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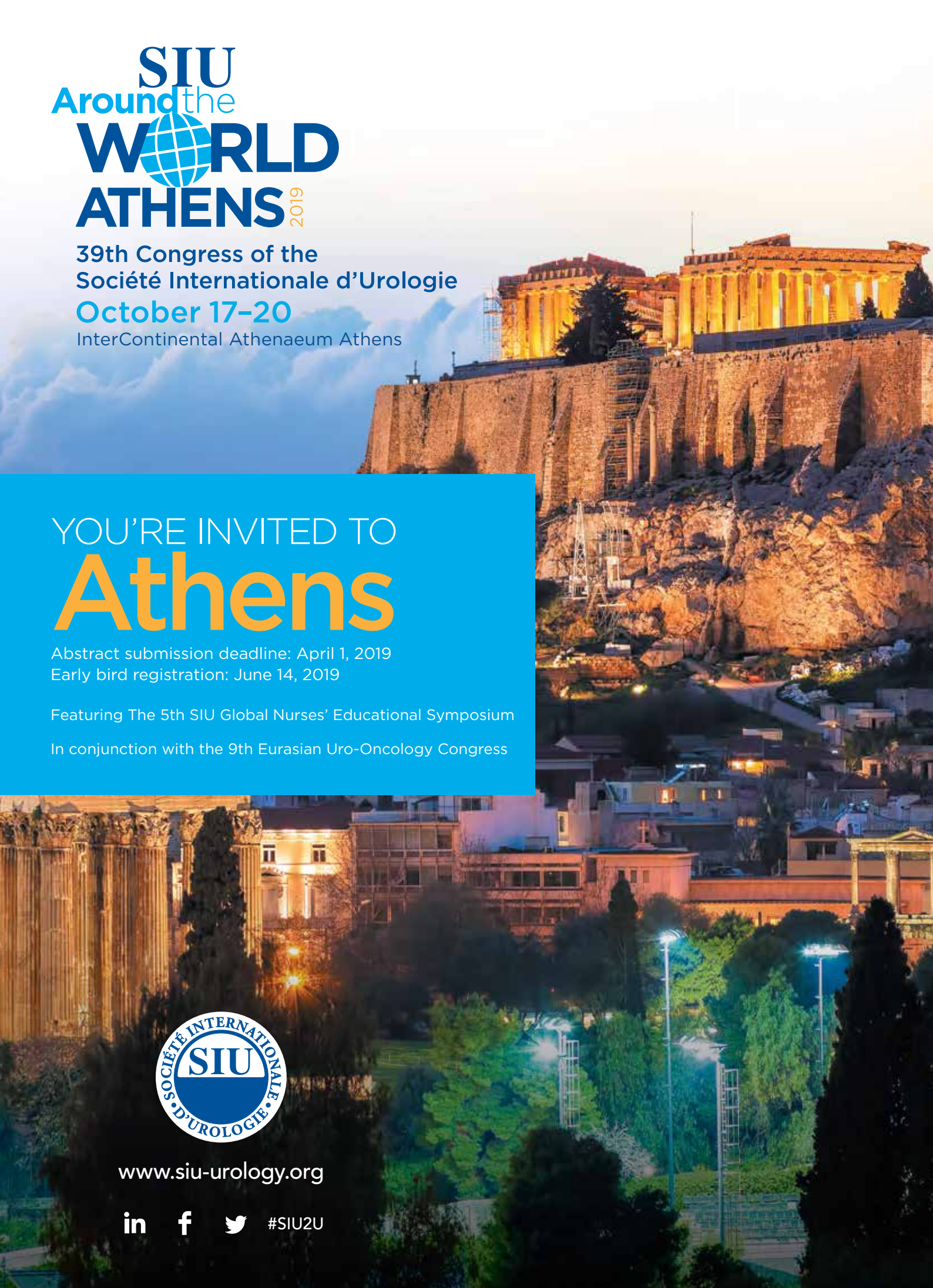

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Contents

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ORIGINAL ARTICLE

Prognostic factors of renal cell carcinoma. A single center experience

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Abstract

Introduction-Objective: A Several algorithms have been developed for the prognosis of renal cancer. Aim of our study was to investigate the prognostic significance of certain clinical and pathological factors of renal cell cancer.

Materials and Methods: 114 patients who underwent radical nephrectomy in our Hospital were examined. Parameters including age, gender, mode of presentation, hematological and pathological parameters. All were evaluated for their role as predictors of disease free and overall survival.

Results: Median follow up was 69 months. Predominant histological type, pathological stage and nuclear grade were clear cell carcinoma, pT1 and Fuhrman II, respectively. 5 year overall and disease free survival were 86% and 82 %, respectively. Only nuclear grade ($p = 0.02$) and preoperative anemia ($p < 0.01$) were correlated with overall survival, while pathological stage, nuclear grade, anemia and neutrophil-to-lymphocyte ratio of 2.7 or greater were associated with disease free survival ($p = 0.02$, $p = 0.038$, $p<0.01$, $p = 0.049$ respectively). In the multivariate setting, anemia ($p = 0.04$) and pathological stage ($p = 0.026$) were the only independent statistically significant predictors of disease-free survival while anemia ($p = 0.018$) and neutrophil to lymphocyte ratio ≥ 2.7 ($p = 0.034$) were the only factors correlated with overall survival.

Conclusions: Due to the wide application of various imaging studies, patients with kidney cancer are diagnosed more often with localized disease and favorable pathological features. Fuhrman nuclear grade, pathological stage, preoperative anemia and neutrophil to lymphocyte ratio are strongly associated with survival. In localized disease, such information could be used to guide the intensity of follow-up and identify high-risk patients who can be targeted for adjuvant therapy trials.

Nikolaos Grivas, Vasilios Kafarakis, Ioannis Tsimaris, Stella Chatzistamou, Xrysanthi Counavou, Apostolis Paxinos, Nikolaos Kalampokis, Konstantinos Hastazeris, Nikolaos Stavropoulos
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Introduction

Key words
Nephrectomy; prognosis; renal cell carcinoma; survival

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and 90-95% of neoplasms arising from the kidney. It represents the sixth most frequently diagnosed cancer in men and the 10th in women [1]. The highest incidences have been recorded in North America, Australia/New Zealand and Europe, with lower rates in Africa, Asia and the Pacific [2]. In men, the mortality rate per 100,000 population fell from 4.8 in 1990-1994 to 4.1 in 2000-2004; in women, the rate fell from 2.1 to 1.8 [3].

Several prognostic models have been created in order to stratify patients in risk groups [4]. Laboratory abnormalities, including anemia, hypercalcemia, liver dysfunction, neutrophilia, neutrophil to lymphocyte ratio (NLR) of 2.7 or greater, thrombocytosis and elevated markers of inflammation, have all been acknowledged as predictors of poor survival in RCC [5,6]. Pathologic features, such as nuclear grade, tumor-node-metastasis (TNM) stage [7] and histologic subtype, have been assessed as potential prognostic factors. Currently the choice of the more appropriate algorithm or nomogram is an unresolved question [8].

In this study, we retrospectively analyzed the clinicopathological factors of patients with non-metastatic RCC treated with radical nephrectomy. Additionally the relationship between survival and each variable was recorded.

Patients and methods

We retrospectively reviewed all patients with RCC who underwent radical nephrectomy in our Hospital. Recorded clinical features included age, gender and mode of presentation. Routine laboratory variables were measured from preoperative blood samples, including hemoglobin, neutrophil count, lymphocyte and platelet count, serum sodium, alkaline phosphatase and calcium. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Anemia was defined as hemoglobin < 13.5 g/dL in males and < 12.0 g/dL in females. Pathologic features assessed included histologic subtype, TNM stage, Fuhrman nuclear grade, tumor size, and presence or absence of sarcomatoid differentiation. Overall survival (OS) and disease free survival (DFS) were recorded and correlated with the above clinical and pathological parameters. OS was the time from date of nephrectomy to the date of death from any cause. DFS was defined as time to the date of progression of disease and/or to the date of death from disease while

No patients received new adjuvant therapy preoperatively and/ or synchronic postoperative adjuvant therapy. All patients had negative margins. Lymphadenectomy was restricted to staging purposes with dissection of palpable and enlarged lymph nodes. Exclusion criteria were the following: pathologically confirmed urothelial carcinoma, specimens with tissue unavailable for accurate evaluation, patients with lymph node or distant metastases and patients treated with partial nephrectomy.

The prognosis of these patients was determined from information from hospital charts and telephone follow up. The data obtained were recorded on a standard research form and filled in a database. All patients were followed up every 6 months in the first three years after surgery and every year thereafter by physical examination, blood chemistry analysis, chest X-ray, and abdominal enhanced computer tomography (CT).

Regarding statistical analysis, univariate and multivariate Cox proportional hazards models were used to assess the predictive ability of the hematologic, biochemical and pathological baseline characteristics on DFS and OS. The Kaplan-Meier technique was used to evaluate OS and DFS and the log rank test was used to compare survival curves with $p < 0.05$ as the significance cutoff. SPSS software ver. 13.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analysis.

Results

Clinicopathological characteristics of the 114 patients who were included in the study are summarized in **Table 1**. There were 80 (70.1%) men and 34 (29.9%) women with a median age of 64 years old. Right kidney was most often (56.9%) affected. Half of the patients presented with a mass identified incidentally in ultrasound or computer tomography examination. Gross hematuria and flank pain were the first symptom in 21.1% and 7.8% of the patients, respectively. Median sodium level was 142.

Histological findings confirmed RCC in 90 (78.9%) patients, while 15 (13.1%) had papillary tumor and 5 (4.4%) chromophobe tumor. One group of 4 patients (3.6%) presented sarcomatoid features. When our pa-

Table 1 *Clinicopathological characteristics of the patients*

Characteristics	Number of patients (%)
Sex	
Male	80 (70.1)
Female	34 (29.9)
Median age at diagnosis	63.5
Symptoms	
Incidental	57 (50)
Hematuria	24 (21.1)
Flank pain	9 (7.8)
Other	24 (21.1)
Histology type	
Clear cell	90 (78.9)
Papillary	15 (13.1)
Chromophobe	5 (4.4)
Sarcomatoid	4 (3.6)
T stage	
T1	71 (62.2)
T2	13 (11.4)
T3	30 (26.4)
Fuhrman grade	
1	23 (20.2)
2	64 (56.1)
3	21 (18.4)
4	6 (5.3)

tients were stratified according to pathological stage there were 71 (62.2%) with stage pT1, 13 (11.4%) with stage pT2 and 30 (26,4%) with stage pT3. Regarding Fuhrman grade, 23 patients (20.2%) were classified as grade I, 64 (56.1%) as grade II, 21 (18.4%) as grade III and 6 (5.3%) as grade IV.

At the time of data analysis, median length of follow up from nephrectomy was 69 months (range, 1-179 months). Survival data existed for 103 patients. OS rates from nephrectomy for all patients were 93% for 1 year, 88 % for 3 years and 85% for 5 years. DFS rates at 1, 3, and 5 years were 94%, 88%, and 82% respectively.

Fuhrman nuclear grade (**Figure 1**) and preoperative anemia (**Figure 2**) were the only factors significantly associated with OS ($p = 0.02$ and $p < 0.01$ respectively). The differences in OS were not significant between histological subtypes ($p = 0.14$) and TNM pathological stage ($p = 0.17$). Additionally, OS was not associated with age ($p = 0.68$), gender ($p = 0.93$), mode of presentation ($p = 0.18$),

Figure 1. *Patients with Fuhrman III-IV had a worse overall survival rate. (Kaplan-Meier log rank test, p = 0.02)*

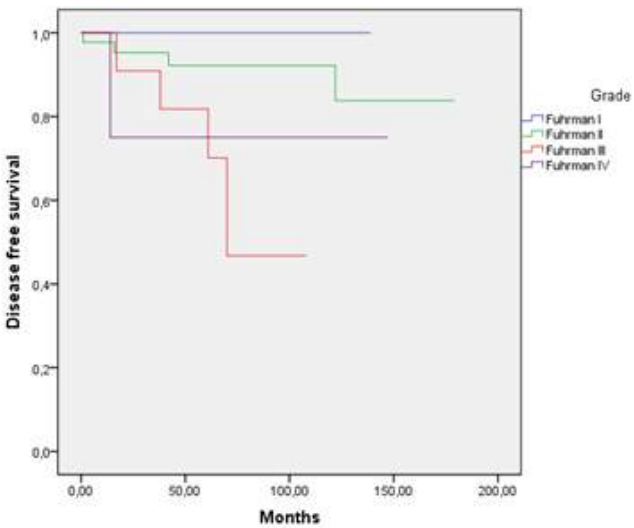


Figure 2. *Patients with preoperative anemia had a worse overall survival rate. (Kaplan-Meier log rank test, p < 0.01)*

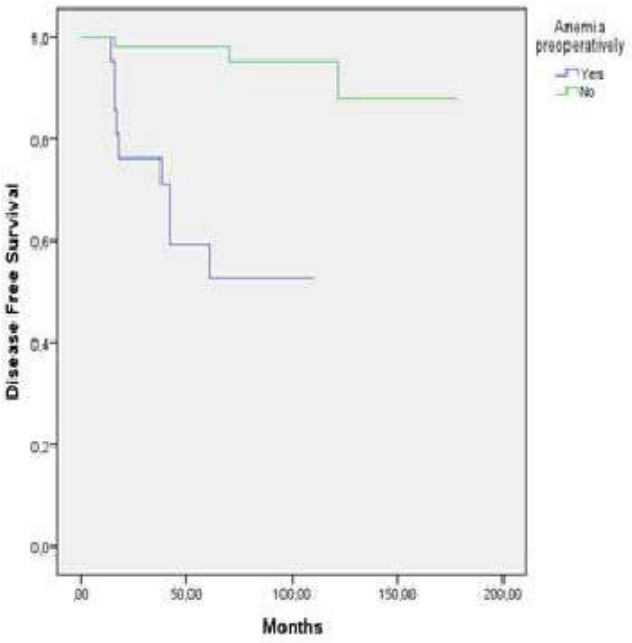


Figure 3. *Patients with pathological stage pT2-pT3 had a worse disease free survival rate (Kaplan-Meier log rank test p = 0.02)*

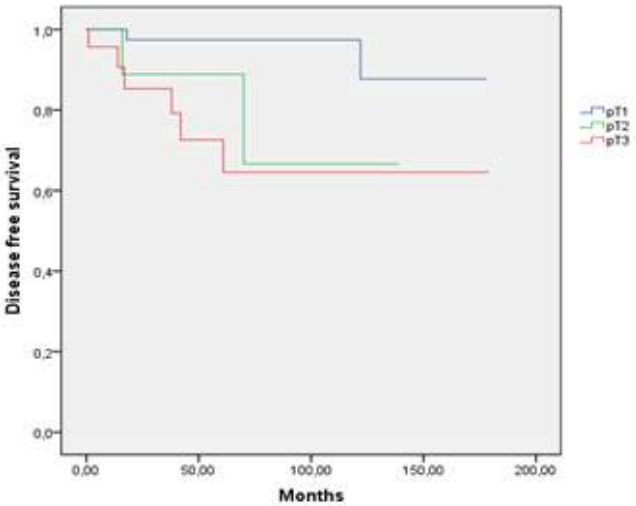


Figure 4. *Patients with Fuhrman III-IV had a worse disease free survival rate (Kaplan-Meier log rank test p = 0.038)*

