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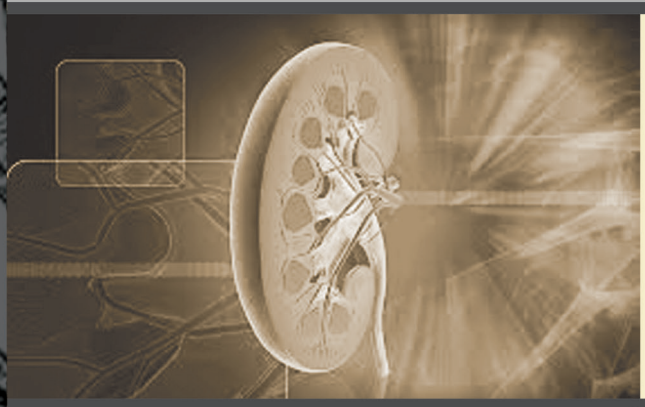

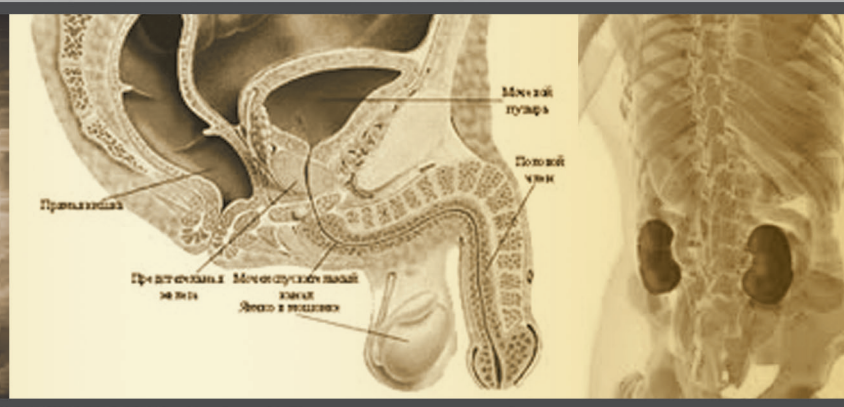

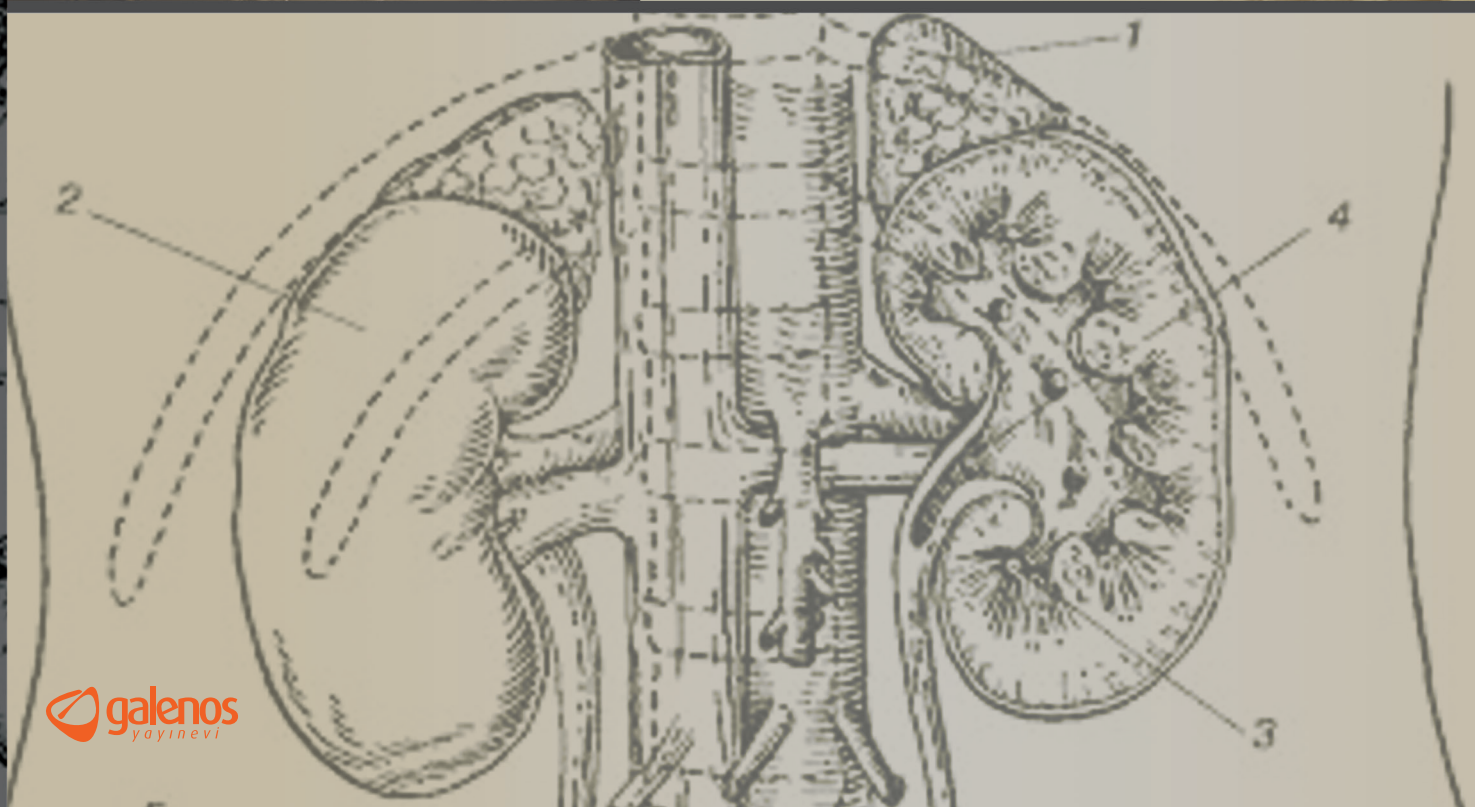

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REVIEW
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Invasion Mechanisms of Bladder Cancer: A Molecular Review

Mesane Kanserinde İnvazyon Mekanizmaları: Moleküler Bakış

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ABSTRACT

Bladder cancer (BC) is a very common cancer and it has high mortality rates, especially in late stages. BC is considered as a different disease in various stages and grades. Non-muscle-invasive BC and muscle-invasive BC have different properties. There are some prognostic factors for progression and recurrence rates of BC and we have some risk assessment methods. These factors are based on clinical findings and histopathological properties. We do not know which factors and molecular processes are effective in the invasion mechanism. In this review, we summarized possible invasion mechanisms of BC.

Keywords

Bladder cancer, invasion, metastasis, molecular

ÖZ

Mesane kanseri farklı evrelerde farklı birer hastalık gibi kabul ve tedavi edilir. Her evre tekrarlama ve ilerleme açısından farklı riskler taşır. Günümüzde bu tekrarlama ve ilerleme risklerini gösteren değişik hesaplama sistemleri tanımlansa da altta yatan moleküler, genetik ve çevresel faktörler net olarak gösterilememiştir. Mevcut risk hesaplama sistemleri klinik, makroskopik ve patolojik değerlendirme temellerine oturmaktadır. Derlemede özetlemeye çalıştığımız olası invazyon mekanizmaları aydınlatıldıkça prognostik yeni moleküler faktörlerin tanımlanması, hatta bu temelde yeni tedavi metodlarının geliştirilmesi mümkün olacaktır.

Anahtar Kelimeler

Mesane kanseri, invazyon, metastaz, moleküler

Introduction

Urothelial tumors are classified as papillary and nonpapillary (solid) tumors. Histopathologically, more than 90% of bladder cancers (BCs) are urothelial (transitional) cell carcinomas (UCC or TCC). At the time of diagnosis, about 75% of BCs are non-muscle-invasive bladder cancer (NMIBC) and remaining 25% are muscle-invasive bladder cancer (MIBC). Phenotypes and genotypes of these cancers in various stages are different. In this context, 30% to 50% of NMIBCs recur after transurethral resection of the primary tumor, and 10% to 20% progress to MIBC. Many of high-grade carcinomas (including carcinoma in situ) invade the bladder wall and may metastasize to other sites. Additionally, nearly 50% of patients with MIBCs have occult distant metastases at the time of diagnosis (1,2). Recently, in the literature, there are many studies in which molecular, genetic and physical factors have been investigated in the progression and recurrence of the BC but it has not been fully outlined. All these factors affect the process of metastasis, invasion and resistance to therapy. Generally, major characteristics of malignant cancer cells are defined as self-sufficiency in growth signals, insensitivity to anti-growth signals, tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis, and evading apoptosis. Additionally, tumor metastasis includes detachment, migration, invasion, intravasation, anoikis, evasion, and extravasation steps. In this review, we aimed to summarize the possible genetic, molecular and physical factors that are responsible for the progression and recurrence.

Epithelial-Mesenchymal Transition and Plasticity

Mechanism of the invasion/metastasis includes separation from the epithelial collective, degradation of the surrounding matrix, migration and invasion through the basement membrane, intravasation and survival in the circulation, extravasation at a secondary site, survival as micrometastasis, and, finally, growth into overt metastases (3). Epithelium is an important member of the growth, differentiation, division, apoptosis, tissue integrity and function. Epithelium is organized as sheets of cells attached to an underlying extracellular matrix (ECM) called basement membrane (BM), especially laminin. Epithelial cells are polarized along an apical basal axis and connected to each other by multiple cell-cell adhesive junctions (4). These ensure mechanical integrity of the epithelium and include adherens

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junctions (zonula adherens) and desmosomes (macula adherens). Both of them include a protein named E-cadherin and it is crucial for the current EMT process. MIBC expresses molecular markers of a developmental process known as 'epithelial-mesenchymal transition (EMT)'. On the contrary, mesenchymal cells do not form a layer neither are they attached firmly to a basement membrane. They contact other mesenchymal cells only focally and can migrate easily. EMT process include specification of a cell, disruption of the BM, change in the cell shape, withdrawal from the epithelial sheet and differentiation to a mesenchymal cell (5). Morphological features of a mesenchymal cell include front end-back end polarity, fibroblast-like view, elongate morphology (spindle-shaped), filopodia (front end cell membrane prominences interacting with the surrounding ECM) and invasive motility (6,7). As we know, cellular plasticity is fundamental to embryologic development and plasticity describes differentiation and transformation ability of a cell. EMT process is not cancer but plays an important role in tissue differentiation, organ development, embryogenesis, inflammation, tissue regeneration and wound healing. On the contrary to the EMT, mesenchymal-epithelial transition (MET) is critical for the later stages of metastasis (8,9). MET is a fundamental embryologic process, especially in the nephrogenesis. As we know, trigone region of the bladder and kidney develop from common embryologic origin and several growth factors are critical regulators of this process as wnt/wingless, bone morphogenic protein (BMP) family, fibroblast growth factor (FGF), fibroblast growth factor receptor (FGFR) and proteoglycans (PGs). There is evidence to suggest that the FGF family plays a fundamental role in cellular differentiation and tumor phenotype in bladder carcinoma via MET process (9). Recently, there is also accumulating evidence that EMT/MET plays important roles in cancer progression, invasion and metastasis, resistance to the apoptosis, and refractory responses to chemotherapy. It is characterized by downregulation of the homotypic adhesion molecule, E-cadherin, and proteins involved in cell polarity, with parallel upregulation of fibronectin (FN), vimentin, certain integrins, matrix metalloproteases (MMP), and several transcriptional repressors of E-cadherin expression (Twist, Snail, Slug, Zeb-1, Zeb-2) (10). These transcriptional factors, after binding to the complexes, translocate to the nucleus and transactivate target genes that include oncogenes and tumor suppressors. Vascular endothelial growth factor (VEGF) and FGF-2 are members of the EMT-related genes. Especially, FGFR plays a role in caellular differentiation and epidermal growth factor receptor (EGFR) is correlated with the transition from superficial to invasive BC. EGFR binds two specific ligands: EGF and transforming growth factor-alpha (TGF-α). Members of the TGF-beta/BMP family of cytokines are the best-characterized inducers of EMT, although many inflammatory cytokines (and their transcriptional target, NFκB) and developmental signaling systems (sonic hedgehog, Notch, and Wnt) play central roles in regulating EMT as well. In this process, polarized epithelial cells progressively alter their junctional and polarity complexes to acquire morphological and biochemical characteristics typical of mesenchymal cells (11). Recently, there have been many studies about tumor-initiating cells (cancer stem cells) in the literature. Sonic hedgehog (SHH)-expressing stem cells in basal cells within precursor lesion become tumor-initiating cells (12). Cells in the EMT process exhibit stem cell-like properties. Otherwise, there is no quantitative measure to assess the interplay between EMT and cancer progression (i.e. Spindle Index) (13).

Cadherins (calcium-dependent; types E, N, P) are transmembrane glycoproteins responsible for cell-cell adhesion. The cytoplasmic domain of the cadherins binds catenins (α, β, γ; plakoglobin) which mediate the connection between epithelial E-cadherin and cytoskeletal protein F-actin in adherens junction and desmosome. Interaction forces between two E-cadherin molecules are reported to be 200 nanoNewtons (14). Baumgart et al. (15) have reported that E-cadherin and N-cadherin were associated with the grade and stage of BC. E-cadherin is one of the hallmarks of an epithelial phenotype and N-cadherin is found in fibroblast and muscle cell connections. 'Cadherin switch' from E- to N-cadherin is descriptive for EMT process (15). P-cadherin is localized to the basal cell compartment. Rb tumor suppressor protein regulates E-cadherin expression. Integrin-linked kinase participates in signaling cascades resulting in E-cadherin repression. Alterations associated with the cadherin/catenin complex often feature at the center of EMT related to increased migration and invasion of cells (16). In addition to the N-cadherin, vimentin expression, the second mesenchymal marker, is linked to EMT and displays fibroblast morphology.

According to the recent studies, EMT is strongly associated with aggressive BC behavior, such as recurrence, progression, and metastasis. In the context of these data, increased possibility of the EMT may be a new target in BC treatment strategies. For example, loss of E-cadherin expression is a marker of poor response to the monoclonal antibody cetuximab, which blocks EGFR binding and thereby downregulates BC proliferation (17). In addition, EGFR and miR-200 family members have been found to be predictive of cisplatin-based chemo-responsiveness. EMT reversal may be associated with the responsiveness of high-risk patients with NMIBC to Bacillus-Calmette-Guerin treatment via tumor necrosis-related apoptosis-inducing ligand association. In the future, N-cadherin and Twist targeting therapies (i.e. ADH-1) will be useful for BC treatment.

There is increasing evidence that glicosphingolipids (GSLs) and glycosylation status of proteins play key roles in oncogenesis (18). GSLs and protein glycosylation are therefore expected to play some role in EMT process. The ability of GSLs and gangliosides to interact with various signal transducers, as well as with receptors for growth factors (GFs) or integrins, to define cell adhesion, motility, and growth were well established in many previous studies (19,20,21).

Cytoskeletal Filaments and Extracellular Matrix

The three major cytoskeletal filaments are the microfilaments (MF) (actin; polymerized highly conserved protein), intermediate filaments and microtubules. MF and microtubules (cytoskeleton) play an important role in cellular communication and intracellular transport and signaling processes, cellular movement and motility (cytokinesis), migration, differentiation, membrane organization, cellular growth, cell division, phagocytosis, and molecular transport between the plasma membrane and the nucleus. Increased motile activity, increased rate of cell proliferation and removal of growth inhibiting cell-cell contacts are hallmarks of tumorigenesis. Actin exists either in monomeric (G-actin) or polymeric forms (F-actin). Most filaments also contain a tropomyosin (TM) polymer that runs along the major groove in the microfilament (22). Microtubules are composed of α/β tubulin heterodimers. Intermediate filaments (IFs) are the principal structural determinants within cells. IFs can be divided into five

classes: keratins, neurofilaments, desmin, laminin, and vimentin. IFs are linked to the ECM and extend to the cytoplasmic interior that surrounds the nucleus.

The process of cell motility (CM) can be broken down into four steps; protrusion, adhesion, contraction and retraction. Successfully crossing many of the physiological barriers to tumor cell metastasis (i.e. basement membrane) requires specialized structures, such as invadopodia and podosomes. There exist different modes of cell migration, such as mesenchymal and amoeboid movement. Activation of CM and migration is caused by activation of receptors, turning on the growth cycle. Increased expression of MMPs, breaking cell-cell contacts allows journey of the malignant cancer cells. Most transmembrane proteins (GF receptors, adhesion proteins, ion channels) are either permanently or transiently associated with the submembranous system of actin MF. Redox control of the actin (MF) system in CM and migration is an emerging field of research. In a few studies, MIBC, which activates RhoA/ROCK signaling pathway, has been shown to promote the enhanced contractility of cells using amoeboid migration (23,24).

In this system, transmembrane proteins, linked to the submembranous actin force generator, are responsible for the first level of the CM, and shape and integrity of cells, whose four steps are:

1) Polymerization of actin into filaments,

2) Organization of filaments into ensembles by cross-linking proteins and by adhesions to extracellular structures,

3) Force-generation for large scale movements through interaction between actin filaments and different myosins,

4) Depolymerization of filaments to reform unpolymerized actin for new rounds of polymerization (25).

During this cycle, MF system is executed in response to interactions between the cell and surrounding environment, i.e., GFs, cytokines, other cells or extracellular matrices (local area network). Cell surface protrusions (lamellipodia and filopodia) are built of actin microfilaments, whose assembly takes place primarily at advancing edges of cells, and it is the polymerization of actin that provides the force for their protrusion (26,27). Myosin-dependent processes translocate molecules and particles along lamellipodial and filopodial MF arrangements. For example, integrins are transported towards the tip of filopodia and they become involved in filament growth and establishment of adhesion sites. Stress fibers (MF and myosin II) are used to move the whole cell (28). In tissues, cell-cell interactions engage different transmembrane proteins, e.g., cadherins which dynamically link actin microfilament arrangements in neighboring cells by mechanisms that are crucial in this process (29,30,31,32). Many of the proteins involved in the control of the MF system are products derived from proto-oncogenes. Endo- and exocytosis and formation of the podosomes, invadosomes, filopodia are major actors in this process. Actin filaments are attached to profilin in the cell. On the other hand, TM may be critically involved in the regulation of actin filament formation and function, as reflected in the alterations in TM isoform expression seen as a result of the development of the malignant state of cancers (33,34). GF-stimulated cells rapidly change their levels of TM isoforms in the cytosol, which coincide with actin polymerization, leading to formation of lamellipodia and filopodia. Gelsolin (fragmentation) and cofilin (disassembly) are important molecules in this phosphoinositides- and CM-cycles. In addition to polyphospho-inositides and small GTPases, transient generation of H_2O_2 seems to play important roles in regulating formation and activity of cell edge protrusions, integrin-mediated adhesion and migration (35,36). Cofilin controls crucial aspects of motility and migration of cells. Malignant cells have strongly altered levels of TMs in the cytosol and cytomatrix. High molecular weight and low molecular weight isoforms appear to influence different aspects of the functioning of the MF-system; one class primarily being involved in controlling the motile activity of lamelliopodia and filopodia, and the other controlling the formation of cell adhesions and stress fibers. Profilin, cofilin, TM, gelsolin, α-actinin, and vinculin, belonging to the MF system, are associated with malignant transformation. Cell migration is executed by repeated cycles of protrusion (actin polimerization), matrix adhesions (formation of focal complexes/ focal adhesions in association with actin filaments) and retraction (actomyosin force generation). Integrins appear at the outer edge of cell protrusions and presumably as a result of integrins interacting with the ECM, focal complexes (integrin, talin, paxilin, vinculin, zyxin, tensin) appear at a distance of about 1µm from the advancing edge (37,38). Recently, it has been discovered that stress forces from outside or actomyosin-dependent forces positively influence (mechanosensing) actin polymerization at the focal adhesions (39). Integrins execute cell-matrix as well as cell-cell interactions, whereas adhesion via the cadherin family of adhesion proteins is preferentially intercellular. Cadherin-cadherin interactions link the MF system of adjacent cells. For example, E-cadherin, the protypic member of the cadherin family, regulates cell adhesion in epithelial cells. During embryonic development, down regulation of E-cadherin function initiates a complex program wherein epithelial cells adopt a fibroblast-like phenotype and display tissue invasive activity, a process called EMT. Repression of E-cadherin appears to play a major role in EMT of epithelial-derived cancer types. E-cadherin repression frequently occurs in tandem with activation of the Wnt-signaling cascade (40).

