seven females (28%), whereas group 2 comprised of 19 (76%) males and six (24%) female patients (p=0.747). Regarding age distribution, the mean age in group 1 was 50.88+/-7.59 yrs and in group 2 it was 55.12+/-8.54 yrs (p=0.054). The mean BMI in group 1 was 25.9+/-1.41 kg/m^2 and in group 2 it was 25.4+/-1.2 kg/m^2 (p=0.177). In group 1, 10/25 (40%) whereas in group 2, 3/25 (12%) had a history of previous abdominal surgery (p=0.024). Some patients had undergone previous CAPD catheter insertion, which had been removed for various indications like outflow failure, CAPD peritonitis and other issues. There were a total four such patients who were equally divided in the two arms of two each (Table 2).

The VAS pain score on D+0 (postop evening) was 8 in group 1 and 8.72 in group 2 (p=0.006). There was no difference in the VAS pain scores in the two groups on D+1, D+2, D+3 and D+7. Patients were followed up in the Nephrology and Urology OPD for catheter training, dialysis or in the event of any complication noticed by the patient or caregiver while administering CAPD.

Table 1. Pre-operative variables

	Laparoscopic	Open
Gender distribution		
Male	18	19
Female	7	6
Age distribution		
35-45	5	3
46-55	13	10
56-65	6	9
>65	1	3
BMI		
20-23	2	1
23.1-25	2	8
25.1-27	14	13
>27	7	3
H/O previous abdominal surgeries		
Yes	10	3
No	15	22
Previous CAPD insertion		
Yes	2	2
No	23	23

CAPD: Continuous ambulatory peritoneal dialysis, BMI: Body mass index

A total of 20 patients, 10 each in both groups (40% of patients in either group) were readmitted for catheter-related complications.

Five patients had pericatheter leakage during the study period. Of these, two were from group 1 (8% of patients) and three were from group 2 (12% of patients) (p=1.0).

There was only one mortality in the entire study population, which was in group 1. Catheter tips were found to have migrated out of the true pelvis in seven cases in total (detected by performing an abdominal X-ray). Of these, three cases were in group 1 (12% of patients) and four were in group 2 (16% of patients) (p=1.0).

Of the total readmissions for CAPD catheter-related complications, 10 were because of catheter-related peritonitis. Four occurred in group 1, whereas six occurred in group 2 (p=0.48).

Four patients had catheter site infections. Of these, three were in group 1 (12% of patients), whereas one was in group 2 (4% of patients) (p=0.1).

At the six-week postoperative follow-up, two patients in group 1 (8% of patients), whereas three patients in group 2 (12% of patients) had a non-functional catheter (p=1.0).

Discussion

Patients with ESRD must be treated with renal replacement therapies, such as haemodialysis or CAPD. CAPD increases the quality of life as it is relatively easy to use, cheaper and less

Table 2. Post-operative outcomes

	Laparoscopic	Open	p-value
Post-operative pain scores			
Day 0	8.0	8.7	0.006
Day 1	6.0	6.8	0.073
Day 2	4.7	5.1	0.093
Day 3	3.5	3.9	0.066
Day 7	2.3	2.5	0.130
Outcome			
Readmission	10	10	-
Leakage	2	3	1.0
Mortality	1	0	1.0
Catheter Migration	3	4	1.0
Peritonitis	4	6	0.48
Catheter site infection	3	1	0.1
Status at 6 weeks			
Non-functional	2	3	-
Functional	23	22	1.0

invasive. For these reasons, approximately 1,20,000 patients use renal replacement with CAPD worldwide (2).

A successful PD programme is dependent on the proper placement of a permanent CAPD catheter, which can be placed by various techniques, including open, percutaneous and laparoscopic. Several studies have found laparoscopic PD catheter placements in wider use with satisfactory success rates and acceptable morbidity in recent years (3). Although some authors have found catheter survival to be better when placed via a laparoscope, the benefit of laparoscopic techniques remains debated. A meta-analysis by Sakurada et al. (4) found no significant advantage in outcomes, such as complication rates, catheter survival rate, pain scores or length of stay in studies comparing laparoscopic versus open CAPD catheter insertion.

In our study, the two groups were well matched regarding age, sex distribution and BMI. BMI of the patient is a major determinant in outcomes of any surgical procedure. Patients with BMI >30 kg/m^2 are generally recommended to lose weight before any elective surgery to reduce the chances of postoperative complications. In the case of ESRD patients requiring CAPD catheter placement, such an option is not feasible. Patients must undergo the surgical procedure at whatever BMI they present. The mean BMI in the laparoscopic group was 25.9+/-1.41 kg/m^2 and that in the open group was 25.4+/-1.2 kg/m^2 (p=0.177). These results are similar to those of van Laanen et al. (5) and Wright et al. (6).

In our study, despite a significantly larger number of patients in the laparoscopic group with a history of prior abdominal surgeries, there was no statistically significant difference in outcome regarding functional status or surgical complications between the two groups. A similar study by van Laanen et al. (5) with 23 patients (52% of total) in the open group and 22 (48% of total) in the laparoscopic group with a history of previous abdominal surgeries and another study by Wright et al. (6), with 5/24 patients in the open group and 11/21 patients in the laparoscopic group with a history of previous abdominal operations have shown comparable functional outcomes between the two groups. Our study population was similar to that in the study by Wright et al. (6) because there was a higher proportion of patients in the laparoscopic group (10/25-40%) who had a history of previous abdominal surgeries compared with the open group, which had only 3/25 (12%) patients with previous abdominal surgeries. Despite the significant difference in this parameter, there was no effect on the primary outcome measure. Although the study is not powered to analyse the comparison of the outcomes of different techniques used to place CAPD catheters in patients with a history of abdominal surgeries, a history of previous abdominal surgeries seems not to reduce success rate of laparoscopic CAPD catheter placement. The technique of CAPD catheter placement by laparoscopy has been advocated at many centres for patients with a history of abdominal surgery. The logic is that laparoscopic visualisation of the intrabdominal milieu helps the surgeon place the catheter tip correctly at a site away from adhesions and perform division of adhesions that may interfere with the proper functioning of the CAPD catheter.

In our study, both groups had 8% of patients who had previously undergone CAPD catheter placement. They had undergone catheter removal for various reasons, like outflow obstruction, peritonitis or other problems. In the study by van Laanen et al. (5), 16% of the patients undergoing laparoscopic or open CAPD catheter insertion had a history of CAPD catheter insertion. In their study, this group of patients with a history of prior implantation of CAPD catheter had a success rate of 83% in the open group and 88% in the laparoscopic group making it a statistically insignificant parameter. Our study population had a very small proportion of patients with such a history. The patients in the laparoscopic group who had a previous history of CAPD catheter insertion had functional CAPD catheters at six weeks. In the open group, of the two patients, one patient had a non-functional CAPD catheter at six weeks. The difference between the two groups was not statistically significant.

For postoperative pain scores measured on D+0, D+1, D+2, D+3 and D+7, there was no significant difference in the scores between the two arms in our study except on the postoperative evening when the patients in the laparoscopic arm had significantly less pain than those in the open surgical placement arm (p=0.006). Similar to the studies by Wright et al. (6) and Jwo et al. (7), postoperative pain and the requirement for analgesics did not differ between the laparoscopic and open groups. A likely explanation is that the pain caused by the limited dissection via the small incision in the open group was equivalent to the mild pain produced by the carbon dioxide pneumoperitoneum during the laparoscopic procedure.

The incidence of catheter tip migration is reported as 2.7% and 15.0% for various catheter insertion techniques (7). We had 12% and 16% catheter tip migration rates in the laparoscopic and open surgical techniques. In our results, the open group's catheter tip migration rate was comparable to that of Jwo et al. (7), but our rate in the laparoscopic arm was higher than theirs. Studies by Soontrapornchai and Simapatanapong (3) have demonstrated a catheter tip migration rate of 0%. However, in this study, fixation of the catheter to the parietal peritoneum was performed, which probably was the reason for the zero-migration rate. We did not perform this fixation suture in the laparoscopic technique as suture fixation is not an option in the open surgical technique. We wanted to compare the outcomes between the two arms without a significant difference in the technique.

In the literature, the dialysate fluid leakage incidence after open or laparoscopic catheter placement has been reported to be between 5% and 13% (8,9). Paramedian placement, oblique catheter course through the abdominal wall, long extraperitoneal tunnel and long duration from catheter placement to dialysis initiation seem to reduce the incidence. Yun et al. (10) reported that minimising the leakage risk was minimised by reducing the trocars' number and size. In our study in place of the 10 mm port, we used an 8 mm port (that did not exceed the catheter cuff diameter) to tunnel in the catheter to reduce fluid leakages, tunnel infection and minimise the incisional hernia rate. We think that loose pericatheter tissue may increase the risk of leakage and catheter infection. Our study had a pericatheter leakage rate of 8% and 12% in the laparoscopic and open surgery arms, respectively. These results are much higher than the rates mentioned in the studies by Soontrapornchai and Simapatanapong (3) and most recently by van Laanen et al. (5). They had leakage rates of 2%/2% and 2%/0%, respectively, in the laparoscopic and open surgery arms. Our results were closer to the rates published by Jwo et al. (7) who had leakage rates of 10%/16% in the laparoscopic and open arms.

One of our patients in the laparoscopic arm died during the 6-week follow-up period due to congestive cardiac failure. This patient did not have any surgical complications, but he died within six weeks of the procedure. Hence, he was considered a surgical mortality. Jwo et al. (7) had a mortality rate of 17.5% and 27% in the laparoscopic and open surgery arms, respectively. However, among all the mortalities in that study, only one mortality was due to catheter-related sepsis, whereas the remaining mortalities were not directly related to surgery.

The exit-site/tunnel infection incidence did not differ between the laparoscopic (12%) and open (4%) insertion technique in our study (p=0.1). The PD catheter was subcutaneously tunnelled in all cases, which reduced the exit-site infection incidence, regardless of the insertion technique. The literature suggests a higher exit-site infection incidence in the open group 6.3%-41% versus the laparoscopic group 2.5%-18% (11,12).