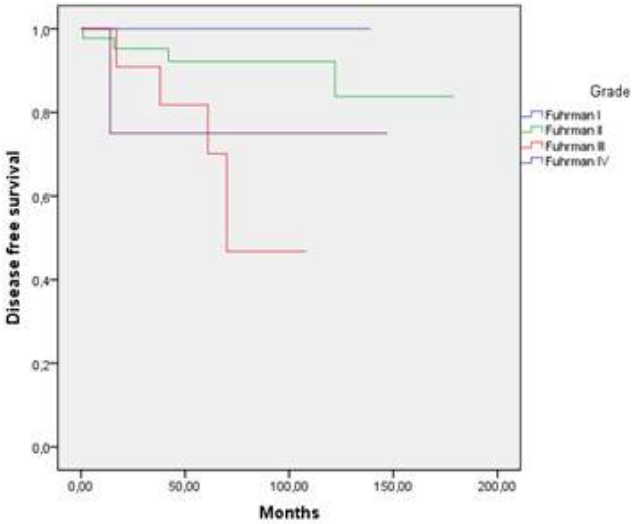
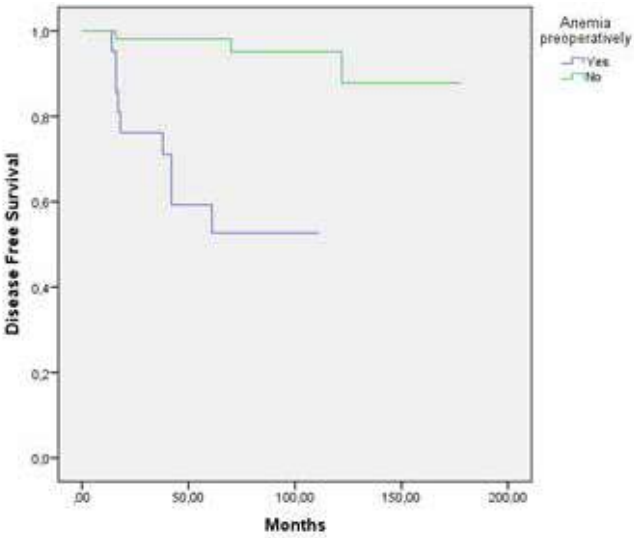


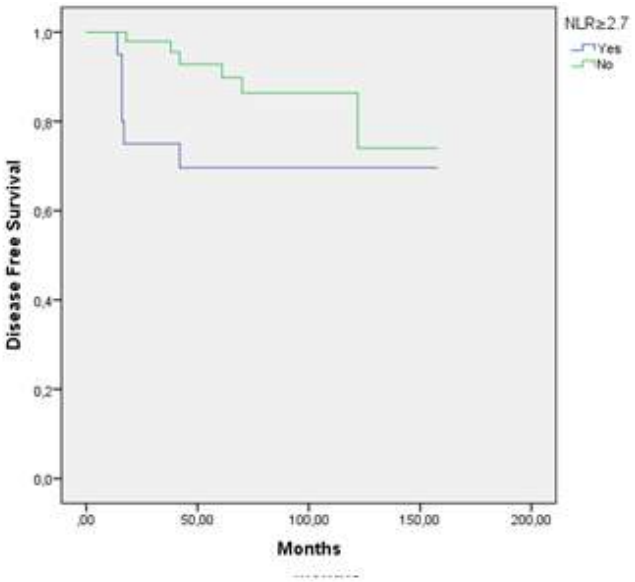
Figure 5. *Patients with preoperative anemia had a worse disease free survival rate. (Kaplan-Meier log rank test, p < 0.01)*



thrombocytosis (p = 0.37), NLR ≥ 2.7 (p = 0.12), sodium levels below median (p = 0.09) hypercalcemia (p = 0.53) and abnormal alkaline phosphate levels (p = 0.59).

Pathological stage (p = 0.02), Fuhrman grade (p = 0.038), preoperatively anemia (p < 0.01) and NLR ≥ 2.7 (p = 0.049) were the only factors predictive of DFS (**Figures 3-6**). Histological subtypes (p = 0.10), age (p = 0.94), gender (p = 0.58), mode of presentation (p = 0.33), thrombocytosis (p = 0.35), sodium levels below median (p = 0.06), hypercalcemia (p = 0.53) and abnormal alkaline phosphate levels (p = 0.57) had no significant impact on DFS.

Figure 6. *Patients with preoperative NLR ≥ 2,7 had a worse disease free survival rate. (Kaplan-Meier log rank test, p = 0.049)*



Among all patients with RCC, the only factors which found to be independent statistically significant predictors of OS in the multivariate setting were preoperative anemia (p = 0.018) and NLR ≥ 2,7 (p = 0.034). On multivariate analysis of DFS, only pathological stage (p = 0.026) and preoperative anemia (p = 0.04) proved to be independent significant predictive factors.

Discussion

The incidence of RCC has clearly risen over the past 20 years, largely due to the widespread utilization of non invasive imaging modalities such as ultrasonography, CT scan and MRI. There is a stage migration to smaller localised renal tumours, which has been stabilized, and better disease specific survival [9]. Surgery remains the only curative therapy despite the introduction of a number of new promising treatment options such as nephron-sparing surgery and thermal ablation [10].

Classical prognostic factors for non-metastatic RCC include anatomical, histological, clinical and molecular features. Kattan et al. were the first authors to develop a nomogram to predict the probability of RCC recurrence after nephrectomy [11]. Currently the most commonly used prognostic models for localized RCC are the University of California Los Angeles integrated staging system (UISS) and the Stage, Size, Grade, and Necrosis (SSIGN) developed at the Mayo Clinic. UISS predicts patient survival by integrating the TNM stage, Fuhrman's grade, and Eastern Cooperative Oncology Group (ECOG) performance status (PS), while SSIGN calculates prognostic score according to Stage, Size, Grade, and Necrosis (SSIGN) [12,13]. The use of prognostic indicators, might play a crucial role in predicting outcome and adopting new adjuvant treatments to the needs of individual patients. Patient profiling and assigning into risk categories, is an important concept as it allows prediction of tumour behaviour and therefore patient prognosis [14]. Additionally, it allows the selection of the most suitable therapeutic option for each of them [15].

As shown in the results, our patients had an excellent prognosis with 5-year OS and DFS of 85% and 82%, respectively. In the present study, we found that 74% of RCCs were pathologically localized at the moment of the initial diagnosis. On univariate analysis Fuhrman nuclear grade and preoperative anemia were independent predictor of OS and DFS while pathological stage and NLR ≥ 2,7 were independent factor of DFS. Notably, histological type of the primary tumour failed to be an independent predictor of OS and DFS. Concerning the other prognostic factors, we found that age, mode of presentation, thrombocytosis, sodium levels below median, hypercalcemia and abnormal alkaline phosphate levels were not associated with OS and DFS.

Only the pathological stage and preoperative anemia remained significantly associated with DFS upon multivariate analysis. OS remained associated with anemia and NLR. Several of our findings confirm previous associations [16,17]. Most authors agree that TNM stage and Fuhrman nuclear grade are the strongest independent prognostic factors for localized RCC [18]. With regard to tumour grade, Fuhrman nuclear grade is widely applied in RCC of all histological subtypes, although little evidence indicates that it has prognostic use for tumour types other than clear cell RCC [19]. Preoperative anemia is established adverse prognostic factor, while recent studies confirm that pre- and post-treatment NLR is a significant prognostic factor for recurrence in patients with clear cell carcinoma [20, 21].

There are recently published results in non metastatic RCC from studies aiming to investigate the use of targeted agents in the adjuvant, postoperative setting in the context of surgical treatment. The S-TRAC study showed improved DFS in high-risk patients (according to the UISS staging system) receiving a nephrectomy prior to randomization to either sunitinib or placebo treatment for 1 year [22]. The PROTECT trial evaluates the efficacy and safety of pazopanib in patients with T2-T4 clinical stage showing improved progression free

survival [23]. In the ASSURE study, patients with stage II-IV disease were stratified and randomized to treatment with sunitinib, sorafenib as adjuvant therapy following nephrectomy, though no difference was shown in DFS [24].

Approximately 20-30% of patients diagnosed with kidney cancer present with metastatic disease and a similar percentage of patients with initially localized disease experience a relapse and develop metastatic disease [25]. The introduction of vascular endothelial growth factor (VEGF)-pathway inhibitors (e.g., sunitinib, sorafenib, pazopanib, and bevacizumab) and mTOR inhibitors (e.g., everolimus and temsirolimus) has substantially improved the outcomes of patients with metastatic RCC [26]. These agents have largely replaced cytokines (immunotherapy) in treatment-naive patients [27]. Despite new promising therapies, metastatic RCC is one of the therapy resistant malignancies. Therefore, methods to predict which patients are likely to develop metastases are needed, and it is also important to identify those that respond to various treatments [28].

The limitations to the present study are inherent to its retrospective nature and the relatively small number of patients. We also could not study some preoperative biological prognostic factors (such as C-reactive protein, Lactate dehydrogenase, Erythrocyte Sedimentation Rate) because of the lack of data. The potential inter-observer variability in the determination of the histological variables may represent limitations in the interpretation of the results obtained in the study.

Prognostic factors that can risk stratify patients, predictive biomarkers that can help individualize treatment selection and predict a patient's response to therapy, facilitate the better understanding and treatment of the disease [29]. Despite their adequate prognostic ability, none of the established prognostic models is 100% accurate. In consequence, the search for more accurate markers continues. Molecular events that can unveil the biologic heterogeneity underlying the varied clinical behaviour of RCC may help improve individualised prognostication and risk-stratified clinical decision making [30]. Novel prognostic factors and more up-to-date models are urgently needed for patients with localized and metastatic RCC, especially in the era of targeted therapies [31].

Conclusion

Our findings confirm the potential role of histologic features and hematological parameters as predictive tools of RCC. Prognostic models should widely be used in the clinical practice to counsel patients, plan surveillance protocols and select appropriate candidates for inclusion in adjuvant treatment protocols. Further improvements in our ability to predict RCC prognosis will rely on the integration of molecular and genetic markers in the currently established models.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

ΕΙΣΑΓΩΓΗ: Έχουν αναπτυχθεί πολλοί αλγόριθμοι για την πρόγνωση του καρκίνου του νεφρού. Στόχος της μελέτης μας ήταν η διερεύνηση της προγνωστικής σημασίας συγκεκριμένων κλινικών και παθολογικών παραγόντων του καρκίνου του νεφρού.

ΥΛΙΚΟ/ΜΕΘΟΔΟΣ: Εξετάστηκαν 114 ασθενείς που υποβλήθηκαν σε ριζική νεφρεκτομή στο Νοσοκομείο μας. Παράμετροι που αξιολογήθηκαν ήταν η ηλικία, το φύλο, το αρχικό σύμπτωμα, καθώς και αιματολογικές και παθολογικές παράμετροι. Καταγράφηκε η συσχέτισή τους με την συνολική και την ελεύθερης νόσου επιβίωση.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Η διάμεση παρακολούθηση ήταν 69 μήνες. Ο κυρίαρχος ιστολογικός τύπος, το παθολογικό στάδιο και ο βαθμός κακοήθειας Fuhrman ήταν το διαυγοκυτταρικό καρκίνωμα, το στάδιο pT1 και το Fuhrman II, αντίστοιχα. Η 5ετής συνολική και ελεύθερης νόσου επιβίωση ήταν 86% και 82%, αντίστοιχα. Μόνο ο βαθμός κακοήθειας ($p = 0.02$) και η προεγχειρητική αναιμία ($p < 0.01$) συσχετίστηκαν με τη συνολική επιβίωση, ενώ το παθολογικό στάδιο, ο βαθμός κακοήθειας, η αναιμία και η αναλογία ουδετερόφιλων-λεμφοκυττάρων ≥ 2,7 συσχετίστηκαν με την ελεύθερης νόσου επιβίωση ($p = 0.02$, $p = 0.038$, $p < 0.01$, $p = 0.049$, αντίστοιχα). Στην πολυπαραγοντική ανάλυση, η αναιμία ($p = 0.04$) και το παθολογικό στάδιο ($p = 0.026$) ήταν οι μόνοι ανεξάρτητοι προγνωστικοί παράγοντες της ελεύθερης νόσου επιβίωσης ενώ η αναιμία ($p = 0.018$) και η αναλογία ουδετερόφιλων-λεμφοκύτταρα ≥ 2,7 ($p =$ ήταν οι μόνοι παράγοντες που συσχετίστηκαν με τη συνολική επιβίωση.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Οι ασθενείς με νεφροκυτταρικό καρκίνο διαγιγνώσκονται συχνότερα με εντοπισμένη ασθένεια και ευνοϊκά παθολογικά χαρακτηριστικά. Ο βαθμός κακοήθειας Fuhrman, το παθολογικό στάδιο, η προεγχειρητική αναιμία και η αναλογία ουδετερόφιλων-λεμφοκυττάρων εμφανίζουν ισχυρή συσχέτιση με την επιβίωση. Τα παραπάνω δεδομένα θα μπορούσαν να χρησιμοποιηθούν για να κατευθύνουν το ρυθμό του follow up και να εντοπίσουν τους ασθενείς υψηλού κινδύνου στους οποίους μπορούν να εφαρμοστούν νέες στοχευμένες θεραπείες.

Λέξεις ευρετηριασμού
νεφρεκτομή, πρόγνωση, καρκίνος νεφρού, επιβίωση

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ORIGINAL ARTICLE

Chronic prostatic infection: Epidemiology and clinical characteristics

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Abstract

INTRODUCTION/AIM: Chronic prostatitis (CP) is an inflammatory condition of the prostate causing a variety of symptoms. Since clinical presentation varies widely and differential diagnosis includes life threating conditions, CP is often overlooked. Moreover, despite having negative impact on patients' quality of life, CP receives a somehow little attention in clinical practice in comparison with other urological conditions. In this paper we present clinical patterns of chronic prostatitis recorded in 1624 visits aiming to determine the incidence of NIH categories of chronic prostatitis among patients referring to a single Hellenic tertiary care center with symptoms of prostatitis and to describe the clinical characteristics of chronic prostatitis on our population.
MATERIAL: The clinical sample used in the study consisted of medical records of individuals with reported pelvic discomfort, genital pain, lower urinary tract symptoms and sexual dysfunction, and from patients with febrile relapses of chronic bacterial prostatitis, visiting the Urology Department of the Tzaneio Prefecture General Hospital of Piraeus, between 03/2009 and 03/2019. Patients with febrile prostatitis were evaluated with a single mid-stream "clean" urine sample culture while in all remaining cases, the Meares and Stamey test –or the two glass test– was performed. Bacterial identification was performed using the Vitek 2 Compact system and the sensitivity test was performed with the disc and the Vitek 2 system. Demographic, microbiological and clinical history of each assessed patient were reviewed.

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RESULTS: 409 patients were presented with a single set of CP like symptoms and were recorded with up to three visits (including follow up) and 160 were presented with one or more relapses. In total, 307 patients were diagnosed with chronic bacterial prostatitis (CBP). More than half of them had history of prostatitis. Of the remaining, thirty one (31) were diagnosed with cystitis-prostatitis, while in 63 patients the EPS/VB3 cultures were negative despite the presence of bacteria in the specimens. These cases were considered as possible CBP cases. In 154 cases symptoms were attributed to diseases other than prostatitis. Forty one (41) patients were initially diagnosed with chronic non-bacterial inflammatory prostatitis (CNBP Inf) and 71 with chronic non-bacterial non-inflammatory prostatitis (CNBP Non-Inf). A wide variety of symptoms and combinations of them were associated with CP. Of note, most patients note some degree of genitourinary pain or discomfort. Common presentations include also dysuria, frequency and new onset sexual dysfunction without other aetiology as well. Few patients were initially presented with febrile relapses of CBP. No differences in symptoms incidence and duration was found among CBP, CNBP Inf and CNBP Non-Inf. Clinical improvement was reported by 267 patients.
CONCLUSIONS: A wide variety of symptoms and combinations of them were associated with CP. Being nonspecific symptoms may confuse diagnosis and for this reason CP may be underestimated and undertreated. It is important to identify these symptoms in order to diagnose CP and select the optimal treatment according to CP category in order to improve the quality of life and the social function of the patient.