Physical Factors and Reciprocity

Elasticity of BC cells (BCC) are strongly linked to the actin cytoskeleton (spatial 3D organization and density, stress fibers). Elasticity measurements are performed with an atomic force microscope at the cellular level. BCC have Young's moduli (Pascal-Pa) about 2-3 times lower than that of non-malignant cells. The low Young's modulus (higher cellular deformability) seems to occur at an earlier stage of cancer progression and it does not include the metastatic phenotype (41). Its occurrence depends on partial lack and/or depolymerization of the actin filaments. Evaluation of the stiffness can be used as a biomarker of BC. This configuration plays a dominant role in controlling the elasticity of BCC to an external force (i.e. intravesical pressure). MRI elastography will be useful instrument for this purpose (42). Effert and Seifert (43) reported that ultrasutructural analysis of microinvasions in the basal epithelial cells may help to evaluate the invasion capability for BCC by electron microscopy. Moreover, for tissue invasion, cancer cells are able to move out and infiltrate adjacent tissues by degrading enzymes. Cancer invasion can be described as a morphological instability that occurs during tumor growth and results in invasive 'fingering' and

branching. This instability may be driven by any physical or chemical condition. Adhesion molecules, such as cadherins are the determinant factor of the physical environment. In recent researches reported that, in 3D environments, E-cadherin deficiency indeed led to a loss of intercellular adhesion and triggered tumor cell invasion by matrix MMP-2 and MMP-9 driven matrix degradation. Surface tension at the tumor-tissue interface, have been extensively studied in the field of fluid dynamics (44,45,46,47). Promoting tumor cell adhesion and thus increasing the tumor surface tension can induce cellular cohesiveness and decreasing of the invasiveness. Microenvironmental pressure and tumor radius can be determinant of the invasion capability. Reducing the tumor size through and accompanying nonsurgical approaches may provide additional contributions by decreasing the invasion. Reducing the confining mechanical pressure exerted on the tumor can affect therapy results (i.e. adjuvant corticosteroid treatment).

Hyaluronan Regulation and Glycosaminoglycan

The urothelium, the epithelial lining of the bladder, also known as the transitional epithelium, is not just a simple barrier. It is now recognized as a specialized tissue that regulates complex bladder function. The surface of the urothelial umbrella cells carry a thin layer of glycoproteins and PGs, together forming a glycosaminoglycan (GAG) layer which constitutes a hydrophilic mucosal coating and a barrier against solutes or noxious substances in the urine (48,49,50). There is evidence that the implantation and seeding of viable tumor cells influence BC recurrence and endeavoring to prevent early implantation would appear to be a worthwhile therapeutic focus (51). The current clinical approach involves chemotherapy with instillations of cytotoxic agents, and two recent proposals under investigation describe an anti adhesive application and an antiangiogenic strategy (52). Providing a more protective barrier or blistering the GAG layer of the urothelium to prevent implantation of tumor cells is another option with therapeutic potential in recurrent BC (53).

Damage to the urothelial GAG barrier layer is thought to underline the pathologies of several chronic bladder pathologies. Penetration of urinary constituents into the bladder wall causes C-fiber activation, mast cell activation and histamine release. Protecting the urothelium or restoring the GAG layer to prevent the inflammation is the basis for clinical use of intravesical instillation (sodium hyaluronate-chondroitin sulfate). GAG replacement therapy in cancer is being investigated.

GAGs are unbranched polysaccharides composed of repeating disaccharide units of alternating uronic acids and amino sugars. Most GAGs are covalently attached to core proteins to form PGs. Dysregulated expression of GAGs can be associated with angiogenesis, cancer, inflammation, GF signaling, proteolysis of the environment, and cell behavior. Four major classes of GAGs have been identified: heparan sulfate, chondroitin sulfate/dermatan sulfate, keratan sulfate, and hyaluronan (HA). PGs are classified based on the amino acid homology of their protein cores, their location (cell surface, basement membrane, ECM) and their GAG substitution (54,55). Some PGs are substituted with more than one GAG chain type, such as syndecan-1 (heparan sulfate and chondroitin sulfate) and aggrecan (keratan sulfate and chondroitin sulfate), versican, perlecan, decorin, biglycan, glypican, etc. Cancer-related functions of GAG receptors and enzymes are involved in GAG synthesis and modification. GAG and PGs play important roles in multiple cancer-related processes. GAGs and PGs are effective in controlling cell proliferation. Cell surface heparan sulfate PGs serve as coreceptors for several GFs. Chondroitin sulfate PGs have a role as modulators of signal transduction and enhance focal adhesion kinase. Dermatan sulfate PGs decorin modulates EGFR signaling and controlling cell proliferation. The ability of cancer cells to invade into surrounding tissues involves changes in expression of cell surface molecules and the expression of ECM-degradative enzymes. GAGs and PGs are major constituents of the ECM and cell surface PGs mediate cell-matrix interactions. Changes in expression of these molecules reduce cell adhesion and promote cancer cell invasion. Versican inhibits cell adhesion to FN, syndecans acting in concert with integrins, HA signaling through CD44 contribute to increased cancer CM through signaling events that activate the cytoskeleton. Cancer cells also secrete matrix metalloproteinase (MMP), heparanase, hyaluronidases to penetrate the BM and ECM to invade surrounding tissues (56,57,58,59). Metastasis includes cancer cell dissemination into the circulation, adhesive interactions with endothelial cells, and colonization. Heparanase promotes invasion and metastasis by degrading heparan sulfate chains in cell surface and matrix heparan sulfate PGs (60,61,62). Syndecan-1 may regulate the adhesion of cancer cells to blood and lymphatic vessel endothelium or promote the association with different host cells during metastatic seeding. HA activates EMT. For a cancer to grow beyond a diameter of 2 mm, primary tumors and metastases require nutrient support from the vascular system. In this process, crucial molecules are VEGF, FGF, angiopoietins, GAGs, and PGs (56,63,64,65,66,67).

Proteinases contribute to all stages of diseases, especially cancer development and progression. ECM is a highly dynamic and functional network. Major ECM components are PGs, as well as fibrillar proteins, such as collagens and elastin, and other glycoproteins. In cancer, PG expression is often altered in the stroma and this might contribute to disease progression that is occurred via matrix proteinase. Extracellular proteases are actively involved in tumor progression and metastasis by degrading the majority of ECM macromolecules. Proteinase enzyme family catalyzes the hydrolytic breakdown of proteins into peptides or amino acids at their terminal ends (exopeptidases) or inside the peptide chain (peptidases). At least 569 proteinases are defined according to the MEROPS database and distributed intra and extracellularly which are classified based on the chemical moiety that participates in the hydrolysis (aspartic, cysteine, threonine, serine and metalloproteinases) (68). A single PG would be expected to interact and modulate more than ten proteases. Proteinases contribute to all stages of tumor progression, including tumor growth and survival, angiogenesis, cell invasion, cell adhesion, migration, EMT, and immune surveillance, and that they are produced not only by the tumor cells themselves, but also by the tumor microenvironment (69,70). Metalloproteinases and cathepsins are among the major families of proteinases implicated in cancer progression. Metzincin family of MMPs (including methionine residue and zinc) is comprised of matrix MMPs, a disintegrin and MMPs (ADAMs), ADAMs with thrombospondin motifs (ADAMTSs), bacterial serralysins, and proteases such as the astacins (including the meprins) (71,72). The current MMPs are classified into six groups as collagenases, gelatinases, stromelysins, matrilysins, membrane type MMPs, and other MMPs (73). MMPs are the main group of regulating proteinases in ECM. MMPs are responsible for the turnover and

degradation of almost all ECM components (collagen, laminin, FN), non-ECM cell regulators, integrin, kinases, chemokines and cytokines (Table 1) (74,75).

Heparin blocks the effect of MIBC exosomes on cell migration and invasion that uptake occurs through a heparin sulfate proteoglycan (HSPG)-dependent mechanism (76). HSPGs often act as a co-receptors for various integrin receptors and integrin receptors are well-established mediators of cell-matrix interactions (including tumor migration and invasion) (77,78,79,80,81). However, this mechanism remains to be elucidated.

Angiogenesis

Angiogenesis is fundamental to tumor growth, invasion and metastasis. Hypoxia plays a key role in tumor progression by modulating gene regulation and expression, such as hypoxia-inducible factor 1 (HIF-1). Another aspect of the tumor microenvironment that has a role in tumor metastasis is inflammation. Dysregulation of the normal wound healing processes in cancer can result in an influx of angiogenic cytokines from nearby immune cells contributing to metastasis.

The VEGF plays pivotal roles in tumor angiogenesis. Blockage of the VEGF signaling as a therapeutic target includes antibodies, aptamers, peptides and small molecules. For tumor clones to grow beyond 100-200 µm, they have to recruit new blood vessels by angiogenesis (82,83,84). Tumor angiogenesis also involves a complex interplay between the tumor and surrounding or supportive cells, including vascular endothelial cells, pericytes, smooth muscle cells, fibroblasts and tumor-associated macrophages (85). In response to hypoxia, tumor tissues produce angiogenic GFs such as VEGF, fibroblast GFs (FGFs), and platelet-derived endothelial cell growth factor. These angiogenic growth factors bind to their corresponding specific receptors located on the endothelial cells of preexisting blood vessels; various signal transduction pathways are activated to promote the activation of endothelial cells (86,87,88). Subsequently, the original vessels undergo characteristic morphological changes, including enlargement of the diameter, BM degradation, a thinned endothelial cell lining, increased endothelial number, decreased number of pericytes, and detachment of pericytes. At the sprouting tips of growing vessels, endothelial cells secrete MMPs to facilitate the degradation of extracellular tumor matrix and cell invasion (89). Cell surface adhesion molecules, such as integrins also play an important role in endothelial cell migration and in contact with the extracellular tumor matrix, facilitating cell survival (90,91). Next, a lumen within an endothelial cell tubule has to be formed, which requires interactions between the ECM and cell-associated surface proteins, among them are galectin-2, PECAM-1, VE-cadherin (92). A fast growing tumor almost always creates a hypoxic environment due to several interconnected reasons

Table 1. Extracellular molecules involved in cancer invasion

Category	Molecule	Type	Molecules co-involved in cancer cell invasion
	HA	Glycosaminoglycan	CD44
ECM molecules	FN	Glycoprotein	eHSP90, HSP90, MMP-9, FAK/PI3K/AKT/ERK/ NF-κB, PEDF
	Sibling	Small Integrin-Binding Ligand, N-linked Glycoprotein	Pro-MMPs, MMP-2, MMP-9, MMP-3, αvβ3 integrin, FAK/MEK/ERK/NF-κb CD44v6
ECM receptors	Integrins	Cell surface receptors	FN, MMP-9, MMP-2, FAK/ILK/ERK/PI3K/ NF-κb, EGFR, osteopontin
	CD44	Cell surface receptors	HA, osteopontin
Growth factors	TGF-β	Growth factors	TBRI, TBRII, Erk, Ras
	Heregulin	EGF-like growth and differentiation factor	ErbB3, ErbB4, PAK-1, AMF
Growth factor receptors	EGFR	Cell surface receptor	TGF-α, Grb-2, Ras/Raf/MEK/MAPK
	HER-2	Cell surface co-receptor	HER-3, eHSP90, MAPK, PI3K/AKT
	IGF-R	Cell surface receptor	IGFs, IRS-2, PI3K/AKT, Ras/Raf/MAPK
Matrix metallo proteinase	MMP-9	Zinc endopeptidase	eHSP90, HASP90, Rab40b, VAMP4, gelatin type IV, collagen, VEGF, bFGF
	MMP-2	Zinc endopeptidase	Gelatine, type IV collagen, eHSP90, HASP90, Rab40b, VAMP4, VEGF, bFGF
	CD-10	Zinc dependent metalloproteinase	Twist 1
Chaperones	eHSP90	Chaperon	Cdc37, FN, HER-2, EGFR, pro-MMP2, pro-MMP9
	eCdc37	Co-chaperon	HSP90, eHSP90, HER2, EGFR, Raf-1, CDK4, EGFRvIII, PJCS-AK
LRP-1	LRP-1	Low density lipoprotein receptor	Nexin-1 (PN-1), Erk pathway, MMP-9, eHSP90, EphA2, AKT1, AKT2

ECM: Extracellular matrix, LRP-1: Low density lipoprotein receptor-related protein 1, EGFR: Epidermal growth factor receptor, IGF-R: Insulin-like growth factor receptor, MMP: Matrix metalloproteases, VEGF: Vascular endothelial growth factor, TGF-α: Transforming growth factor-alpha, TGF-β: Transforming growth factor-beta, FN: Fibronectin, HA: Hyaluronan

including unsynchronized growth rates of tumor and endothelial cells, disorganized vascular architecture, sluggish blood flow and high interstitial fluid pressure (IFP) (93,94). Hypoxia leads to increased levels of HIF-1 alpha which increases VEGF expression. High level of VEGF could further increase vascular disorganization, permeability and IFP, leading to severe hypoxia in turn (95).

Tumor associated endothelial cells can acquire cytogenetic abnormalities while in the tumor microenvironment (intratumor ecosystem). Altered expression of VEGF has been observed in urothelial carcinoma of the bladder (UCB) cells (96). Elevated levels of VEGF expression have also been detected in urine samples from UCB patients and correlated with disease recurrence and progression (97). High level of VEGF expression in tumors and in serum samples from patients with UCB also predicted poorer prognosis and increased frequency of disease recurrence (98). Altered VEGF expression has been found to be associated with advanced pathological stage and lymph node metastasis (99). It is suggested that VEGF, in combination with other angiogenic factors such as angiogenin and MMPs, may serve as a biomarker for the diagnosis and prognosis of patients with UCB.

Conclusion

Each BC in various stages and grades is considered as a different disease. NMIBC is a well curable cancer, potentially it can display recurrence or progression. Moreover, 30% to 50% of these patients have recurrences after transurethral resection of the primary tumor, and 10% to 20% progress to MIBC. We do not know which factors are exactly responsible for recurrence and progression in BC. In this review, we summarized possible molecular factors in this process. In the future, there is need for more experimental studies on these processes for prognostic evaluation and treatment options of BC.

Ethics

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Fehmi Narter, Concept: Fehmi Narter, Design: Fehmi Narter, Data Collection or Processing: Fehmi Narter, Analysis or Interpretation: Fehmi Narter, Literature Search: Fehmi Narter, Kubilay Sabuncu, Writing: Fehmi Narter, Kubilay Sabuncu.

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Effect of Age on Outcome of High-Risk Non-Muscle-Invasive Bladder Cancer Patients Treated with Second Transurethral Resection and Maintenance Bacillus Calmette-Guerin Therapy

İkinci Transüretral Rezeksiyon Yapılan ve İdame Bacillus Calmette-Guerin Tedavisi Alan Yüksek Riskli Kasa İnvaze Olmayan Mesane Kanseri Hastalarının Sonuçlarına Yaşın Etkisi

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

High risk non-muscle invasive bladder cancer patients should be treated with maintenance Bacillus Calmette-Guerin (BCG) to obtain a reduce the risk of progression. The exact mechanism of action of BCG has not been clearly understood. However, there is clearly an action of immune system. Capacity of immune system decreases with advanced age and age has been shown to be associated with increased progression rates and decreased survival rates in patients receiving BCG. Previous studies are heterogeneous with respect to their population and they did not evaluate the effect of age on maintenance BCG response with the definition of progression involving Ta upstaging to T1.

ABSTRACT

Objective

To determine the effect of age on recurrence and progression rates in a population of high-risk non-muscle invasive bladder cancer (NMIBC) patients treated with a second transurethral resection (TUR) and at least 1 year of maintenance Bacillus Calmette-Guerin (BCG) therapy.

Materials and Methods

In this multicenter study, we reviewed the data of patients treated for high-risk NMIBC between 2005 and 2012. Patients without a muscle-invasive cancer on second TUR and received induction BCG and at least one year of maintenance BCG therapy and at least 12 months of follow-up after completion of maintenance BCG were included. Effect of age was analyzed both dichotomously (<70 or ≥70 years) as well as

ÖZ

Amaç

Bu çalışmada yüksek riskli kasa invaze olmayan mesane kanseri (KİOMK) nedeniyle ikinci transüretral rezeksiyon (TUR) yapılan ve idame Bacillus Calmette-Guerin (BCG) tedavisi alan hastalarda nüks ve progresyon oranlarına yaşın etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem

Bu çok merkezli çalışmada 2005-2012 yılları arasında yüksek riskli KİOMK nedeniyle tedavi edilen hastaların verileri incelendi. İkinci TUR da kasa invaziv olmayan, indüksiyon sonrası en az 1 yıl süre ile idame BCG tedavisi alan ve en az 12 ay tedavi alan hastalar dahil edildi. Yaşın etkisi hem iki grup olarak (<70 vs ≥70 yaş) hem de on yıllık artan gruplarda incelendi. Ki-kare, Student T-test ve ANOVA testi grupların karşılaştırılması için

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by 10-year increments. Chi-square test, Student's T-test and analysis of variance (ANOVA) were used for comparison of the groups. Univariate and multivariate logistic regression analyses were performed to identify predictors of recurrence and progression.

Results

Overall, 242 eligible patients were included. Baseline parameters were similar. With a mean follow-up of 29.4±22.2 months, neither 3-year recurrence-free survival nor 3-year progression-free survival differed between the age groups when examined either dichotomously or by 10-year increments.

Conclusion

In high-risk NMIBC patients treated with a second TUR and received maintenance BCG therapy, age was not associated with increased rates of neither recurrence nor progression. Until a randomized prospective clinical trial assess the appropriate adjuvant intravesical therapy in the elderly, elderly patients should probably be treated in the same manner as younger patients.

Keywords

Bacillus Calmette Guerin, age, nonmuscle-invasive bladder cancer, second transurethral resection

kullanıldı. Nüks ve progresyonu öngören faktörlerin belirlenmesi için tek değişkenli ve çok değişkenli lojistik regresyon analizi uygulandı.

Bulgular

Çalışmada 242 hastanın verileri değerlendirildi. Yaş gruplarının temel özelliklerinde fark izlenmedi. Ortalama 29,4±22,2 aylık takipte 3 yıllık nükssüz ve progresyonsuz sağkalım oranları açısından hem ikili grup hem de 10 yıllık artışlar ile yaş gruplanması ile fark saptanmadı.

Sonuç

İkinci TUR ve idame BCG ile tedavi edilen yüksek riskli KİOMK olgularında yaşın nüks ya da progresyon oranlarına etki etmediği görüldü. Ancak takip sürelerinin kısa olması nedeniyle fark gösterilememiş olabilir. Yaşlı hasta grubunda uygun intravezikal tedavinin belirleneceği bir randomize prospektif çalışma yapılana kadar yaşlı hastaların da büyük ihtimalle genç hastalar gibi tedavi edilmesi uygun olacaktır.

Anahtar Kelimeler

Bacillus Calmette Guerin, yaş, kasa invaze olmayan mesane kanseri, ikinci transüretral rezeksiyon

Introduction

Bladder cancer is the second most common malignancy of urinary system and non-muscle-invasive bladder cancer (NMIBC) accounting for about 75% of the cases (1). High-risk NMIBC patients should be treated with intravesical Bacillus Calmette-Guerin (BCG) therapy including a maintenance schedule after a 6 weekly induction to obtain a reduction in the risk of progression. Another important aspect of treatment is performing a second transurethral resection (TUR) performed within 2-6 weeks after initial resection to decrease the recurrence and progression rates (2,3,4).

The exact mechanism of action of BCG has not been clearly understood. However, detection of immune cells in the bladder wall and cytokines in urine clarifies the action of immune system (5). However, the capacity of immune system decreases with advanced age and age has been shown to be a parameter associated with increased progression rates and decreased survival rates in patients receiving BCG (6,7,8).

In the above mentioned trials, the study populations are heterogeneous as two important factors, maintenance BCG and a second TUR, were not performed in all patients (6,7,8). Besides, in these trials, progression was defined as upstaging to T2 or higher or presence of metastatic disease (6,7,8). However, in NMIBC, progression of Ta disease to T1 disease has been shown to be important (9) and the International Bladder Cancer Group involved progression of Ta disease to T1 disease in the definition of progression (10).

To our knowledge, there is no clinical trial evaluating the effect of age on response to maintenance BCG with the definition of progression involving Ta upstaging to T1. In this retrospective multicenter trial, we aimed to identify the effect of age on recurrence and progression rates in a population with high-risk NMIBC treated with maintenance BCG therapy.