A large case series did not report any difference in the peritonitis incidence when using the open insertion technique (2.9%-31%) or the laparoscopic technique (2.5%-31%) (1). Our study's data also showed no significant difference in the peritonitis incidence in agreement with these studies. The differences in peritonitis incidence in various reports might be partly due to differences in the prophylactic antibiotic regimens used. There is no consensus about which and when antibiotics should be administered to prevent peritonitis. The type of antibiotic used might influence the peritonitis incidence. Gadallah et al. (13) reported in a large randomized controlled trial that the use of 1 gm vancomycin preoperatively significantly reduced the peritonitis risk compared with 1 gm cefazolin and no antibiotic at all.

Mechanical obstructions that impair the functionality of CAPD catheters are an omental wrap, adhesions or catheter migration out of the pelvis (3). Catheter fixation to the peritoneum in the laparoscopic method might decrease the risk of this complication (14,15). Gadallah et al. (16) found catheter survival rates to be 77.5% and 62.5%, respectively, in the laparoscopic and open groups and reported the laparoscopic group to be better. Gajjar et al. (17) showed that the functionality rate of catheters inserted by laparoscopy was 97.8%, whereas it was 80% for the conventional method, with no statistical significance. In our study, the 6-week survival for catheters was 92% in laparoscopy and 88% in open surgery group with no significant difference.

Study Limitations

A limitation of our study is that, despite randomisation, there was a statistically significant difference in patients with a previous abdominal surgery favouring the open surgery group. This could have negatively influenced the clinical success rate in the laparoscopic group. It also makes a comparison between open and laparoscopic surgery more hazardous. Larger study populations with longer follow-up are required to reach more definitive conclusions.

Conclusion

The specific advantages of open surgery are shorter operative times and more basic equipment requirements and those of the laparoscopic technique are the opportunities to do adhesiolysis and place the catheter tip in the pelvis under direct vision. Our study shows no significant difference between these two modalities regarding functional outcomes and perioperative complication rates. However, it was only a short-term outcomes study and further trials focusing on long-term outcomes are needed.

Ethics

Ethics Committee Approval: After obtaining institutional ethical committee approval (Institutional Ethics Committee, Army Hospital (R & R), Delhi Cantt, IEC Regn no: 93/2016).

Informed Consent: All patients for PD were included in this trial after obtaining written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.J., G.M., Concept: R.T., G.S., Design: R.T., N.S., Data Collection or Processing: G.S., Analysis or Interpretation: N.S., Literature Search: G.S., Writing: A.J., G.S.

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ORIGINAL RESEARCH
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The Effective Way in Answering the IPSS: Patients Themselves or with the Physician?

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What's known on the subject? and What does the study add?

The International Prostate Symptom score (IPSS) is an evaluation form used in the diagnosis of benign prostate hyperplasia in clinical practice. It has been translated into Turkish and thus may not be fully understood by patients. In this regard, there may be differences in the treatment of the patients. When the IPSS form was filled with the help of a physician, the results were different from those of forms that were filled by the patients themselves. Based on our clinical experience, the IPSS form answered with the help of a physician gives more useful results in treatment regulation. This procedure would better guide treatments in such patients.

Abstract

Objective: This study aimed to compare the answers given to the International Prostate Symptom score (IPSS) questionnaire by patients with the help of a physician according to age and education level.
Materials and Methods: The study included 204 patients, aged 50-75 years, who presented for the first time at the Urology Department with complaints of lower urinary tract symptoms and had not previously completed an IPSS form. The patients were given IPSS questionnaires and asked to complete them. Then the patients completed the IPSS forms again with the help of their physicians. The results were compared statistically.
Results: When the education level was assessed separately, a significant difference was observed regarding the IPSS form completed with the help of a physician ($p<0.001$). When the patients were divided by age as <60 years and ≥60 years, a statistically significant difference was seen in the IPSS values ($p<0.001$).
Conclusion: Regardless of age and education level, a difference was found between filling the IPSS form with the assistance of a physician and by patients alone. Clinicians should consider this situation.
Keywords: Benign prostate hyperplasia, IPSS, questionnaire forms

Introduction

The appropriate application of certain algorithms, and the quantification of these, are extremely crucial in the diagnosis, treatment, and follow-up of diseases for both the patient and physician. Several questionnaires have been created for this purpose and are used worldwide (1). The use of the International Prostate Symptom score (IPSS), is recognised as a symptom index for benign prostate hyperplasia (BPH). The IPSS has been approved as a questionnaire for the evaluation of lower urinary tract symptoms (LUTS) in males with BPH (2). Although these types of questionnaires are extremely beneficial in medical practice, the educational level of the patient, ability to understand the questions on the form, age, and mental state when completing the form can contribute in the mathematical differences, and this can change the form of treatment (3). This study aimed to evaluate the relationship between the age and educational level of the patient and IPSS scores when the form is completed alone or with the assistance of a physician.

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Materials and Methods

After the institutional review board approval was obtained (Karadeniz Technical University Ethics Committee approval no: 2019/334), the prospective study enrolled 204 patients, aged 50-75 years, who presented for the first time at the Urology with complaints of LUTS and had not previously completed an IPSS form. The patients were classified by age (<60 and ≥60 years) and by educational level (primary school, middle school, high school, and university). The patients were given the IPSS forms, for which the Turkish translation has been confirmed, and were instructed to complete it on their own, without help. Moreover, uroflowmetry was done to all patients who participated in the study. Voided urine with volumes ≥150 mL was used for the study. Qmax values >15 mL/s were excluded. To avoid bias, the physician did not evaluate the uroflowmetry and IPSS scores before the patients filled the forms alone.

Further, the IPSS form was completed with the assistance of a physician (a single physician, HT, for all cases), and the time taken was recorded. Statistical analysis was conducted to determine differences between the results of IPSS questionnaires completed by the patient alone and those of forms completed with the help of the physician according to the age and educational level classifications.

Patients were excluded from the study if they had any lower urinary tract infection, ureteral stricture, a history of urinary system surgery, diabetes mellitus, and urinary malignancy or if they had previously completed an IPSS questionnaire.

Statistical Analysis

To assess the normal distribution, all continuous variables were analysed with the Kolmogorov-Smirnov test and histogram. The Wilcoxon-Rank test was used to compare the variables. Data obtained in the study were analysed statistically using SPSS for Windows vn 20.0 software (SPSS, Chicago, IL, USA).

Results

The mean age of the whole patient group was 61.6 years. The educational level was determined to be high school and university in 62 (30.3%) cases, middle school in 82 (40.1%), and primary school in 60 (29.4%) (Table 1). When the patients alone completed the IPSS, the mean scores for the subgroups of primary school, middle school, and high school and above were 14.8±1.7, 16.0±1.1, and 17.5±1.4, respectively. When the IPSS was completed with the assistance of the physician, the mean scores for the subgroups of primary school, middle school, and high school and above were 21.2±3.1, 21.3±2.5, and 18.5±1.8, respectively. A statistically significant difference was found between all the groups as regards the IPSS score (p<0.001).

When classified according to age, the IPSS values of patients aged <60 years were 16.4±2 when the questionnaire was completed alone and 19.7±2.9 when completed with the assistance of a physician. For patients aged >60 years, the IPSS values were 15.9±1.5 when the questionnaire was completed alone and 21.0±2.5 when completed with the assistance of a physician. The difference between the two age groups was determined to be statistically significant (p<0.001) (Table 2). The mean quality of life score according to the urinary symptoms in item 8 of the IPSS was determined to be 2.6 when completed by the patient alone and 2.8 when completed with assistance from the physician. The mean time taken to complete the form with the assistance of the physician was 4.20 mins. The mean uroflowmetry values of the patients are summarised in Table 3.

Table 1. Education level and IPSS values

Education level	Number (n)	Patient IPSS (mean ± SD)	Doctor IPSS (mean ± SD)	p-value
Primary	60 (29.4%)	14.8±1.7	21.2±3.1	<0.001
Middle	82 (40.2%)	16.0±1.1	21.3±2.5	<0.001
High and above	62 (30.4%)	17.5±1.4	18.5±1.8	<0.001

SD: Standard deviation, IPSS: International Prostate Symptom score

Table 2. IPSS values by age

Age	Number (%)	Patient IPSS	Doctor IPSS	p-value
<60	82 (40.1%)	16.4±2	19.7±2.9	<0.001
≥60	122 (59.9%)	15.9±1.5	21±2.6	<0.001

IPSS: International Prostate Symptom score

Table 3. Mean uroflowmetric scores

Uroflowmetry	mean ± SD
Voided volume (mL)	183.0±69.7
Maximum flow rate (Qmax, mL/s)	13.2±14.4
Mean voiding time (second)	52.7±19.1
Flow time (second)	41.0±13.2
Average flow rate (Qave)	5.6±3.4
Time to maximum flow (second)	9.8±4.9

SD: Standard deviation

Discussion

Just as in several different branches, several questionnaires are used in urology practice. One of these forms, which was created after extremely extensive studies and was prepared to be short and clear and in a concise language, is the IPSS questionnaire which is used in BPH diagnosis and is the most commonly used form in urology practice. The IPSS has been translated into several languages and has started to be used in other countries (4). Seven items are related to bladder capacity and urination

symptoms. The symptom scores are classified as mild degree, 1-7 points; moderate, 8-19 points; and severely symptomatic, 20-35 points (5). Item 8 of the IPSS is related to quality of life; previous studies have shown that quality of life is the most significant predictor of improvement with treatment (6).

Studies conducted after the IPSS came into use have reported it to be a simple and reliable evaluation method not affected by educational level and sociodemographic variables (1,7). However, observations in our clinic have shown that several patients have difficulty in completing the IPSS questionnaire and the level of treatment is affected by the IPSS score. Therefore, this study aimed to classify patients according to age and educational level and show the effect of assistance from the physician on IPSS scores.

A study by Cam et al. (8) revealed that patients with a primary school educational level did not fully complete the IPSS questionnaire. Moreover, Van der Walt et al. (9) reported that when the educational level of the patient was low, more help was needed to complete the IPSS. In contrast, Netto Júnior and de Lima (10) reported that educational level had no effect on IPSS scores; however, in the study, the patients were given information regarding the questions and how to answer them before they completed the questionnaire.