Key words
Chronic prostatitis, prostate, infection, epidemiology, symptoms

Introduction/Aim

Chronic prostatitis (CP) is an inflammatory condition of the prostate causing a variety of symptoms. As it rather consist a clinical diagnosis, the decision for microbiological confirmation depends on clinicians' suspicion. However, recognizing CP can be difficult, as history, examination and clinical presentation are highly variable[1]. In addition differential diagnosis includes some life threatening conditions that attract attention while CP fails to do so. Moreover, although the Meares-Stamey test is the gold standard to diagnose CP, it is rarely used in practice due to time constraints and the difficulty obtaining samples[2]. For these reasons, CP is often overlooked and many cases remain undiagnosed. Finally, despite having negative impact on patients' quality of life, CP receives a somehow little attention in clinical practice in comparison with other urological conditions as shown by the relatively low numbers of relative publications[3]. The aim of our study was to determine the incidence of NIH categories of chronic prostatitis among patients referring to a single Hellenic tertiary care center with symptoms of prostatitis and to describe the clinical characteristics of chronic prostatitis on our population.

Material

The clinical sample used in the study consisted of medical records of individuals with reported pelvic discomfort, genital pain, lower urinary tract symptoms and sexual dysfunction, and from patients with febrile relapses of chronic bacterial prostatitis (CBP), visiting the Urology Department of the Tzaneio Prefecture General Hospital of Piraeus, between 03/2009 and 03/2019.

Demographic, microbiological and clinical history of each assessed patient, were reviewed. Patients suffering from conditions that influence bacterial virulence or host response (eg. immunodeficiency, abnormalities of the urogenital system) and patients who received antibiotics or immunosuppressive treatment within 4 weeks of the visit were excluded from the study.

Included patients were clinically evaluated and underwent the Meares-Stamey "4-glass" test, based on cultures of first-void (VB1), midstream/pre-prostatic massage (VB2), expressed prostatic secretions (EPS) and post-prostatic massage urine (VB3) specimens. Few cases underwent the "two-glass" test[4], assessing the sole VB2 and VB3 specimens. Depending on medical history and specific symptoms, urethral smear cultures and total ejaculate cultures were additionally obtained from several patients. Patients presenting with febrile prostatitis were investigated by a midstream urine culture (MUC) only. Given that no standard cut-off level of the number of bacteria in both urine and prostate secretion samples is defined by consensus for the diagnosis of chronic bacterial prostatitis, we defined no lower acceptable level for either one.

Table 1 *Patient demographic and clinical data*

Clinical sample	N
Number of visits	1624
Number of patients	759
Lost to follow up	92
Diseases other than prostatitis	154
CBP	307
Cystitis-prostatitis	31
Possible CBP	63
CNBP Inf	41
CNBP Non-Inf	71
Demographics	**N**
Average Age	45.1
Chronic prostatitis history	271

Bacterial identification was performed using the Vitek 2 Compact system and the sensitivity test was performed with the disc and the Vitek 2 system.

Appropriate antimicrobials were administered to confirmed cases of CBP accordingly to antibiogram for a period of 4 weeks (a few patients received a 2 week treatment regimen) and the remaining received treatment based on the UPOINT phenotypic classification system. Follow-up included interview, physical examination and the Meares-Stamey test.

The local Ethical Committee approved the research protocol for the present retrospective study.

Results

Clinical patterns of chronic prostatitis recorded in 1624 visits (between 03/2009 and 03/2019) owing to prostatitis like symptoms investigation and ordinary follow up were reviewed. Ninety out of 659 recorded patients were lost to follow up and were excluded from the study. Most (409) were presented with a single set of CP like symptoms and were recorded with up to three visits (including follow up) and 160 were presented with one or more clinical relapses. In total, 307 patients were diagnosed with CBP. More than half of them had history of prostatitis. In 63 patients the EPS/VB3 cultures were negative despite the presence of bacteria in the specimens. These cases were considered as possible CBP cases. In 54 cases symptoms were attributed to diseases other than prostatitis. Of the remaining, thirty one (31) were diagnosed with cystitis-prostatitis (bacterial colonies in VB1 and VB2 samples were higher in number compared to VB3), forty one (41) patients were diagnosed with chronic non-bacterial inflammatory prostatitis (CNBP Inf) and 71 with chronic non-bacterial non-inflammatory prostatitis (CNBP Non-Inf) (**Table 1**). A wide variety of symptoms and symptoms combinations were associated with CP. Main symptoms were reported to begin slowly and in mild form, alternating periods of absence with moments of worsening. In most cases, symptoms lasted more than three months before the diagnosis. However, during relapse phases, the patients could promptly recognise the symptoms. Almost all patients note some degree of genitourinary pain or discomfort. Common presentations included also dysuria, frequency and new onset sexual dysfunction without other aetiology. Few patients were initially presented with febrile relapses of CBP (**Table 2**). No differences in symptoms incidence and duration were found among CBP, CNBP Inf and CNBP Non-Inf.

As far as the outcomes of follow-up visits are concerned, 267 patients reported elimination of symptoms/clinical improvement; though only 149 were completely cured (**Table 3**).

Discussion

Traditionally, category II chronic bacterial prostatitis (CBP) is defined as recurrent symptomatic UTIs caused by the same organism detected in prostatic secretions, occurring between asymptomatic periods[5]. Diagnosis is easy and is primarily based on history, physical examination and urine culture. Nonetheless, current evidence shows that CP and CBP patients are mainly presenting

Table 2 *Main symptoms*

N	Main symptom	CBP	CNBP Inf	CNBP Non-Inf
273	Scrotal and/or testicular pain and coexisting symptoms, if any	√	√	√
119	Pain in the pelvic area and coexisting symptoms, if any	√	√	√
82	Perineal discomfort and coexisting symptoms, if any	√	√	√
56	High fever or low-grade fever associated with a history of prostatitis	√		
44	Penile burning and coexisting symptoms, if any	√	√	√
27	Pain localized to the prostate and coexisting symptoms, if any	√	√	√

Table 3 *Outcomes of follow up visits*

Diagnosis	Treated	N
Cystitis & CBP	29 (93.54%)	31
CNBP Inf	15 (39.47%)	41
CNBP Non-Inf	20 (28.16%)	71
CBP	189 (61.56%)	307
Possible CBP	14 (22.22%)	63
N	267	

with symptoms comprising genitourinary pain and urinary, sexual and/or ejaculatory disturbances[6]. In such a case, differential diagnosis is difficult and includes acute cystitis, benign prostatic hyperplasia, urinary tract stones, bladder cancer, prostatic abscess, enterovesical fistula, and foreign body within the urinary tract[7]. Diagnosis requires additional tests such as imaging, cytology, endoscopy and prostatic secretion culture, and urine specimen testing pre- and post-prostatic massage. The key symptom that poses the suspicion for CP is pain. In fact, the majority (89.48%) of our study population showed a complex clinical presentation combining pain with genitourinary symptoms. However, while perineal discomfort, suprapubic pain and pain localized to the prostate can be easily attributed to prostatitis, other symptoms such as scrotal/testicular pain, premature ejaculation and penile burning cannot. Actually, the most frequent symptom in our study was nonspecific scrotal/testicular pain (36% of cases). In a similar study, testicular pain was highlighted as the patients' main clinical manifestation (44.3%), followed by ejaculatory discomfort (27.9%) and haemospermia (26.2%)[8].

Given that the diagnostic workup of chronic orchialgia not includes systematic methods for evaluating underlying prostatitis, many cases can be easily misinterpreted. Thus, the aetiology of chronic orchialgia remains currently unknown with up to 50% of the cases attributed to an idiopathic aetiology[9]. Yet, the pathophysiology of chronic nonspecific scrotal/testicular pain is not well understood, but reminds that of prostatitis-induced pelvic pain, as it involves nerve sensitization following repeated stimulation leading to modulation of these pathways, ultimately resulting in spontaneous firing[10].

Premature ejaculation was characterized as being psychogenic in origin and so the diagnostic workup is focused on IELT assessment, perceived control and distress. In patients with hematospermia, the diagnostic workup is usually limited to urinalysis and testing for sexually transmitted infections[11]. Since the workup of both conditions does not include systematic methods for evaluating a possibly underlying CBP, we only evaluated those cases with some association with CBP. As a matter of fact, in our study only 4 patients presented with hematospermia and one with acquired premature ejaculation. All these patients reported a history of CBP and 3 of them had coexisting symptoms that overlap with those of chronic prostatitis.

While hematospermia is mainly caused by genitourinary inflammatory disorders, very few studies provide data regarding CBP-associated hematospermia, diagnosed with the use of robust prostatitis evaluation methods. Two recent studies associated more than half of the evaluated hematospermia cases with evidence of CBP[12,13]. The pathogens most frequently associated with hematospermia appear to be *Staphylococcus aureus* and *Ureaplasma urealyticum*[9].

Previous studies demonstrated a quite similar prevalence (47.8 and 52% respectively) of CBP in patients with premature ejaculation[14, 15]. Therefore, examination of the prostate, both physically and microbiologically, should be considered during assessment of patients with hematospermia and premature ejaculation.

In our study 10.52% of the patients were presented with episodic or persistent relapsing urinary tract infections. This finding is in accordance with the general perception about the development of CBP, since after an episode of acute bacterial prostatitis approximately 5-10% of patients may progress to chronic infection[16,17]. However, more than 50% of the patients presenting with pain accompanied or not by urinary, sexual and/or ejaculatory disturbances reported a previous diagnosis of prostatitis (either acute or chronic).

Up to 25% of men receive a diagnosis of prostatitis in their lifetime, but <10% have a proven bacterial infection[18]. Contrary to the general concept, in this study the bacteriologically proven incidence of CBP among men with prostatitis symptoms was high. The reason explaining such finding is possibly the fact that we defined no lower acceptable level for bacterial colonies in both urine and prostate secretion samples for the diagnosis of chronic bacterial prostatitis. Moreover, the fact that we recognised certain Gram-positive bacteria as pathogenic may have also contributed to this difference. It should be also mentioned the possibility of false negative CBP diagnosis. In our study 12.37% of the patients had negative EPS/VB3 cultures despite the presence of bacteria in the specimens. It is possible that the rate of false negative CBP diagnoses could be even greater given that obligate intracellular parasites and intracellular bacterial communities in human urinary tract are non-visible in urinalysis[19]. Therefore, if urine cultures show no growth, a nucleic acid test for C. trachomatis and culture of prostatic fluid for ureaplasmas could be considered. If these tests are also negative, an alternative diagnosis should be considered[20].

To our best knowledge, published studies examining CBP epidemiology in Greece are extremely rare with one from the same geographical region (Attica) reporting diagnosis of CBP to be established in 26.9% of the total cohort[21]. A higher frequency of CBP in Greece is not to be excluded since significant variations in CBP incidence exist even among limitrophe geographical arias. In Italy for example, the prevalence appear to be higher in central than in central-northern, northern and southern regions and the Isles as well[22].

Clinical improvement is as successful as the underlying etiology is simpler and clear. In fact in our study, cystitis and CBP showed the higher success rate and CNBP Non-Inf and Possible CBP the lower.

Conclusions

Chronic prostatitis syndromes share similar clinical characteristics but vary widely in response to treatment. The wide variety of nonspecific symptoms and symptoms combinations associated with CP may confuse diagnosis. Thus recognizing and managing clinical features that raise the *suspicion* of this entity is important for *clinicians in order* to diagnose it and select the optimal treatment according to CP category.

Περίληψη

ΕΙΣΑΓΩΓΗ / ΣΚΟΠΟΣ: Η χρόνια προστατίτιδα (ΧΠ) είναι μια φλεγμονώδης κατάσταση του προστάτη που προκαλεί μια ποικιλία συμπτωμάτων. Δεδομένου ότι η κλινική παρουσίαση ποικίλλει ευρέως και η διαφορική διάγνωση περιλαμβάνει ορισμένες απειλητικές για τη ζωή καταστάσεις, η ΧΠ συχνά παραβλέπεται. Επιπλέον, παρά το γεγονός ότι έχει αρνητικό αντίκτυπο στην ποιότητα ζωής των ασθενών, η ΧΠ γίνεται αντικείμενο μικρής προσοχής στην κλινική πρακτική σε σύγκριση με άλλες ουρολογικές καταστάσεις. Στην παρούσα εργασία παρουσιάζουμε κλινικά μοντέλα χρόνιας προστατίτιδας που καταγράφηκαν σε 1624 επισκέψεις με στόχο τον προσδιορισμό της επίπτωσης των κατηγοριών χρόνιας προστατίτιδας NIH μεταξύ ασθενών που αναφέρονται σε ένα ενιαίο κέντρο τριτοβάθμιας φροντίδας με συμπτώματα προστατίτιδας και την περιγραφή των κλινικών χαρακτηριστικών της χρόνιας προστατίτιδας στον πληθυσμό της περιοχής μας.

ΥΛΙΚΟ: Το κλινικό δείγμα που χρησιμοποιήθηκε στη μελέτη περιελάμβανε ιατρικά αρχεία ατόμων με αναφερθείσα πυελική δυσφορία, πόνο γεννητικών οργάνων, συμπτώματα από το κατώτερο ουροποιητικό σύστημα και σεξουαλική δυσλειτουργία και από ασθενείς με υποτροπιάζουσες υποτροπές χρόνιας βακτηριακής προστατίτιδας, που επισκέφθηκαν το Τμήμα Ουρολογίας του Τζανείου Γενικού Νοσοκομείου Πειραιά, μεταξύ 03/2009 και 03/2019. Οι ασθενείς με εμπύρετη προστατίτιδα αξιολογήθηκαν με ένα μόνο δείγμα μέσης ούρησης ενώ σε όλες τις υπόλοιπες περιπτώσεις πραγματοποιήθηκε η δοκιμή Meares και Stamey ή η δοκιμή των δύο δειγμάτων. Διεξήχθη βακτηριακή ταυτοποίηση χρησιμοποιώντας το σύστημα Vitek 2 Compact και δοκιμή ευαισθησίας που πραγματοποιήθηκε με διάχυση δίσκου και το σύστημα Vitek 2. Προσδιορίστηκε το δημογραφικό, μικροβιολογικό και κλινικό ιστορικό κάθε εκτιμούμενου ασθενούς.

ΑΠΟΤΕΛΕΣΜΑΤΑ: 409 ασθενείς με συμπτώματα ΧΠ καταγράφηκαν σε έως και τρεις επισκέψεις (συμπεριλαμβανομένης της επίσκεψης παρακολούθησης) και 160 σε περισσότερες από τρεις επισκέψεις καθότι παρουσίασαν μία ή περισσότερες υποτροπές. Συνολικά, 307 ασθενείς διαγνώστηκαν με χρόνια βακτηριακή προστατίτιδα (ΧΒΠ). Περισσότεροι από τους μισούς είχαν ιστορικό προστατίτιδας. Από τους υπόλοιπους, τριάντα ένα (31) διαγνώστηκαν με κυστίτιδα-προστατίτιδα, ενώ σε 63 ασθενείς οι καλλιέργειες EPS / VB3 ήταν αρνητικές παρά την παρουσία βακτηριδίων στα δείγματα. Αυτές οι περιπτώσεις θεωρήθηκαν πιθανές περιπτώσεις ΧΒΠ. Σε 154 περιπτώσεις τα συμπτώματα αποδόθηκαν σε άλλες ασθένειες εκτός από προστατίτιδα. Σαράντα ένας (41) ασθενείς διαγνώστηκαν με χρόνια μη βακτηριακή προστατίτιδα φλεγμονώδους τύπου (ΧΜΒ Φλεγμονωδης) και 71 με χρόνια μη βακτηριακή προστατίτιδα μη-φλεγμονώδους τύπου (ΧΜΒ Μη Φλεγμονωδης). Και τα τρία είδη ΧΠ συσχετίστηκαν με μια μεγάλη ποικιλία συμπτωμάτων και συνδυασμών αυτών. Δεν παρατηρήθηκαν διαφορές όσον αφορά την εμφάνιση και τη διάρκεια των συμπτωμάτων. Αξιοσημείωτα, οι περισσότεροι ασθενείς αναφέρουν κάποιο βαθμό ουρογεννητικού πόνου ή δυσφορίας. Άλλα κοινά συμπτώματα είναι η δυσουρία, η συχνουρία και η νεοεμφανιζόμενη σεξουαλική δυσλειτουργία. Λίγοι ασθενείς παρουσιάστηκαν με εμπύρετη υποτροπή ΧΒΠ. Κλινική βελτίωση αναφέρθηκε από 267 ασθενείς.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Μια ευρεία ποικιλία συμπτωμάτων σχετίστηκε με την ΧΠ. Καθότι είναι μη ειδικά η ΧΠ μπορεί να υποεκτιμηθεί και να παραμείνει αδιάγνωστη. Είναι λοιπόν σημαντικό να εντοπιστούν τα συμπτώματα αυτά προκειμένου να διαγνωστεί η ΧΠ. και να επιλεγεί η βέλτιστη θεραπεία σύμφωνα με την κατηγορία ΧΠ προκειμένου να βελτιωθεί η ποιότητα ζωής και η κοινωνική λειτουργία του ασθενούς.