Materials and Methods

The study was planned and performed by the Association of Urooncology of Turkey bladder cancer study group. Retrospective data of patients, who were treated for high-risk NMIBC between 2005 and 2012 and received induction BCG and at least one year of maintenance BCG, were collected from ten participating centers.

Patients were included if;

1) A high grade Ta or any T1 urothelial carcinoma with or without carcinoma in situ (CIS) was present in the first TUR specimen,

2) A complete first TUR (reported by the surgeon to be complete resection) of bladder carcinoma and a second TUR were performed,

3) Received 6 weekly instillations of BCG therapy and at least 1 year of maintenance BCG therapy,

4) At least 12 months of follow-up after completion of maintenance BCG.

Patients with a histology other than pure urothelial carcinoma (urothelial carcinoma together with other histologic variants were also excluded), incomplete resection at initial TUR, a diagnosis of muscle invasive cancer on second TUR, a time interval of >90 days between first and second TUR, and those who did not complete 1 year of maintenance therapy were excluded. During the second TUR, aggressive resection of all visible and suspected tumors with adequate sampling of muscle layer was performed. The patients were assessed with cystoscopy, cytology and tumor resection every 3 months for the first 2 years and then biannually for a minimum of 5 years and annually thereafter as indicated. Progression was defined as an increase in pathological stage (Ta to T1 or T1 to ≥T2).

Individual patient data were requested for the following patient and tumor characteristics and were included in the database: age, gender, tumor grade, T stage, concomitant CIS, primary or recurrent

tumor, number of tumors, main tumor size, application of early single dose intravesical chemotherapy, recurrence, and progression. Central pathological review of the specimens was not performed.

Association of age with recurrence-free survival (RFS) and progression-free survival PFS) rates was the primary outcome measure of the study. Effect of age was analyzed both dichotomously (<70 or ≥70 years) as well as by 10-year increments (<50, 50-59, 60-69, ≥70 years) with regard to previous trials (6,11). Cox univariate and multivariate proportional hazards regression models were fit with end points, time to recurrence and time to progression.

Statistical Analysis

Statistical analysis was performed using SPSS v. 20.0. A Chi-square test was used to compare categorical variables and student's t-test and analysis of variance were applied for continuous variables of the groups based on time to second TUR. Univariate and multivariate logistic regression analyses were performed to identify predictors of recurrence and progression. Kaplan-Meier curves were constructed for RFS and PFS and the groups were compared with the log-rank test. A p value of less than 0.05 was considered statistically significant.

Results

Out of 264 retrospectively evaluated patients, a total of 242 patients fulfilled the inclusion criteria. Twenty-two patients were excluded; 13 due to incomplete initial TUR, 6 for elapsed time >90 days between first and second TUR, 2 for having histology other than urothelial cancer and 1 due to a short follow-up (<6 months) period after completion of BCG. The mean age of study population was 64.7±10.7 years and the mean follow-up period was 29.4±22.2 months (range 12-96) without a significant difference between the groups. Of the patients, 212 (87.6 %) were male and 30 (12.4%) were female. Stage Ta and T1 tumors were present in 40 (16.5%) and 202 (83.5%) patients, respectively. Concomitant CIS was present in 19 patients. High-grade tumors were present in 214 (88.4%) patients and immediate postoperative single-dose intravesical chemotherapeutic instillation was given to 162 (66.9%) patients. Pathological evaluation of the surgical specimens of the second TUR revealed NMIBC in 104 (42.9%) patients.

Regarding the age groups, there were 150 patients <70 years of age and 92 patients ≥70 years of age. The number of patients in age groups <50, 50-59, 60-69, and ≥70 years was 20, 49, 81, and 92 respectively. There were no differences between the groups in age, sex, T stage, concomitant CIS, tumor grade, largest tumor diameter, tumor multiplicity, tumor status (primary, recurrent) or instillation of immediate postoperative intravesical chemotherapy (all p values=>0.05) (Table 1).

Survival Analysis

The 3-year RFS rates were 63.3%, 68.1%, 68.1% and 59.7% in age groups of <50, 50-59, 60-69, and ≥70 years, respectively (p=0.701, Figure 1a). When age groups of <70 years and ≥70 years were compared, RFS rates were 81.9% and 72.8%, respectively (p=0.257, Figure 1b).

The 3-year PFS rates were 80.0%, 87.7%, 83.1% and 77.5% in age groups of <50, 50-59, 60-69, and ≥70 years, respectively (p=0.393, Figure 2a). No significant difference was observed between the age groups <70 years and ≥70 years in terms of PFS (PFS: 94.4% vs 86.3%, p=0.100, Figure 2b). On univariate analysis, tumor grade [(odds ratio (OR)] 3.107, 95% confidence interval (CI) 1.724-7.918, p=0.0008) and concomitant CIS (OR 1.933, 95% CI 1.302-5.267, p=0.001) were found to be associated with a higher risk of recurrence (Table 2). Tumor grade (OR 2.221, 95% CI 1.488-6.178, p=0.002) was the only factor identified as predictor of progression on univariate analysis (Table 3).

Table 1. Baseline patient characteristics by age groups

Variables	<50 years n=20	50-59 years n=49	60-69 years n=81	≥70 years n=92	p value	<70 years n=150	≥70 years n=92	p value
Sex								
Male, n (%)	18 (90)	39 (79.6)	71 (87.7)	82 (89.1)	0.680	128 (85.3)	82 (89.1)	0.397
Female, n (%)	2 (10)	10 (20.4)	10 (12.3)	10 (10.9)		22 (14.7)	10 (10.9)	
Stage								
Ta, n (%)	2 (10)	7 (14.3)	13 (16.0)	18 (19.6)	0.551	22 (14.7)	18 (19.6)	0.319
T1, n (%)	18 (90)	42 (85.7)	68 (84.0)	74 (80.4)		128 (85.3)	74 (80.4)	
High grade tumor, n (%)	17 (85.0)	42 (85.7)	74 (87.6)	81 (88.0)	0.481	133 (88.7)	81 (88.0)	0.883
Concomitant CIS, n (%)	2 (10)	4 (8.2)	6 (7.4)	7 (7.6)	0.229	12 (8.0)	7 (7.6)	0.912
Tumor size, mean ± SD	2.69±1.3	2.56±1.2	2.73±1.2	2.66±1.3	0.644	2.67±1.3	2.66±1.3	0.905
Patients with multiple tumors, n (%)	5 (25)	14 (28.6)	24 (29.6)	30 (32.6)	0,900	43 (28.7)	30 (32.6)	0.516
Patients with primary tumors, n (%)	17 (85.0)	43 (87.7)	67 (82.7)	80 (86.9)	0.449	127 (84.7)	80 (86.9)	0.623
Immediate postoperative intravesical chemotherapy, n (%)	12 (60)	31 (63.2)	52 (64.2)	57 (61.9)	0.598	95 (63.3)	57 (61.9)	0.829

CIS: Carcinoma in situ, SD: Standard deviation

On multivariate analysis, tumor grade (OR 2.533, 95% CI 1.121-5.822, p=0.003), and concomitant CIS (OR 1.534, 95% CI 1.078-2.544, p=0.008) were detected as predictors of recurrence.

Discussion

Treatment of high-risk NMIBC is of importance as the disease has a significant potential of progression. The current practice involves performance of a second TUR and application of maintenance BCG. Verification of prognostic factors for response to maintenance BCG is important to detect patients that must be followed closely to not lose the chance of more aggressive treatments in case of progression. Patients with progression to muscle invasive disease from a NMIBC have unfavorable prognosis even after radical cystectomy (12).

Prognostic factors for this patient population has recently been investigated (6,7). In the study of European Organisation for Research and Treatment of Cancer (EORTC) 30911, data of patients undergoing maintenance BCG have been evaluated. The authors evaluated the value of age as a prognostic factor and accepted 70 years of age as the cut of value. Age was not found to be a predictor of recurrence, however, patients older than 70 years of age were found to have a shorter time to progression as well as shorter overall and cancer-specific survival rates. The authors mentioned the reduced activity of immune system by age as the cause of poorer survival rates and higher risk of progression (6). In that study, the authors did not mention any information on performing a second TUR in their population, a factor which is associated with decreased recurrence and progression rates as well as better response to BCG (13,14). In our study, all patients similarly received maintenance BCG, besides, all patients underwent a second TUR.

Another important point is the definition of progression. In the EORTC 30911 study, progression was defined as muscle invasion or distant metastasis. However, the International Bladder Cancer Group defined progression as: an increase in T stage from CIS or Ta to T1 (lamina propria invasion); development of ≥T2 or lymph node (N+) disease or distant metastasis (M1); or an increase in grade from low to high, and concluded that Investigators should consider the use of this new definition to help standardize protocols and improve the

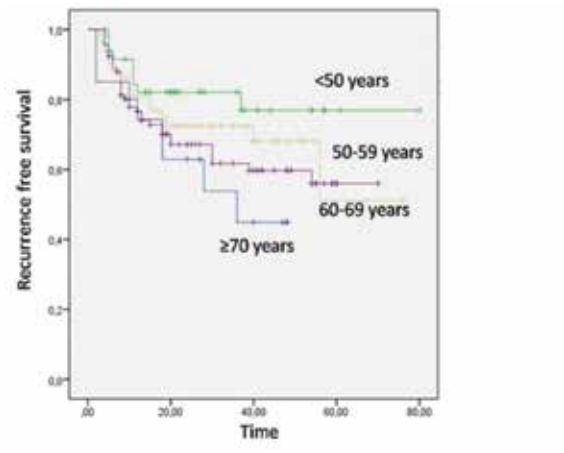

Figure 1. Kaplan-Meier curves of the recurrence free survival rates for the groups according to 4 groups
Kaplan-Meier curves of the recurrence free survival rates for the groups according to 2 groups

Table 3. Univariate analysis for detection of predictors for progression

Variables	OR	95% CI	p value
Age (<70 years vs ≥70 years)	1.007	0.326-1.174	0.997
Age (regarding 4 groups)	1.002	0.297-1.228	0.998
Sex	1.127	0.485-1.777	0.866
Stage (Ta vs T1)	1.218	0.687-1.792	0.708
Grade (high vs low)	2.221	1.488-6.178	0.002
Concomitant CIS	1.286	0.703-2.114	0.662
Tumor size	1.215	0.617-1.887	0.694
Tumor focality (solitary vs multiple)	1.116	0.471-1.684	0.905
Tumor status (primary vs recurrent)	1.187	0.606-1.903	0.601
Immediate postoperative intravesical chemotherapy	1.147	0.551-1.874	0.667

CI: Confidence interval, OR: Odds ratio, CIS: Carcinoma in situ

Table 2. Univariate analysis for detection of predictors for recurrence

Variables	OR	95% CI	p value
Age (<70 years vs ≥70 years)	1.011	0.455-1.396	0.844
Age (regarding 4 groups)	1.003	0.341-1.228	0.954
Sex	1.147	0.692-2.189	0.814
Stage (Ta vs T1)	1.209	0.780-2.802	0.428
Grade (low vs high)	3.107	1.724-7.918	0.0008
Concomitant CIS	1.933	1.302-5.267	0.001
Tumor size	1.325	0.856-2.887	0.308
Tumor focality (solitary vs multiple)	1.165	0.498-1.942	0.738
Tumor status (primary vs recurrent)	1.225	0.597-2.867	0.318
Immediate postoperative intravesical chemotherapy	1.366	0.603-2.955	0.299

CI: Confidence interval, OR: Odds ratio, CIS: Carcinoma in situ

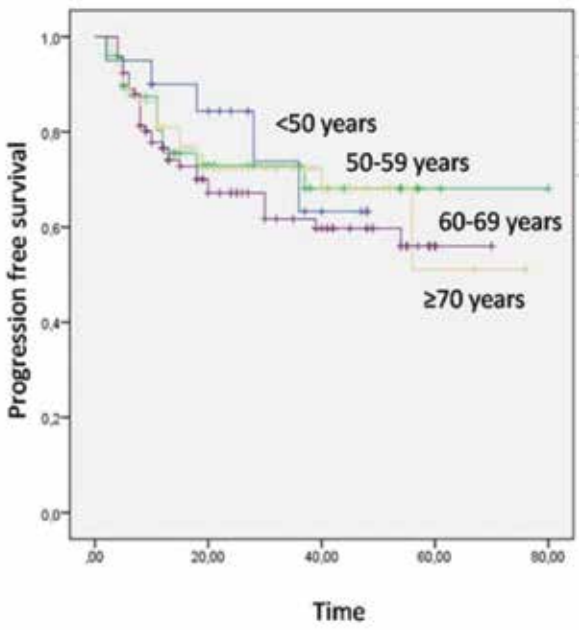

Figure 2a. Kaplan-Meier curves of the progression free survival rates for the groups according to 4 groups

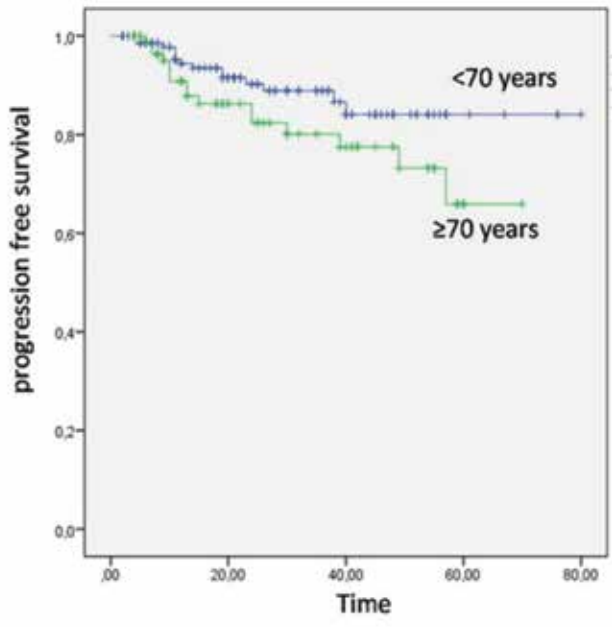

Figure 2b. Kaplan-Meier curves of the progression free survival rates for the groups according to 2 groups

reporting of progression (10). Our study is the first study investigating prognostic factors for recurrence and progression in high-risk NMIBC patients receiving maintenance BCG together with the definition of progression involving progression of Ta to T1 stage but not low-grade to high-grade disease.

In another study on the highest number of T1G3 patients, prognostic factors were evaluated to define risk groups. In that study Restaging TUR prior to BCG was performed in only 38.2% of patients and maintenance BCG was given to only another 38.2% of patients (7). Besides, progression was defined as progression to muscle-invasive disease. The results of multivariate analysis revealed that maintenance BCG and tumor size were the factors associated with increased recurrence and progression rates and decreased overall and cancer-specific survival rates. Additionally, age (≥70 years) was associated with increased progression rates and decreased overall and cancer-specific survival rates.

In our study, effect of age on recurrence and progression rates was evaluated and age (both categorically and as a continuous variable) was not found to be associated with increased recurrence and survival rates. There are important differences between our study and the previous cohorts. Our cohort involved patients who underwent a second TUR and received maintenance BCG therapy. In addition, in our study, the definition of progression involved progression from Ta to T1 disease as suggested by the International Bladder Cancer Group. RFS and PFS rates in the ≥70 years group were slightly lower compared to that in the <70 years group, however, this difference did not reach statistical significance (RFS: 72.8% vs. 81.9% and PFS: 86.3% vs 94.4%). This may be associated with the definition of progression and other properties of the population, however, more importantly, our cohort had a relatively lower duration of follow-up and also due to lower number of patients, power of the current study may not be sufficient to detect an underlying significant difference.

Concomitant CIS was found to be an important prognostic parameter in a previous study (15) and it was found to be associated with increased recurrence rates in our study. It was observed to be associated with increased progression but not with increased recurrence rates in a study by Gontero et al. (7). Tumor grade was the only parameter associated with higher progression rates in our series.

This study is limited by its retrospective nature. The patients were included from 10 different centers and therefore quality of TUR was probably variable. However, this aspect represents the real life much better. In addition, although the sample size of 242 patients may be insufficient to provide desirable power level, our data includes relatively homogeneous patient population consisting of high-risk NMIBC patients and all underwent second TUR and were treated with a maintenance BCG. Therefore, cautious use of these findings is recommended in patients who receive only induction BCG after second TUR. Additionally, central pathological review was not performed and this may affect especially the tumor grade results of the patients.

Conclusions

In high-risk NMIBC patients treated with a second TUR and received maintenance BCG, age was not found to be associated with increased rates of neither recurrence nor progression. However, the duration of follow-up was short and a significant difference has not been found. Prospective randomized studies with longer follow-up are needed to validate the effect of age on the rates of response to BCG with the definition of progression involving Ta to T1 progression.

Acknowledgement

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Ethics

Ethics Committee Approval: The study was performed retrospectively and ethical committe approval was not done, Informed Consent:

Informed consent has been received from all of the patients prior to surgery.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Sümer Baltacı, Murat Bozlu, Levent Türkeri, Mehmet İlker Gökçe, Cavit Can, Aydın Mungan, Güven Aslan, Asıf Yıldırım, Uğur Kuyumcuoğlu, İlker Tinay, Concept: Sümer Baltacı, Levent Türkeri, Cavit Can, Aydın Mungan, Güven Aslan, Design: Sümer Baltacı, Levent Türkeri, Cavit Can, Aydın Mungan, Güven Aslan, Data Collection or Processing: Mehmet İlker Gökçe, Asıf Yıldırım, Uğur Kuyumcuoğlu, Analysis or Interpretation: Sümer Baltacı, Mehmet İlker Gökçe, Literature Search: Sümer Baltacı, Mehmet İlker Gökçe, Aydın Mungan, Writing: Sümer Baltacı, Levent Türkeri, Mehmet İlker Gökçe.

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Does Morbid Obesity Adversely Affect Success and Complication Rates in Percutaneous Nephrolithotomy?

Morbid Obezite Perkütan Nefrolitotomide Başarı ve Komplikasyon Oranlarını Etkiler mi?

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

Efficacy of percutaneous nephrolithotomy in morbid obese patients is still debatable. We believe that this study may give valuable information about this topic.

ABSTRACT

Objective

To investigate percutaneous nephrolithotomy (PNL) results of morbid obese patients with a body mass index (BMI) of ≥40 kg/m^2 by comparing with a control group of normal BMI (20-25 kg/m^2).

Materials and Methods

Thirty patients with a BMI of ≥40 kg/m^2 were randomly assigned to group 1 and 30 patients with a normal BMI (20-25 kg/m^2) constituted group 2 as controls. We compared the groups with regard to baseline characteristics, intraoperative parameters, and stone-free and complication rates.

Results

A total of 60 patients were included in the study. Demographic data and stone burden were similar in both groups. We found no significant differences in access number and success, operative time, and stone-free and complication rates.

Conclusion

PNL is a safe and effective treatment even for patients with a BMI of ≥40 kg/m^2.

Keywords

Kidney, kidney calculi, percutaneous nephrolithotomy, morbid obesity

ÖZ

Amaç

Vücut kitle indeksi (VKİ) 40 kg/m^2 üzerinde olan hastaların perkütan nefrolitotomi (PNL) sonuçlarını VKİ normal sınırlarda olan (20-25 kg/m^2 hastalardan oluşmuş kontrol grubu ile kıyaslamak amaçlandı.

Gereç ve Yöntem

VKİ 40 kg/m^2 üzerinde olan 30 hasta grup 1 olarak adlandırıldı. İstatistiksel olarak uygun kıyaslama yapabilmek için VKİ normal sınırda olan hastalar arasından random olarak 30 hasta seçildi ve grup 2 olarak adlandırıldı. Gruplar temel demografik veriler, intaoperatif parametreler, taşsızlık ve komplikasyon oranları açısından kıyaslandı.

Bulgular

Toplam 60 hasta çalışmaya dahil edildi. Demografik veriler ve taş yükü iki grup arasında benzerdi. Gruplar arasında akses sayısı, akses başarısı, operasyon zamanı gibi preoperatif data, taşsızlık ve komplikasyon oranları açısından anlamlı fark saptanmadı.

Sonuç

PNL morbid obez hastalarda bile güvenli ve etkili bir yöntemdir.

Anahtar Kelimeler

Böbrek, böbrek taşı, perkütan nefrolitotomi, morbid obezite

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Introduction

Kidney stone formation is a common disease and its lifetime prevalence varies between 1% and 15%. With considerably high stone-free rates and acceptable complication rates, percutaneous nephrolithotomy (PNL) is accepted as the gold standard treatment method for kidney stones larger than 2 cm, according to the European Association of Urology and American Urological Association guidelines (1).