This approach may have affected the results, especially for the group of patients with a low education level. In another study conducted in Portugal and Brazil, a significantly low rate of form completion by the group with a low education level was noted. Bozlu et al. (11) demonstrated that educational level did not affect the IPSS and QOL results when the questionnaire was administered either by the physician or patient alone. In the current study, when the evaluation was made according to the classification of primary school, middle school, and high school and above level of education, although all the groups completed the form fully, the IPSS results were statistically significant when the form was completed with the assistance of the physician.

In a study by Johnson et al. (12), majority of the patients completed the form on their own, and it was determined that majority of them were young and with a high level of income. In the current study, the income level was not examined; however, the mean IPSS value was found to be higher in the patient group aged <60 years compared to those aged >60 years. This result can be attributed to a higher level of education in the younger group.

When the different ethnic origins of those living in a society are considered, several people with different native languages living in different countries can be seen. Even if questionnaires such as the IPSS are translated into different languages, it may not be completely translated into the native language of the individual, and this could imply a controversy on the extent to which the patient has understood the questions, and correct responses may not be given. Despite the high education level of many people, words used in the original IPSS form are not frequently encountered and routinely used words (13). Although the IPSS is better understood and completed as education level of the respondent increases, the accuracy of the responses may not always be guaranteed. The reason for the difference seen between all the education level groups in the current study could be due to this.

One of the questions which was difficult to understand and interpret for patients is the question on quality of life according to urinary symptoms. Words such as "pleased", "delighted", and "happy" may not be clearly defined in local languages. However, in the current study, the quality of life values according to urinary symptoms were similar when the patient completed the form alone and with the assistance of the physician.

Due to an intense work tempo and patient numbers, several urologists avoid completing the IPSS together with the patient. In literature, there is no report that provides information about the time taken to complete the IPSS. In the current study, as there was the uncertainty that a true result could be obtained from timing the patient completing the form alone, only the time taken to complete the form together with the physician was recorded, and a mean time of 4.20 mins was determined. This can be considered an extremely short time to ensure the correct diagnosis and treatment for a BPH patient.

Study Limitations

This study had some limitations, primarily its small sample size. Additionally, because of the range of ethnicities, there may have been difficulties for some patients in understanding the IPSS as it was completed in the frequently spoken language rather than their native language. To be able to complete the form correctly, it is crucial to correctly understand the questions first. Although factors such as age and education level have an effect on understanding the questionnaire correctly, they are not sufficient, and the cognitive capacity of the patient should be evaluated. In the current study, cognitive capacity was not assessed. With a correct scale, further extensive studies could provide objective results.

Additionally, although it is clear from the results of the study that assistance increases the IPSS score, it cannot be concluded that these higher IPSS scores obtained by the help of physician show clinical symptoms better than self-filled scores. Further studies evaluating the correlations between Qmax, post-void residual, etc., should be conducted to reveal the correctness of each method.

Conclusion

When it is considered that the IPSS was completed by the physician in a short time, it can be deduced that irrespective of age and educational level, completion of the form together with the physician can result in accurate diagnosis and treatment. In addition, the translation of questionnaires such as the IPSS into concise and understandable language and various local languages could increase accuracy rates.

Ethics

Ethics Committee Approval: After the institutional review board approval was obtained (Karadeniz Technical University Ethics Committee approval no: 2019/334).

Informed Consent: Informed written consent was obtained from all patients before participating in the study.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: H.T., Design: H.T., G.K.Ö., Data Collection and/or Processing: H.T., G.K.Ö., Analysis and/or Interpretation: G.K.Ö., Literature Search: H.T., Writing: H.T., Critical Review: G.K.Ö.

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ORIGINAL RESEARCH
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Comparison of Supine and Prone Positioning in Female Patients Undergoing Urethral Diverticulum Excision

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What's known on the subject? and What does the study add?

Excision of female urethral diverticulea (UD) has been traditionally performed in standard lithotomy position. It has been recently suggested that a prone patient positioning might improve surgeon's access to the surgical field and result in improved surgical outcomes. However, up to date there has not been any direct comparison of supine and prone patient positioning during urethral diverticulectomy. This study compares the surgical outcomes of patients undergoing UD excision in supine and prone positions.

Abstract

Objective: Transvaginal excision of urethral diverticulum (UD) is the gold standard treatment for symptomatic women with UD. Complete UD excision can be challenging due to poor access to the surgical field, especially with proximal, circumferential and recurrent UD. Prone patient positioning has been suggested as an effective way of improving surgical access and vision compared to the traditional supine positioning. However, direct comparison of the two positions is yet to be performed. This study aimed to compare patients who underwent UD excision in prone and supine positions.

Materials and Methods: Prospectively recorded data of 79 women undergoing urethral diverticulectomy between 2004 and 2017 in a single referral centre were reviewed. Patients were operated either in supine or prone positions based on the surgeon's preference. Data collected included patient demographics, UD characteristics on magnetic resonance imaging, intraoperative details and postoperative outcomes. Operative time was calculated from the electronic theatre records starting from the entry of the patient into the operating room to their exit.

Results: The mean patient age was 42.38 (±15.24) years. More than half of the patients had a recurrent UD at presentation (51.89%). The mean size of the diverticulum was 25.06 (±1.2) mm, and the mean operative time was 146.18 (±6.0) min. UD excision was undertaken in prone position in 50 (63.3%) and supine position in 29 (36.7%) patients. Patients in the prone position group were older and had relatively larger and proximal UD. In the multivariable analysis, it was found that a proximally located UD was the main indicator for undergoing surgery in the prone position.

Conclusion: Despite longer operative times, prone patient positioning appears to be the preferred option for patients with larger and proximal UD, presumably because it offers better access to the surgical field.

Keywords: Urethral diverticulum, prone position, surgical outcomes

Introduction

A urethral diverticulum (UD) is an epithelium lined, cystic outpouching of the urethra. UD is thought to arise from repeated infection and dilatation of the Skene's (paraurethral) glands. UD can occur anywhere in the female urethra; however, it mostly affects the middle and distal parts. UD is rare and thus, overlooked. Patients mostly present at ages 30-50 years with a classical triad of postvoid dribbling, dysuria and dyspareunia. In a population based study in the United States, the annual incidence of UD is reported to be 17.9% per 10,00,000 women per year (1).

Current evidence on the natural history and clinical presentation of UD is based on data from retrospective case series, making the evidence base relatively weak. Nevertheless, transvaginal diverticulectomy is the most commonly performed surgical procedure for symptomatic UD treatment. Success rates for urethral diverticulectomy have been around 70%-86% with

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reported complications of urethrovaginal fistula (1%-8%), *de novo* stress urinary incontinence (1%-16%), recurrent UD (5%) and recurrent urinary tract infections (UTI) (7%-31%) (2).

Many of these complications can be prevented by meticulous surgical dissection around the urethra and sphincter mechanism and by repairing UD in layers. This can be challenging for the surgeon especially in complex cases of circumferentially large and recurrent UD. Vaginal diverticulectomy for female UD is mostly performed in a standard lithotomy position (3,4). Recently, we have described an alternative patient positioning strategy, the modified jackknife position, to optimise surgical access and facilitate surgical excision (5), with equal success and complication rates. However, direct comparison of supine and prone patient positioning during female UD excision has not been performed so far.

In this study, a retrospective analysis was done for perioperative outcomes of patients undergoing UD excision in prone and supine positions.

Materials and Methods

1.1. Study Population

Prospectively recorded case notes of women undergoing a urethral diverticulectomy for symptomatic UD in a single referral centre were reviewed. Patients with complete electronic records from 2004 to 2017 were included. Patient characteristics, diverticulum characteristics on magnetic resonance imaging (MRI) and perioperative data were extracted and recorded.

1.2. Surgical Technique

All surgeries were performed by two specialised reconstructive urologists. The decisions to undertake the operations at supine or prone positions were mainly made by the operating surgeon and anaesthetists based on patient and diverticulum factors.

All operations started in supine lithotomy position with rigid cystourethroscopic examination using a 17 Fr cystoscope. Two ureteric catheters were placed in cases where the diverticula were large and/or extended towards the bladder neck to reduce the risk of ureteric injury. After cystoscopy a suprapubic catheter was inserted into the bladder in all patients together with a 16 Fr urethral Foley catheter. Afterwards, the patient was either brought into a prone position or the operation continued in supine position. Prone positioning was performed in close co-operation between the anaesthesiologist and surgical team with the involvement of 4-6 personnel in logrolling the patient into a prone position. Operative time was calculated from the central database starting from the entry of the patient into the operating room to their exit after the operation.

Excision of the diverticulum started by placing a vaginal retractor and injecting 1:200.000 adrenaline/lignocaine solution underneath the vaginal mucosa for hydrodissection. Then, a UD shaped vaginal flap was raised with a sharp dissection. The vaginal mucosal flap was mobilised off the underlying tissues to the level of the bladder neck, and the raised flap was retracted off the field by placing it underneath the central blade of the retractor. Periurethral tissues around the diverticular sac were developed, after which the diverticulum was dissected off the urethral muscle and excised. The urethra was then reconstructed over the Foley catheter using 4/0 Monocryl and figure-of-eight sutures. A watertight closure without any tension on the suture line was achieved. Tissue interposition was performed using preserved periurethral tissues or a Martius flap. Eventually, the vaginal mucosal flap was closed, and the vaginal packs were left inside the vagina.

1.3. Postoperative Care

The vaginal pack was removed at the first postoperative day. Intravenous antibiotics were administered for 48 hours after the surgery followed by oral antibiotics for 21 days. Both urethral and suprapubic catheters (SPC) were kept *in situ* for 21 days. After which a trial without catheter was performed in the clinic. The SPC was removed after a successful trial without catheter. All patients were followed up for 3 months and then discharged to a general practitioner's care if well and symptom free.

1.4 Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences v17.0 software. Descriptive statistics were analysed for statistical significance ($p<0.05$) using chi-square test and Student's t-test for categorical and continuous variables, respectively. Normal distribution of data was checked using Kolmogorov-Smirnov test.