Λέξεις ευρετηριασμού
Χρόνια προστατίτιδα, προστάτης, λοίμωξη, επιδημιολογία, συμπτώματα

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ORIGINAL ARTICLE

Detection of circulating tumor cells in bladder cancer patients. Assessing the potential use of SURVIVIN, hTERT, and CK20 in aiming urine cytology and in diagnosis and monitoring of bladder cancer

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Abstract

AIM: This study aimed to analyse the presence of circulating tumor cells (CTCs) in bladder cancer patients using Multiplex polymerase chain reaction (PCR) Assays and to assess its potential use for clinical applications. Materials and Methods: Urine samples were collected from 208 patients (169 patients and 39 healthy volunteers). After RNA extraction and cDNA synthesis, the samples were analyzed for the expression of SURVIVIN, human telomerase reverse transcriptase (hTERT), cytokeratin 20 (CK20) mRNA in urine, using multiplex-PCR assays.
RESULTS: SURVIVIN, hTERT and CK20 alone or in combination correlated well with histological grade, primary tumor size (T≥3) and significantly worse progression-free survival.
CONCLUSION: Multiplex-PCR assays can be a useful tool for staging and monitoring purposes in patients with bladder cancer.

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Key words
Circulating tumor cells, bladder cancer, SURVIVIN, h-TERT, CK20

Introduction & objectives

Bladder cancer is the most common malignancy of the urinary tract, the eleventh most commonly diagnosed cancer and a leading cause of cancer morbidity and mortality (1). The standard procedure for diagnosing bladder cancer includes cystoscopy combined with cytological examination (2). Cystoscopy is an invasive, high-cost method and is considered the gold standard for detecting and monitoring bladder tumors, with a sensitivity of 70%, whereas cytology is a low-sensitive operator-dependent method (3, 4). There is a need for sensitive and specific non-invasive urinary markers that might reduce both cystoscopy and cost. An ideal bladder cancer marker should have high sensitivity and specificity; it should be noninvasive and easy to interpret (5). Several markers are commercially available, but none of them alone is sensitive and specific (6).

The presence of circulating tumor cells (CTCs) in the peripheral blood was first reported by Ashworth in 1869 (7). Malignant cells are detached from primary tumors, become invasive and may then intravasate into the blood or lymphatic circulation. Subsequently, extravasate from the circulation and establish a secondary tumor in another organ far from the primary tumor (8). The detection of CTCs has been well demonstrated in breast, lung, colon, prostate, bladder, melanoma and other malignancies (9,10). CTC detection can contribute to tumor diagnosis and identify patients with advanced bladder cancer, but such assays should not be used as initial screening diagnostic tests due to their low sensitivity (11). Polymerase chain reaction (PCR)-based methods are commonly used rapid and low-cost methods for the detection of CTCs (12).

Cytokeratins (CKs) are intermediate filaments expressed in epithelial cells. *CK20* is more highly expressed in urothelial tumors compared with normal transitional epithelium and can thus be considered as a marker of urothelial differentiation (13). SURVIVIN mRNA detection using reverse transcriptase polymerase chain reaction (RT-PCR) can be used as an important adjunct method for cystoscopy in early screening and postoperative monitoring of bladder cancer (14,15). In addition, urinary human telomerase reverse transcriptase (hTERT) activity is a good marker for the early diagnosis of bladder tumors in symptomatic patients (16), having the same specificity as urinary bladder cytology but higher sensitivity (17), while the combination of hTERT with cytology increases sensitivity to 95% (18).

This study aimed to analyse the presence of CTC in bladder cancer patients using Multiplex PCR Assays and to assess its potential use for clinical applications.

Materials and Methods

A total of 208 patients (177 men and 31 women) from one tertiary university hospital, prior to surgical or any other therapeutic intervention were enrolled in the study and categorized into three groups. Group A included patients newly diagnosed with bladder cancer (n = 105), group B included patients with a history of bladder cancer (n = 64), and group C included healthy volunteers (n = 39). People without clinical or laboratory suspicion, without a known history of malignancy or who were operated for another reason entirely irrelevant (e.g., inguinal hernia), considered as healthy volunteers. Patients were excluded from the study if they had another histological type of urothelial cancer, had received neoadjuvant or adjuvant chemotherapy, and had a medical history of the same or another type of cancer.

In the group of patients with a history of bladder cancer, less than five years had passed from the last occurrence, without any recurrence noted, meanwhile. Samples were collected before their admission to the hospital either for regular follow-up or early workup due to suspicion of recurrence. Clinical staging was based on pathological findings at the time of transurethral resection, examination under anesthesia, cross-section imaging of the abdomen and pelvis with either CT or Magnetic resonance imaging (MRI), and chest X-ray. Transurethral resection and radical cystectomy specimens were graded and staged according to TNM classification. Patients were also categorized based on the American Joint Committee on Cancer (AJCC) staging.

The clinical and demographic characteristics of the patients are shown in **Table 1**. All participants provided written informed consent to this research protocol and this study was conducted under the approval of the local Ethics Committee and conforms to the Declaration of Helsinki.

Regarding follow-up, an appropriate schedule for disease monitoring of the patients (sometimes confirming, reminding, and re-scheduling appointments by phone, in case of older patients or patients with-

Table 1 *Clinical and demographic characteristics of the three study groups*

	Group		
	Newly diagnosed (n = 105)	History of bladder Ca (N = 64)	Control (n = 39)
	n (%)	n (%)	n (%)
Gender			
Men	90 (85.7)	58 (90.6)	29 (74.4)
Women	15 (14.3)	6 (9.4)	10 (25.6)
Mean age (SD), years	68.4 (10.5)	68.5 (10.9)	67.2 (18.0)
Primary tumor stage (T)			
0a	36 (34.3)	20 (31.3)	-
0is	1 (1)	4 (6.3)	-
1	34 (32.4)	34 (53.1)	-
2	20 (19)	4 (6.3)	-
3	9 (8.6)	1 (1.6)	-
4	5 (4.8)	1 (1.6)	-
Infiltrated Nodes (N)			
No	97 (92.4)	62 (96.9)	-
Yes	0 (0)	0 (0)	-
Anatomical stage*			
0a	35 (33.3)	20 (31.3)	-
0is	3 (2.9)	4 (6.3)	-
1	33 (31.4)	34 (53.1)	-
2	16 (15.2)	3 (4.7)	-
3	7 (6.7)	1 (1.6)	-
4	11 (10.5)	2 (3.1)	-
Histological grade			
1	8 (7.6)	5 (7.8)	-
2	46 (43.8)	(45.3)	-
3	50 (47.6)	26 (40.6)	-
In situ	1 (1)	4 (6.3)	-

* By American Joint Committee on Cancer (31).

out spouses, relatives or care givers), based on regular cystoscopy, urinary cytology and imaging techniques, according to the EAU Guidelines was performed (19, 20). There were three patients who have been lost to follow-up. However, the number was not considered statistically significant and that is why they were not included in the tables.

Primers for the selected markers were designed using FastPCR software. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used to evaluate the performance of complementary DNA (cDNA) synthesis (housekeeping gene). Fifty milliliters of spontaneously voided urine (second void of the day) was taken from each patient before they received any treatment or underwent surgery.

Samples were processed within 3 hours of collection. They were centrifuged at 2000x g for 10 min. The cell pellet was homogenized in 1 ml Tri-Reagent RT-111. Total cellular RNA was then extracted, according to the manufacturer's instructions. Diethylpyrocarbonate water (DEPC-treated H2O) was used for RNA pellet dilution. Total RNA concentration and quality were determined by ultraviolet spectophotometry (measurements at 260 nm, 280 nm).

cDNA was synthesized using Moloney Murine Leukemia Virus (M-MLV) Reverse Transcriptase. The resulting complementary DNA was then used for multiplex PCR reaction.

All PCR reactions were performed using the Qiagen Multiplex PCR Kit. The reaction mixture contained 1X Qiagen Multiplex PCR Mix, 0.125 μM CK20 primers, 0.3 μM SURVIVIN primers, 0,3 μM hTERT primers and DEPC-treated water up to 23 μl. Complementary DNA (2 μl) was added to the reaction volume.

For GAPDH detection, the PCR reaction was performed using the Qiagen Taq PCR Kit. The reaction mixture contained 1x Qiagen PCR Buffer, 0.66 μM GAPDH primers and DEPC-treated water. Cycling conditions were the same as for multiplex PCR.

PCR products were analyzed by electrophoresis in a 2% agarose gel (ethidium bromide stained) and were then captured under UV light in KODAK EDAS 290 Imaging System (CareStream Health, Rochester, NY, USA).

We proceed to a qualitative analysis. Before developing multiplex PCR, first, we performed single PCR for each gene using bladder cancer tissue as a positive control and urine from healthy volunteers as a negative control, normalizing the PCR so that there is no expression of any of these genes in the healthy controls. Urine samples with detectable GAPDH band together with the positive marker product were considered positive for any gene expression. Samples were considered negative when GAPDH-band were identified alone. In cases of missing GAPDH signal, samples were excluded from analysis.

Statistical analysis

Quantitative variables are expressed as mean values +/- standard deviation (SD)/median values (interquartile range). Qualitative variables are expressed as absolute and relative frequencies. For comparisons of proportions, chi-square and Fisher's exact tests were used. Analysis of variance (ANOVA) was used for the comparison of the mean age between the study groups. Recurrence-free survival was defined as the time from diagnosis of bladder cancer to the date of the first bladder recurrence (same or lower disease stage or grade). Progression-free survival was defined as the time from diagnosis of bladder cancer to the date that higher disease grade or stage were detected. Log-rank tests were used for the comparison of survival curves. Sensitivity, specificity, negative and positive predictive values were calculated to estimate the discriminative ability of study markers between the group with a history of bladder cancer and controls (no cancer) as well as between the newly diagnosed group and controls. All reported p-values are two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using the Statistical Package or the Social Sciences Predictive Analysis Software 19.0.

Results

Of the newly diagnosed group, 17.2% were categorized as having disease of anatomic stage III or IV (AJCC), and the corresponding proportion was 4.7% for the group with history of bladder cancer ($p = 0.017$). Recurrence was recorded in 20 patients (19.2%) from the newly diagnosed group and in 26 patients (40.6%) from the group with history of bladder cancer ($p = 0.002$), while disease progression was recorded in 12 of the patients with newly diagnosed bladder cancer (11.8%) and in 11 (18.0%) with history of bladder cancer ($p > 0.050$). The mean follow-up period was 26.9 months (SD = 11.9), with a median of 32 months (interquartile range from 15 to 37 months).

The detection of all markers and their respective combinations in the three study groups is presented in **Table 2**.

Expression of hTERT, CK20 and SURVIVIN in urine. Urine detection of SURVIVIN, CK20, the combined positive detections of SURVIVIN plus CK20, SURVIVIN or/and hTERT-positive (that is: SURVIVIN-hTERT-positive), SURVIVIN-CK20-positive, hTERT-CK20-positive and SURVIVIN-hTERT-CK20-positive were frequent in the newly diagnosed group and the group of patients with history of bladder cancer, and rare in the control group (Table 2).

Sensitivity, specificity, negative and positive predictive value of markers used for discriminating newly diagnosed and control groups (**Table 3**). Urinary markers and their combinations had high positive predictive values ranging from 91.7% to 100% and high specificity rates ranging from 94.9% to 100%. The sensitivity was low, the highest being detected for combined positive detection of hTERT-CK20-positive (35.9%), and SURVIVIN-hTERT-CK20-positive (36.2%).

Sensitivity, specificity, negative and positive predictive values of marker detections in patients with history of bladder cancer and control group **(Table 4)**. Urinary markers also presented high specificity and positive predictive values, while the highest sensitivity rates were found for CK20, SURVIVIN-CK20-positive, hTERT-CK20-positive and SURVIVIN hTERT-CK20-positive.

Table 2 *Expression of all study markers and their combinations in the three study groups*

	Group			
	A	B	C	
	Newly diagnosed	History of bladder cancer	Control	*p*-Value
	n (%)	n (%)	n (%)	
SURVIVIN	22 (21)[C]	13 (20.3)[C]	2 (5.1)[A, B]	0.043*
hTERT	11 (10.5)	5 (7.8)	0 (0.0)	0.099**
CK20	35 (33.3)[C]	22 (34.4)[C]	1 (2.6)[A, B]	< 0.001*
SURVIVIN and *hTERT*	9 (8.6)	4 (6.3)	0 (0)	0.175**
SURVIVIN and *CK20*	22 (21)[C]	13 (20.3)[C]	1 (2.6)[A, B]	0.026*
hTERT and *CK20*	9 (8.6)	4 (6.3)	0 (0)	0.175**
SURVIVIN and *hTERT* and *CK20*	9 (8.6)	4 (6.3)	0 (0)	0.175**
SURVIVIN-hTERT-positive	25 (23.8)[C]	14 (21.9)[C]	2 (5.1)[A, B]	0.038*
SURVIVIN-CK20-positive	35 (33.3)[C]	22 (34.4)[C]	2 (5.1)[A, B]	0.002*
hTERT-CK20-positive	38 (36.2)[C]	23 (35.9)[C]	1 (2.6)[A, B]	< 0.001*
SURVIVIN-hTERT-CK20-positive	38 (36.2)[C]	23 (35.9)[C]	2 (5.1)[A, B]	0.001*

Table 3 *Percentage sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of study markers for the discrimination between newly diagnosed patients with bladder cancer and controls*

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
SURVIVIN	21.0 (13.6-30.0)	94.9 (82.7-99.4)	91.7 (73.0-99.0)	30.8 (22.7-39.9)
hTERT	10.5 (5.4-18.0)	100.0 (91.0-100.0)	100.0 (71.5-100.0)	29.3 (21.8-37.8)
CK20	33.3 (24.4-43.2)	97.4 (86.5-99.9)	97.2 (85.5-99.9)	35.2 (26.2-45.0)
SURVIVIN and *hTERT*	8.6 (4.0-15.7)	100.0 (91.0-100.0)	100.0 (66.4-100.0)	28.9 (21.4-37.3)
SURVIVIN and *CK20*	21.0 (13.6-30.0)	97.4 (86.5-99.9)	95.7 (78.1-99.9)	31.4 (23.3-40.5)
hTERT and CK20	8.6 (4.0-15.7)	100.0 (90.97-100.0)	100.0 (66.4-100.0)	28.9 (21.4-37.3)
SURVIVIN and *hTERT* and *CK20*	8.6 (4.0-15.7)	100.0 (90.97-100.0)	100.0 (66.4-100.0)	28.9 (21.4-37.3)
SURVIVIN-hTERT-positive	23.8 (16.0-33.1)	94.9 (82.7-99.4)	92.6 (75.7-99.1)	31.6 (23.3-40.9)
SURVIVIN-CK20-positive	33.3 (24.4-43.2)	94.9 (82.7-99.4)	94.6 (81.8-99.3)	34.6 (25.7-44.4)
hTERT-CK20-positive	36.2 (27.0-46.2)	97.4 (86.5-99.9)	97.4 (86.5-99.9)	36.2 (27.0-46.2)
SURVIVIN-hTERT-CK20-positive	36.2 (27.0-46.2)	94.9 (82.7-99.4)	95.0 (83.1-99.4)	35.6 (26.4-45.6)