On the other side, today, obesity is also a common heath problem worldwide. Its incidence is increasing day by day due to inappropriate dietary patterns and decreased physical activities (2). Outcomes of PNL which is frequently performed in stone surgery today are controversial for obese patients There have been some studies reporting that obesity adversely affects the results while some others showed no effect (3,4). We investigated outcomes of PNL in morbid obese patients [body mass index (BMI) ≥40 kg/m^2] using the data of our clinic by comparing with a control group.

Materials and Methods

The data of 1150 patients who underwent PNL between the years 2008 and 2015 in our clinic were retrospectively analysed. We evaluated 958 patients whose demographical, perioperative and postoperative data were completely accessible and met the inclusion criteria. Patients under 18 years of age and those having urinary system anomaly or a history of ipsilateral open stone surgery or PNL were excluded. A total of 60 patients were included. The patients were divided into two groups: 30 patients with a BMI ≥40 kg/m^2 were included in group 1 and 30 patients with a normal BMI (20-25 kg/m^2), who served as controls, constituted group 2.

Demographic characteristics, such as age, gender, height, and weight of the included patients were accessed. Preoperative imaging of all patients was implemented by non-contrast computed tomography (NCCT) of the abdomen. On imaging, only calyx or only pelvic stones were called as simple stones; whereas the stones occupying one or more calyces in addition to the pelvis as well as staghorn stones were named as complex stones.

The period from contrast material administration to the placement of nephrostomy catheter was recorded as operation time. In addition, how many seconds the fluoroscopic imaging was used throughout the operation, how many accesses were made and the presence of peroperative complications, if any, were recorded.

At the end of the operation, a 14 Fr re-entry Malecot catheter was placed in all patients. Malecot catheter was removed on the 1st-3rd day postoperatively and the patients without any complications were discharged. Postoperative complications and additional interventions, if any, were also recorded separately. All the patients were reassessed by NCCT which is routinely taken at postoperative 1st month. Observing stones of 4 mm or smaller size or no stones were accepted as operational success.

Statistical Analysis

The chi-square test was used to examine the differences with categorical variables and the Mann-Whitney U test to compare the differences between two independent groups. In the analysis "α", p≤0.05 was taken into account. We used simple random sampling method in this paper. Simple random sampling is the basic sampling technique where we select a group of subjects (a sample) for a study from a larger group (a population). Each individual is chosen entirely by chance and each member of the population has an equal chance of being included in the sample. Every possible sample of a given size has the same chance of selection. Excel was used to generate a random sample with n=30, without replacement in this study. IBM SPSS (Statistical Package for the Social Sciences) software SPSS Inc (version 15.00) was used for statistical analysis.

Results

A total of 60 patients were included in the study. Of the patients in group 1, 13 (43%) were male, 17 (57%) were female and 10 (33%) of the patients in group two were male, 20 (67%) were female. There was no difference between the groups in terms of gender (p=0.426).

The average age of the patients was 44.7±2.36 years in group 1 and 46±3.30 years in group 2. There was no significant difference between the groups in terms of age (p=0.871).

Twenty-four patients had simple stones and 6 patients had complex stones in both group 1 and group 2. Therefore, two groups were identical in regard to stone burden (p=1).

The average operation time was 64.5±8.03 minutes in non-obese group, while it was 56±7.8 minutes in morbid obese group. We did not determine any significant difference between the two groups with respect to operation time (p=0.148).

The average fluoroscopy time was 149±35.2 seconds in group 1 and 162±36.8 seconds in group 2. There was no significant difference in fluoroscopy time between the groups (p=0.673).

Single access was performed in 27 patients and double access was done in three patients in group 1. In group 2, however, single access was performed in all the patients. There were no patients with no access. There was no difference in the number of access between the groups (p=0.237) (Table 1). There were no postoperative complications in either groups. Two patients (6.6%) in morbid obese group and three patients (10%) in group 2 required blood transfusion due to postoperative hemodynamic instability. There was no difference in postoperative bleeding between the groups (p=1). Postoperative fever

Table 1. Patient demographics and intraoperative variables

	Group 1 (n=30)	Group 2 (n=30)	p value
Average age (year)	44±2.36	46±3.30	0.871
Gender (%) Male Female	 13 (43) 17 (57)	 10 (33) 20 (67)	0.426
Stone burden (%) Simple Complex	 24 (80) 6 (20)	 24 (80) 6 (20)	1
Number of access Single Double	 27 3	 30 -	0.237
Operation time (min)	56±7.8	64.5±8.03	0.148
Fluoroscopy time (sec)	149±35.2	162±36.8	0.673

Table 2. Postoperative outcomes and complications			
	Group 1 (n=30)	**Group 2 (n=30)**	**p value**
Stone-free rates (%)	3 (10)	8 (26.6)	0.181
Postoperative transfusion (%)	2 (6.6)	3 (10)	1
Postoperative fever (%)	2 (6.6)	5 (16.6)	0.424
Additional intervention (%) DJS	1 (3.3)	-	1
DJS: Double-J stent			

exceeding 38 °C was observed in two patients in morbid obese group and in five patients in non-obese group. Those patients with high fever were discharged after appropriate monitoring and treatment. There was no significant difference in fever between the groups (p=0.424). Sepsis developed in none of the patients, no patients required intensive care and no patients were lost due to operation-related complications.

When the groups were analysed in regard to operational success, we observed postoperative residual stones in three patients (10%) in group one and in eight patients (26.6%) in group 2. There was no significant difference between the groups in terms of operational success (p=0.181).

The groups were also evaluated with respect to additional postoperative interventions. In the non-obese group, double-J stent was inserted in one patient due to fluid discharge coming out of incision site. No patients required additional intervention in the morbid obese group. The two groups were identical with respect to any requirement for additional intervention (p=1) (Table 2).

Discussion

Today, obesity is increasing worldwide. The rate of increase in the last three decades is even higher, particularly in high-income countries (5). Obesity has multiple roles in the formation of kidney stones.

Obese patients have a rather more inactive life in comparison to non-obese patients. Furthermore, higher prevalence of gout disease in obese patients, as well as high amount of purine, carbohydrates and animal fat content in their diet have adverse effects on stone formation. Impaired ammonia metabolism as the result of insulin resistance as well as transport problems in renal tubular cells pave the way for renal stone formation (6).

Obesity, while increasing the susceptibility to urolithiasis, creates complications in treatment. Extracorporeal shock wave lithotripsy poses a problem for these patients due to the increased f2 distance. Success rate is low in patients with high stone burden (7). Recently, retrograde intrarenal surgery appears to be a good treatment alternative due to low complication rates. However, considering low stone-free rate in single sessions, longer operational time as well as necessitating additional intervention, it is arguable that this is a good alternative to PNL for high stone burden patients (8,10).

Anesthesia can be problematic in obese patients. With the additional adverse contribution of prone position, respiratory troubles are encountered at a higher rate in obese patients due to the decrease in total lung capacity, expiratory lung volume and functional residual capacity as well as the problems related to mechanical endotracheal intubation (11). For this reason, PNL operation was performed in some centers in supine position instead of prone position, and it was shown that operation time was shorter while stone-free, complication, blood transfusion and postoperative fever rates were similar (12,13). In our clinic, PNL was performed in prone position since we had no experience of PNL in supine position. There was no anesthesia-related complication in any of the patients.

In their study of 530 patients, Faerber and Goh (14) determined that the complication rate in 93 obese patients was considerably higher than in patients having normal BMI. Besides that, Paerle et al. (15) reported that blood transfusion was required more in the obese group. In our study, there was no difference in transfusion requirement between the groups (p=1). When the groups were compared for other complications, there were also no differences between the groups in terms of postoperative fever and any need for additional intervention after PNL (p=0.424, p=1).

Koo et al. (3) determined no difference between groups with respect to operative duration and hemorrhage in their series of 181 patients divided into 4 groups according to the World Health Organization classification of BMI. In our study, we observed no difference in operative duration between the morbid obese and normal weight groups (p=0.148). At the same time, no difference was found in fluoroscopy requirement between the groups (p=0.673).

In their study including 546 obese patients, El-Assmy et al. (16) found a success rate of 84.8% in obese patients. They found no difference vin success rates between the patients that they studied in 4 groups. In our study, the success rate in morbid obese group was around 90% and no statistically significant difference was determined between the groups (p=0.181)

The Clinical Research Office of the Endourological Sovciety study group published the first prospective study including 3.709 patients (17). PNL-operated patients were sorted with respect to their BMI. Contrary to many publications, they expressed that as BMI increased, stone-free rate decreased and operation time increased. In our study, the success rate in morbid obese patients was similar to that in normal BMI group.

Conclusion

Even though this was a retrospective study, we determined that morbid obesity had no effect on operational complications in PNL and operational success. Further studies are required with higher number of patients in order to have a definite conclusion on this matter.

Ethics

Ethics Committee Approval: Ethics committee approval was not obtained because this was a retrospective study, Informed Consent: Written informed consent can not be obtained from patients because this was a retrospective study.

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tufan Süelözgen, Cemal Selcuk İşoğlu, Concept: Cemal Selcuk İşoğlu, Yusuf Özlem İlbey, Design: Tufan Süelözgen, Ferruh Zorlu, Data Collection or Processing: Hakan

Türk, Mehmet Yoldaş, Batuhan Ergani, Mustafa Karabıçak, Analysis or Interpretation: Cemal Selçuk İşoğlu, Hayal Boyacıoğlu, Literature Search: Okan Nabi Yalbuzdağ, Yusuf Özlem İlbey, Writing: Cemal Selçuk İşoğlu, Tufan Süelözgen.

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The Effect of Charlson's Comorbidity Index on Clavien-Dindo Classification of Surgical Complications in Percutaneous Nephrolitotomy

Perkütan Nefrolitotomide Charlson Komorbidite İndeksi'nin Postoperatif Clavien Komplikasyon Skalası Üzerine Etkisi

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

In this series the remarkable feature is that about 50% of patients had various comorbidities. Advanced age and comorbidity makes patients more susceptible to surgical complications. In this study, achievement similar complication rate between the groups suggest that the presence of preoperative comorbidities do not create a major risk factor on com.

ABSTRACT

Objective

Percutaneous nephrolithotomy (PCNL) in comorbid patients is challenging due to the high susceptibility to complications. In our study, by taking the age of patents into account, we have tried to figure out the impact of comorbid conditions on complications identified after PCNL operations in our clinic.

Materials and Methods

Three hundred-sixty patients, who underwent PCNL in our clinic between June 2002 and June 2012, were retrospectively analyzed. The patients were assessed in terms of demographic characteristics, access locations, preoperative comorbidity using the age-adjusted Charlson's Comorbidity Index (ACCI) and postoperative complications using the Clavien-Dindo classification of surgical complications.

Results

The mean age of the patients was 46 (10-83) years. Two hundred-twenty (61.1%) patients were male and 140 (38.9%) were female. According to preoperative ACCI, 169 (46.9%) of the cases were classified as group 1 and 191 (53.1%) of the cases as group 2. In 212 (58.8%) patients, entry into the lower calyx, in 136 (37.7%) - into the middle calyx and in 12 (3.3%) patients, entry into the upper calyx was done. The rate of complications in ACCI group 1, grade 1, grade 2 and grade 3a was 12.4%, 18.9%, 8.28% and in group 2, it was 6.8%, 26.7%, 6.28%, respectively. There was no significant difference between the groups (p=0.098, p=0.16 and p=0.49, respectively). Grade 3b and grade 4a complications were seen only in

ÖZ

Amaç

Perkütan nefrolitotomi (PNL), komorbiditesi olan hastalarda komplikasyonlara daha duyarlı olmaları nedeniyle zorludur. Bu çalışmada, kliniğimizde PNL operasyonları sonrası belirlenen komplikasyonlar üzerinde eşlik eden durumların etkisini hastaların yaşlarını da dikkate alarak dikkate alarak incelemeye çalıştık.

Gereç ve Yöntem

Haziran 2002 ve Haziran 2012 tarihleri arasında kliniğimizde, PNL uygulanan 360 hasta retrospektif olarak incelendi. Bu çalışmada hastalar, demografik özellikleri, akses giriş yerleri, yaşa göre düzeltilmiş Charlson Komorbidite İndeksi'ne (ACCI) göre preoperatif komorbiditeleri ve Clavien-Dindo Sınıflandırma Sistemi kullanılarak gelişen postoperatif komplikasyonları açısından değerlendirildi.

Bulgular

Çalışmaya alınan 360 hastanın yaş ortalaması 46 idi (10-83 yıl). Hastaların 220'si (%61,1) erkek ve 140'ı (%38,9) kadındı. ACCI sınıflamasına göre hastaların 169'u (%46,9) grup 1 ve 191'i (%53,1) grup 2 olarak tanımlandı. Olguların 212'sine (%58,8) alt kaliks, 136'sına (37,7%) orta kaliks ve 12'sine (3,3%) de üst kaliks girişi uygulandı. Komplikasyonlara bakıldığında ACCI grup 1 hastalarda %12,4 sınıf 1, %18,9 sınıf 2, %8,28 sınıf 3a ve ACCI grup 2 hastalarda %6,8 sınıf 1, %26,7 sınıf 2, % 6,28 sınıf 3a komplikasyon görüldü (p=0,098; 0,16; 0,49). Sınıf 3b ve sınıf 4a komplikasyonlar sadece ACCI grup 2 hastalarda görüldü. Sınıf 4b ve 5 komplikasyon her iki grup hastalarda da görülmedi.

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group 2 (1.04%, 0.52%, resceptively). Grade 4b and 5 complications were not observed in both groups.

Conclusion

Considering the age of patients, we have not observed a significant difference in the rate of postoperative complications between the groups. Therefore, we assume that the recognized preoperative comorbidities are not risk factors for PCNL procedures and operations.

Keywords

Percutaneous nephrolithotomy, the age-adjusted Charlson's Comorbidity Index, the Clavien-Dindo Classification of surgical complications

Sonuç

Biz hastaların yaşlarını da dikkate aldığımızda, ameliyat sonrası komplikasyon oranları arasında anlamlı bir fark gözlemlemedik. Bu nedenle, tanımlanmış preoperatif komorbiditelerin PNL işlemleri ve operasyonları için risk faktörleri olmadığını düşünmekteyiz.

Anahtar Kelimeler

Perkütan nefrolitotomi, yaşa göre düzeltilmiş Charlson Komorbidite İndeksi, Clavien-Dindo sınıflandırma sistemi

Introduction

Urinary tract stone disease is widely seen in our country occupying an important place in the practice of urology. It has been reported that 10% of people live with this disease throughout their lives (1). Treatment options for kidney stones include extracorporeal shock wave lithotripsy (ESWL), ureterorenoscopy, percutaneous nephrolithotomy (PCNL), and open and laparoscopic surgery. PCNL is a minimally invasive surgical procedure for the treatment of kidney stones. Since Rupel and Brown extracted an calculus via an operatively established nephrostomy in 1941, owing to the development of novel techniques and equipment through years, PCNL today has become a preferred method in the treatment of large-volume stones in cases where stone extraction is difficult for reasons depending on the anatomical structure or stone localization. The method is not completely innocent although overall success rate of >90%; it has been reported in the Clinical Research Office of the Endourological Society (CROES) PCNL Global Study that 20.5% of 5724 subjects (n=1175) experienced one more complications (2,3). Although extravasation (7.2%), hemorrhage requiring blood transfusion (11.2-17.5%) and fever (21-32.1%) are common complications; septicemia (0.3-4.7%), colon injuries (0.2-4.8%) and pleural injury (%0-3.1) are among the rare major complications (4). Conversion to open surgery is rare and is usually required during the first experience with PCNL (5). In PCNL operation, the reported mortality rate is between 0.3% and 0.046% (6).

In the literature, although there are studies investigating the effects of patients' co-morbid conditions on PCNL complications (4), there have been no study examining the effects of multiple co-morbid factors including patient age on complications.

In our study, taking into account patients' age, we discussed the relationship between complications and pre-existing comorbid conditions in patients undergoing PCNL operations in light of the literature.

Materials and Methods

Three hundred-sixty patients who underwent PCNL in our clinic between June 2002 and June 2012 were retrospectively analyzed. Written informed consent was obtained from all subjects. Demographic characteristics, preoperative comorbidity, preoperative and postoperative hemoglobin values, access locations, and intraoperative and postoperative complications were evaluated. Patients with a history of previous operations on the same side of the kidney, solitary kidney, PCNL made simultaneously on both kidney and those with operations with more than one access were excluded from the study. Preoperative comorbidities were obtained from hospital records and age-adjusted Charlson's comorbidity index (ACCI) scores were calculated by using the existing 19 comorbid parameters including the patients' age (Table 1) (7). The patients were divided into two groups according to their preoperative comorbidities as ACCI group 1 (0 points) and ACCI group 2 (points 1 and above). The protocol for this study was reviewed and approved by the Ethics Committee (Institutional Review Board) of the Faculty of Medicine, Bülent Ecevit University (date: 16/04/2013, meeting number: 2013/09, protocol number: 2013-49-16/04).

Two grams of ceftriaxone was given as prophylactic antibiotic in patients with negative urine cultures. Patients with positive urine culture were treated with antibiotics based on the antibiogram at least 48 hours before surgery. The percutaneous access was performed with the patient in the prone position following the contrast media injection via the open-ended ureteral catheter which was placed transurethrally in the supine position prior to the renal access. Both working and safety guide wires were inserted after successful access. Tract dilatations were performed by Amplatz fascial dilators until 30 Fr and Amplatz sheath was used in all cases. A standard nephroscope was used with pneumatic lithotripsy for stone disintegration. At the end of the procedure, 20 F nephrostomy tubes were inserted for 48 to 72 hours. All patients had postoperative direct urinary system graphy and laboratory investigation.

Postoperative complications were defined as adverse events occurred in 30 days and were graded by the Clavien-Dindo classification of surgical complications (CDCSC) that provides an objective and practical way to grouping complications (8). The complications were divided into 7 groups according to the classification (1, 2, 3a, 3b, 4a, 4b, 5). Underarm measurement of 37.5 degrees and above was evaluated as fever.

Statistical analysis was performed using SPSS version 19.0. Descriptive statistics for continuous variables were shown as mean and standard deviation and descriptive statistics of categorical variables were shown as frequency and percentage. Pearson's Chi-Square, Yates-corrected Chi-Square and Fisher's exact tests were used for comparison of categorical variables.

Results

The average age of the 360 patients (220 (61.1%) male and 140 (38.9%) female) was 46 (10-83) years. According to preoperative ACCI, 169 (46.9%) patients were classified as group 1 and 191 (53.1%) as group 2. In 212 (58.8%) patients, entry into the lower calyx, in 136 (37.7%) - into the middle calyx, and in 12 (3.3%) patients, entry into the upper calyx was done. The demographic characteristics of the patients and intra-postoperative findings are summarized in Table 2. All patients underwent standard PCNL under general anesthesia. In 40 (11.1%) subjects intraoperative complications and in 50 (13.8%), postoperative complications were observed.

In Table 3 ACCI groups and scores CDCSC are compared. The most common complications were fever and mild bleeding (Table 4). Fourteen (3.8%) of complications were due to surgery, 47 (13.0%) were due to medical reasons. There was no significant difference in the complication rate though patients co-morbidity index (ACCI scores) increases. Minor complications as CDCSC grade 1 and 2 were seen in the foreground. Fever seen after operation, blood transfusion because of a fall in hemoglobin level as a result of surgical procedure, DJ catheter application secondary to extravasation because of surgeon, surgical procedure and stone burden were independent factors of comorbidities.

The relationship between complications and calyceal entry sides are described in Table 5 and 6.

In ACCI group 2 after the middle caliceal entry, in 1 case grade 3b (0.5%) and in 1 case grade 4a (0.5%) complication has been seen that were not significant (Table 5). In 1 patient of ACCI group 1, after the upper caliceal entry, pneumothorax followed by deep vein thrombosis due to pulmonerthromboembolism was seen (p=0.032) (Table 6).

Discussion

Table 1. The age-adjusted Charlson's Comorbidity Index (7)

Point	Comorbid conditions
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcers Mild liver disease Diabetes
2	Hemiplegia Moderate/severe renal disease Diabetes with end-organ damage Any tumor Leukemia Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumors AIDS
1	Over 40 years for every decades

AIDS: Acquired immune deficiency syndrome

This study emphasizes that patients with kidney stones treated with PCNL also have preoperative comorbidities. In about half of patients, there are a variety of comorbidities. However, an increased comorbidity score does not show an increase in the rate of complications.