Table 1. Preoperative characteristics of patients undergoing urethral diverticulectomy

	n	%
Age (± SD)	42.38 (±15.24)	
ASA score (%)		
ASA 1	48	60.8
ASA 2	31	39.2
Previous surgical intervention		
Yes	41	51.9
No	38	48.1
MRI localisation		
Distal	19	24.1
Mid-urethral	41	51.9
Proximal	17	21.5
Full length	2	2.5

SD: Standard deviation, MRI: Magnetic resonance imaging, ASA: American Society of Anesthesiologists

Results

2.1. Patient Characteristics

A total of 79 patients were included in the analysis. The age at presentation was 42.38 (minimum: 18 maximum: 72) years. More than half of the patients (41/79) had previous surgical intervention for UD at the time of presentation (Table 1). All patients had an American Society of Anaesthesiologists score of either 1 or 2 on preoperative evaluation, and all but 1 patient were considered to be unfit for the prone position.

2.2. MRI Features of the Diverticulum

All patients underwent postvoid MRI scan to confirm the diagnosis and plan the surgery. The mean size of the diverticulum was 25.0 mm (minimum: 8 maximum: 48), and most of the diverticula were located in the mid-urethra (51.9%) followed by distal urethra (24.1%) and proximal urethra (21.5%).

2.3. Perioperative Characteristics

UD excision was undertaken in prone position in 50 (63.3%) and supine position in 29 (36.7%) patients. The mean duration of operation was 97.7 (±44.6) and 171.6 (±38.5) min in supine and prone position groups, respectively. Patients in the prone position group were older and had relatively larger and proximal UD (Table 2). On the multivariable analysis of factors of "size of the UD, age and location of the UD", only those with distal UD indicated undergoing a surgery in the prone position.

2.4. Outcomes

Table 2. Comparison of peroperative characteristics of patients undergoing excision of urethral diverticulum in supine and prone positions

	Supine (n=29)	Prone (n=50)	p-value
Mean operative time, minutes (± SD)	97.7 (44.6)	171.6 (38.5)	0.001
Mean diverticulum size (± SD)	19.9 (8.5)	27.6 (11.2)	0.002
Diverticulum localized at mid/ proximal urethra	12/28	47/50	0.001
Patients with prior surgery	14/28	27/50	0.39
Age	33.8 (18.4)	46.7 (11.2)	0.01

SD: Standard deviation

The median length of hospital stay was 5.2 (±3.5) days, and the mean time for removal of catheters was 18.8 (±8.5) days. The mean follow-up was 7 (±6.8) months. In 93.6% of patients, complete resolution of symptoms was achieved. Only 3 (6.4%) patients continued to have symptoms after excision.

With regards to postoperative complications, one patient had a Martius flap infection that resolved after intravenous antibiotic treatment, one patient had a postoperative UTI needing hospitalisation and one patient failed to empty her bladder in the first trial without catheter. No anaesthesia-related complications were noted.

Discussion

Urethral diverticulectomy can safely and effectively be performed both in prone and supine positions. Anticipated advantages of prone position include better exposure of the surgical field and tissue planes visualisation especially in cases with more proximal UD. Meticulous dissection of the UD from the surrounding tissues is important in these surgeries as the nerves and blood vessels of the vaginal mucosa are concentrated in the lamina propria (6). Excessive bleeding can occur together with inadvertent damage to the nerves if the anterior vaginal wall dissection is not performed properly avoiding this area. Therefore, dissecting through the avascular plane is essential to achieve better surgical outcomes in UD excision.

In this retrospective series, prone patient positioning seems to prolong the operation time; however, patients in the prone position group had significantly bigger and more proximal UD. The multivariable analysis showed that in our centre, the prone position was preferred over supine positioning in patients with more proximal UD.

We have previously described prone positioning in UD excision. Several other steps were taken to improve surgical field exposure. These include the use of Park's anal retractor and retraction of the buttocks with an adhesive tape. All these measures might have had an effect on surgical outcomes. Additionally, being a referral centre, all the theatre staff and anaesthetists on these surgeries were quite experienced. One can assume that first time users of this position can expect longer operative times with less experienced staff and anaesthetists. Close collaboration and effective communications within the surgical team is essential for the success of this approach.

Study Limitations

The main limitation of this study is its retrospective nature and selection bias. Patients appear to be selected to prone group when they had a larger and more proximal UD. Also patients in the prone position group were older. Therefore, a selection bias is found in this study.

Conclusion

Prone patient positioning can be performed safely and effectively when excising urethral diverticulum in females.

Prone positioning appears to prolong the operative time; however, patients in the prone position group have diverticula that are more difficult to excise. Therefore, a conclusion was not made on why exactly operative times are longer in the prone group in this study. Further studies that compare these two positions are necessary.

Ethics

Ethics Committee Approval: Ethics committee approval is not necessary for this study as it does not involve any experimentations in animal or human tissues.

Informed Consent: This is a retrospective chart review.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.M., Design: N.M., Data Collection or Processing: N.M., R.I., Analysis or Interpretation: N.M., Literature Search: N.M., Writing: N.M., R.I., C.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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Challenges in Laparoscopic Simple Nephrectomy of Non-functioning Kidneys Due to Urolithiasis

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What's known on the subject? and What does the study add?

Laparoscopic simple nephrectomies due to atrophic kidneys may be challenging owing to the presence of fibrotic and inflammatory adhesions. Especially, nephrectomies for xanthogranulomatous pyelonephritis are associated with various difficulties. This study found that xanthogranulomatous pyelonephritis was the main pathology of all cases converted to open surgery. In addition, 19% of the complications had Clavien-Dindo score>1, which is relatively less than reported in the literature.

Abstract

Objective: Simple nephrectomies may be challenging owing to the fibrotic and inflammatory processes that extend to the renal hilum and perirenal adipose tissue. This study aimed to investigate the complications of laparoscopic nephrectomies for atrophic kidneys.

Materials and Methods: Data of patients who underwent laparoscopic nephrectomy for atrophic kidneys were retrospectively evaluated. Preoperatively, all patients had undergone biochemical examinations, computed tomography and scintigraphic studies. The localisation of the stone, affected side, size of the atrophic kidney and presence of fistula and abscess were evaluated radiologically in the preoperative period. The pathology results of the patients were also assessed.

Results: A total of 53 patients were included. Conversion to open surgery was necessary in 3 (6%) patients. Pathology reports of these patients revealed xanthogranulomatous pyelonephritis. Moreover, 10 (19%) patients had Clavien-Dindo score >1. Postoperative fistula or abscess formation was not observed in any patient. None of patients had dialysis or sepsis in the postoperative period. Compared with the preoperative data, postoperative creatinine and blood urea nitrogen values were significantly increased.

Conclusion: Although laparoscopic nephrectomy is a gold standard treatment option, especially for atrophic kidney, nephrectomies for xanthogranulomatous pyelonephritis can become challenging even for the most experienced surgeons. Thus, surgeons should be always ready to transition to open surgery and be aware of the occurrences of complications in the perioperative and early postoperative periods.

Keywords: Laparoscopy, nephrectomy, urolithiasis, atrophic kidney, xanthogranulomatous pyelonephritis

Introduction

The incidence of upper urinary tract stones is increasing worldwide (1). Clearly, minimally invasive treatment options have increased in parallel with technological developments in the last 30 years. However, still, in Turkey, many patients have not received treatment or have delayed treatment due to stone-related diseases. In patients with severe renal impairment due to stone-related diseases, nephrectomy may be required in some cases. Nephrectomies were performed for recurrent urinary tract infection, pain, severe hydronephrosis (pouch kidney), abscess formation and fistula formation (2).

The level of surgical difficulty increases because of the fibrotic and inflammatory processes extending to the renal hilum and perirenal adipose tissue. Therefore, complications may be encountered more often in simple nephrectomies than in kidney

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tumour nephrectomies because of the non-functioning kidneys. Perhaps, the most challenging procedure in this scenario is laparoscopic nephrectomy performed in patients with xanthogranulomatous pyelonephritis. In some cases, the chronic inflammatory process may have caused the development of squamous urothelial cancer, which had been overlooked with preoperative imaging techniques (3). The complication rates in these patients are higher than in patients who underwent nephrectomies for renal tumours. These complications include conversion to open surgery, bowel injuries (most importantly duodenum injury), solid-organ injuries (such as the liver and spleen), major vascular injuries (e.g. renal vessels, aorta, vena and cava), pneumothorax, port site infection and subcutaneous emphysema (3-5). If the procedure requires a laparoscopic approach, the surgeon must have a high level of experience.

Clayman described the first laparoscopic nephrectomy in 1991 (6). This procedure demonstrated shortened hospitalization time, short recovery time, less bleeding, postoperative pain as well as cosmetic advantages (7). Because of these advantages, the laparoscopic method has become the gold standard for nephrectomy for acute benign and malignant diseases (2,8). However, simple nephrectomies performed by a laparoscopic approach can be very challenging and complicated than renal tumour nephrectomies, because of the aforementioned conditions. To our knowledge, only a few studies have examined the complications of simple nephrectomies and problems encountered in these surgeries (9). Thus, in this study, we aimed to investigate the difficulties and complications that we have encountered during laparoscopic simple nephrectomy for kidney atrophy due to urolithiasis.

Materials and Methods

Data of patients who underwent laparoscopic nephrectomy for atrophic kidneys between January 2013 and November 2018 were retrospectively evaluated. Informed consent was obtained for all patients. The local institutional review board approved the study (49109414-64.02).

All patients were over 18 years old, and their preoperative comorbidities and biochemical and radiological data were examined. Preoperatively, all patients underwent biochemical examinations, including renal function tests, complete urinalysis, urine culture examination, analysis of bleeding parameters, computed tomography (CT) and scintigraphic studies. Patients with positive urine culture were treated according to the antibiogram and then underwent surgery. In patients with clean urine culture, second-generation cephalosporin was administered as preoperative prophylaxis. Stone localization, affected side, size of the atrophic kidney and presence of fistula and abscess were evaluated radiologically in the preoperative period. Preoperative comorbidities were assessed according to American Society of Anesthesiologist (ASA) score (10), and perioperative and postoperative complications were evaluated according to the Clavien-Dindo Classification (11). The pathology results of the patients were also assessed.