Association with progression-free survival. Patients in the newly diagnosed bladder cancer group with positive urine SURVIVIN detection had worse progression-free survival compared to those that were negative for SURVIVIN (logrank test, p = 0.011). Specifically, three of the newly diagnosed patients with negative SURVIVIN (8.8%) had disease progression and the corresponding proportion was 26.9% in cases that SURVIVIN was detected. The positive detection of urinary CK20 was also associated with worse progression free-survival in newly diagnosed patients (logrank test, p = 0.050). Worse progression free-survival was found in the newly diagnosed group with combined positivity for the detection of urinary SURVIVIN and hTERT (log-rank test, p = 0.048), urinary SURVIVIN and CK20 (log-rank test, p = 0.011), urinary hTERT and CK20 (log rank test, p = 0.048), urinary SURVIVIN with hTERT and CK20 (log-rank test, p = 0.048), urinary SURVIVIN and hTERT (log-rank test, p = 0.029), and urinary SURVIVIN and CK20 (log rank test, p = 0.050). In addition, recurrence-free rates were worse in the cases of newly diagnosed patients with combined positivity for urinary SURVIVIN and hTERT

Table 4 *Percentage sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of study markers for the discrimination between the group with history of bladder cancer and controls*

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
SURVIVIN	20.3 (11.3-32.2)	94.9 (82.7-99.4)	86.7 (59.5-98.3)	42.1 (31.6-53.1)
hTERT	7.8 (2.6-17.3)	100.0 (91.0-100.0)	100.0 (47.8-100.0)	39.8 (30.0-50.2)
CK20	34.4 (23.0-47.3)	97.4 (86.5-99.9)	95.7 (78.1-99.9)	47.5 (36.2-59.0)
SURVIVIN and *hTERT*	6.3 (1.7-15.2)	100.0 (91.0-100.0)	100.0 (39.8-100.0)	39.4 (29.7-49.7)
SURVIVIN and *CK20*	20.3 (11.3-32.2)	97.4 (86.5-99.9)	92.9 (66.1-99.8)	42.7 (32.3-53.6)
hTERT and *CK20*	6.3 (1.7-15.2)	100.0 (91.0-100.0)	100.0 (39.8-100.0)	39.4 (29.7-49.7)
SURVIVIN and *hTERT* and *CK20*	6.3 (1.7-15.2)	100.0 (91.0-100.0)	100.0 (39.8-100.0)	39.4 (29.7-49.7)
SURVIVIN-hTERT-positive	21.9 (12.5-34.0)	94.9 (82.7-99.4)	87.5 (61.6-98.5)	42.5 (32.0-53.6)
SURVIVIN-CK20-positive	34.4 (23.0-47.3)	94.9 (82.7-99.4)	91.7 (73.0-99.0)	46.8 (35.5-58.4)
hTERT-CK20-positive	35.9 (24.3-48.9)	97.4 (86.5-99.9)	95.8 (78.9-99.9)	48.1 (36.7-59.6)
SURVIVIN-hTERT-CK20-positive	35.9 (24.3-48.9)	94.9 (82.7-99.4)	92.0 (74.0-99.0)	47.5 (36.0-9.1)

Table 5 *Mean recurrence-free survival (in months) in newly diagnosed and patients with a history of bladder cancer based on various markers*

		Newly diagnosed patients			Patients with a history of bladder cancer		
		Mean	SE*	P Log-rank	Mean	SE*	P Log-rank
Total		34,06	1,23		28,93	1,65	
SURVIVIN	Negative	34,94	1,31	0,098	28,42	1,86	0,472
	Positive	30,99	3,07		31,00	3,53	
H-TERT	Negative	34,59	1,26	0,157	28,34	1,76	0,329
	Positive	29,32	4,28		36,00	2,68	
CK20	Negative	34,60	1,44	0,475	27,93	2,09	0,555
	Positive	33,07	2,31		30,82	2,63	

* Standard Error

(log-rank test, p = 0.050), urinary hTERT and CK20 (log-rank test, p = 0.050), and urinary SURVIVIN plus hTERT plus CK20 (log-rank test, p = 0.048).

Correlation of positive detections with various clinicopathological parameters of patients with bladder cancer. In newly diagnosed patients, positive hTERT detection in urine was associated with primary tumor size ≥3 (that is T3 or T4) as compared to those with tumor size <3 (that is T1 or T2) (28.6% vs. 7.7%, p = 0.032) and with AJCC stage 2 or greater as compared with stage <2 (50.0% vs. 6.3%, p = 0.028). Similarly, the combined positive detection of SURVIVIN and hTERT (50.0% vs. 6.3%, p = 0.028), hTERT and CK20 (50.0% vs. 6.3%, p = 0.028), and SURVIVIN with hTERT and CK20 (50.0% vs. 6.3%, p = 0.028) were associated with AJCC stage 2 or greater. In addition, all marker detections in urine samples and their respective combinations were associated with histological grade 3 or carcinoma in situ (for SURVIVIN 31.4% vs. 11.1%, p = 0.011; for hTERT: 19.6% vs. 1.9%, p = 0.003; and for CK20: 54.9% vs. 13.0%, p < 0.001).

Disease recurrence (**Tables 5, 6**). In the group of the newly diagnosed patients, 20 patients had a recurrence (19.2%), whereas in the group of patients with a history of bladder Ca, the corresponding number was 26 (40.6%) and was significantly higher = 0.002). Primary patients who were positive in the SURVIV and HTERT, H-TERT and CK20, and SURVIV and HTERT and CK20 combinations had a relapse significantly earlier than those who had negative markers (HR = 2.77, 95% SD:

Table 6 *Mean recurrence-free survival (in months) in newly diagnosed and patients with a history of bladder cancer based on various marker combinations*

		Newly diagnosed patients			Patients with a history of bladder cancer		
		Mean	SE*	P Log-rank	Mean	SE*	P Log-rank
SURVIV and HTERT	Negative	34,70	1,24	**0,050**	28,52	1,73	0,487
	Positive	27,33	4,97		30,75	1,95	
SURVIV and CK20	Negative	34,94	1,31	0,098	28,42	1,86	0,472
	Positive	30,99	3,07		31,00	3,53	
H-TERT and CK20	Negative	34,70	1,24	**0,050**	28,52	1,73	0,487
	Positive	27,33	4,97		30,75	1,95	
SURVIV and HTERT and CK20	Negative	34,70	1,24	0,**048**	28,52	1,73	0,487
	Positive	27,33	4,97		30,75	1,95	
SURVIV and/or HTERT	Negative	34,74	1,35	0,221	28,20	1,88	0,347
	Positive	32,08	2,75		31,57	3,32	
SURVIV and/or CK20	Negative	34,60	1,44	0,475	27,93	2,09	0,555
	Positive	33,07	2,31		30,82	2,63	
HTERT and/or CK20	Negative	34,35	1,50	0,694	27,66	2,12	0,426
	Positive	33,64	2,14		31,18	2,54	
SURVIV and/or HTERT and/or CK20	Negative	34,35	1,50	0,694	27,66	2,12	0,426
	Positive	33,64	2,14		31,18	2,54	

* Standard Error
**All cases are censored

1.01-8.29 for all combinations, see Kaplan-Meier curves in **figures 1 to 3**). In contrast, in patients with a history of bladder cancer, there was no significant difference in recurrence-free survival depending on whether they were positive or negative for the various combinations of urine markers.

In the multifactorial Cox models, having as independent variables the positive detection of tumor markers, sex, age, tumor stage, tumor grade and haematuria, only the tumor grade (as expected) and the combination of urine markers SURVIVIN and HTERT and CK20 were found to be independently associated with the recurrence of the newly diagnosed patients. ***Progression of the disease*** (**Tables 7, 8**). In the group of the newly diagnosed patients, 12 patients had a progression of the disease (11.8%), whereas in the group of patients with a history of bladder Ca, the corresponding number was 11 (18.0%), without any statistically significant difference between the two groups (p = 0.266).

In the group of the newly diagnosed, mean progression-free survival time was 36.60 months (SE = 0.97). Patients who were SURVIVIN-positive had a progression of the disease significantly earlier than the negative

Figure 1. *Kaplan-Meier estimates for disease recurrence in the newly diagnosed group according to the expression of SURVIVIN and HTERT*

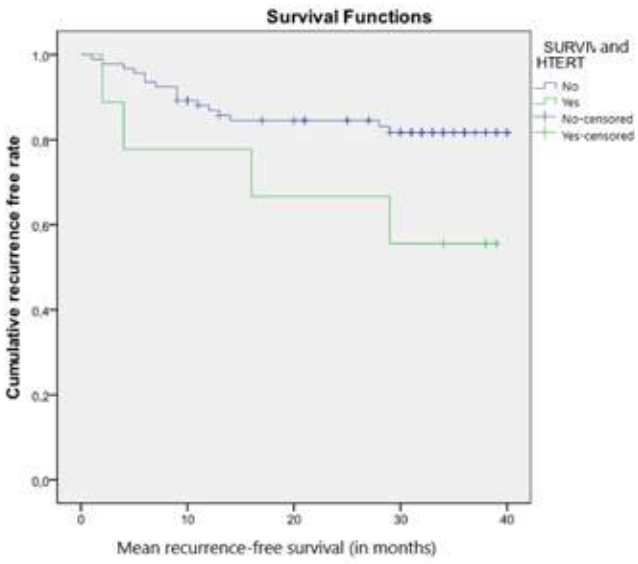


Table 7 *Mean progression-free survival (in months) in newly diagnosed and patients with a history of bladder cancer based on various markers*

		Newly diagnosed patients			Patients with a history of bladder cancer		
		Mean	SE*	P Log-rank	Mean	SE*	P Log-rank
Total		36,60	0,97		35,27	1,10	
SURVIVIN	Negative	37,72	0,93	**0,011**	35,80	1,10	0,475
	Positive	32,58	2,83		33,15	3,17	
H-TERT	Negative	37,07	0,97	0,109	35,20	1,17	0,929
	Postive	32,16	3,72		36,00	2,68	
CK20	Negative	37,89	0,94	**0,050**	35,67	1,23	0,813
	Positive	34,07	2,15		34,50	2,15	

* Standard Error

Table 8 *Mean progression-free survival (in months) in newly diagnosed and patients with a history of bladder cancer based on various marker combinations*

		Newly diagnosed patients			Patients with a history of bladder cancer		
		Mean	SE*	P Log-rank	Mean	SE*	P Log-rank
SURVIV and HTERT	Negative	37,13	0,95	**0,048**	35,27	1,15	0,745
	Positive	30,78	4,39		31,50	2,16	
SURVIV and CK20	Negative	37,72	0,93	0,011	35,80	1,10	0,475
	Positive	32,58	2,83		33,15	3,17	
H-TERT and CK20	Negative	37,13	0,95	**0,048**	35,27	1,15	0,745
	Positive	30,78	4,39		31,50	2,17	
SURVIV and HTERT and CK20	Negative	37,13	0,95	**0,048**	35,27	1,15	0,745
	Positive	30,78	4,39		31,50	2,17	
SURVIV and/or HTERT	Negative	37,63	0,96	0,029	35,74	1,21	0,580
	Positive	33,47	2,53		33,57	2,97	
SURVIV and/or CK20	Negative	37,89	0,94	0,050	35,67	1,23	0,813
	Positive	34,07	2,15		34,50	2,15	
HTERT and/or CK20	Negative	37,79	0,98	0,092	35,59	1,26	0,908
	Positive	34,55	1,99		34,70	2,06	
SURVIV and/or HTERT and/or CK20	Negative	37,79	0,98	0,092	35,59	1,26	0,908
	Positive	34,55	1,99		34,70	2,06	

* Standard Error
**All cases are censored

patients (log-rank test, p = 0.011, HR = 3.91, 95% CI: 1.26-12.14; Kaplan-Meier curves in **Figure 4**). In particular, three of the newly diagnosed SURVIVIN-negative patients (8.8%) had a progression of the disease, and the corresponding ratio was 26.9% when the SURVIVIN was positive. Correspondingly, the newly diagnosed CK20-positive patients showed progression significantly earlier than those who were negative (log-rank test, p = 0.050, HR = 2.96, 95% CI: 1.03-9, 32 – see Kaplan-Meier curves in **Figure 5**). In all patients with a history of bladder Ca, the mean free progression time was 35.27 months (SE = 1.10). There was no significant difference in progression-free survival whether they were positive or negative on the various indicators.

The newly diagnosed patients who were positive in the SURVIV and HTERT, H-TERT and CK20, and SURVIV

Figure 2. *Kaplan-Meier estimates for disease recurrence in the newly diagnosed group according to the expression of HTERT and CK20*

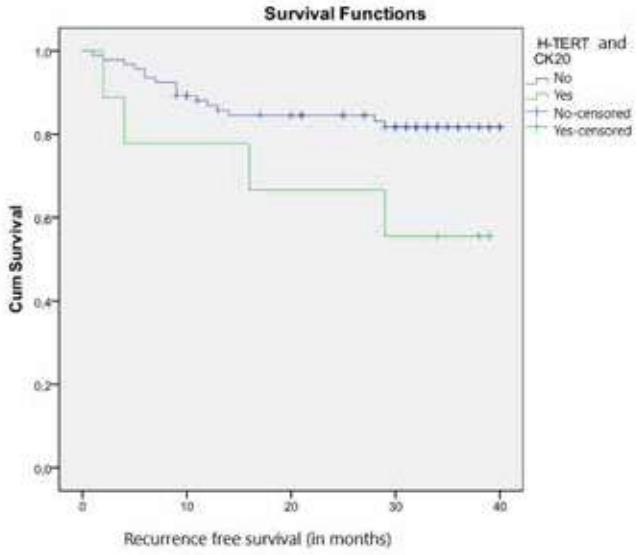


Figure 3. *Kaplan-Meier estimates for disease recurrence in the newly diagnosed group according to the expression of SURVIV and HTERT and CK20*

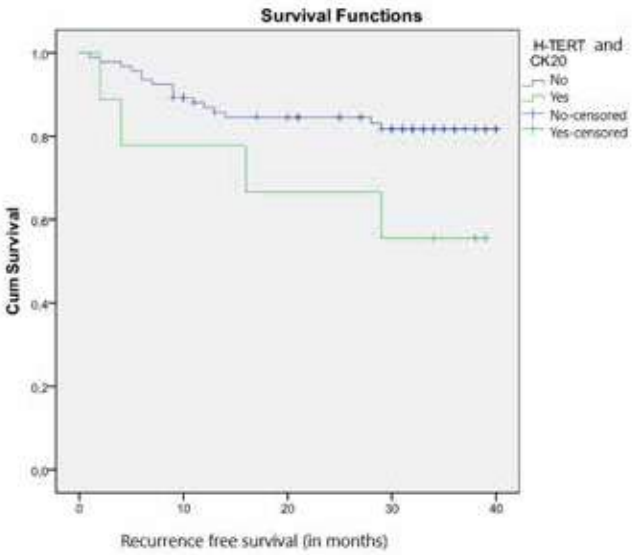


Figure 4. *Kaplan-Meier estimates for disease recurrence in the newly diagnosed group according to the expression of SURVIV*