According to the American Urological Association and the European Association of Urology (EAU) guidelines on nephrolithiasis, ESWL is considered as the first-line treatment modality The main indications for PCNL include stones not responding to ESWL and stones especially over 2 cm in size and hard (cystine, COM) (9).

ACCI was created to estimate the long-term mortality and is a method to classify existing comorbid conditions (10). Charlson and colleagues have created a variety of disease categories and have identified certain points in each category. They gave 1 point to comorbid conditions, such as myocardial infarction, congestive heart

Table 2. The demographic characteristics of the patients and intra-postoperative findings

		n	%
Gender Fale	Female	140	38.9
	220	61.1	
Mean age	46±14	(10-83 years)	
Calyceal entrance Middle calyx entry Upper calyx entry	Lower calyx entry	212	58.8
	Middle calyx entry	136	37.7
	Upper calyx entry	12	3.3
Mean nephrostomy withdrawal period	2.92±1.09	(1-8 day)	
Mean length of stay in hospital	4.5±1.62	(2-17 day)	
ACCI group 1	169 (46.9%)		
ACCI group 2	191 (53.1%)		

	Lower calyx	Middle calyx	Upper calyx	Total
ACCI group 1	103 (60.7%)	62 (36.9%)	4 (2.4%)	169 (100%)
ACCI group 2	109 (56.8%)	74 (38.9%)	8 (4.2%)	191 (100%)

(p<0.01, comparison of values between lower calyx, middle calyx, upper calyx), ACCI: Age-adjusted Charlson Comorbidity Index

Table 3. Comparison of age-adjusted Charlson Comorbidity Index groups and Clavien-Dindo Classification of surgical complications

CDCSC	ACCI group 1 (n=169)	ACCI group 2 (n=191)	p*
Grade 1	21 (12.4%)	13 (6.8%)	0.098
Grade 2	32 (18.9%)	51 (26.7%)	0.16
Grade 3a	14 (8.28%)	12 (6.28%)	0.49
Grade 3b	-	2 (1.04%)	NS**
Grade 4a	-	1 (0.52%)	NS**

*p<0.05, Chi-square tests, **NS: Non specific, ACCI: Age-adjusted Charlson Comorbidity Index, CDCSC: Clavien-Dindo Classification of Surgical Complications

failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcers, mild liver disease, and diabetes. The sum of all points of comorbid conditions constitute the final score (Table 1).

Geriatric population constitutes the fastest growing segment in many parts of the world. Although age itself is not a disease, but in elderly patients with reduced functional reserve of organs makes them more sensitive to stress factors, such as bleeding, sepsis and medical complications (11,12). The effects of age on complications have been addressed in several studies (13,14,15,16). Koppie et al. (7), for the first time, formed the ACCI scores by including the patients' age to estimate the outcomes of patients who underwent radical cystectomy when calculating the Charlson's comorbidity index scores (Table 1).

In a retrospective series published by Sahin et al. (14), the complication rate of percutaneous nefrolitototmy operation in patients aged over 60 years has been reported to be similar to that in younger patients. Similarly, in a series published in 2012, Okeke and colleagues (15) have reported similar complication rates in younger patients compared to those in patients aged 70 years and older. Stoller et al. (13) have reported higher transfusion rates in elderly after PCNL. In their study published in 2012, Unsal et al (16) have reported that there was an increase in preoperative comorbidities and postoperative complications in parallel with age.

In this study, when patients were divided into two groups according to ACCI based on the preoperative comorbid conditions and taking into consideration the age, similar postoperative complication rates were observed between ACCI group 1 and ACCI group 2.

Oner et al. (17) have reported in their study of 1750 cases that large stones, stone complexity, multi tract entry, lack of experience and a prolonged period of PCNL operations increased the rate of complications. Similarly, in a study of 2.318 subjects made by Olvera-Posada et al. (18), it has been reported that older age and upper pole access were associated with an increased risk of major complications.

The pleura and the lungs are reported to be the most injured organs during PCNL operations especially in those via intercostal entry above the 12th rib. Hopper and Yakes (19) in their series reported that intercostal entry made after full expiration was responsible for 86% of the pleura and 29% of the lung injuries. In their series published in 2007, Sukumar et al. (20) assessed the success of supracostal

Table 4. Age-adjusted Charlson Comorbidity Index groups and Clavien-Dindo Classification of Surgical Complications were compared

		ACCI group 1 (n=169)	ACCI group 2 (n=191)		
CDCSC	Type of complication	Number of patients		p*	Treatment
Grade 1	Fever	21 (12.4%)	13 (6.8%)	0.098	Antipyretic therapy
Grade 2	Mild bleeding	29 (17.1%)	40 (209%)	0.45	Blood transfusion
	Mild respiratory distress	1 (0.6%)	2 (1.0%)	0.63	Follow-up
	Urinary infection	1 (0.6%)	2 (1.0%)	0.63	Antibiotics
	Hypertension	1 (0.6%)	7 (3.7%)	0.053	Antihypertensive therapy
Grade 3a	Pelvis perforation	5 (2.95%)	6 (3.1%)	0.92	Double J ureteral stent insertion for 4 weeks
	Persistent urine leakage	7 (4.1%)	6 (3.1%)	0.62	Double J ureteral stent insertion for 4 weeks
	Pneumothorax	1 (0.6%)	-	NS**	Insertion chest tube
	Perirenal hematoma (requiring medical follow-up)	1 (0.6%)	-	NS**	Follow-up
Grade 3b	Perirenal hematoma	-	2 (1.0%)	NS**	Selective angioembolization
Grade 4a	Shortnes of breath	-	1 (0.5%)	NS**	Intensive care follow-up

*p<0.05, Chi-square tests, **NS: Non specific, ACCI: Age-adjusted Charlson Comorbidity Index, CDCSC: Clavien-Dindo Classification of surgical complications

Table 5. Comparison of age-adjusted Charlson Comorbidity Index groups and Clavien-Dindo Classification of Surgical Complications According to the calyx of entry

	ACCI group 1 (n=169)			ACCI group 2 (n=191)			
CDCSC	Lower calyx	Middle calyx	Upper calyx	Lower calyx	Middle calyx	Upper calyx	p
Grade 1	16 (9.5%)	5 (2.9%)	-	8 (4.2%)	4 (2.1%)	1 (0.5%)	0.326
Grade 2	21 (12.4%)	11 (6.5%)	-	30 (15.7%)	19 (9.9%)	2 (1.0%)	0.347
Grade 3a	7 (4.1%)	6 (3.5%)	1 (0.6%)	9 (4.7%)	3 (1.6%)	-	0.435
Grade 3b	-	-	-	1 (0.5%)	1 (0.5%)	-	-
Grade 4a	-	-	-	-	1 (0.5%)	-	-

ACCI: Age-adjusted Charlson Comorbidity Index, CDCSC: Clavien-Dindo Classification of surgical complications

Table 6. Complications and statistical p values according to the calyx of entry in all cases

	Lower calyx	Middle calyx	Upper calyx	p*
Mild respiratory distress	-	3 (2.2%)	-	0.054
Hypertension	4 (1.9%)	4 (2.9%)	-	0.626
Severe hematuria	1 (0.5%)	1 (0.7%)	-	0.891
Fever	24 (11.4%)	9 (6.6%)	1 (8.3%)	0.326
Perirenal hematoma	1 (0.3%)	2 (0.5%)	-	0.725
Deep vein thrombosis	-	-	1 (0.5%)	0.586
Pulmonerthromboembolism	-	-	1 (8.3%)	0.032
Urinary infection	1 (0.5%)	2 (1.5%)	-	0.569
Pneumothorax	-	-	1 (8.3%)	0.032
Arteriovenous fistula	-	1 (0.7%)	-	0.379
Convertion to open surgery	2 (0.9%)	-	-	0.343
Intensive care follow-up	-	1 (0.7%)	-	0.379

*p<0.005

entry in 110 patients and reported that the overall complication rate was 11.8%. In 10 patients, hydrothorax/hemothorax, in one patient - perinephric collection, in two patients - infection/sepsis and in 2, massive bleeding were observed. As a result, they have reported high success rates in selected patients with acceptable morbidity. In a study of 597 cases published in 2011 by Mousavi et al. (21) investigating the complication rate of supracostal and infracostal entry in 123 patients, total complication rate and the rate of perioperative bleeding as the most common complication were reported to be 13% and 5.7%, respectively. In supracostal access applications, the incidence of complications requiring intervention, such as pleural effusion and pneumothorax ranges from 12% to 4% (22,23). Intrathoracic complication rate has been reported to increase when entry was done over the 11th rib compared to that over the 12th rib (1.4% versus 34.6%) (24). Mousavi-Bahar et al. (21) has reported the pneumothorax rate as 2.4%. These results show that supracostal entry should not be done unless required. In a study of 318 cases published in 2011 by Honey et al. (25) that examined the complication of supracostal and infrakostal access, the total complication rate, independent from tract enty, was reported to be 11.6%. Pleural complication rate was reported to be 3.2% in supracostal entry application although even higher than literature. (p=0.038). However, in the same study, it was reported that in patients undergoing infracostal puncture febrile infection as complication was observed more frequently with the rate of 5.6% (p=0.043).

In this study, similar to the literature, pulmonary complications occurred most often in supracostal entry cases with a rate of 8.3% (p=0.032). Likewise, febrile complication rates were more frequently observed in infracostal entry with a rate of 11.4% (p=0.326), though not significant (Table 6). In subjects who underwent supracostal entry, no perirenal bleeding and severe hematuria were seen (p=0.891). Our study also appears to support the reliability and minimal morbidity of supracostal entry, as (because of) pleural injury risk for supracostal entry seems to be low. Despite less number of subjects, we believe that our complication rate was in parallel with the literature data.

While trying to treat urinary tract stone disease, causing death is the most feared complication. The rate of mortality after PCNL was reported to be 0% to 0.3% in the 2013 EAU guideline (26). A few cases of death occurring after bleeding have been reported in the published first series (6). Although Segura et al. (27) reported no cases of deaths in their study of 1.000 PCNL cases published in 1985, in the series issued in 1987 by Lee et al. (6), 1 (0.2%) death due to respiratory failure in a patient with previous lung disease and other 1 (0.2%) death due to acute myocardial infarction were reported.

Although CDCSC was used in several studies in the field of general surgery, in those related to urology was used only in retroperitonoscopy, laparoscopic radical prostatectomy and laparoscopic live donor nephrectomy (28,29,30). Attempting to classify the PCNL complications according to the CDCSC is based on the very near future.

Although CDCSC brings standardization to the rating of postoperative complications, when placed in the urology practice, it seems to have some limitations. In the world of urology, creating a novel classification system that can cover urological operations might be more beneficial or CDCSC can be revised slightly to strictly include complications after urological operations.

Study Limitations

The factors that limit our study were the electively good evaluation of patients, not to use multiple tract entrance, and though the main goal was to achieve stone-free status, the limited number of complications we have seen compared to the number of cases. The second limitation of this study was that although there was not an exact age cutoff point in the literature to make the differentiation between young and old, we tried to overcome this issue by using the classification system used in the study of Koppie et al. (7).

Conclusion

In this series, the remarkable feature is that about 50% of patients had various comorbidities. Advanced age and comorbidity makes patients more susceptible to surgical complications. In this study, achieving similar complication rate between the groups suggests that the presence of preoperative comorbidities do not create a major risk for complications after PCNL. Further studies with larger samples and multiple tract entry are warranted.

Ethics

Ethics Committee Approval: The study were approved by the Bülent Ecevit University of Local Ethics Committee (Date: 16/04/2013, meeting no: 2013/09), Informed Consent: Consent form was filled out by all participants.

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Reha Girgin, Bülent Akduman, Concept: Bülent Akduman, Reha Girgin, Design: Bülent Akduman, Reha Girgin, Data Collection or Processing: Reha Girgin, Analysis or Interpretation: Reha Girgin, Ramazan Topaktaş, Literature Search: Selçuk Altın, Ali Akkoç, Writing: Reha Girgin, Cemil Aydın.

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Effect of Bariatric Sleeve Gastrectomy Technique on Women's Lower Urinary Tract Symptoms and Quality of Life: A Prospective Study

Bariatrik Sleeve Gastrektomi Tekniğinin Kadın Alt Üriner Sistem Semptomları ve Yaşam Kalitesi Üzerine Etkisi: Prospektif Bir Çalışma

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

The effect of bariatric surgery on lower urinary tract symptoms in obese women.

ABSTRACT

Objective

Obesity triggers lower urinary tract symptoms (LUTS) secondary to accumulation of excess fat which may lead to increase in intra-abdominal/intravesical pressures and subsequent impairment in pelvic floor muscles. However, it is considered that weight loss resolve these symptoms. In this study, we aimed to investigate the effects of bariatric surgery and especially Sleeve gastrectomy (SG) on women's LUTS, and quality of life.

Materials and Methods

A total of 53 patients who have undergone laparoscopic SG in our clinics between April 2014 and March 2015 were included in this prospective study. Age, body weight and body mass index (BMI) of the participants were preoperatively and postoperatively recorded. The patients have pre/post-operatively filled the Beck depression inventory (BDI), International prostate symptom score (IPSS), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) and the 36-Item Short Form health survey (SF-36) scores were recorded. Additionally, post-operative decrease in body weight and BMI of the patients was recorded.

Results

There was a statistically significant decrease in mean BDI, IPSS and ICIQ-SF scores and SF-36 (prominent increment in physical and mental

ÖZ

Amaç

Obezite; yağlanma artışı nedeniyle intraabdominal/intravesikal basınçta artışa neden olarak pelvik taban kaslarını zayıflatır ve alt üriner sistem semptomlarının (AÜSS) oluşmasını tetikler. Kilo kaybının ise bu semptomlarda düzelmeye yol açacağına inanılmaktadır. Bizim bu çalışmadaki amacımız günümüzde gittikçe artan sayılarda uygulanan bariatrik cerrahinin özellikle Sleeve gastrektomi (SG) tekniği uygulanarak sağlanan kilo kaybının kadınlarda AÜSS ve yaşam kalitesine olan etkilerini araştırmaktır.

Gereç ve Yöntem

Nisan 2014 ila Mart 2015 tarihleri arasında merkezimizde obezite nedeniyle laparoskopik SG cerrahisi geçiren hastalardan dışlama kriterleri sonrasında uygun olan 53 kadın hasta çalışmaya dahil edildi. Hastaların operasyon öncesi yaş, boy, kiloları ve vücut kitle indeksleri (VKİ) preoperatif ve postoperatif olarak kaydedildi. Hastalara preoperatif ve postoperatif olarak Beck depresyon ölçeği (BDI), Uluslar arası prostat semptom skoru (IPSS), Uluslar arası idrar kaçırma sorgulama formu (ICIQ-SF) ve short form-36 (SF-36) doldurularak verileri kaydedildi. Ayrıca hastaların operasyon sonrası kilo kayıpları ve VKİ düşüşleri de kaydedildi.

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component summary (PCS and MCS) scores), when compared with pre-operative values. A positive correlation was found between BMI and parameters including age, BDI and IPSS. However, no significant correlation was present between BMI and the parameters including ICIQ-SF, PCS and MCS.

Conclusion

Negative effect of obesity on LUTS and quality of life cannot be ignored. We assume that bariatric surgery can induce dramatic weight loss, amelioration in symptoms of urinary dysfunction and increase in quality of life of women.

Keywords

Obesity, lower urinary system, bariatric surgery, Sleeve gastrectomy, quality of life

Bulgular

Operasyon öncesine göre operasyon sonrası BDI, IPSS, ICIQ-SF ortalamalarında görülen düşüş ve SF-36'nın mental ve fiziksel ortalama skorlarında görülen artış istatistiksel olarak anlamlı bulundu.

Sonuç

Bu çalışmada bariatrik obezite cerrahisinin kadınlarda dramatik kilo kaybı ile birlikte AÜSS üzerinde düzelme ve yaşam kalitesinde artış sağlayabileceğini düşünmekteyiz.

Anahtar Kelimeler

Obezite, alt üriner sistem, bariatrik cerrahi, Sleeve gastrektomi, yaşam kalitesi

Introduction

Obesity is among the most important problems both in developed and developing countries due to its related comorbidities. From the year 1980 up to now, the number of obese individuals has increased nearly two-fold. Based on 2008 data of The World Health Organization, 1.6 billion overweight adults are living worldwide. This figure also includes 300 million obese female individuals (1,2). In the United States, approximately 67% of the population is either overweight or obese, whereas the prevalence of obesity is 40-50% in many European countries (3). More than 40 million children under five years of age were overweight according to 2011 data (1,2). It is estimated that there are 500 million obese adults globally and this number is increasing every year. Annually, nearly 2.8 million people are lost because of the complications related to obesity (4). The Turkish Diabetes Epidemiology Study-I (TURDEP-I), reported that the prevalence of obesity was 22.3% in 1997 (5). However, it has been reported in TURDEP-II that the obesity rate raised up to 32% in 2010 and this fact reflects a worrisome increment (6). Although it is possible to lose weight using non-surgical methods, within a short time, such as 24 months, 66% of patients regain their lost weight. Patient's compliance to diet during medical treatment can give an idea about the postoperative compliance of the patient to the prescribed treatment. Since comorbidities associated with obesity result in premature deaths. Surgery has become the first choice in the treatment of morbid obesity (7). Nowadays, bariatric surgery is the only treatment modality which produces 15% weight loss in long term (8). When mortality, morbidity, cost, patient's satisfaction and, most importantly, amount of weight loss are considered, laparoscopic Sleeve gastrectomy (LSG) is one of the most frequently preferred surgical procedures (9,10). In the USA, nearly more than 220.000 of bariatric surgical procedures are being performed annually (11). Theoretically, obesity triggers lower urinary tract symptoms (LUTS) due to accumulation of excess fat, leading to increases in intra-abdominal and intravesical pressures and resultant weakening of pelvic floor muscles. However, weight loss is thought to resolve these symptoms (12,13,14). In this study, we aimed to investigate the effect of weight loss achieved by bariatric surgery, especially using LSG technique, on women's LUTS and quality of life.

Materials and Methods

A total of 53 female obese patients who underwent LSG between April 2014 and March 2015 were included in this prospective study. Ethical approval was obtained from the Local Ethics Committee prior to commencing the study. Patients who did not give informed consent, those with a history of treatment for sexual dysfunction, with a known mental or psychiatric disease, a history of weight loss treatment, surgery for incontinence, medical treatment for LUTS, respiratory tract diseases (e.g. chronic obstructive pulmonary disease) or a neurological disorder which might be associated with urinary symptoms, and those younger than 18 years of age were excluded. 53 female patients were included in this study and pre- and post-operative data were evaluated. Preoperative data on age, height, body weight and body mass index (BMI) were recorded. Before and after the operation (6 months after surgery) the patients completed the International prostate symptom score (IPSS), International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), Beck depression inventory (BDI) and the 36-Item Short Form health survey (SF-36), and the scores were recorded. Besides, postoperative decrease in body weight and BMI were determined in all patients. All the participant patients were advised to follow the dietary program according to the bariatric surgery diet guidelines for six months before and after the surgical intervention and to avoid some foods, such as caffeine, spices and citrus fruits which may cause irritation in the bladder.

IPSS: Its former name was American Urological Association Symptom Index. This scoring system consists of 8 items, which are rated as mild (0-7), moderate (8-19) and severe (20-35) symptomatic. Severity of symptoms and their progression within a specific time period are compared.

ICIQ-SF: This scoring system measures severity and effects of symptoms of incontinence on quality of life and contains 4 questions. The cut-off scores are as follows: slight=1-5, moderate=6-12, severe=13-18 and very severe=19-21.

BDI: It is a multiple-choice self-assessment scale consisting of 21 items used to measure severity of anxiety in children and adults. The levels of anxiety are scored as follows: 0-13=minimal depression, 14-19=mild depression and 20-28=moderate depression, 20-63=severve depression.

SF-36: This is a reliable and very frequently used validated scale in the evaluation of health status and quality of life. The scale consists of 36 items and enables measurements of 8 domains which include vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Scoring is summarized under two headings namely Physical summary scores (PCS) and Mental summary scores (MCS).