All surgeries were performed through a transperitoneal laparoscopic approach. The standard laparoscopic nephrectomy procedure was performed with four trocars (one for the retraction of the liver) on the right side and three trocars on the left side. Renal pedicle vessels were clipped with hem-o-lock clips. Pathological specimens were usually removed by enlarging the incision through the trocar or using an Endo Catch specimen retrieval bag through the Pfannenstiel route.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences version 22 (IBM Corp., Armonk, NY, USA). Quantitative values are given as mean ± standard deviation for parametric data, while quantitative values for nonparametric data are presented as median [minimum-maximum (min-max)]. Categorical variables are presented as numbers and percentages. Shapiro-Wilk and Q-Q plots were used to check the normality of the variables. Data were expressed as mean ± standard deviation (range, min-max) or median (interquartile range) for continuous variables and described as counts (n) and percentages (%) for categorical variables. Since the preoperative and postoperative haemoglobin values conformed to a normal distribution, the difference between the two values was compared with the significance test. Serum creatinine and blood urea nitrogen values were compared using the Wilcoxon test because they were not normally distributed in the Shapiro-Wilk test. A p-value of less than 0.05 was considered significant for all data.

Results

In total, 53 patients who underwent simple laparoscopic nephrectomy due to non-functioning kidneys were included. Scintigraphic evaluation data were available, and patients had <10% of kidney functions. The mean age was 55 (39-73) years. The mean operation time was 153 (75-215) min. The average body mass index was 28.3 (23-35) kg/m2. Thirty (57%) of the nephrectomies were performed on the left and 23 (43%) were performed on the right side (Table 1). Conversion to open surgery was necessary in 3 (6%) patients. Pathology reports of these patients revealed xanthogranulomatous pyelonephritis. However, preoperative CT results were not definitive for xanthogranulomatous pyelonephritis. In these cases, the renal pedicle could not be dissected because the renal hilum was very adherent. Therefore, open surgery was performed. Overall, four patients had Clavien-Dindo IIIb complications. One patient had a

colon injury, which was found intraoperatively and repaired by a general surgeon laparoscopically. One patient had minimal vena cava injury, which was endoscopically repaired and checked for haemostasis. One patient had a very minimal duodenal injury, which was repaired laparoscopically by the general surgeon. One patient developed ileus due to intestinal obstruction and underwent surgery to remove the bridges 72 hours later. As regards complications, 10 (19%) patients had Clavien-Dindo score >1. Postoperative fistula or abscess development was not observed in any patient. None of the patients were on dialysis or had sepsis in the postoperative period. Blood transfusion was performed in three patients, and postoperative fever was also observed in three patients. No significant difference was found between the mean preoperative and early postoperative haemoglobin values [t (52)=-1.284, p=0.205]. Clavien-Dindo classification of the complications is summarised in Table 2. In total, pathology reports of 48 (91%) patients revealed chronic pyelonephritis. Xanthogranulomatous pyelonephritis was reported in 5 (9%) patients (Table 1). Kidney function tests of the patients were checked at the third month after surgery; the preoperative median creatinine level was 1.01 (0.78-1.23), and the postoperative level was 1.32 (0.88-1.61), presenting a significant difference (z=-6.301, p=0.000). Similarly, the median blood urea nitrogen levels in the preoperative and postoperative periods were 29 (14-41) and 33 (13-80), respectively, and the difference was significant (z=-5.648, p=0.000).

Table 1. Demographic, clinical, surgical, and pathological characteristics of the patients

Characteristics	Patients
Age (year)	
Mean (min-max)	55 (39-73)
Gender	
Female	33 (62%)
Male	20 (38%)
BMI (kg/m$^{2)}$	
Mean (min-max)	28(23-35)
Kidney	
Right	23 (43%)
Left	30 (57%)
Renal Size, mm	
Mean (min-max)	107 (69-133)
ASA	
I	22 (41%)
II	29 (55%)
III	2 (4%)
IV	0
Operation duration (min)	
Mean (min-max)	153 (75-215)
Pathology report	
Chronic pyelonephritis	48 (91%)
Xanthogranulomatous pyelonephritis	5 (9%)
Conversion to open surgery	3 (6%)

BMI: Body mass index, ASA: American Society of Anesthesiologists, Min: Minimum, Max: Maximum

Table 2. Postoperative complications data according to the Clavien-Dindo Classification

Clavien-Dindo	N (%)
I	0
II	6 (11%)
IIIa	0
IIIb	4 (8%)
IVa	0
IVb	0
V	0

Discussion

Urolithiasis is the most common benign disease that requires nephrectomy by impairing renal function. Recurrent infection, chronic pain and hypertension that cannot be corrected by antibiotic therapy necessitate nephrectomy in patients with urolithiasis (12,13). However, laparoscopic nephrectomy can be much more challenging than radical nephrectomies. This is because recurrent infections cause an intense inflammatory reaction and the kidneys become adherent to the surrounding tissues. Besides, severe inflammatory reactions developed around the renal pedicle in these patients, which may make the dissection of the renal pedicle difficult and sometimes impossible via the laparoscopic route.

Laparoscopic surgery has become a gold standard treatment modality, especially for nephrectomy, in the last two decades. However, given the mentioned difficulties, serious complications can occur following laparoscopic simple nephrectomies. Recently, Zelhof et al. (2) analysed 1093 benign nephrectomies and reported the highest complication rate of 23.9% in patients with non-functioning kidneys caused by stones. In the same study, compared with radical nephrectomies performed only for T1 tumours, the overall complication rates (11.9% vs 10%), open surgery rates (5.9% vs 3.3%) and blood transfusion rates (4.8% vs 2.8%) were higher in benign nephrectomies (2). Again, in a recent study that included 149 patients, 19.3% of the patients developed complications of Clavien-Dindo score >1, and the vascular injury rate was 3.3% (9). In our study, the overall complication rate was 19%, that is, 10 patients had complications with Clavien-Dindo score >1. A vena cava injury with minimal area occurred in one patient during surgery, and it was repaired laparoscopically.

Among other conditions, kidney size has been reported to increase the complication rates. Manohar et al. stated that the complication rate was high in patients (n=84) with kidney size >10 cm (14). In another study, the kidney size associated with increased risk of complications was >12 cm. In the present study, the mean kidney size was 107 mm; however, when patients were evaluated in terms of complications, the kidney size was not a factor affecting the complication rate. In the literature, studies have indicated that the risk of complications significantly increases with a high ASA score, which is essential in predicting preoperative complications (9,15). We cannot comment on this issue because only two of our patients had ASA 3 and none had ASA 4.

Conversion to open surgery is often observed in laparoscopic benign nephrectomies. Its rate is even higher in patients with xanthogranulomatous pyelonephritis. In a series of 62 patients, the rate of conversion to open surgery was 7.2% (3). In addition, this rate was as high as 28% in a series of 50 patients (16), but it was 19.2% in the study by Danilovic et al. (9). In their extensive research, Permpongkosol et al. (17) reported 5.9% and 2.9% for laparoscopic simple nephrectomy and radical nephrectomy in 2775 patients, respectively. In our study, the rate of conversion to open surgery was 6%, and all pathology results of these cases revealed xanthogranulomatous pyelonephritis.

Radical nephrectomy is an independent risk factor for decreased renal function. Acute renal failure accounted for 0.4% of radical nephrectomy. However, few studies have evaluated renal function after nephrectomies for atrophic kidneys (17,18). A study stated that 6.7% of patients who had undergone laparoscopic simple nephrectomy need dialysis in the first 6 months of follow-up (9). In our study, at 3 months postoperatively, both creatinine and blood urea nitrogen levels indicated a deterioration in renal functions.

Study Limitations

This study has certain limitations. First, we included a small number of patients. Second, our patients were not compared with those who underwent laparoscopic radical nephrectomies. Finally, the hospital where the surgeries were performed is not tertiary medical centre; this may have caused a tendency to perform surgery in patients with less comorbidity, albeit involuntarily. Although laparoscopic nephrectomy is a multidimensionally evaluated and established surgical method, very few studies have precisely assessed the complications of laparoscopic nephrectomies for non-functioning kidney urolithiasis; thus, the results of the present are valuable.

Conclusion

Although laparoscopic nephrectomy is a gold standard treatment option for nephrectomy, especially atrophic kidney, nephrectomies for xanthogranulomatous pyelonephritis can become challenging even for the most experienced surgeons. In our study, xanthogranulomatous pyelonephritis was found to be the main pathology of all cases converted to open surgery. However, preoperative CT results did not specifically present in any of these cases that the diagnosis could be xanthogranulomatous pyelonephritis. In the light of our study and the literature, laparoscopic simple nephrectomies performed primarily for xanthogranulomatous pyelonephritis can be challenging and complicated.

Ethics

Ethics Committee Approval: This retrospective study was approved by the institutional review board and was performed in accordance with the ethical standards.

Informed Consent: Informed consent was obtained for all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Y., Concept: G.Y., Design: G.Y., Data Collection or Processing: G.Y., A.F.B., Analysis or Interpretation: A.F.B., Literature Search: Ö.K., A.F.B., Writing: Ö.K., A.F.B., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
General Urology

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Extremely Rare Localization of Bladder Stone: Scrotal Bladder Hernia

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Abstract

Inguinoscrotal bladder hernia is rarely encountered relative to the common occurrence of inguinal hernia. Most patients are asymptomatic and diagnosed perioperatively; however, lower urinary tract symptoms along with swelling in the inguinal region and two-stage urination may suggest herniated bladder. Co-occurrence of inguinoscrotal bladder hernia and herniated bladder stone is extremely rare, and there is no consensus on its treatment. Herein, we will present the case of an 81-year-old male patient with an inguinoscrotal bladder hernia and herniated bladder stone. To our knowledge, this is the seventh case reported in the literature thus far.
Keywords: Bladder stone, stone, scrotal hernia

Introduction

An inguinal hernia is common among all hernias (80-83%); however, herniation of the bladder into the inguinal canal is a rare condition, which accounts for 1%-3% of hernia cases and occurs in 10% of men aged 50-70 years with obesity (1). Symptoms generally include inguinal pain or swelling associated with lower urinary tract symptoms (LUTS) and a decrease in scrotum size after voiding. Findings of ultrasonography (USG), computed tomography (CT) and cystography, as well as a physical examination, are used for diagnosis. Surgical repair is the best treatment option in large and symptomatic bladder hernias (1). Co-occurrence of an inguinoscrotal bladder hernia (IBH) and herniated bladder stone is considerably rarer, and few cases have been reported in the literature (2-7). This paper aimed to present a patient who had IBH and herniated bladder stone and underwent surgery. To the best of our knowledge, this is the seventh case reported in the literature thus far.