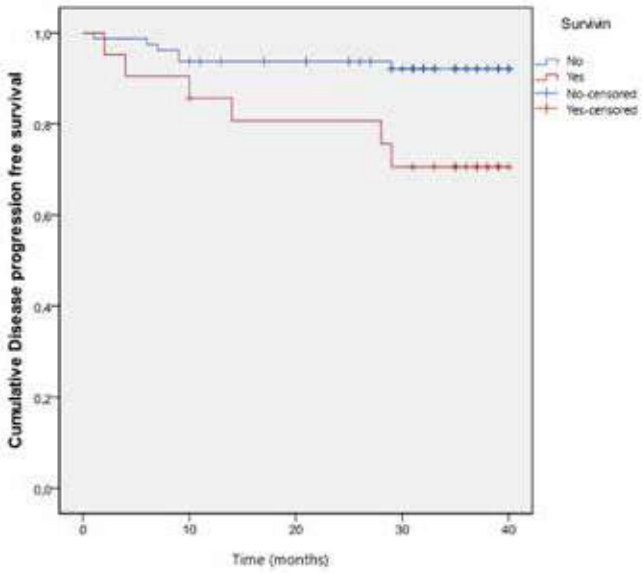
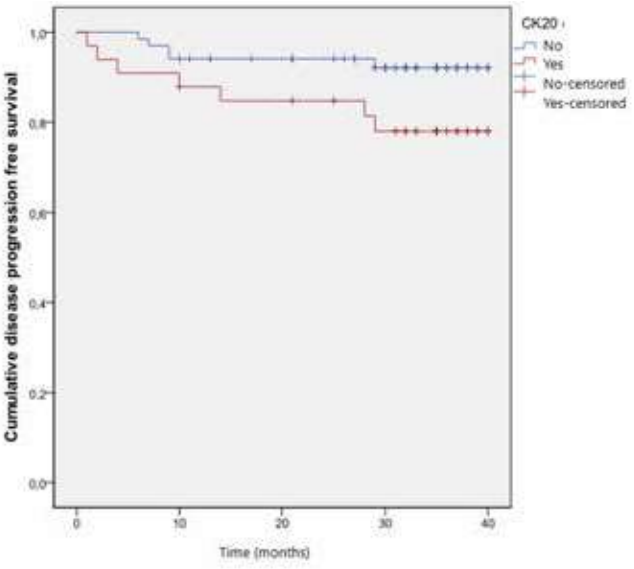


Figure 5. *Kaplan-Meier estimates for disease recurrence in the newly diagnosed group according to the expression of CK20*



and HTERT and CK20 combinations showed a progression of the disease significantly earlier compared to those with negative markers (HR = 3.45, 95% SD: 1.03-12.7 for all combinations). Also, the newly diagnosed patients who were positive in the SURVIV and CK20 combination experienced a progression of the disease significantly earlier than those who were negative (HR = 3.91, 95% CI: 1.26-12.1). The newly diagnosed patients who were positive for the combination of SURVIVIN and/or HTERT had a progression of the disease significantly

Table 9 *Mean recurrence and/or progression-free survival (in months) in newly diagnosed and patients with a history of bladder cancer based on various markers*

		Newly diagnosed patients			Patients with a history of bladder cancer		
		Mean	SE*	P Log-rank	Mean	SE*	P Log-rank
Total		33,86	1,23		32,03	1,43	
SURVIVIN	Negative	34,57	1,34	0,146	31,92	1,57	0,633
	Positive	31,37	2,92		32,46	3,39	
H-TERT	Negative	34,27	1,29	0,221	-	-	-**
	Positive	30,05	3,90		-	-	
CK20	Negative	34,17	1,48	0,611	31,55	1,79	0,794
	Positive	33,32	2,22		32,98	2,36	

* Standard Error
**All cases are censored

earlier than those who were negative (HR = 3.28, 95% CI: 1.06-10.16). Additionally, the newly diagnosed patients who were positive in the SURVIVIN and CK20 combination had a progression of the disease significantly earlier compared to the negative ones (HR = 2.96, 95% ΔE: 1.03-9.32). In contrast, in patients with a history of bladder Ca there was no significant difference in recurrence-free survival depending on whether they were positive or negative in the various marker combinations.

In the multifactorial Cox models, having as independent variables, the positive detection of tumor markers, sex, age, tumor stage, tumor grade and haematuria, only gender, and SURVIVIN-positive urine were found to be independently associated with the progression of the disease in the newly diagnosed patients. In particular, women had a 8.18-fold higher risk (95% CI: 1.93-34.68, p = 0.004) compared to men. Also, the newly diagnosed SURVIVIN urine-positive patients had a 7.48-fold higher risk (95% CI: 1.93-28.97, p = 0.004) compared to the previously diagnosed patients who were negative in SURVIVIN.

Recurrence and/or progression of the disease (**Table 9**). In the group of newly diagnosed patients, 21 patients experienced recurrence and/or progression of the disease (20.6%), whereas in the group of patients with a history of bladder Ca, the corresponding number was 19 (31.7%), with no significant difference between the two groups (p = 0.114).

In the total amount of the newly diagnosed patients, the mean recurrence and/or progression-free survival was 33.86 months (SE = 1.23). There was no significant difference in the recurrence and progression-free survival depending on whether they were positive or negative for the tumor markers. In all patients with a history of bladder Ca, the mean time for recurrence and/or progression of the disease was 32.03 months (SE = 1.43). There was also no significant difference in the time of recurrence and/or disease progression depending on whether they were positive or negative for the various urine markers.

Discussion

Although the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group has developed a scoring system and risk tables (21), more intensive research is required in the field of CTCs in order to improve the predictive accuracy of the currently existing risk tables (22). We should not only be able to use these molecular markers as a screening test in populations at higher risk for bladder cancer (23) but to also achieve better surveillance (24, 25) and perhaps a better understanding of the biological behavior of the disease. Especially when interobserver variability exists in the classification of stage T1 versus Ta tumors and tumor grading in both 1997 and 2004 classifications. In such difficult cases, where an additional review by an experienced genitourinary pathologist is recommended, an objective, easy to perform and highly specific assay would be of great importance.

Rink et al. showed significantly worse overall progression-free survival and cancer-specific survival in CTC-positive compared with CTC negative patients (26). Msaouel and Koutsilieris further performed a systematic review and metaanalysis of the value of CTC detection in the bladder and urothelial cancer, high-

lighting the potential clinical role of CTCs as a marker of advanced bladder cancer (11). It has also been shown that CTC status may provide prognostic information in the face of negative imaging (23). CTC status could provide clinicians with valuable information that might be applied to preoperative management algorithms and potentially identify patients who would be most appropriate for neoadjuvant chemotherapy or clinical trial protocols. The advantages of multi-marker use for CTC detection in patients with colorectal cancer (CRC) have already been described (28). Many previous studies have shown that the use of more than one marker independently increases the sensitivity and the specificity of CTC detection and thus the correlation with disease stage in patients with CRC (29, 30). Implementation of multiplex RT-PCR, which allows the examination of multiple marker expression in a single reaction, could be advantageous, in contrast with the application of separate PCR reactions for each marker, which can be time-consuming and costly. Moreover, it represents an easily applied, noninvasive technique for the detection of CTCs in patients with cancer.

The aim of the present study was to evaluate the clinical significance of a multiplex PCR-based detection of CTCs using primers for SURVIVIN, hTERT, and CK20 in urine samples and to assess the possible clinical applications of these markers in patients with bladder cancer. With a substantial follow-up period, we were able to estimate several clinical parameters (sensitivity, specificity, positive predictive value, negative predictive value, progression-free survival) and assess their prognostic relevance.

Our data highlight the known correlation between primary tumor (T stage) and high grade with worst prognosis regarding recurrence and progression in patients with bladder cancer. Beyond these, there seems to be a statistically significant correlation of those clinical parameters with the evaluated mRNA markers. Urine markers also demonstrated high specificity and positive predictive values, both in the newly diagnosed group and in patients with a history of bladder cancer. Therefore CTCs detection may be useful in confirming the cancer diagnosis.

Positive SURVIVIN detection in the urine of newly diagnosed patients revealed worse prognosis. The positive detection of CK20 was also associated with worse progression free-survival in newly diagnosed patients. Furthermore, in newly diagnosed, positive hTERT detections correlated more with primary tumor size (T) ≥3 and with AJCC stage 3 or greater as compared with stage <3. In addition, all marker detections and their respective combined positivity correlated with high grade cancer (histological grade 3 or carcinoma in situ), in the newly diagnosed patients. There is thus a considerable connection with the conclusion of Rink et al., that that the presence of CTC may be predictive for early systemic disease (26).

Multiplex RT-PCR assay can provide useful information concerning bladder cancer stage, grading and progression-free and recurrence-free survival. The combination of the mRNA markers in a single reaction could be beneficial in the early detection of high-grade/clinically relevant disease and monitoring of bladder cancer patients (mainly those with a high possibility to progress or recurrence), as it has previously been documented in other malignancies (31, 32).

This study does have several limitations. The overall number of patients needs to be greater. Therefore, the results must be interpreted with caution. The usage of CTCs seems promising, but for the moment is mainly study-based and no large trials have been performed yet; therefore, no clinically usable markers have been identified. Relatively large-scale studies and longer follow-up surveys would prove the clinical significance and prognostic importance of multiplex PCR based detection of CTCs using hTERT, CK20, and SURVIVIN in urine and mainly their combinations in patients with bladder cancer. Despite the relatively low number of patients, to our knowledge, it is one of the largest studies to date in patients with bladder cancer. There is also a need for large quantitative studies, which will allow us to evaluate the optimal cut-off CTC count for increased sensitivity and specificity.

The future of marker development seems bright and new techniques are emerging. Beyond finding good markers, the financial cost-effectiveness will be an important issue, and that has not been studied sufficiently yet. Currently, no single marker can guide us in surveillance and lower the frequency of urethrocystoscopy. Whether the use of a set of markers will be the answer will have to be studied.

Περίληψη

ΣΚΟΠΟΣ: Ο σκοπός της μελέτης ήταν να αναλύσει την παρουσία κυκλοφορούντων καρκινικών κυττάρων (CTCs) στα ούρα ασθενών με καρκίνο της ουροδόχου κύστης χρησιμοποιώντας πολλαπλή αλυσιδωτή αντίδραση πολυμεράσης (Multiplex PCR) και να αξιολογήσει την πιθανές κλινικές εφαρμογές τους.

ΥΛΙΚΑ ΚΑΙ ΜΕΘΟΔΟΙ: Έγινε συλλογή δειγμάτων ούρων από 208 συμμετέχοντες (169 ασθενείς και 39 υγιείς εθελοντές). Μετά από λήψη του RNA και τη σύνθεση του συμπληρωματικού DNA, έγινε ανάλυση των δειγμάτων για την έκφραση SURVIVIN, κυτοκερατίνης 20 (cytokeratin 20 - CK20), και της ανθρώπινης τελομεράσης ανάστροφης τρανσκριπτάσης (hTERT), με τη χρήση multiplex-PCP.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Οι SURVIV, h-TERT and CK20 μόνοι τους ή σε συνδυασμό σχετίστηκαν με τον ιστολογικό βαθμό κακοήθειας, το επίπεδο του όγκου και την πρόγνωση των ασθενών. **ΣΥΜΠΕΡΑΣΜΑ:** Η ανίχνευση CTCs με τη βοήθεια της Multiplex PCR μπορεί να αποτελέσει ένα χρήσιμο εργαλείο στη σταδιοποίηση και στον έλεγχο των ασθενών με ουροθηλιακό καρκίνο της ουροδόχου κύστης.

Λέξεις ευρετηριασμού

Κυκλοφορούντα καρκινικά κύτταρα, καρκίνος ουροδόχου κύστης, PCR, SURVIVIN, hTERT, CK20

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Case report

Neglected Gluteal Area Pressure Ulcer evolved into Fournier's Gangrene: a rare complication

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Abstract

Fournier's Gangrene is a fulminant polymicrobial infection of the fascia with high mortality rate. A rare case of a paraplegic 48-year-old male who developed Fournier's Gangrene due to neglected gluteal area pressure ulcer is reported. The patient was referred to our emergency department in case of high fever, hemodynamic instability and neglected, malodorous left gluteal area pressure ulcer during the last 24 hours. Clinical examination revealed intense cellulitis around the ulcer, foul odor, incipient skin necrosis and crepitus on palpation of the left hemiscrotum. Computed Tomography scan confirmed the diagnosis of Fournier's Gangrene. The patient underwent immediate, extensive surgical debridement of the necrotic tissues. Pus cultures revealed Proteus mirabilis and Pseudomonas aeroginosa. Postoperatively, repeated debridement of necrotic tissue and administration of vacuum-assisted wound closing device had as a result the progressive patient's recovery, who was discharged on the 32rd postoperative day, following surgical trauma reconstruction by plastic surgeons.

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Neglected Gluteal Area Pressure Ulcer evolved into Fournier's Gangrene: a rare complication
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Introduction

Key words
Fournier's gangrene, Gluteal Ulcer, NSTI (necrotizing soft-tissue infection), Wound V.A.C.

Fournier's gangrene (FG) was first described in 1883, by the French venereologist Jean Alfred Fournier who described five cases of previously healthy, young men who developed gangrene of the penis and scrotum rapidly, without apparent cause. FG is a rare, rapid and potentially fatal soft tissue infection of the genitalia, perineum, perianal region and abdominal wall. Our aim is to present a rare case of extensive FG due to neglected left gluteal pressure ulcer and to underline the significance of early intervention and diligent postoperative care, as well as the importance of cooperation of the multi disciplinary team (MDT) in the management of extensive necrotising fasciitis.

Case report

A 48-year-male was referred to our emergency department because of 24-hours history of high fever and malodorous left gluteal area pressure. He suffered from paralysis of the lower extremities caused by a machine accident 18 years ago and he is on wheelchair since then. During the last year, he had developed a left gluteal area pressure ulcer and recurrent local infection.

Figure 1. *Preoperative photo demonstrating left gluteal ulcer which demonstrated redness, localized warmth around the neglected gluteal ulcer*

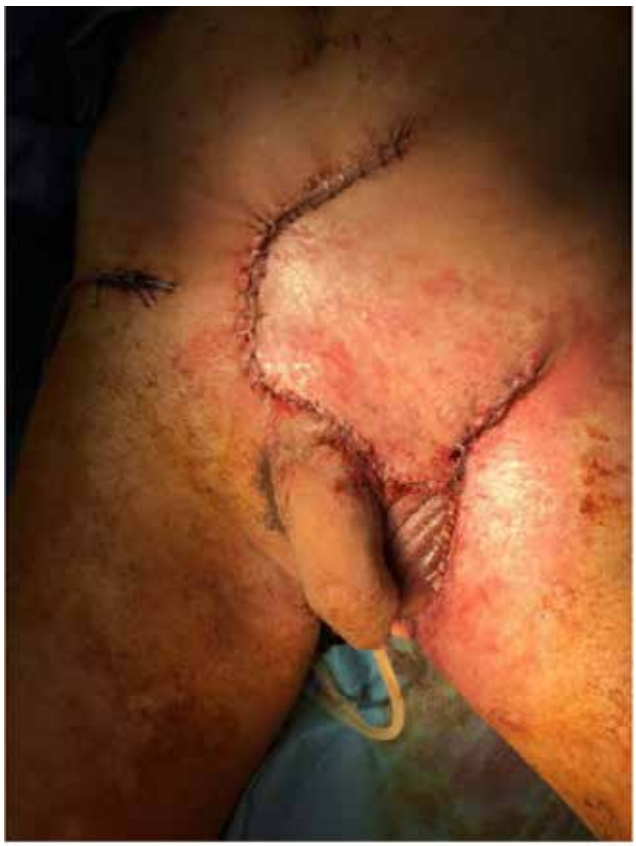
Clinical examination revealed intense cellulitis around the ulcer (7 x 5 cm in dimension), foul odor, and incipient skin necrosis and crepitus on palpation of the left hemiscrotum (**figure 1**). Redness and warmth were extended to sacral area, anal area, perineum and left hemiscrotum. On admission, he was hemodynamically unstable and his temperature was 39.5°C. White blood cell count was 19200/μL (NORMAL VALUES 4000-10000/μL) and a C-reactive protein value was 90 mg/dL(NORMAL VALUE 5-10 mg /dL). Computed Tomography (CT) scan revealed hyperemia, gas in the area of sacrum - rectum, and retroperitoneum and confirmed the diagnosis of extensive necrotising fasciitis (**figure 2**).

Blood, urine and pus cultures were obtained and fluid resuscitation and broad-spectrum antibiotic therapy were administered (meropenem, vancomycin and clindamycin), according to Internal Medicine consultation. The patient underwent immediate surgical debridement of the necrotic tissues to bleeding edges, under general anesthesia.: Necrotic tissue was extended to coccygeal bone, left gluteus maximus muscle, anal sphincter muscle, levator ani muscle, perineum and left scrotum region (**figures 3, 4**). Samples were collected for culture and the wound was left open.