Surgical technique: SG was firstly started to be performed as a restrictive component of duodenal switch operation. It was introduced into surgical practice as a risk-decreasing method in high-risk patients who cannot tolerate prolonged procedures (15). LSG has become a safe and effective primary method of bariatric surgery, which has gained high popularity among surgeons and patients (16). In this method, a narrow tubular neo-stomach is constructed. Greater curvature is freed from 2-3 cm proximal to the pylori up to "His angle" (incisuracardiaca), then gastric resection is realized. In order not to leave a large fundus pouch behind, posterior dissection should be very well performed so as to make His angle visible. Sleeve tube is fixated by suturing it to the omentum or gastrocolic adipose tissue. This procedure prevents kinking of the stomach from incisura angularis. Restrictive nature of LSG, decrease in ghrelin hormone production, rapid passage of food into distal segments and increase in peptide-YY and glucagone-like peptide-1 hormones are thought to induce weight loss (17,18). LSG is preferred in super obese patients, and those with a BMI of <50 kg/m^2 who want to be operated with this method. In a systemic analysis of 2.500 patients (median BMI: 51.2 kg/m^2) who had been operated with this method, the average weight loss was 55%, complication rate was 8%, and mortality rate was 0.19% (19). Diabetes remission rate was found to be 66.2% among patients who underwent LSG and it was thought that 15% these patients might again require a bariatric intervention at a later date (20,21). LSG has become a very frequently preferred method alone or in combination with other methods in the treatment of morbid obesity (22).

Statistical Analysis

The study was planned as a prospective trial. For statistical analysis of the results obtained in the study, SPSS Statistics 22 (IBM, Chicago, USA) program was used. The fitness of parameters to normality of distribution was evaluated using the Shapiro-Wilks test. In the comparison of the study data, descriptive statistical methods (mean, standard deviation) were used. Besides, for intergroup comparisons of quantitative data with normal distribution Student's t-test and those with non-normal distribution, the Mann-Whitney U test were used. A p-value of less than 0.05 was considered statistically significant. For intra group comparisons of parameters with normal distribution, the paired samples t-test, and for parameters with non-normal distribution, the Wilcoxon signed-rank test was used. In the analysis of correlations between parameters with normal distribution, Pearson's correlation analysis was employed.

Results

The study was performed on 53 female patients who underwent LSG between April 2014 and March 2015. The mean age of the subjects was 34.85±9.38 years (range: 18-54) (Table 1). Statistically significant decreases in average postoperative BMI values, BDI scores, body weights, IPSS, and ICIQ-SF scores were detected relative to the preoperative estimates (for all, p=0.001). When compared with preoperative values, statistically significant increases were observed in average postoperative PCS and MCS (for all, p=0.001) (Table 2). When compared with preoperative values, a positive correlation at a level of 29.5% was found between postoperative amount of percent change in BMIs and age (p=0.032). When compared with preoperative values, there was no statistically significant correlation between postoperative amount of percent change in BMIs, and changes in ICIQ-SF, PCS and MCS values (p=0.054). When compared with preoperative values, a statistically significant positive correlation was observed at a level of 27.8% between postoperative amount percent change in BMIs, and changes in BDI scores (p=0.044). When compared with preoperative values, a statistically significant positive correlation was found at a level of 33.5% between postoperative amount of percent change in BMIs and changes in IPSS values (p=0.014) (Figure 1).

Discussion

Theoretically, obesity triggers LUTS due to accumulation of excess fat which causes increases in intraabdominal and intravesical pressure

Table 1. Comparative evaluation of pre and postoperative study parameters of female patients

	Preoperative	Postoperative	p
	Mean±SD (median)	Mean±SD (median)	
BMI (kg/m^2)[2]	47.39±6.4	37.76±5.14	0.0012
Body weight (kg)	126.64±17.69	100.17±12.98	0.0012
BDI[3]	14.66±4.67 (15)	9.15±2.81 (8)	0.0012
IPSS[4]	4.13±3.41 (3)	1.91±2.19 (1)	0.001**
ICIQ-SF[5]	5.64±4.99 (6)	2.34±2.92 (1)	0.001**
PCS[6]	36.72±9.96	45.01±6.01	0.0012
MCS[7]	44.36±6.43	49.7±4.82	0.0012

SD: Standard deviation, [2]Wilcoxon signed-rank test, [3]Paired samples t test, **p<0.01, [2]BMI: Body mass index, [3]BDI: Beck depression inventory, [4]IPSS: International prostate symptom score, [5]ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form, [6]PCS: Physical summation score, [7]MCS: Mental summation score

Table 2. Evaluation of percent changes detected in postoperative Body mass index values relative to preoperative values and their correlations with changes in some selected parameters

Postoperative changes in some postoperative parameters relative to preoperative values	BMI[2] percent change (%)	
	r	p
Age (years)	0.295	0.032*
BDI[3]	0.278	0.044*
IPSS[4]	0.335	0.014*
ICIQ-SF[5]	0.266	0.054
Body weight	0.859	0.001**
PCS[6]	-0.244	0.078
MCS[7]	-0.266	0.055

Pearson correlation analysis *p<0.05, **p<0.01, SD: Standard deviation, [2]Wilcoxon signed-rank test, [3]Paired samples t test, **p<0.01 [2]BMI: Body mass index, [3]BDI: Beck depression inventory, [4]IPSS: International prostate symptom score, [5]ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form, [6]PCS: Physical summation score, [7]MCS: Mental summation score

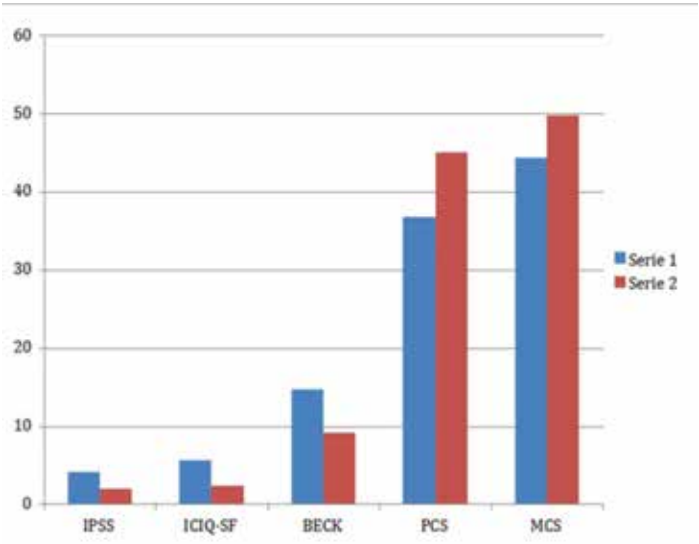

Figure 1. Comparative evaluation of pre and postoperative International prostate symptom score, International Consultation on Incontinence Questionnaire-Short Form, Beck depression inventory, physical component summary and mental component summary of patients
Serie 1: Pre-gastrectomy, Serie 2: Post-gastrectomy, IPSS: International prostate symptom score, ICIQ-SF: International consultation on incontinence questionnaire short form, BECK: Depression inventory scoring, PCS: Physical summary scores, MCS: Mental summary scores

and resultant weakening of pelvic floor muscles. However, weight loss is thought to resolve these symptoms (12-14).

Vella et al. (23) underlined BMI as an independent risk factor for urinary system symptoms. In our study, a significant correlation could not be found between change in BMI, and ICIQ-SF, while a positive correlation was detected between changes in BMI, and IPSS scores.

Ranasinghe et al. (24) performed laparosopic gastric banding in 653 female patients, and reported postoperative improvements in their ICIQ-SF scores. In our study, we also detected improvements in postoperative ICIQ-SF scores when compared with the preoperative values.

Palleschi et al. (25) reported higher incidence of overactive bladder symptoms in obese people and asserted that women were more severely affected by these symptoms. They recorded improvements in overactive bladder symptoms in patients who had undergone LSG at the 6. postoperative month.

In their study on 421 cases, Merrell et al. (26) reported that women with pelvic floor deformities had higher psychiatric concerns about the postoperative outcomes of bariatric surgery relative to other candidates of bariatric surgery. However, in our study, evaluations performed by means of BDI and we observed that preoperative high BDI scores had decreased and hence improved during the postoperative period.

Snyder et al. (27) analyzed physical and mental quality of life of women athletes and non-athletes in the year 2010 and found that average PCS and MCS sin control group were 53.3 and 46.6, respectively.

However, in our study, average preoperative PCS and MCS in obese participants were found to be 36.72 and 44.36, which were apparently lower than the average scores detected in normal population. Whereas, postoperative PCS and MCS statistically significantly improved, and raised to 45.01 and 49.7 points, respectively.

IPSS rating scale was not used in LUTS evaluation in the current study. However, it has also been reported in the literature that IPSS, which was a well-known approach in evaluation of the male patients, was used in female patients. In our study, IPSS rating scale was applied for LUTS of our patients and, after assessments, the patients were categorized in the mildly symptomatic (0-7) group. However, when compared with the preoperative values, the decrease in postoperative mean IPSS scores was statistically significant. Besides, a statistically significant and positive correlation at a level of 33.5% was found between amount of percent change in BMI and changes in IPSS scores. In our study in female patients who had undergone LSG and lost weight, LUTS ameliorated with resultant improvement in patients quality of life.

In the future, studies incorporated with urodynamic studies, which will explain postoperative improvements in LUTS following bariatric surgery, and relevant correlations should be conducted.

Unfavorable effects of increasingly prevalent obesity on sexual functions cannot be denied. We assume that bariatric surgery induces dramatic weight loss, and also decreases urinary dysfunction in women with resultant improvement in their quality of life.

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Ethics

Ethics Committee Approval: 2014/16 study, Fatih Sultan Mehmet Training and Research Hospital-Local Ethics Committee 2014/36, Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Concept: Fatih Uruç, Bekir Aras, Design: Fatih Uruç, Bekir Aras, Data Collection or Processing: Serkan Akan, Aytaç Şahin, Elif Uruç, Özgür Haki Yüksel, Analysis or Interpretation: Ahmet Ürkmez, Çağlar Yıldırım, Literature Research: Ahmet Ürkmez, Çağlar Yıldırım, Writing: Fatih Uruç, Bekir Aras.

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CASE REPORT
GENERAL UROLOGY

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A Case of Iatrogenic Ureter Injury: Recent Diagnostic and Treatment Methods

Bir Olgu Eşliğinde İyatrojenik Üreter Yaralanmaları Güncel Tanı ve Tedavi Yöntemleri

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ABSTRACT

The ureters are rarely exposed to trauma. Ureteral injuries are generally in the form of iatrogenic, blunt injuries, and rarely penetrating injuries. Iatrogenic injuries often occur during surgical procedures. They do not present with specific findings and symptoms, therefore, they have late-onset symptoms. Imaging modalities of choice are usually intravenous pyelography and computed tomography. Treatment is tailored to the location of the trauma.

Keywords

Ureter, trauma, iatrogenic ureteral injury, duplicated ureter

ÖZ

Üreterler nadiren travmaya maruz kalırlar. Üreter yaralanmaları iyatrojenik, künt travmalar ve nadiren penetran yaralanma şeklindedir. İyatrojenik yaralanmalar genellikle cerrahi işlemler ile birlikte olur. Üreter yaralanmalarının spesifik bulgu ve semptomları yoktur. Bu nedenle geç belirti vermektedir. Görüntüleme yöntemi olarak sıklıkla intravenöz pyelografi ve bilgisayarlı tomografiden yararlanılır. Tedavi, travmanın lokalizasyonuna göre belirlenir.

Anahtar Kelimeler

Üreter, travma, iyatrojenik yaralanma, çift üreter

Introduction

Ureteral traumas are rare representing almost 1-2.5% of all urogenital system injuries (1,2). Percent of seventy-five ureteral injuries are iatrogenic, 18% are blunt traumas and 7% penetrating injuries (3). Iatrogenic injuries are generally reported to be caused by endourological interventions (42%), gynecological (34%) and intra-abdominal surgeries (24%) (4). Iatrogenic ureteral injuries do not present with specific findings and symptoms, often with delayed diagnosis and only 1/3 are recognized during surgery (5). This study presents a case of ureteral injury during surgery and discusses the diagnosis and treatment procedures.

Case Presentation

A 30-years old female patient was admitted to our emergency department with the complaints of extensive abdominal pain, bloating and belching. Her history revealed that she underwent total abdominal hysterectomy + bilateral salpingo-oophorectomy for myoma uteri in another center about 20 days ago. Three days after surgery, she underwent percutaneous nephrostomy for left sided hydronephrosis in a different center that she was referred to with the complaint of abdominal pain. Her physical exam revealed findings of hard abdomen with rebound tenderness. Laboratory workup indicated anemia (hemoglobin=10.1 gr/dl), leukocytosis (white blood cell=15200) and thrombocytosis (platelet=520 thousand). Antegrade pyelography showed partial filling of the ureter with opaque substance with the contrast matter not reaching the distal portion (Figure 1). The patient was admitted to the hospital upon computed tomography (CT) results indicating collection to the superior of the bladder (Figure 2).

The patient was taken to operation following preoperative preparations. During the operation, the left ureter was found to be sutured and excised at around 5 cm to the distal. During dissection, it was also noted that the patient had duplicated collective system (Figure 3). Ureteroureterostomy was performed after removal of the necrotized portion of the distal end of the excised ureter following enteroanastomosis lateral to the other ureter. An ureteral stent was placed to the injured ureter and the procedure was completed. Drain was taken off on post-op day 15. The stent was removed based on her CT findings in the first month showing no signs of leak (Figure 4). The patient is in her 6th post-op month and does not have any complaint.

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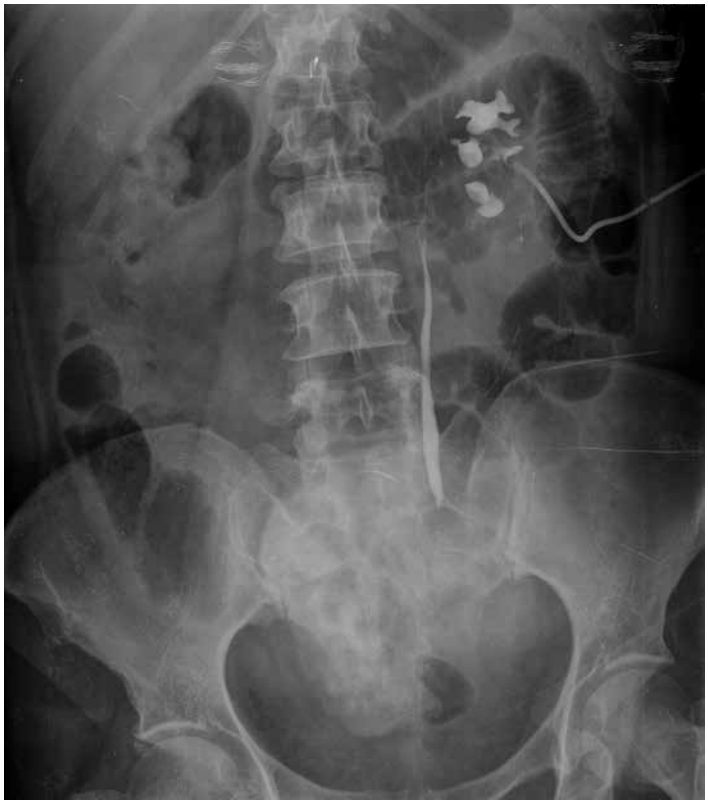

Figure 1. Contrast agent passage through distal ureter was not mentioned by preop antegrade pyelography

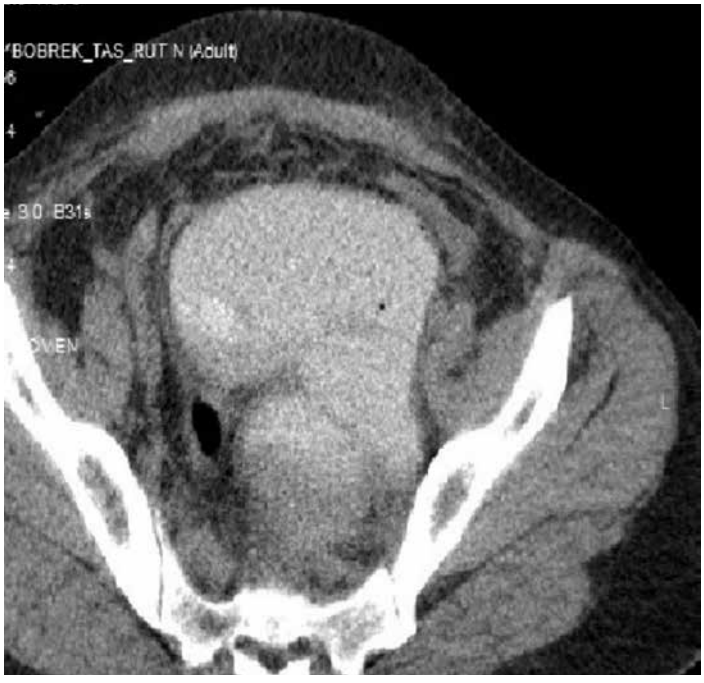

Figure 2. Urinoma formation at the superior part of bladder by computered tomography

Discussion

Ureter anatomy, supply network and adjacencies should be well-recognized to avoid ureteral injuries. The ureters are in close adjacency to female genital organs and are threatened during liberation. The most frequently injured portion of the ureters is the distal parts, as in our case (4,6).

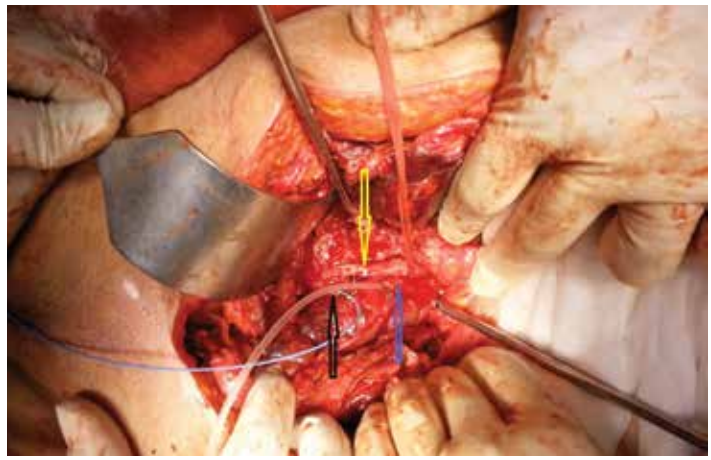

Figure 3. Patient had a duplex collecting system yellow sign healthy ureter blue sign proximal part of the injured ureter black sign distal part of the injured ureter

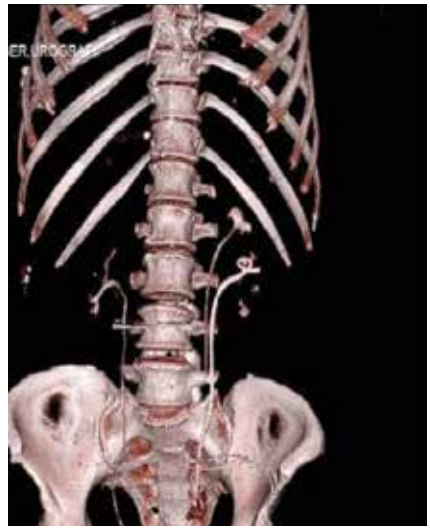

Figure 4. After 1 month computed tomography urography there is no urine leakage

The most common findings of ureteral injuries are side pain and tenderness, hematuria, oliguria, anuria, delayed recovery or increased fluid discharge from drains (for post-op patients), and vaginal fluid leak when the cervical stump remains open. Urinary peritonitis is a chemical peritonitis mostly presenting with extensive abdominal pain, distention and ileus (7). It is sometimes confined by being surrounded with a leaking fibrous capsule to the retroperitoneum causing urinoma (8). Urinoma may get infected and may cause sepsis and electrolyte imbalance.

Radiologic diagnostic tools are ultrasonography (USG), CT or intravenous pyelography in case of an injury. If the ureteral orifices are visible on cystoscopy, presence of urinary flow therein may indicate at least absence of obstruction yet cannot exclude other types of injuries. Outflow of blood or air (in laparoscopic operations) from the orifice during cystoscopy are indirect findings of injury (9). If post-op ureteral injury is suspected, urinomas, abscess formations and hydronephrosis may be detected by USG and/or contrast-enhanced CT, whereas CT urography may contribute to localization of the injury.

In the order of frequency, the most common locations for ureteral injuries are distal, middle and proximal parts of the ureter (4,6). General principles applicable to organ injuries also apply to ureteral injuries. There are various treatment options depending on the type of ureteral injuries. In minor injuries (clamp crush, needle injuries, etc.), conservative treatment may be applied unless there is suspicion of ureter vitality and leak, and presence of peristalsis (9). As for injuries due to ligation and other basic injuries, stenting should be preferred to avoid potential stenosis and leaks (10,11). Stents should be in place for 2-6 weeks depending on the condition of the patient (12). In complete lacerations of the ureter suturing in addition to stenting, as we did in our case, would be a more favorable method (5).