Case Presentation

An 81-year-old male patient presented with swelling in the right groin for approximately 1 year, pollakiuria, difficulty in urination intermittently for 3 years and two-stage urination. He also had to squeeze his scrotum to complete urination. He had hypertension and had not undergone any surgeries. On physical examination, the patient had a large right inguinoscrotal hernia, and the swelling significantly decreased after micturition. Digital rectal examination revealed a large and smooth prostate. His body mass index was 31 kg/m^2, and his serum creatinine level and prostate-specific antigen were 0.9 mg/dL and 3.1 ng/dL, respectively. The residual urine volume was 310 mL, and the residual volume after voiding was 90 mL with a two-stage voiding pattern. Hernia sac and bladder herniation with stone were suspected on USG. CT showed that the bladder was herniated to the right scrotal region, and there was a 22 mm stone in the herniated part of the bladder (Figure 1). Cystoscopy was performed before right open inguinal hernioplasty and cystolithotomy under spinal anesthesia. The prostate was hypertrophic, the bladder mucosa was normal and no tumors or stones were detected in the bladder during cystoscopy. Thereafter, a right inguinal incision was performed, and the spermatic cord was found and retracted. The bladder was primarily repaired after the bladder was incised, and the stone was removed (Figure 1). The defect in the inguinal canal was repaired with polypropylene mesh, and the procedure was terminated after the herniated bladder

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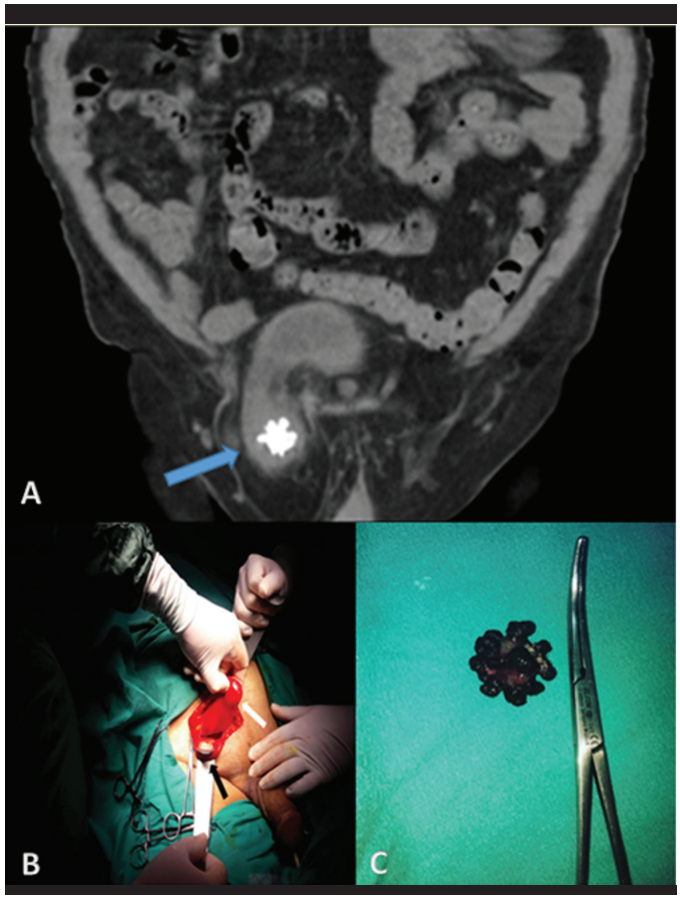

Figure 1. (A) Non-contrast CT coronal view demonstrates herniation of bladder into the right scrotum and view of the calculus inside the scrotum (blue arrow); (B) Spermatic cord (black arrow) and stone inside the herniated bladder (white arrow); (C) The stone removed from the herniated part of the bladder

CT: Computed tomography

was returned to its anatomical position. No problems were encountered in the postoperative follow-up, and the patient was discharged 3 days after the operation. The urinary catheter was removed on the seventh postoperative day. The two-stage voiding pattern disappeared at the six-week follow-up. Post voiding residual urine volume was 60 mL. Written informed consent was obtained from the patient to report this case study and publication of images.

Discussion

Bladder herniation is usually observed on the right side (8). Older age, obesity, surgical history in the inguinal region, increased perivesical adipose tissue, and diseases that increase intravesical pressure such as benign prostatic hypertrophy (BPH) and neurogenic bladder are considered predisposing factors for herniation (9). In this case, similar to most reports, the hernia was on the right side, and age, obesity and clinical symptoms of BPH were considered predisposing factors.

While cystography is the golden standard diagnostic method, USG and CT can provide valuable information about the location and content of the hernia (8). As in this case, the preoperative diagnosis was made only in less than 7% of IBH cases in patients undergoing inguinal hernia repair (8). CT should be performed prior to inguinal hernia repair in men aged >50 years with obesity, voiding symptoms and history of inguinal hernia repair. The standard treatment for IBH with bladder stone has not been established. Therefore, the patient's clinical conditions must be taken into consideration to determine the treatment method. Bladder resection can only be performed in cases with bladder wall necrosis, narrow hernia neck and tumors in the hernia bladder (10).

Postma and Smith (3) reported the first case of IBH with a herniated bladder stone. An 82-year-old male patient, who had LUTS and two-stage urination, was diagnosed with multiple calculi in the enlarged scrotum on direct radiography. Open hernia repair and open cystolithotomy were performed. Ptochos and Iosifidis (4) described a 67-year-old man who presented with acute retention of urine and opacity in the right groin, and this patient underwent open prostatectomy as well as open hernia repair and open cystolithotomy. In another study, a 77-year-old male patient who presented with acute urinary retention also had two-stage urination and open hernia repair and endoscopic cystolithotomy were performed (2). Moreover, a 55-year-old male patient presented with LUTS and swelling in the left hemiscrotum. His CT revealed two calculi in the herniated bladder, one of which was at the left ureterovesical junction. Open hernia repair, cystolithotomy in the region of the herniated bladder and extraction of the calculi from the bladder and ureter were performed (6). In a recent study, although an 82-year-old male patient was investigated for anemia, his CT showed a mass in the colon, right IBH and three stones with a diameter of 5-10 mm in the herniated bladder. The patient underwent open hernia repair, radical cancer surgery and endoscopic cystolithotomy (5). Two cases were reported in the latest study. The first case was not clinically different from previous cases. Unlike other cases, the 86-year-old patient was admitted with LUTS, hematuria and scrotal swelling. Dilatation was detected in the left renal pelvis and ureter on USG. CT showed that the herniating part of the bladder contained multiple calculi with a bladder tumor in the left wall. Open hernia repair, endoscopic cystolithotomy and bladder tumor resection were performed on this patient (7).

Although scrotal herniation of the stone-containing bladder is extremely rare, it should be considered in older men with LUTS who have an inguinal hernia. Urologists and general surgeons should be aware of the diagnosis and complications IBH.

Ethics

Informed Consent: Written informed consent was obtained from the patient to report this case study and publication of images.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., H.D., Concept: Y.K., S.T., T.N.Y., Design: Y.K., S.T., T.N.Y., Data Collection or Processing: M.B.D., Analysis or Interpretation: M.B.D., Literature Search: M.B.D., Writing: M.B.D., Y.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Endourology

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A Case of Incidentally Detected Urothelial Carcinoma of Renal Pelvis

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Abstract

Urothelial carcinomas of the renal pelvis are rare malignancies presenting commonly in older individuals and are characterised by flank pain, haematuria and palpable mass. Squamous differentiation is a common urothelial carcinoma and is usually associated with factors causing chronic irritation such as renal stone, infection and inflammation. We report a case of a young male patient who was incidentally diagnosed with right pelvic-ureteric junction obstruction during evaluation for Hodgkin lymphoma. After completion of chemotherapy for Hodgkin lymphoma, the patient underwent laparoscopic Anderson-Hynes pyeloplasty. The resected adynamic segment part of the pelvic-ureteric junction was sent for histopathological examination, which showed high-grade urothelial carcinoma with extensive squamous metaplasia. The patient was further managed with laparoscopic radical nephroureterectomy and lymphadenectomy. Our report is the first case of an incidental histologically detected urothelial carcinoma in a young patient without any radiological mass lesion.
Keywords: Urothelial carcinoma, pelvic-ureteric junction obstruction, squamous metaplasia, renal pelvis, pyeloplasty

Introduction

Upper urinary tract tumours involving the renal pelvis and ureter are relatively rare and seen in less than 5% of renal tumours. In a study, renal pelvic tumours accounted for 11.1% of all tumours, with the majority of urothelial origin (1). We report a rare case of urothelial carcinoma with extensive squamous metaplasia presenting as pelvic-ureteric junction obstruction that was diagnosed in the resected stenotic segment during Anderson-Hynes pyeloplasty. This histological diagnosis determined in the absence of typical symptoms or radiological mass lesions is notable from a clinical standpoint.