Figure 2. *Preoperative CT scan SHOWING gas around the sacrum, rectum and retroperitoneum*

Figures 3, 4. *Intraoperative image demonstrating surgical debridement of the (1) left gluteal and (2) scrotum region. There are two points in left gluteal region which were debrided due to infection (arrows)*

Figure 5. *At 16th postoperative day plastic surgeons , wound reconstruction by using skin flaps by plastic surgeons was performed under general anesthesia with free subcutaneous flap*



Postoperatively, the patient remained afebrile and we repeat dressings on surgical trauma twice a day. Pus cultures revealed Proteus mirabilis and Pseudomonas aeroginosa. On the 4th postoperative day, we observed the appearance of necrosis on the left testicle and the patient was transferred to the operation room, where he underwent left orchiectomy under general anesthesia. On the following days, repeated debridement of the surgical trauma and administration of vacuum-assisted closure device administration had as result the progressive patient's recovery, who was transferred to the plastic surgeons' department on the 14th postoperative day. Two days later, plastic surgeons reconstructed the surgical trauma by using skin flaps under general anesthesia and the patient was discharged on 32rd postoperative day (**figure 5**).

Discussion

FG is a type of necrotizing fasciitis affecting usually the perineum and scrotum. FG is a life-threatening disease and is characterized by a very rapid progression and mortality rate ranging from 3% to 67% [1].

Bacterial infection spreads quickly from the urinary tract (or the perianal, abdominal, or retroperitoneal tissues), often following a trauma. The gangrene is due to thrombosis of small blood vessels below the skin and the most frequent predisposing factor is diabetes mellitus. The prevalence of diabetes mellitus in patients with any type of NF ranges between 40 and 60%. Other common co-morbidities include liver cirrhosis, chronic heart failure, obesity, alcohol abuse, immunodeficiency, systemic lupus erythematosus, Addison's disease, pre-existing hypertension, and peripheral vascular disease [3, 4].

The microorganisms that tend to be found in FG are species that normally exist in the perineum and genitalia, that consist aerobic and anaerobic bacteria. The most commonly isolated aerobic microorganisms are Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus, while the most commonly isolated anaerobic microorganism is Bacteroides fragilis. Other organisms include, Enterococcus, Pseudomonas and Proteus species as in our case [7, 8].

Furthermore, several cases of severe sacral pressure ulcer-induced FG extending to the pelvic cavity and retroperitoneum have been reported. Two infection routes have been reported for pressure ulcer-induced FG: (a) the sacral pressure ulcer becomes advanced, forms a retroperitoneal abscess, and finally induces FG; and (b) the sacral pressure ulcer directly induces FG [5, 6].

Many underlying conditions have been reported to be associated with FG, such as immunosuppression, trauma, and genitourinary infections, malignancy, chronic steroid use, cytotoxic drugs, lymphoproliferative disease, malnutrition and human immunodeficiency virus (HIV) infection [9]. In addition, sacral pressure ulcers can cause FG. Retroperitoneal necrotizing fasciitis is uncommon, and it was reported that the primary sources of infection in such cases are chronic pyelonephritis, diverticulitis, colonic cancer, and perianal abscesses [9].

Patients with NF usually present with the classic triad of symptoms: local pain, swelling, and erythema [10].

However, in the fulminant form of disease, the patient is critically ill with signs and symptoms of septic shock and multiple organ dysfunction, along with extensive necrosis of soft tissue. In this case, the clinical picture deteriorates rapidly within a few hours [11].

Imaging investigation can help to establish the diagnosis of NF. Although plain radiography has low sensitivity and specificity, it is capable of showing gas in the soft tissue, in almost half of all patients. CT and MRI are more sensitive and specific than plain radiography. A CT scan can show the extent of tissue infection, fascial swelling, inflammation, and gas formation [11].

There are a lot of researches that suggest the effect of combining hyperbaric oxygen therapy with conventional therapy that offers advantages in the management of Fournier's gangrene [12, 13].

Treatment consists of rapid and aggressive surgical debridement of the necrotic tissue under general or spinal anesthesia, suprapubic catheter insertion, removal of foreign bodies, and fluid resuscitation. Broad-spectrum antibiotics are given empirically and according to the result of the cultures. Serial necrotic tissue debridement may be needed [14].

Conclusions

A rare and severe case of fg due to neglected gluteal pressure ulcer extending to the scrotum is presented. FG was treated with emergent debridement and continuous wound cleansing, coordinate with the use of wound V.A.C which proved to be very beneficial for patient's recovery. The authors consider that the combination of emergently debridement with wound cleansing, vacuum devices obtain good infection control and reconstruction. Over the last decade, there has been increasing awareness of the importance of the multi-disciplinary team (MDT) in the management of a number of surgical conditions.

Περίληψη

Η γάγγραινα Fournier είναι μια ασυνήθης νεκρωτική λοίμωξη των περιτονιών των έξω γεννητικών οργάνων και του περινέου , πολυμικροβιακής συνήθως αιτιολογίας. Στόχος μας είναι να παρουσιάσουμε μια σπάνια περίπτωση εκτεταμένης FG λόγω του παραμελημένου έλκους στον αριστερό γλουτό και να υπογραμμίσουμε τη σημασία της πρώιμης παρέμβασης και της επιμελής μετεγχειρητικής φροντίδας, καθώς και τη σημασία της συνεργασίας της πολυεπιστημονικής ομάδας (MDT) στη διαχείριση της εκτεταμένης νεκρωτικής λοίμωξης.

Λέξεις ευρετηριασμού

Γάγγραινα, Νεκρωτική απονευρωσίτιδα, Εσχάρα, Έλκος κατάκλισης

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Review

Ureteral stents. A review of the different polymeric types, their characteristics and their connection to stent related symptoms

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Abstract

Introduction: The purpose of this article is to review the different available polymeric stent types. Furthermore, an analysis of their basic bioqualities is carried out and a correlation of their physical characteristics (length, size, material) with stent related complications is investigated. A thorough Medline, PubMed and literature research was performed for this review.

Results: The available reviews and articles associating materials to stent related symptoms provide conflicting results and most of the studies don't clearly state the characteristics of the materials used. Moreover, although there are a significant number of studies in the literature concerning stent length and diameter, results about their association to stent related symptoms, are also conflicting.

Conclusion: Many studies suggest that an association exists, between the different types and the characteristics of the stents used and stent related symptoms. Nevertheless, current evidence is not sufficient to support this statement and further investigation is needed.

Themistocles Ch. Bellos, Nikolaos A. Kostakopoulos, Athanasios G. Papatsoris
Ureteral stents. A review of the different polymeric types, their characteristics and their connection to stent related symptoms
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Ureteral stents. A review of the different polymeric types, their characteristics and their connection to stent related symptoms., p. 46-54

Introduction

Key words
ureteral stents,
stent related symptoms,
stent materials,
stent properties

Ureteral stents have become an important part of urologic practice since Finney on the one hand and Hepperlen and colleagues on the other, first described the double-J® (American Cystoscope Makers [ACMI], Southborough, MA) stent and single-pigtail stent, respectively [1, 2, 3]. Stenting of the urinary tract began as an adjunct to open surgery to facilitate upper tract drainage or to align the ureter. Gustav Simon performed the first reported case during the 19th century by placing a tube in the ureter during open cystostomy, and Joaquin Albarrano created the first catheter intended for use in the ureter in the early 1900s. Although vulcanization of rubber was first reported in 1839, early catheters were constructed from fabric coated with varnish [4].

The indications and materials used for stenting were summarized by Davis [5, 6] while Macaluso summarized the state of the art for external urinary diversion [7]. Zimskind et al suggested the insertion of long-term indwelling silicone rubber ureteral splints into the ureter to bypass obstruction since he noted the inconvenience of an external device [8]. Subsequently there have been refinements in catheter placement and design [9, 10, 11]. The issue of internal coil retention was addressed by Gibbons, Mardis, Finney and Hepperlen [1, 12, 13, 14]. Since that time, there have been many advances in design as well as in materials, which have been directed in improving biocompatibility and reducing stent-related morbidity. [3]

Stent properties

The basic properties of a ureteral stent have been reviewed by Mardis et al.[15] "Memory" produces the ability to maintain the position within the ureter and is a consequence of polymeric crosslinking, which results from physical or chemical bonding between macromolecular chains. [3, 15].

"Durometer" refers to the strength of the memory, which can be varied within the same material and depends on the type of cross-linking used. As cross-linking increases, the durometer changes from soft to hard. [3, 15] Elasticity allows the shape of the stent to be manipulated [3, 15].

The elongation capacity is the percentage of elongation at stent breakage. Thermoplastic elastomers, such as polyurethanes and a variety of other proprietary copolymers, generally have more elongation capacity than thermoset elastomers, such as silicone [15].

Biodurability refers to the ability to exist within the body without degradation of stent structure and function. Stent degradation within the urinary tract has been reported for polyethylene, polyurethane, and silicone internal ureteral stents [15].

Biocompatibility is the utopian state at which the material present within the ureter has no significant effect on the interface between itself and the urothelium, such as the ability to resist encrustation and infection, thus producing no symptoms and complications.

The biocompatibility of a stent may be enhanced with use of hydrophilic polymers that have low protein absorption and low bacterial adherence [16].

The coefficient of friction describes how easily a stent is passed or exchanged. Applying a hydrophilic coating reduces the surface coefficient of friction [3, 15].

Radiopacity refers to the ease of stent visualization during fluoroscopy. All stents are radiopaque and some contain fillers that further enhance radiopacity [3, 15].

Stent types

A double-J stent (the original, silicone, closed tipped stent) has an open hook configuration at either end of the ureteral stent, and a double pigtail stent has a full retentive coil at either end [1].

All stent manufacturers produce a basic double-pigtail stent, which have a variety of names, designs, and compositions. Standard double-pigtail stents must be sized correctly because those that are too long can cause bladder irritation, and those that are too short can migrate up the ureter. A 24-cm ureteral stent is well suited for most adults, but should be individualized according to the ureteral length of the patient. Multiple-coil stents were designed to meet the "one size fits all" concept, that leave redundant length in the bladder coiled, so the trigone is not irritated [17].

Some stents are manufactured with a nylon suture attached to the distal end, which can be left at the urethral meatus, allowing for removal after short term drainage without the need for repeat cystoscopy [17].

Open-ended ureteral stents have no coils and thus are not suitable for long-term urinary drainage. However, they can be secured externally to provide temporary drainage. Open-ended stents are useful in helping

Table 1 *Basic terms of materials used in stents*

Terms	Definitions
Biomaterial	**A substance natural or synthetic, which at some stage in treatment interfaces with tissue**
Polymer	A substance consisting of molecules characterized by the repetition of one or more types of chemical units (monomers)
Copolymer	A substance formed of repeated sequences of polymers with differing chemical structure (a.k.a blocks)
Elastomer	A macromolecular polymer that can reform to an original configuration after substantial deformation
Thermoplastic	A polymer that can be softened by heating and hardened by cooling and that in soft state can be shaped by molding or extrusion
Thermoset	A polymer that can be treated by heat to the extent that it is substantially non meltable

Mardis H.K., Kroeger R.M., Morton J.J. et al.: Comparative evaluation of materials used for internal ureteral stents. *J Endourol* 7: 105-115, 1993.

to direct and advance a guidewire into a ureteral orifice as well as assist in collecting upper urinary tract urine samples and permitting retrograde pyelography. They are commonly placed intraoperatively to identify ureters to avoid inadvertent injury during abdominal or pelvic surgery [17].

Other types of stents include: Transilluminating ureteral stents, spiral stents, dual durometer stents, and magnetic stents [3].

Dual durometer stents incorporate a smooth transition from a firm biomaterial at the renal end to a soft biomaterial at the bladder end. They have long tapered tips at the renal end and are coated with a hydrophilic-bonded hydrogel that decreases their coefficients of friction. Their firm proximal end and hydrophilic coating allow for ease of access through the ureteral orifice and facilitate negotiation past obstruction, and the soft distal end results in decreased patient discomfort [3].

Stent materials

There are three main materials used for ureteral stents in clinical practice: silicone-based, polyurethane based and a third class, percuflex.

Silicone is composed of alternating silicone and oxygen atoms and has a high coefficient of friction, making it difficult to use when negotiating strictures or tortuous ureters. [16] Proprietary modifications to silicone led to the development of C-Flex, a silicone-modified styrene/ethylene/butylene block thermoplastic copolymer. [4]

Polyethylene was the first synthetic polymer used to fashion ureteral stents. It consists of polyolefin and is flexible, odorless, translucent, and nonreactive in the body. The stiffness of polyethylene made it useful for the management of ureteral strictures, but it was found to promote protein deposits, leading to an increased likelihood of crystalloid adherence, encrustation, and infection [18].

Polyurethane, a common generic class of condensation polymers derived from polyisocynate and a polyol has been used in an effort to combine the flexibility of silicone with the stiffness of polyethylene. Polyurethane is highly versatile and inexpensive [19].

Percuflex (Boston Scientific, Natick, Mass) is a proprietary olefinic block copolymer developed by Boston Scientific/ Microvasive that becomes soft and flexible at body temperature. This material also has excellent memory and strength [4].

Tecoflex (Thermedics, Woburn, Mass) is a proprietary aliphatic thermoplastic polymer that is not silicone based. Stents made with this material have a smooth surface and a comparatively large inside diameter. This material allows for ink labeling instead of laser labeling, which may theoretically decrease the likelihood of encrustation from the rough surface created by the laser [4].

Pellethane (C.R. Bard, Covington, Ga) is a proprietary copolymer from Bard used in their Inlay stents. Flexima is a newer proprietary material (Boston Scientific/ Microvasive) designed to resist buckling during insertion. Vertex (Applied Medical, Rancho Santa Margarita, Calif) is a proprietary material from Applied Medical [4].

Bioabsorbable polymeric materials are designed to retain their tissue-supporting properties for defined periods. After placement, they are gradually biodegraded into tissue-compatible compounds that are absorbed and replaced by healing tissue [20].

These stents will be most useful for clinical situations in which temporary upper urinary tract drainage is desired. Bioabsorbable materials used in urologic stents are high-molecular-weight polymers of polylactic and polyglycolic acid. [20] However, these stents have less

favorable biocompatibility than standard stents because of inferior healing of the incised ureteral musculature. Temporary ureteral drainage stents (Boston Scientific/ Microvasive) have been shown to dissolve in a benign fashion [21].

Metallic, superalloy titanium and nickel/titanium are materials currently used for permanently implanted stents, such as the Wallstent or Memokath 051 to relieve conditions such as malignant obstruction and ureteral stricture [22, 23, 61, 62]. The problems associated with metal stents include collagenous ingrowth, hyperplastic epithelium, distal ureteral narrowing, intense fibrosis, and subsequent obstruction [24, 26, 61, 62]. The **Memokath 051™** (PNN Medical A/S, Kvistgaard, Denmark) has better patency rates, but also higher migration rates, than other metallic stents [61].

The development of tissue-engineered stents is still under development. Cartilaginous stents have been successfully created in vitro and in vivo using chondrocyte-seeded polymer matrices [25].

Biodegradable Ureteral Stents have mainly been tested in animal models and show promising results. In recent studies conducted in pigs, two biodegradable copolymers with different degradation rates were used. Polymer-I was Glycomer-631™ and Polymer-II was pure polyglycolic acid PGA. Polymer-II was only used for the central section, and was braided with Polymer-I. The distal and proximal anchoring systems were manufacture exclusively with Polymer-I, since it has better biomechanical characteristics and a slower degradation rate. This allows the stent to remain for 3-6 weeks. The ureters receiving biodegradable stents showed no evidence of vesicoureteral reflux (VUR). Degradation took place in a controlled and predictable fashion from the third to the sixth week, and no obstructive fragments appeared. Significant advantages of these stents were absence of VUR and of ureteral orifice damage. Also they always maintained distal ureteral peristalsis [63].

The goals of **coating ureteral stents** are to facilitate passage over a guidewire beyond an obstruction and to reduce or eliminate biofilm formation and encrustation. The main types are the hydrophilic coatings, phosporylcholine and heparin coatings.