There also exist various treatment options depending on the location of ureteral injuries. The most commonly injured location is the distal one third of the ureter (4,6). End-to-end anastomosis (ureteroureterostomy) may be performed in injuries at a distance of 3-4 cm to the ureterovesical junction. In injuries, which are localized closer to the ureterovesical junction, on the other hand, the best option is ureteroneocystostomy (10). Psoas hitch (6-8 cm) or boari flap (11-15 cm) methods may be applied to achieve more length in patients who cannot be treated with ureteroneocystostomy alone. In mid-ureter injuries, end-to-end anastomosis (ureteroureterostomy) should be tried at first. If the injury is severe and there is no possibility of performing the repair without tightening, then, psoas hitch, boari flap or transureteroureterostomy may be applied (13,14). Transureteroureterostomy is performed by anastomosing the injured ureter to the contralateral intact ureter. This should be a method of last resort since an iatrogenic injury is created on the intact ureter. As for upper end injuries, end-to-end anastomosis should be tried at first (13).

Ureteroureterostomy should first be tried in complete or partial ureteral detachments. If ureteroureterostomy is not possible, although rarely used, placement of ileal colonic segment in between may be the first option to follow (15,16). Nephrostomy is often used when primary repair is not possible (16,17). Autotransplantation is the procedure to option for in the absence of the other kidney or in case of impaired renal functions and only if the other options are not favorable (17). Nephrectomy, on the other hand, is an option to be applied quite rarely, and should be preferred only after making sure that the functions of the contralateral kidney are normal.

Our case had ureteral injury that occurred during a gynecological operation and underwent conservative or minimally invasive methods since this injury was not a full-thickness incision. The interesting part of the case was that she had a duplicated ureter. This may, in itself, be the intrinsic reason that misled the surgeon during the gynecological operation to bind the ureter. That's why binding or excising should never be performed unless the surgeon is totally sure about the tissues being bound during any surgical procedure. If it is not possible to be sure, it may be an option to check the presence of vessels or ureters by using a fine needle. If the patient did not have a duplicated collective system, the procedure to follow would have been ureteroneocystostomy and psoas hitch as in the case of distal ureteral injuries.

Conclusion

Iatrogenic ureteral injuries constitute a major complication that may be experienced even by experienced surgeons. Ureteral anatomy should be well-recognized by all surgeons from all disciplines who are interested in pelvic surgery. Surgery should be meticulously done by extreme attention. In case of a ureteral injury, treatment planning should be done according to anatomical location and operative experience.

Ethics

Informed Consent: Consent form was filled out by all participants, Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Hakan Türk, Ferruh Zorlu, Concept: Hakan Türk, Batuhan Ergani, Design: Batuhan Ergani, Mustafa Karabıçak, Data Collection or Processing: Batuhan Ergani, Cemal Selçuk İşoğlu, Analysis or Interpretation: Hakan Türk, Ferruh Zorlu, Literature Search: Batuhan Ergani, Hakan Türk, Writing: Batuhan Ergani.

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CASE REPORT
UROONCOLOGY

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Combined Radiation and Hormonal Therapy for Squamous Cell Carcinoma of the Prostate: A Case Report and Review of the Literature

Prostatın Skuamöz Hücre Karsinomu Tedavisinde Kombine Hormonoterapi ve Radyoterapi: Olgu Sunumu Eşliğinde Literatür Değerlendirmesi

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ABSTRACT

Squamous cell carcinoma (SCC) of the prostate is a rare entity, with a prevalence of 0.6-1% among all prostatic carcinomas. Prostatic SCC has a poor prognosis. Although there are a number of treatment modalities, none of them have promised a long-term survival. Herein, we report a case of SCC coexisting with adenocarcinoma of the prostate treated with a combination of hormonal therapy, leuprolide acetate, and radiotherapy. Twenty-four months after treatment, the patient did not progress into metastatic or end-stage disease with the combination treatment modality. The treatment modalities for SCC are still limited. Comparisons of surgery and radiotherapy, and chemotherapy and hormonal therapy showed that they were all ineffective. Combined radiotherapy and hormone therapy may hold promise for longer survival.

Keywords

Hormonal therapy, squamous cell carcinoma of prostate, radiotherapy

ÖZ

Prostatın skuamöz hücreli karsinom (SHK) tüm prostat karsinom arasında %0,6-1 prevalansı ile nadir görülen bir durumdur. SHK kötü prognoza sahiptir. Çeşitli tedavi modaliteleri olmasına rağmen, bunların hiçbiri uzun süreli yaşam vaat etmezler. Bu yazıda hormon tedavisi ve radyoterapi kombinasyonu ile tedavi olan adenokarsinom birlikteliği ile olan prostatik SHK olgusu sunuldu. Yirmi dört ay tedavi sonrası, hastada kombinasyon tedavi yöntemi ile metastatik ya da son evre hastalık haline ilerleme olmadı. SHK için tedavi yöntemleri hala sınırlı olmasına rağmen kombine radyo ve hormonoterapi bu hastalık için uzun yaşam süresini vaat edebilir.

Anahtar Kelimeler

Hormonoterapi, prostatın skuamöz hücre karsinomu, radyoterapi

Introduction

It has been well-known that the majority of prostate cancers are adenocarcinomas (up to 95%), and pure squamous cell carcinoma (SCC) of the prostate is an extremely rare entity with an incidence of 0.6-1% among all prostatic carcinomas (1). One third of patients with SCC present with normal prostate-specific antigen (PSA) values, and digital rectal examination (DRE) may be more predictive for those patients (2). Prostate SCC has a poor prognosis, and the median survival is about 14 months after diagnosis (3). Approximately 50% of cases present with pure SCC, and SCC coexists with adenocarcinoma in 25-50% of cases (4). Although a number of treatment modalities including radical surgical approaches, chemotherapy, hormone and radiation therapy have been used, however, none of them have promised a long-term survival. In this paper, we report a patient who was diagnosed with prostatic SCC coexisting with adenocarcinoma and treated with hormonal therapy combined with radiation therapy.

Case Presentation

A 69-year-old male patient was admitted to our urology outpatient clinic with a 6-month history of lower urinary tract symptoms (January

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2011). His serum PSA level was 0.43 ng/ml. A transrectal ultrasound-guided prostate biopsy had been performed previously due to stony hard DRE, and the histopathological examination revealed focal squamous metaplasia areas with dysplastic differentiation, without any adenocarcinomatous component, in two of 12 cores. The patient had been treated with an alpha blocker. Two years later (January 2013), the patient complained of voiding difficulty, dysuria, and macroscopic hematuria. A computed tomography (CT) was obtained due to a stony hard and enlarged prostate on DRE, and a normal PSA value (0.65 ng/ml). CT showed an irregularly enlarged prostate, a prostatic mass extending into the bladder neck, bilateral moderate hydronephrosis, and no lymph node enlargement (Figure 1A). Bone scintigraphy was normal. Serum urea and creatinine levels were high (48 mg/dl and 1.73 mg/dl, respectively). After obtaining written informed consent from the patient, transurethral resection of the prostate, cystoscopy and transureteral resection of the suspicious areas of the bladder were performed in one session. Nephrostomy tubes were placed bilaterally. Biopsy revealed moderately differentiated adenocarcinoma with a Gleason score of 5+4, and SCC of the prostate. It was also reported that SCC component of prostatic adenocarcinoma infiltrated epithelial lining of the bladder (Figure 2).

The patient was diagnosed with local-invasive disease, and has been managed with radiotherapy and hormonal therapy with leuprolide acetate since February 2013. He received leuprolide acetate 22.5 mg followed by radiotherapy gray (Gy) 56 Gy to the pelvis, and 10 Gy to the prostatic area. He tolerated the treatment well, and no acute toxicities were seen. Bilateral nephrostomies were removed 6 months after surgery.

He complained of infrequent voiding difficulty and recurrent macroscopic hematuria at postoperative 2nd year follow-up visit. Bilateral severe hydroureteronephrosis has been persisting and his serum urea and creatinine levels did not increase (48 mg/dl and 2.3 mg/dl, respectively), therefore, he did not require dialysis. No bone metastasis was detected on control bone scintigrapy. Our patient's local-invasive disease has not progressed to metastatic or end-stage disease after combination treatment with radiation and hormonal therapy (Figure 1B, C).

Discussion

SCC of the prostate usually presents with outlet obstruction symptoms, similar to other prostatic diseases. Three-tiered classification of prostate cancer includes well-, moderately- and poorly-differentiated categories. The Gleason grading may be used for glandular component, but not for squamous component (2). Primary SCC of the prostate is an aggressive neoplasm found in less than 1% of men worldwide. The histopathological characteristics of prostatic SCC were first described by Mott (5). Those criteria are important to differentiate prostate SCC from non-neoplastic squamous metaplasia (secondary to infarct, acute/chronic prostatitis, granulomatous prostatitis due to Bacillus Calmette-Guerin, estrogen therapy, or radiation therapy) (3). Clinical features pointing towards the diagnosis of prostate SCC include a variable consistency of prostate on DRE; prostate is not always hard on palpation. Different from primary adenocarcinoma of the prostate, serum PSA and acid phosphatase levels are usually within the normal ranges, even in the presence of metastasis. In most of the cases, degree of histological differentiation is moderate. Squamous

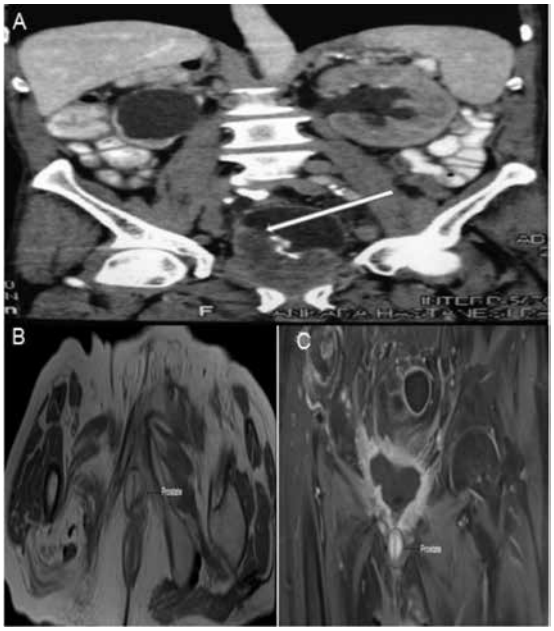

Figure 1. A) Sagittal computerized tomography section demonstrating extension of mass to soft tissues, to the base of bladder (arrow), and moderate hydronephrosis on the left and severe hydronephrosis on the right sides. B) Axial T1-weighted spin echo magnetic resonance image demonstrating reduced volume of the prostate after combination of radiotherapy and hormonal therapy. C) Coronal T1-weighted turbo-spin echo fat-sat magnetic resonance image of the prostate, 24 months after combination therapy. Note the lack of infiltration in bladder soft tissues

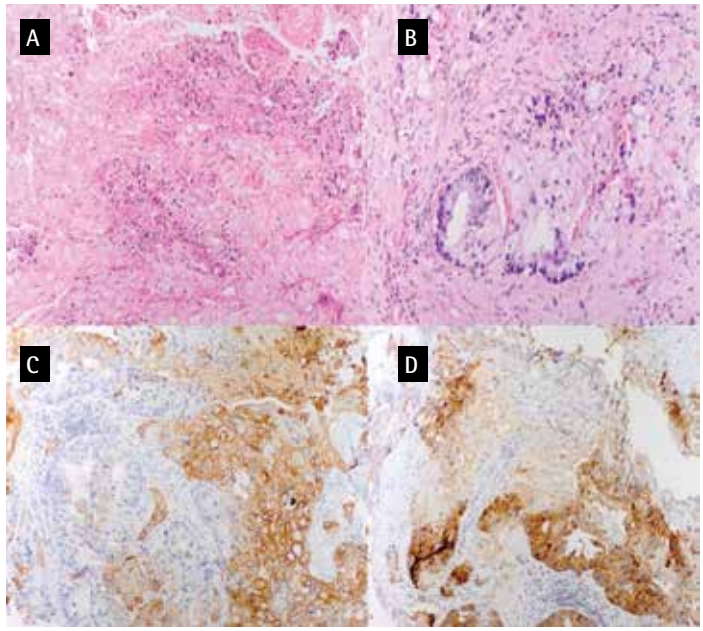

Figure 2. Sections stained with hematoxylin and eosin show only sheets of squamous cell carcinoma, A) original magnification x100) with adjacent focal areas of adenocarcinoma B) original magnification x200). Immunohistochemistry was positive for high molecular weight cytokeratin C) original magnification x100) and prostate-specific antigen D) original magnification x100) in squamous cell carcinoma, however adenocarcinoma cells were negative for high molecular weight cytokeratin and prostate-specific antigen (C, D)

component is together with adenocarcinoma in 5-95% of cases. The morphology does not have any prognostic significance when adenosquamous carcinoma and pure SCC are compared. However, SCC antigen might be elevated, allowing a serologic monitoring of treatment effectiveness or progression of the disease (6).

Primary SCC of the prostate may spread along the nerves, locally extend to periprostatic tissues, bladder and seminal vesicles, and metastasize to lymph nodes and bone. In contrast to adenocarcinoma, metastatic bone lesions are osteolytic (5). The average estimated survival time for prostatic SCC is not long (6-24 months) (2). There have been several studies reporting multimodal therapy for prostate SCC. Munoz et al. (7) reported a long survival (60 months) with a combination of chemotherapy and radiotherapy. They administered 3 courses of chemotherapy with cisplatin and 5-fluorouracil followed by radiotherapy, 46 Gy to the pelvis, and 20 Gy to the prostatic area. Uccibayashi and colleagues (8) showed a survival time of 21 months with a combination of radiotherapy and chemotherapy. Their patient received 54 Gy radiation to the pelvis, and chemotherapy with bleomycin and cisplatin. Majeed et al. (9) reported 18 months of survival with a combination therapy including radical retropubic prostatectomy and bilateral pelvic lymphadenectomy, external beam radiotherapy (2520 cGy) to the prostate bed, and chemotherapy with mitoxantrone and cisplatin. Similarly, Okada and Kamizaki (10) achieved an 18-month survival using a multimodal treatment approach in a patient with lymph node involvement. They treated their patient with 50 Gy radiation to the pelvis, and a 10 Gy boost to the prostate, along with chemotherapy with prednisone, etoposide, procarbazine and cisplatin.

Conclusion

In conclusion, treatment modalities for prostatic SCC are still limited. Comparisons of surgery and radiotherapy, and chemotherapy and hormone therapy showed that they were all ineffective. Combination therapy provides overall survival advantage over monotherapy. However, the origin of prostate SCC has long been a topic for debate, and a better understanding of its biology might help development of effective, novel therapies.

Ethics

Informed Consent: Consent form was filled out by all participants. Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yasin Aydoğmuş, Demirhan Orsan Demir, Concept: Muhammet Fatih Kılınç, Ömer Gökhan Doluoğlu, Design: Tolga Karakan, Ömer Gökhan Doluoğlu, Data Collection or Processing: Elif Özer, Demirhan Orsan Demir, Analysis or Interpretation: Elif Özer, Tolga Karakan, Literature Search: Yasin Aydoğmuş, Muhammet Fatih Kılınç, Writing: Muhammet Fatih Kılınç. Conflict of Interest: No conflict of interest was declared by the authors.

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J Urol Surg 2016;3:101-107

Andrology

doi: 10.4274/jus.2016.03.019

Re: Could Testosterone Replacement Therapy in Hypogonadal Men Ameliorate Anemia, a Cardiovascular Risk Factor? An Observational, 54-week Cumulative Registry Study

Zhang LT, Shin YS, Kim JY, Park JK

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J Urol 2016;195:1057-1064. doi: 10.1016/j.juro.2015.10.130. Epub 2015 Oct 28.

EDITORIAL COMMENT

Testosterone deficiency syndrome may associate with erectile dysfunction, increased abdominal fat and reduced muscle mass. Low serum testosterone is also related with anemia, metabolic syndrome and cardiovascular disease. In this study, the authors investigated if testosterone undecanoate (TU) reduces anemia and the risk of cardiovascular disease in patients with hypogonadism A total of 58 participants with a total testosterone level of less than 2.35 ng/ml received an injection of 1.000 mg TU 6 times; at initial visit, 6, 18, 30, 42 and 54 weeks. They observed that total testosterone and free testosterone levels were restored by TU. Hemoglobin and hematocrit levels significantly increased while anemia and total cholesterol levels significantly reduced. Although there are some limitations of this study e.g. it is not a randomized controlled and a long-term study, TU treatment in hypogonadal men decreased the prevalence of anemia, improved lipid profiles and lowered the risk of cardiovascular disease.

Emre Bakırcıoğlu, MD

Andrology

doi: 10.4274/jus.2016.03.020

Re: A Randomized Prospective Double-Blind Comparison Trial of Clomiphene Citrate and Anastrozole in Raising Testosterone in Hypogonadal Infertile Men

Helo S[1], Ellen J[1], Mechlin C[2], Feustel P[3], Grossman M[4], Ditkoff E[4], McCullough A[1]

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J Sex Med 2015;12:1761-1769. doi: 10.1111/jsm.12944. Epub 2015 Jul 14.

EDITORIAL COMMENT

It has been reported that the prevalence of low testosterone (<300 ng/ml) in infertile men was as high as 41% and low testosterone did not always correlate with impaired seminal parameters (1). Although previous studies have shown that clomiphene citrate (CC) and anastrozole (AZ) were effective in increasing testosterone levels, randomized double blind comparisons are lacking. In this study, the authors aimed to investigate the equivalence of CC versus AZ with respect to improvement in testosterone levels in hypogonadal infertile men. It was shown that there was a significantly larger increase in T level in CC group vs AZ group at 6 and 12 weeks whereas estradiol levels increased in CC group compared to AZ group. Both groups did not demonstrate significant changes in seminal parameters or patient-reported outcomes, This study shows that CC would be a better choice to increase testosterone levels for hypogonadal men with low estradiol levels.

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Emre Bakırcıoğlu, MD

doi: 10.4274/jus.2016.03.021

Re: Causes of Hospital Readmissions after Urologic Cancer Surgery

Schmid M[1], Chiang HA[2], Sood A[3], Campbell L[3], Chun FK[4], Dalela D[3], Okwara J[2], Sammon JD[3], Kibel AS[2], Menon M[3], Fisch M[4], Trinh QD[2]

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Urol Oncol 2016;34:236.e1-236.e11. doi: 10.1016/j.urolonc.2015.11.019. Epub 2015 Dec 23.

EDITORIAL COMMENT

Unplanned readmissions after surgery are a cause for anxiety and inconvenience for the patient and financial burden for the healthcare system. It has been advocated that unplanned readmission rates can be used as a metric for quality of patient care. In the light of the changes in health care policy with an emphasis on reducing readmissions, Schmid and coworkers used the American College of Surgeons National Surgical Quality Improvement Program database to examine the causes and predictors of readmissions after urologic oncology surgical procedures, namely radical prostatectomy (RP), radical nephrectomy (RN), partial nephrectomy (PN), and radical cystectomy (RC). The overall unplanned 30-day readmission rate was 5.5%. Approximately two thirds of readmissions occurred within the first 10 days following hospital discharge. Comparing with the other procedures, RC patients experienced the highest rate (15.9%) for readmissions. For RP and PN, minimally invasive approach was associated with decreased odds for readmissions. Better analyzing the causes and developing strategies to prevent early readmissions after urologic cancer surgery would undoubtedly help to improve patient outcomes and decrease the health care costs.

Özgür Yaycıoğlu, MD

doi: 10.4274/jus.2016.03.022

Re: Metastatic Prostate Cancer in Men Initially Treated with Active Surveillance

Yamamoto T, Musunuru B, Vesprini D, Zhang L, Ghanem G, Loblaw A, Klotz L

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J Urol 2016;195:1409-1414. doi: 10.1016/j.juro.2015.11.075. Epub 2015 Dec 18.