Case Presentation

A 28-year-old male, non-smoker, driver by occupation, presented with complaints of breathlessness, cough and 1-month weight loss. He had no history of abdominal pain, fever, haematuria or lower urinary tract symptoms. General and systemic physical examination were unremarkable. Routine haematological, biochemical and urinalysis findings were normal. Contrast-enhanced computed tomography (CT) chest and whole-body positron emission tomography (PET) scan revealed fluorodeoxyglucose (FDG) avid level IV cervical lymph nodes, mediastinal lymph nodes and gross dilatation of the right renal pelvis with cortical thinning (5-8 mm); the normal ureter was diagnosed with pelvic-ureteric junction obstruction (Figure 1). No FDG lesion was noted in the right pelvis, ureter and hilar region. Excisional biopsy of the right supraclavicular lymph node showed nodular sclerosis Hodgkin lymphoma (stage III). The patient was started on chemotherapy for Hodgkin

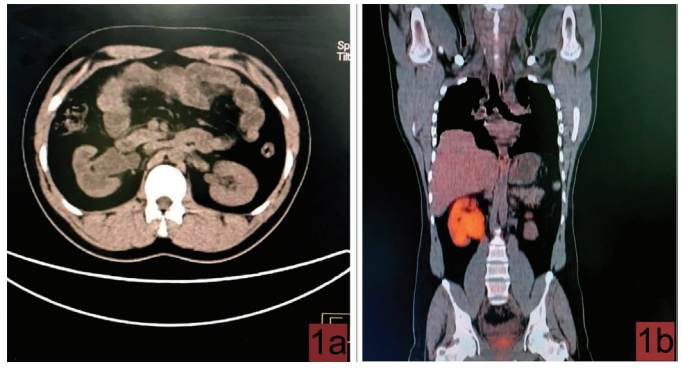

Figure 1. 1a. Axial section of computed tomography scan showing dilated right renal pelvis with parenchymal thinning. 1b. Coronal section of positron emission tomography scan showing physiological uptake in the right renal pelvis

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lymphoma; after completion of six sessions of adriamycin, bleomycin sulphate, vinblastine sulphate and dacarbazine chemotherapy, he was referred for obstruction management. Diethylenetriaminepentacetate scan revealed type 2 obstructive renogram curve with T1/2 of right kidney 26 min, glomerular filtration rate of 26.4 mL/min and split function of 35%. The patient underwent laparoscopic Anderson-Hynes dismembered pyeloplasty. Intraoperatively, large dilated pelvis was seen with tapering at the pelvic-ureteric junction, the stenotic segment was resected at approximately 1 cm, and reduction pyeloplasty was performed. Crossing vessels, peri-pelvic adhesions, or enlarged lymph nodes were not noted. No growth or any abnormal area was observed in the pelvis. Histopathology of the specimen showed high-grade transitional cell carcinoma with extensive squamous metaplasia. The underlying stroma showed extensive infiltrate by atypical squamous cells. Focal keratinisation was identified, and on immunohistochemistry, both p63 and GATA3 were positive in neoplastic cells (Figure 2). The patient then underwent laparoscopic radical nephroureterectomy with excision of the bladder cuff with lymph node dissection. No growth or abnormal area was visible in gross specimen. Histological examination revealed urothelial lining high-grade dysplasia at the pelvic-ureteric junction, with no lymph node invasion. The post-operative period was uneventful. The patient was asymptomatic during the 6-month follow-up, with no evidence of radiological or biochemical recurrence. Cystoscopy findings of the lower urinary tract were normal.

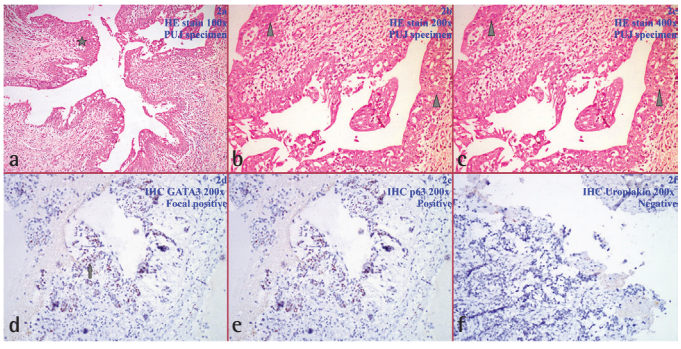

Figure 2. Microphotographs of Haematoxylin-Eosin stained sections of pelvic-ureteric junction lesion show urothelial lining (star 2a;100x) with foci of squamous differentiation (arrowhead 2b;200x, 2c;400x). Tumour cells show immunopositivity for GATA3 (arrow 2d; 200x) and P63 (arrow 2e; 200x) and immunonegativity for uroplakin (2f; 200x)

Discussion

Urothelial carcinoma with squamous differentiation of the renal pelvis are rare malignancies of the upper urinary tract. The common causes for squamous metaplasia in the urothelium are long-standing renal calculi, chronic analgesic abuse, chemicals, vitamin A deficiency, smoking, schistosomiasis and radiotherapy (2).

Urothelial tumours of the renal pelvis are most common in older individuals aged 60-65 years. Men are mostly affected, accounting for >70% of cases. Most patients present with pain due to local extension or pelvic-ureteric junction obstruction, palpable mass and haematuria. Paraneoplastic syndromes such as hypercalcaemia and thrombocytosis may be associated in few cases. Radiological findings include a solid infiltrating mass with hydronephrosis, with or without calcifications (3).

Cases of squamous metaplasia associated with primary pelvic-ureteric junction obstruction have been reported; however, in most of them, a radiological mass lesion was detected or was non-functional due to large hydronephrosis (4,5). In our case, the patient had no risk factors associated with urothelial carcinoma and no radiological mass lesion was seen on CT scan or any FDG avid lesion on PET scan. Gross inspection of the renal pelvis did not show any mass lesion or calcification.

This histopathological diagnosis remains a diagnostic challenge. True squamous differentiation requires evidence of keratinisation, intercellular bridges, or both on routine haematoxylin-eosin staining (6). There are certain immunohistochemical differences between these areas and a conventional urothelial tumour component. In this case, focal areas of keratinisation were present and GATA-3 stain highlighted the presence of neoplastic urothelial cells.

The standard treatment for these tumours is surgery. Radiotherapy/chemotherapy provides marginal benefits only. Radical nephroureterectomy with excision of the bladder cuff is the treatment of choice in these patients (7).

We report a rare incidental diagnosis of urothelial carcinoma with extensive squamous differentiation in resected stenotic segment of pelvic-ureteric junction obstruction in a young patient with no risk factors. This case report highlights the significance of histopathological examination of resected stenotic segment and need for meticulous sampling of the renal pelvis by the pathologist in such specimens.

Ethics

Informed Consent: No specific patient photographs were used in this manuscript, so no informed consent for publication was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.C.D., N.S., Concept: A.H., G.S., Design: A.H., G.S., Data Collection or Processing: N.S., K.V.S., G.P.S.G., Analysis or Interpretation: S.C.D., Literature Search: A.H., G.S., K.V.S., Writing: A.H., S.C.D., G.S., G.P.S.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Urooncology

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Urothelial Carcinoma of the Upper Urinary Tract That Becomes Resectable After Neoadjuvant Chemotherapy: A Case Report and Review of the Literature

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Abstract

Upper tract urothelial carcinoma (UTUC) is less common than bladder cancer, but its incidence is increasing. Neoadjuvant chemotherapy (NAC) has been the treatment focus for locally invasive and high-grade UTUC. Herein, we aimed to present a case of a locally advanced non-metastatic UTUC, which was thought to be unresectable due to local invasion, but surgically treated successfully after NAC. A 64-year-old male patient was admitted to another hospital because of right flank pain, which was not accompanied by macroscopic haematuria. He did not have comorbidities in his anamnesis, but he had a history of smoking 40 packs/year. A locally invasive right kidney tumour was detected in cross-sectional imaging performed at another hospital. He underwent surgery in that hospital, but radical nephroureterectomy could not be performed because of local invasion. He presented to our urology department. He was subsequently started with cisplatin-based NAC, which led to the resolution of local invasion. After NAC, right radical nephroureterectomy and ipsilateral bladder cuff excision with subcostal and Gibson incisions were performed. No signs of mass invasion or lymph node involvement were detected intraoperatively. He was examined 3 months after surgery. On cystourethroscopy, the bladder was normal and cytology was benign. No recurrence or metastasis was detected on the whole-body computed tomography. NAC is one of the valuable multimodal treatment options, enables surgery in locally invasive UTUC and contributes positively to survival rate.
Keywords: Oncology, urooncology, urothelial carcinoma, nephrectomy, nephroureterectomy, neoadjuvant chemotherapy

Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5% of urothelial cancers. Although UTUC is less common than bladder cancer, its incidence is increasing recently (1,2). Radical nephroureterectomy (RNU) and excision of the ipsilateral bladder cuff is the standard surgical procedure for the treatment of UTUC, and surgical treatment can often be curative alone (3). In recent years, organ-sparing approaches have also been considered in some selected cases. Although the standard treatment is RNU, recurrence rates after the surgical approach in locally advanced diseases are quite high, and growing evidence shows the role of both adjuvant chemotherapy (AC) and neoadjuvant chemotherapy (NAC) (4,5). Especially in locally advanced disease, the pathological downstaging (PD) rates by NAC have been shown to contribute positively to survival (6).

Herein, we will present a case of a locally advanced non-metastatic UTUC, which was thought to be unresectable due to local invasion but successfully surgically treated after NAC.

Case Presentation

A 64-year-old male patient was admitted to another hospital because of right flank pain, which was not accompanied by macroscopic haematuria. He did not have comorbidities in his anamnesis, but he had a history of smoking 40 packs/year.

Computed tomography urography was performed after ultrasonography and detected a mass in the right kidney. A 60×85×100 mm^3 infiltrative mass extending to the renal pelvis was detected in the upper and middle calices of the kidney (Figure 1). At the level of the renal hilus, two lymph nodes of 25 mm and 26 mm in diameter were observed anterior to the inferior vena cava. The mass infiltrated the perirenal fat. No metastatic focus or extra pathology was detected in chest computed tomography.

On cystourethroscopy, no tumour was observed in the bladder, so RNU was arranged in the first hospital, but RNU could not be performed. His operation report stated that the abdominal wall muscles were cut through the right subcostal incision and

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entered into the abdominal cavity. The right colon was released, and the right kidney was reached. The surgery was terminated because renal pedicle release was not possible due to inferior invasion of the vena cava.

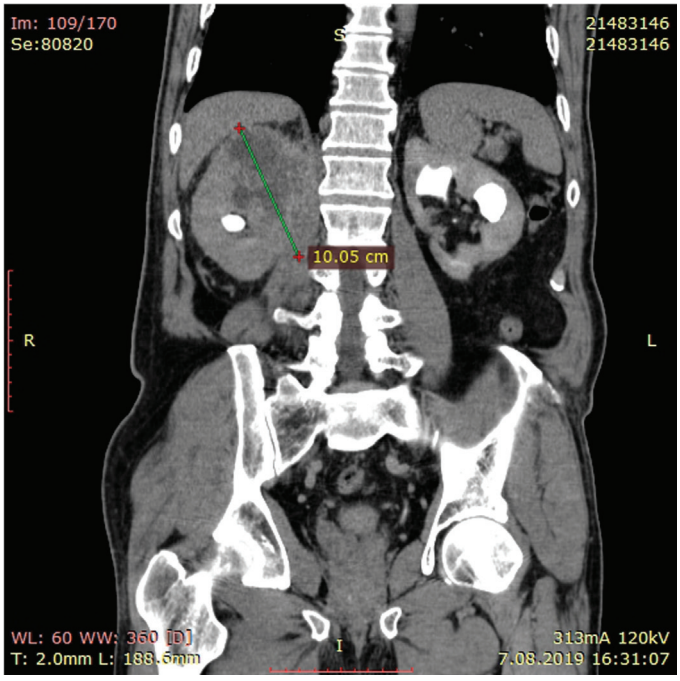

Figure 1. Before neoadjuvant chemotherapy

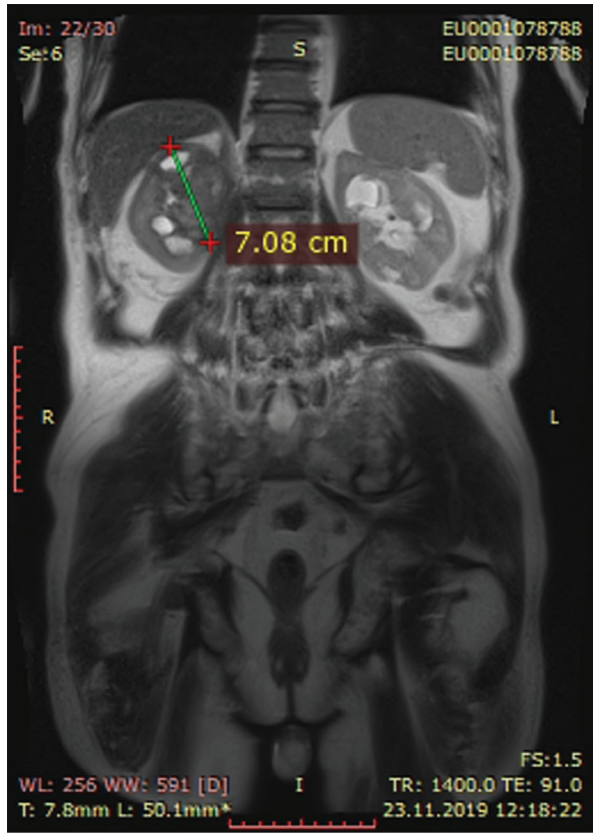

Figure 2. After neoadjuvant chemotherapy

He was referred to our urology department, and a renal biopsy was then performed. NAC was initiated because his renal biopsy histopathological examination finding was compatible with urothelial carcinoma and a local invasive mass was found in the right kidney. The patient received two cycles of gemcitabine (1,000 mg/m^2) and cisplatin (80 mg/m^2). Magnetic resonance imaging was performed for restaging after NAC, which revealed that the mass in the right kidney regressed to 53×60×70 mm^3, and the two pre-existing lymph nodes disappeared (Figure 2).

Right RNU and ipsilateral bladder cuff excision with subcostal and Gibson incisions was performed. No signs of mass invasion or lymph node involvement were detected intraoperatively (Figure 3). Histopathological diagnosis was interpreted as pT4 urothelial carcinoma, and the surgical margins were clear (Figure 4).

The patient was examined 3 months after surgery. On cystourethroscopy, the bladder was normal and cytology was benign. No recurrence or metastasis was detected on the whole-body computed tomography. Written informed consent was obtained from the patient.

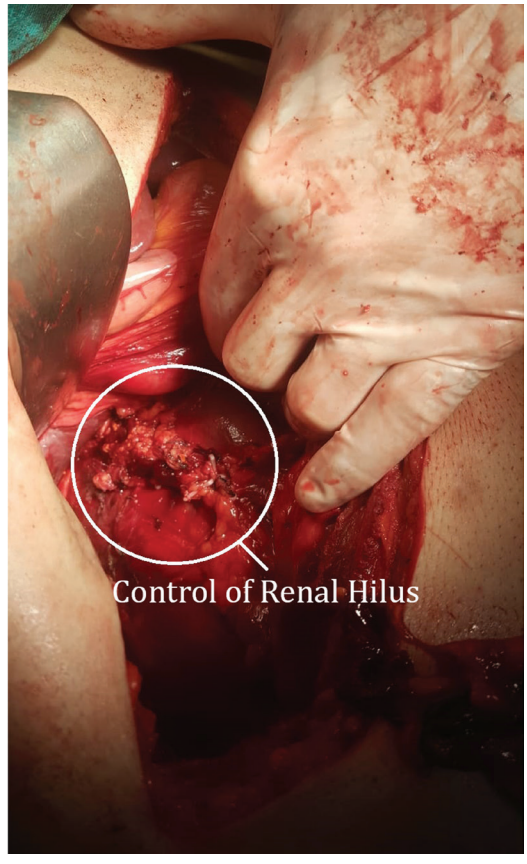

Figure 3. Renal hilus control

Discussion

Evidence on the effectiveness of NAC is based on the results of AC treatment for bladder cancer (1). Compared with AC, NAC may be

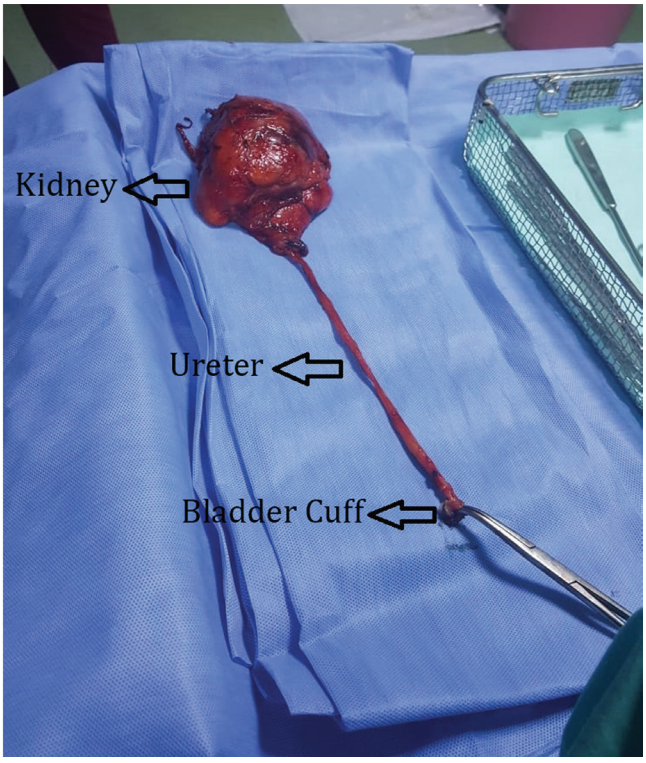

Figure 4. Postoperative view of specimen

considered as a more effective treatment option for UTUC, because some patients cannot receive cisplatin-based AC due to postoperative kidney function impairment (7-9). Cisplatin-based NAC can result in higher pathological complete response (PCR) and PD rates than other chemotherapy regimens, but creatinine clearance must be >50 mL/min for the suitability of this treatment (10). Therefore, preoperative chemotherapy treatment may be more advantageous.

Although UTUC is morphologically similar to bladder cancer, different phenotypically and genotypically malignancies exist because of the high rate of locally advanced disease development (11). The 5-year overall survival (OS) rates of locally invasive UTUC stage T2 and T3 were 73% and 40%, respectively. The median survival time was 6 months in T4 stage (12). Although RNU is the standard treatment for high-grade and locally advanced UTUC, its recurrence rate is quite high. Thus, NAC as treatment for bladder cancer might be considered to treat occult micrometastasis and provide PDs (8). In a recent meta-analysis, OS, cancer-specific survival and progression-free survival in patients receiving NAC were 57%, 59% and 45%, respectively, and PDs increased by 4.76-fold in the NAC-treated group (13). Compared with PCR after NAC, the PD is a stronger prognostic factor for survival rates (6,14). In a prospective study investigating the pathological response to NAC, the PCR rate was 14% and the PD was 60% (10). In our case, the pathological lymph nodes disappeared in magnetic resonance imaging performed after NAC.

As stated in the European Association of Urology guideline, the NAC regimen used in bladder cancer is also effective in the treatment of UTUC (15). However, some patients may lose their chance to undergo surgery, or surgical treatment may be delayed due to the toxicity of chemotherapy after NAC (16). In a study of 61 patients who received NAC for high-grade UTUC, only one patient developed sepsis, but he eventually recovered, and none of the patients had lost their chances for surgery and they have progressive disease (17).

NAC cycle is still controversial for UTUC. A delay of >90 days for radical cystectomy was reported to be associated with a poor prognosis (18). In studies investigating NAC for UTUC, the tumour response was evaluated after two cycles of NAC within 90 days, in line with the recommendations for invasive bladder cancer treatment, and surgery was planned (19,20). Patients with insufficient tumour response (stable or progressive disease) received three or four cycles of NAC (20). Currently, only a few prospective randomised trials are underway for UTUC (21,22). These studies will shed light on NAC for UTUC. In our case, re-imaging was performed to evaluate tumour response after two cycles of NAC. After obtaining a tumour response, we decided to perform surgery.

Despite these data, NAC, which has level 1 evidence in locally advanced BC, has not been the standard treatment in locally advanced and high-grade UTUC, owing to the lack of prospective randomised studies (23).

Upon presentation to our department, we considered that the patient was an RNU candidate, but the case was judged as unresectable due to local invasion. As a result, we decided to initiate NAC. Thereafter, local invasion was resolved, and surgery was feasible and successfully performed. NAC is one of the valuable multimodal treatment options that should be kept in mind because it facilitates surgery in locally invasive UTUC and contributes positively to survival rate.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D., F.K., S.K., A.Ş., Concept: M.D., Design: M.D., Data Collection or Processing: M.D., Analysis or Interpretation: F.K., S.K., A.Ş., Literature Search: M.D., Writing: M.D.

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