EDITORIAL COMMENT

Active surveillance (AS) in prostate cancer has been advocated as a treatment modality to reduce overtreatment of patients with clinically insignificant disease while appropriately offering radical treatment to those in whom the disease is reclassified as high-risk during surveillance. Yamamoto and coworkers have analyzed their prospective cohort of 993 patients treated with AS and analyzed the characteristics of those who eventually progressed to metastatic disease. Out of 980 evaluable patients, 133 (13.6%) had Gleason score (GS) 7 disease. During AS, 30 patients (3.1%) developed metastases. Of note, metastases developed in 13 of 133 (10%) patients with GS 7 disease. The median time to metastasis was 6.3 years. On univariate analysis, GS 7, number of positive cores, core positivity greater than 50% at initial biopsy, intermediate risk group, and short prostate-specific antigen (PSA) doubling time (DT) were significant risk factors for metastases. On multivariate analysis, GS 7, a total of 3 or more positive cores, and PSA DT remained significant. The presence of Gleason pattern 4 on diagnostic biopsy conferred a threefold to fourfold increased risk of metastatic disease. Even though the authors concluded that GS seven patients should be offered AS with caution, the safety of such a suggestion is quite questionable.

Özgür Yaycıoğlu, MD

doi: 10.4274/jus.2016.03.023

Re: Perioperative Complications after Living Kidney Donation: A National Study

Lentine KL[1], Lam NN[2], Axelrod D[3], Schnitzler MA[1], Garg AX[4], Xiao H[1], Dzebisashvili N[3], Schold JD[5], Brennan DC[6], Randall H[1], King EA[7], Segev DL[7]

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Am J Transplant 2016;16:1848-1857. doi: 10.1111/ajt.13687. Epub 2016 Mar 10.

EDITORIAL COMMENT

The authors have investigated the perioperative complications after donor nephrectomy integrating the US transplant registry with administrative records from an academic hospital consortium (97 centers, 2008-2012). 14.964 patients were verified as live donors through linkage with the Organ Procurement and Transplantation Network registry. Overall, 16.8% of donors experienced a perioperative complication, including Clavien grade 2 or higher events in 8.8%, Clavien grade 3 or higher in 7.3%, and Clavien grade 4 or higher events in 2.5%. The most common complications were gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), and surgical/anesthesia-related injuries (2.4%). After adjustment for demographic and clinical factors, African American donors were 26% more likely to experience any perioperative complication and 56% more likely to experience the most severe complications. Other factors associated with increased risk of any perioperative complication, and with the most severe complications included predonation hematologic and psychiatric conditions and more recent years of donation. Donation at centers with the highest annual volume of living donor nephrectomies (>50 cases/year) was associated with approximately 45% lower risk of any perioperative complication and of the most severe complications. Donors who underwent robotic nephrectomy were twice as likely to experience severe perioperative complications (adjusted odds ratio 2.07 for Clavien grade 4 or higher events). To conclude, the authors found that while one in six US living kidney donors experienced a perioperative complication, the most severe complications were infrequent, affecting only 2.5% of donors.

Serkan Akıncı, MD

doi: 10.4274/jus.2016.03.024

Re: Timing of Pregnancy after Kidney Transplantation and Risk of Allograft Failure

Rose C[1], Gill J[1,2], Zalunardo N[1], Johnston O[1], Mehrotra A[3], Gill JS[1,2,4]

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Am J Transplant 2016;16:2360-2367. doi: 10.1111/ajt.13773. Epub 2016 Apr 4.

EDITORIAL COMMENT

The authors have investigated the risk of allograft failure due to the timing of pregnancy after kidney transplantation. Of the 21.814 women aged 15-45 who have received a first kidney-only transplant in the United States Renal Data System, 729 pregnancies were identified using medicare claims. In multivariate analyses, pregnancy in the first posttransplant year was associated with an increased risk of allograft failure from any cause including death (ACGL) (HR: 1.18) and death censored graft loss (DCGL) (HR: 1.25), while pregnancy in the second posttransplant year was associated with an increased risk of DCGL (HR: 1.26). Pregnancy in the third posttransplant year was not associated with an increased risk of ACGL or DCGL. The cause of allograft failure was limited by incomplete data, but changes in immunosuppressant medications and unstable drug levels leading to acute and chronic rejection may be in the causal pathway resulting in graft loss after pregnancy. These results may be useful for physicians providing counseling to women wanting to conceive after transplantation.

Serkan Akıncı, MD

doi: 10.4274/jus.2016.03.025

Re: Long-Term Outcome of Low Scrotal Approach Orchiopexy without Ligation of the Processus Vaginalis

Hyuga T, Kawai S, Nakamura S, Kubo T, Nakai H

Jichi Medical University, Children's Medical Center Tochigi, Department of Pediatric Urology, Tochigi, Japan

J Urol 2016;196:542-547. doi: 10.1016/j.juro.2016.02.2962. Epub 2016 Mar 2.

EDITORIAL COMMENT

Dealing with pre-scrotal cryptorchidism is a common practice for pediatric urologists. Surgical correction is the standard care for these children. There are several surgical techniques which can be performed with no definitive long-term results presented in the literature. In general practice, ligation of patent processus vaginalis (PV) is routinely performed during orchiopexy to avoid an inguinal hernia. In this retrospective study, the authors present their long-term outcomes for patients who underwent low scrotal approach orchiopexy without PV ligation. Intraoperative findings show 10 testes with widely patent PV and not widely patent in 217 testes. The authors choose to ligate only these 10 widely patent PV and, in these other 217 testes, only low scrotal orchiopexy was performed. In a median follow-up of 44 months (range 20-73), only one complication in 'no widely patent PV' group (wound infection) and one complication (reascending testis) in 'widely patent PV' group occurred. As the authors mentioned in their paper, two major concerns with ligation of PV are to obtain a sufficient cord length for appropriate orcihopexy and prevent an inguinal hernia. During their follow-up, there were no reascending testis or hernia occurred in 'non-ligated PV' group. In conclusion, low scrotal approach ochiopexy is a safe procedure for patients with prescrotal crytorchidism and ligation of PV is not absolutely indicated when the PV is not widely patent.

Tukut Doğanca, MD

doi: 10.4274/jus.2016.03.026

Re: Factors Predicting Outcomes of Micropercutaneous Nephrolithotomy: Results from a Large Single-Centre Experience

Ganpule A, Chhabra JS, Kore V, Mishra S, Sabnis R, Desai M

Muljibhai Patel Urological Hospital, Gujarat, India

BJU Int 2016;117:478-483. doi: 10.1111/bju.13263. Epub 2015 Sep 30.

EDITORIAL COMMENT

The recently developed micropercutaneous nephrolithotomy (microperc) is the miniaturized version of mini-percutaneous nephrolithotomy (PCNL) and standard-PCNL that allows for safe access and stone disintegration under direct vision. In this single-centre study, the authors aimed to define the role of microperc in the management of renal calculi and analyse factors predicting outcomes. A total of 139 patients, who underwent microperc between June 2010 and November 2014, were enrolled in this study. Microperc was successful in 119 (91.53%) patients, while in 11 patients (8.46%) some residual fragments were seen on imaging. Of the total study group, conversion to mini- or standard PCNL was required in nine patients (6.47%). Overall complication rate of 11.53%, primarily minor complications comprising renal colic and urinary tract infection. On multivariate analysis, stone density (HU), stone number and stone volume were significantly associated with the dependent variable stone clearance. Multivariate analysis showed that intra-operative complications and stone number were significantly associated with conversion to mini- or standard PCNL. Stone volume threshold of 1.000 mm^3 was a significant predictor of stone clearance in univariate and multivariate analyses, regardless of the stone location.

Some limitations of this study, relatively small sample size and particularly the retrospective and non-comparative design, should be highlighted. EAU guidelines recommend shockwave lithotripsy (SWL) or retrograde intrarenal surgery as the primary treatment modality for stones <10 mm in size. Although microperc is presently being used for small to moderate stones, the very indication that holds for SWL as well, it is notable that SWL is influenced by stone location and pelvicalyceal anatomy, and may require multiple sessions. Nevertheless, microperc has an inherent limitation in that the stone fragments cannot be retrieved for analysis. It has been noted that the closed system leads to a pressure rise, especially in scenarios of impacted pelvic stones and longer operating times. This problem may be even more serious in pediatric patients.

Yakup Bostancı, MD

doi: 10.4274/jus.2016.03.027

Re: Current Standard Technique for Modern Flexible Ureteroscopy: Tips and Tricks

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J Urol 2016;196:542-547. doi: 10.1016/j.juro.2016.02.2962. Epub 2016 Mar 2.

EDITORIAL COMMENT

The prevalence of urinary stone disease is increasing worldwide. The dissemination of the clinical use of ultrasound has improved the diagnosis of stones at an earlier stage. It has increased the expansion of the indications of flexible ureterorenoscopy (fURS). With the advances in flexible ureteroscopy (FU), more successful outcomes are being reported. The most recent EAU guidelines state that for all stones smaller than 2 cm, fURS can be the first choice of treatment. Especially for lower pole stones, the stone free rate is better than that with extracorporeal shock wave lithotripsy. For stones larger than 2 cm staged procedures may be necessary. This paper recommends a standardized technique for fURS to decrease the rate of possible complications, and increase the success rate. Endourological techniques are widely adopted by most of the urological surgeons, hence fURS is an expansion of our surgical armamentarium. In this paper, an experienced group recommends some tips and tricks for each step of the procedure. The authors recommend general anesthesia over spinal anesthesia for two reasons: larger tidal volume during spinal anesthesia may cause movement, which can make the procedure harder. Secondly, the duration of the spinal anesthesia may be too short for some cases. The placement of ureteral access sheath (UAS) should be done under fluoroscopic guidance and proper force should be applied. Ideally, the distal tip of the UAS should be just below the ureteropelvic junction.

For preventing functional deterioration of the FU, the tip of the laser probe should be out of the scope as far as one-quarter of the screen diameter. For preventing excessive prolonged deflections, the stones in the lower pole should be repositioned in order to allow a more straight working channel. Pulverization of the stone is preferred over fragmentation since it decreases the operation time and risk of injury during removal of fragments. A power setting of low frequency (10-15 Hz) and high energy (1-2J) is recommended for kidney stones. It is advised to keep the laser tip 1-2 mm to the stone and start from the outer part of the stone rather than causing holes and tunnels in the center, which leads to larger fragments. The use of small fiber diameters (200-275 nm) is recommended. However, since they are more prone to fiber degradation, it should be cleaved at each 10 minutes of firing with a simple metallic scissor by protruding from the tip of the FU without removing and replacing the laser probe.

When extraction of fragments is necessary, zero tip nitinol baskets are recommended.

The most important exit strategy is the endoscopic inspection of the ureter wall during the removal of UAS by keeping the tip of the scope a few centimeters out of the UAS. Routine stenting whenever a UAS has been used is recommended. When the surgery is uneventful, and the endoscopic examination of the ureter seems normal, short-term stenting is offered.

Selçuk Keskin, MD

doi: 10.4274/jus.2016.03.028

Re: Multicenter External Validation and Comparison of Stone Scoring Systems in Predicting Outcomes after Percutaneous Nephrolithotomy

Tailly TO[1,2], Okhunov Z[3], Nadeau BR[4], Huynh MJ[1], Labadie K[3], Akhavein A[5], Violette PD[1], Olvera-Posada D[1], Alenezi H[1], Amann J[4], Bird VG[5], Landman J[3], Smith AD[6], Denstedt JD[1], Razvi H[1]

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J Endourol 2016;30:594-601. doi: 10.1089/end.2015.0700. Epub 2016 Feb 5.

EDITORIAL COMMENT

There was no stone scoring system for preoperative patient counseling and standardization until Guy's stone score was developed in 2011. S.T.O.N.E Nephrolithometry and Clinical Research Office of Endourological Society nomogram have been developed, respectively. The present study is the largest multicenter cohort study including 586 patients, retrospectively evaluating and comparing these three scoring systems at four academic institutions. The authors reported similar results regarding estimation of stone-free rates (SFR) with all the three scoring systems after a single session percutaneous nephrolitotomy (PCNL). They also noted that none of these scoring systems have significantly added predictive accuracy over stone size alone as a predictor of SFR. The patients were stratified into low-, intermediate-, high- and very high-risk groups for relative risk for residual stone for all scoring systems and it was seen that residual stone risk after PCNL surgery increases with increased risk group stratification. With regard to complications, none of the scoring systems strongly predicted complications. Only S.T.O.N.E score was found to be an independent predictor of operation time. As a result, all the three scoring systems are useful and equally effective in prediction of SFR despite specific limitations. Urological surgeons may benefit from these scoring systems for estimating case complexity and preoperative patient counseling. Further researches on scoring systems are mandatory especially for prediction of complications.

Ozan Bozkurt, MD

Basic Science

doi: 10.4274/jus.2016.03.029

Re: Chemokines in Cancer

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Cancer Immunol Res 2014;2:1125-1131. doi: 10.1158/2326-6066.CIR-14-0160.

EDITORIAL COMMENT

Chemokines are chemotactic cytokines that regulate the trafficking and positioning of cells by activating the seven-transmembrane spanning G protein-coupled chemokine receptors (GPCR) or non G protein-coupled seven-transmembrane spanning receptors called atypical chemokine receptors (ACKR). Chemokines are basic proteins that also bind to glycosaminoglycans which play important roles in their biology. Chemokines are divided into four subfamilies based on the position of the first two N-terminal cysteine residues, including the CC, CXC, CX3C and XC subfamilies. Nearly 50 chemokines and 20 signaling chemokine receptors and 4 AKCRs have been identified. Dysregulated expression of chemokines and their corresponding receptors is implicated in many diseases, such as autoimmune and inflammatory diseases and cancer. Chemokines are essential coordinators of cellular migration and cell-cell interactions and, therefore, have great impact on tumor development. In the tumor microenvironment, tumor-associated host cells and cancer cells release an array of different chemokines, resulting in the recruitment and activation of different cell types that mediate the balance between antitumor and pro-tumor responses. In addition to their primary role as chemoattractants, chemokines are also involved in other tumor-related processes, including tumor cell growth, angiogenesis and metastasis. Therefore, further studies of the distinctions between the pro-tumor and antitumor activities of chemokines are warranted in order to develop more effective therapies against cancer.

Fehmi Narter, MD

doi: 10.4274/jus.2016.03.030

Re: Engineered Nanoparticles Induce Cell Apoptosis: Potential for Cancer Therapy

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Oncotarget 2016:2. doi: 10.18632/oncotarget.8553. [Epub ahead of print]

EDITORIAL COMMENT

Engineered nanoparticles (ENPs) have been widely applied in industry, biology and medicine recently (i.e. clothes, sunscreens, cosmetics, foods, diagnostic medicine, imaging and drug delivery). There are many kinds of manufactured nanomaterial products including TiO_2, ZnO, CeO_2, Fe_2O_3, and CuO (as metal oxide nanoparticles) as well as gold, silver, platinum and palladium (as metal nanoparticles), and other carbon-based ENP's such as carbon nanotububes and quantum dots. ENPs with their sizes no larger than 100 nm are able to enter the human body and accumulate in organs and cause toxic effects. In many researches, ENP effects on the cancer cells of different organs with related cell apoptosis were noted (AgNP, nano-Cr_2O_3, Au-Fe_2O_3 NPs, nano-TiO_2, nano-HAP, nano-Se, MoO_3 nanoplate, Realgar nanoparticles). ENPs, with their unique properties, such as surface charge, particle size, composition and surface modification with tissue recognition ligands or antibodies, has been increasingly explored as a tool to carry small molecular weight drugs as well as macromolecules for cancer therapy, thus generating the new concept "nanocarrier". Direct induction of cell apoptosis by ENPs provides an opportunity for cancer treatment. In the century of nanomedicine that depends on development of the nanotechnology, ENPs have a great potential for application in cancer treatment with minimal side effects.

Fehmi Narter, MD

PATHOLOGY PAGE

doi: 10.4274/jus.1131
J Urol Surg 2016;3:108-109

MiT Family Translocation Renal Cell Carcinomas

MiT Ailesi Translokasyon Renal Hücreli Karsinomlar

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Introduction

MiT family translocation renal cell carcinomas (RCCs) are particular neoplasms with their clinically aggressive behavior and histopathologically distinctive appearance (1). These tumors tend to occur in young age group and consist of nearly 40% of pediatric and 1.6-4% of adult RCCs (1,2).

These tumors are caused by two types of translocations involving TFE3 (transcription factor E3) and TFEB genes which are belong to the Microphtalmia-associated transcriptional factor family (MiT family) (2,3). TFE3 is located on Xp11.2, while TFEB is on chromosome 6. Tumors showing Xp11 translocation are much more common than those involving TFEB translocations. The most common subtypes of gene fusions are ASPSCR1-TFE3 and PRCC-TFE3 (1,3). t(6:11) RCC is the rare form of translocation RCCs which harbors gene fusion among TFEB and MALAT-1 (2). These gene rearrangements result in overexpression of several fusion proteins including TFE3 and TFEB which can be demonstrated with a nuclear labeling by immunohistochemistry as a sensitive and specific diagnostic method for each subtype.

The gross morphology is similar to other RCCs; they do not show a distinct appearance (1). Histopathologically, Xp11 translocation RCC is characterized by papillary structures lined by cells with large, usually clear, sometimes eosinophilic cytoplasm (Figure 1). Immunohistochemically, these tumors are usually negative for epithelial markers [pancytokeratins, epithelial membrane antigen (EMA)], pax-8, and positive for cathepsin K and TFE3 (Figure 1,inset) (4). The diagnosis of Xp11 translocation RCCs is based on microscopic characteristic findings, nuclear immunostaining with TFE3 and/or genetic analysis. Microscopic appearance of t(6;11) RCCs is different from Xp11 translocation RCC (2). The most distinctive pattern is composed of nests of larger epithelioid cells admixed with smaller cells grouped around basement membrane material and also entrapped native renal tubules at the periphery (2). Immunohistochemically, tumour cells show nuclear reactivity for TFEB and cytoplasmic reactivity for cathepsin K and melanocytic markers (HMB-45 and Melan-A) (2).

The differential diagnosis of MiT family translocation RCCs includes a variety of renal neoplasm demonstrating clear cell and papillary features. Conventional clear cell RCC demonstrates diffuse positive expression with epithelial markers and is negative with melanocytic markers. Papillary RCC is positive for cytokeratin 7 and alpha-methylacyl-CoA racemase. In addition, clear cell RCC is characterized by chromosome 3p25 deletion, papillary RCCs by trisomy 7/17. Some of the Xp11 translocation carcinomas include melanin pigment (5). Therefore, epithelioid angiomyolipomas should be considered in the differential diagnosis. Since TFE3 and TFEB gene rearrangements are not present in other neoplasms, fluorescent in situ hybridization can also be useful and helpful in diagnostically challenging cases.

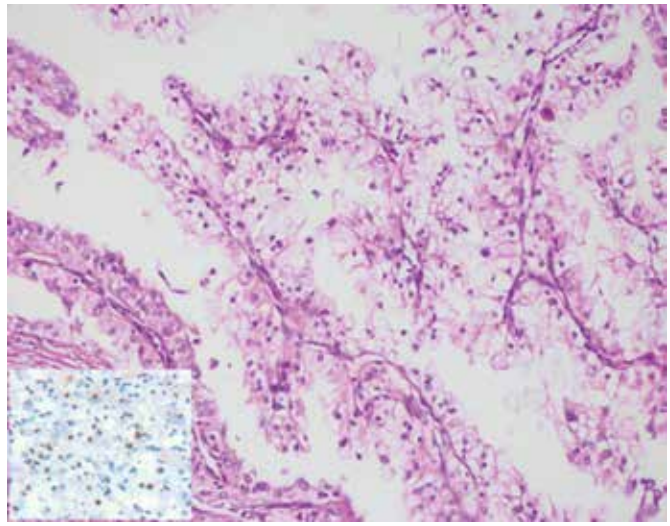

Figure 1. A Xp11 translocation carcinoma having cells with prominent large clear cytoplasms lining papillary structures (x200, Hematoxylin&Eosin) Inset: TFE3 nuclear positivity (x200)

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The prognosis of the Xp11 translocation RCCs is similar to clear cell RCCs but worse than PRCCs. t(6;11) RCCs are indolent than Xp11 translocation RCCs. To be aware of these neoplasms on microscope would provide correct diagnosis and predicting of prognosis.

Ethics

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ayça Tan, Nalan Neşe, Concept: Ayça Tan, Nalan Neşe, Design: Ayça Tan, Nalan Neşe, Data Collection or Processing: Ayça Tan, Nalan Neşe, Analysis or Interpretation: Ayça Tan, Nalan Neşe, Literature Search: Ayça Tan, Nalan Neşe, Writing: Ayça Tan, Nalan Neşe.

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Keywords

Translocation, renal cell carcinomas, MiT family

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