Hydrophilic coatings consist of nondissolvable polymers that swell on contact with water and retain water within their polyanionic structure that layers on its surface. The surface water not only reduces the coefficient of friction, but also contributes to biocompatibility by reducing frictional irritation and cell adhesion at the biomaterial- urothelial interface [4]. Some hydrophilic coatings (e.g. polyvinylpyrrolidone) have been shown in vitro to decrease both hydroxyapatite encrustation and adherence of a hydrophobic Enterococcus faecalis isolate [27].

Phosphorylcholine-coated stents have been shown to be less vulnerable to encrustation and colonization by bacterial biofilm than the uncoated stents at 12 weeks after implantation [28]. According to recent studies, heparin-like coatings can reduce biomaterial encrustation, while heparin-coated stents have been shown absence of biofilm formation or encrustation after 6 weeks. [29] A new approach involves coating biomaterials with oxalate-degrading enzymes derived from Oxalobacter formigenes. [30] Furthermore, the silver nitrate coating was effective in preventing biofilm formation and stent encrustation [4].

Drug eluting metal stents (DESs) have been extensively used in coronary and vascular disease. This type of stents has been proven to provide significantly lower restenosis rates due to the reduction of neo-intimal hyperplasia in comparison to the traditionally used bare metal stents (BMSs). Although the initial results were promising, long-term experience revealed significant complications, which are mainly attributed to stent-related hyperplastic reaction compromising stent patency. A variety of different stent designs, pharmacological agents and coatings have been introduced and are under experimental as well as clinical evaluation. [64] Ureteral stent impregnated with Triclosan a broad spectrum antibiotic by Boston Scientific Corporation (BSCI) was assessed both in vitro and in vivo for its ability to inhibit bacterial survival, biofilm formation and infection development associated with the device. [65] Moreover, polymer-free and bioabsorbable DESs are under development with promising perspectives for the future. The use of DESs in the ureter and urethra has been limited to few experimental studies. Further experimental investigation will decide the potential use of DESs in clinical trials [64].

Ureteral stent related symptoms

Ureteral stenting is applied to prevent the obstruction of the kidney by residual stone fragments, edema and hematoma, to avoid urine extravasation and to relieve pain [31, 32] Some of the indications are summarized in **table 2**.

Trigonal and renal irritation by ureteral stents, vesicorenal reflux through the stent, stent size, stent length, stent position and stent materials are potential factors

Table 2 *Indications for the use of ureteral stents*

1. Ureteral surgery
a. Preoperetively
Stone bypass, adjunct to ESWL, ureteral dilatation prior to ureteroscopy or balloon/wire endopyelotomy or endoureterotomy
b. Postoperatively
Adjunct to ureteroscopy, percutaneous nephrolithotomy, endopyelotomy, endoureterotomy and various open/laparoscopic ureteral operations
2. Ureteral obstruction management
a. Intrinsic
Stone disease, strictures, post instrumentation, oedema, fistulas, tumors
b. Extrinsic
Retroperitoneal neoplasms, retroperitoneal fibrosis, pregnancy, hydronephrosis

Mardis H.K.: Self retained internal ureteral stents. *J Urol.* 1978 Oct; 120:4, pp. 512.

for ureteral stent-related symptoms [33, 34] while principal sources of patient discomfort are a long intravesical segment, inefficient drainage, displacement, and stiffness of the ureteral stent [35].

Pain, lower urinary tract symptoms [frequency (60%), urgency (60%), dysuria(40%)] , flank pain, body pain, hematuria (54%), and fever are usually signs of early complications related to double-J stents [36, 37]. More than 80% of the patients report significant stent related pain affecting daily activities while 78% will report irritative voiding symptoms. Stent related flank pain (25%) is likely due to reflux of urine up the stent during increased intravesical pressures while voiding. As pressure is transmitted up the stent, intrarenal pressures rises, causing pain and discomfort in the flank. This phenomenon is sometimes called the "water hammer". Stent removal can result in pain and LUTS due to irritation of bladder mucosa [38].

Hematuria or gross hematuria immediately after stent placement is common and usually self-limiting, while microscopic hematuria may be present while the stent is still in place. It can be a symptom of uretero-arterial fistula, an uncommon but severe complication of stent placement. It often presents with intermittent gross hematuria and massive hemorrhage during stent exchange. Predisposing factors for fistula formation include: having a stent for longer than one year (even with routine changes), previous pelvic surgery, radiation therapy and underlying vascular disease [38].

Stent related urinary tract infections are reported in 20-30% of patients which will occur despite the use of prophylactic antibiotics. They are difficult to diagnose because of the similarities with simple discomfort due to stent placement. The greater risk factor is long stent indwelling time, with bacteria rates less than 20% in most series at 1 month rising to more than 40% after 3 months. Rates of colonization were much higher than bacteriuria and also increased precipitously with longer indwelling times. [38] In a report there were found bacterial colonies in 44% (25 of 57) of patients with stents. Of the multiple pathogens identified, Enterococcus species (6 of 25) was the most common, followed by Escherichia coli (5 of 25). After short-term antibiotic prophylaxis, the bacteria did not colonize within the first 2 weeks of stent placement. However, the colonization rate increased as the duration of the stent placement lengthened. Colonization of the stent was followed by colonization of urine [39]. Thus it would be prudent to change stents more frequently in patients with recurrent UTI [38] Infections and bacterial colonization are caused by the formation of biofilms and encrustation of the stent. The processes provide bacteria with an environment protected from antibiotics. Dwell time, a history of diabetes, female gender, chronic renal failure and pregnancy are also risk factors for colonization by bacteria [38].

Possible late stent complications include stent migration, encrustation, stone formation, and fragmentation. Stent occlusion may be frequent and requires simple catheter exchange. [36] Other complications include poor work performance and sexual dysfunction [33].

To assess ureteral stent-related symptoms, Joshi et al. described and validated the Ureteral Stent Related Symptom Questionnaire (USSQ) in 2003 [40]. This self-administered questionnaire includes questions in six sections: urinary symptoms, body pain, gen-

eral health, work performance, sexual matters, and additional problems. The total score is the sum of all questions. This questionnaire can define and compare stent-related symptoms [41, 42]. This questionnaire has been validated in different languages to standardize the ureteral stent-related symptoms in the literature [33].

The cause of encrustation is multifactorial. Common risk factors for stent encrustation are long indwelling time, urinary sepsis, history of stone disease, chemotherapy, pregnancy, chronic renal failure, and metabolic or congenital abnormalities.[36] In order to avoid encrustation, it has been reported that a time period of between 2 and 4 months is considered optimal for double-J stent removal or replacement [17, 38, 43].

Migration is an uncommon complication. It can occur proximally toward the kidney or distally toward the bladder. Factors related to distal stent migration include shape and stent material. Stents with a full coil are less prone to migrate than those with a J-shape, and stent materials with great memory, such as polyurethane, are less prone to migrate than those with less memory, such as silicone. [44] Conversely, proximal migration occurs when the stent is too short for the ureter; an adequate choice of the stent length is therefore recommended [45].

Since 1970s stent migration is an uncommon problem with 2-8% incidence, even more so proximal migration (1-4%) [38].

Spontaneous fracture of an indwelling double-J stent is rare but can occur, so stent exchange every 6 months is recommended by the manufacturer [46]. The diagnosis for the patient who presented with this complication was revealed by the smooth stretching on the stent. The clinical presentation of a fragmented ureteral stent may vary, with septic, irritative, and hemorrhagic symptoms [47]. Various causes were proposed to explain the stent breakage: fragmentation of a stent has been attributed to the hostility of the urine. Interaction with urine and extensive inflammatory reaction in situ may play an important role in the initiation and promotion of degradation. [48] Several studies showed that long-indwelling stents mostly appear in a fragmented state; however, Mardis and Kroeger [49] suggested that fragmentation occurs at a site previously allowed to kink during stent insertion. Kinking during stent insertion must therefore be avoided.

In a study conducted by Zisman and colleagues, [50] all breakage lines passed through the side holes, suggesting that this area is a weak point conducive to kinking and may lead to fragmentation. Another factor associated with stent fragmentation is stent composition. There is no consensus on what is the ideal material for ureteral stents. Silicone stents may be more advantageous than polyurethane stents due to the lower risk of calcification and prolonged maintenance of tensile strength for up to 20 months [22]. However, these theories cannot explain why some stent fragmentations occur early following stent insertion. In the study by Kumar and associates [23], a few stents had fragmented into multiple pieces over a mean indwelling time of only 3.5 months.

Sexual dysfunction is also common in the context of ureteral stents, even if under reported or under recognized, it was recognized in 32-86% of patients with indwelling stents. Females report this symptom more readily due to the distress of having a foreign body in the bladder [38].

Correlation between stent materials and complications

Polyurethane has been shown to induce more epithelial ulceration and erosion than other materials. It has limited durability and demonstrates slow in vivo biodegradation [19].

Silicon is nonirritating and resistant to encrustation. However, silicone stents migrate easily and have poor mechanical strength. [16] The partial silicone composition of C-Flex makes these stents softer than polyurethane and theoretically less likely to develop encrustation [4]. It has good biodurability and biocompatibility however larger stent diameters (7 or 8 Fr) are required to maintain a good urinary flow [15].

Percuflex has long term biodurability and biocompatibility [15] Marx and associates have shown that placement of a stent within a canine ureter produces local reactions (oedema, inflammation, epithelial hyperplasia, and ulceration with erosion).Those reactions were mild around C-flex, silicone and polyurethane. It was however nonexistent around Percuflex [51, 52].

Hydrophilic materials (hydrogel coated) are more biocompatible and resistant to encrustation [51]. However there are no currently available materials that avoid biofilm formation and encrustation completely [38].

The first trial assessing the influence of stent rigidity was published by Proyor et al. The authors found no difference in stent- related symptoms (SRS) for 4 stent types with different rigidity [37, 53]. In 1995, Lennon et al reported on a higher incidence of dysuria, renal and suprapubic pain in patients with firm stents compared to those with soft ones with a randomized trial of 155

patients. However, they did not find differences in the aspects of urgency, dysuria or hematuria [37, 54].

Correlation between other stent characteristics and complications

A number of studies have looked at ways to improve stent related pain and voiding dysfunction, which is caused by trigonal irritation. Patients with the distal coil crossing the midline of the bladder report more pain, voiding symptoms, decreased work performance, worsened sexual function, and more analgesia requirements than patients with appropriately placed stents. [38] Overall stents that cross the midline, have longer amount of time in situ, and develop urinary tract infections (UTI), have all been associated with patient pain and discomfort due to the caliceal position of the upper renal coils [38].

Stent diameter does not appear to influence the severity of stent related symptoms. A larger sized diameter stent does not appear to cause more symptoms of pain, hematuria or even LUTS. A number of studies have compared various stent sizes ranging from 4.8 Fr up to 14 Fr endopyelotomy stents, and have shown that symptoms do not improve even when smaller diameter stents are used [38, 55, 56, 57], while other studies suggest that with larger diameters there are increased symptoms [58] particularly affecting the pain levels and patient comfort but not the rest of the stent associated symptoms [59]. Among the risk factors for proximal migration of the stents are smaller diameter stents (4.8 Fr are more likely to migrate or dislodge than 6 Fr). Other include indwelling time, shorter length or improper stent positioning. [38] Despite appropriately placing and sizing the stent, patients will still experience stent related urinary symptoms and pain [38].

The use of stents carrying a suture string is sometimes used to facilitate the extraction of the stent. In a systematic review by Dellis et al. non-string stents caused less stent related pain in cases of stent in situ. On the contrary, string stents caused less pain at extraction. Stent dislodgement was more frequent in the string group. There was no difference between the groups concerning the rate of UTIs [60].

Conclusion

Although significant advances in basic science research involving biocompatibility issues and biofilm formation have been achieved, SRS remain problems with stents in the urinary tract and therefore limit their long-term use. The perfect stent from the ideal materials is yet to be produced so urologists must choose the most suitable stent for every patient and each set of parameters.

Περίληψη

Εισαγωγή: Ο σκοπός του άρθρου είναι να ανασκοπήσει τα διαφορετικά είδη πολυμερικών stent. Επίσης, αναλύονται τα βασικά βιολογικά και φυσικά τους χαρακτηριστικά (μήκος, μέγεθος, υλικό) και μελετάται η συσχέτισή τους με τις επιπλοκές από την χρήση των ουρητηρικών stent. Για τη συγγραφή της ανασκόπησης διενεργήθηκε μια εκτενής αναζήτηση στο PubMed, Medline και σε συγγράμματα.

Αποτελέσματα: Οι υπάρχουσες μελέτες που συνδέουν τα υλικά των stent με τα συμπτώματα που προκαλούνται από την χρήση τους, προσφέρουν αντικρουόμενα αποτελέσματα και οι περισσότερες μελέτες δεν δηλώνουν ξεκάθαρα τα χαρακτηριστικά των υλικών των ουρητηρικών καθετήρων που χρησιμοποιήθηκαν. Επίσης, παρόλο που υπάρχουν αρκετές μελέτες στη βιβλιογραφία, αντικρουόμενα αποτελέσματα προκύπτουν αναφορικά και με τη διάμετρο και το μήκος των stent, σε σχέση με τις επιπλοκές τους.

Συμπέρασμα: Αρκετές μελέτες υποστηρίζουν πως υπάρχει συσχέτιση μεταξύ των διαφορετικών τύπων ουρητηρικών αυτοσυγκρατούμενων καθετήρων που χρησιμοποιούνται και των συμπτωμάτων που προκύπτουν από αυτά. Παρόλα αυτά, τα μέχρι τώρα δεδομένα δεν επαρκούν, για να υποστηρίξουν αυτή τη συσχέτιση και περαιτέρω διερεύνηση είναι απαραίτητη.

Λέξεις ευρετηριασμού

ουρητηρικοί αυτοσυγκρατούμενοι καθετήρες, συμπτώματα σχετιζόμενα με τα στεντ, υλικά στεντ, ιδιότητες στεντ

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GDPR Issue

The new General Data Protection Regulation: practical implications in daily practice

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Abstract

With the introduction of the General Data Protection Regulation (GDPR), the use of personal data is limited and protected in medical practice. Key elements of the new regulation include the need for clear and affirmative consent by the patient concerned, destruction of data if storage is no longer necessary for the initial purpose, the right to be forgotten, the right to obtain rectification of personal data, the right of the patient to transfer personal data to another institution and the right of the patient to be informed when data have been hacked. This article explains the consequences of the new regulations in a practical manner for private practices, community hospitals, university hospitals and medical institutions.

In an age of increasing use of social media, big data analyses and evolving technical possibilities to communicate the hazard is that we may lose control over our privacy. The new law has been set up to protect the individual patient against this in a transparent manner. In scientific research and disease or implant registration, this has major consequences for health organisations. In daily clinical practice, some simple adjustments usually are sufficient to comply with this new law.

Introduction

On 25 May 2018, the General Data Protection Regulation (GDPR) of the European Union was effectuated (1). With the introduction, a huge media campaign was executed and stellar fines were announced if organizations would not meet the new criteria. Protection of personal data is of particular importance in the health sector, and the basic requirement of confidential-

Key words
General Data Protection Regulation, general urology, privacy, consent, registration, audit

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ity of diagnostic and therapeutic information requires special attention in the digital environment. The new GDPR implies that all health organizations processing personal data must be able to prove that they comply with the rules. So, our full attention was drawn, but what are the consequences for our daily work as physicians?

Key elements

Although the new GDPR applies to all domains of the public and private sectors, some specific derogations (legal exemptions) are defined for data concerning health, meant to protect the rights of patients and confidentiality of their personal health data (2). The main purpose of the GDPR is to define and update several basic rights of patients regarding control of and access to their personal data, and to implement common rules for data protection in all member states. Key elements of the new regulation include the need for clear and affirmative consent by the patient concerned; destruction of data if storage is no longer necessary for the initial purpose or after withdrawal of consent by the data subject ('the right to be forgotten'); the right to obtain rectification of his/her personal data; the right of the patient to transfer personal data to another institution ('data portability'); the right of the data subject to be informed when his/her data have been hacked.

The GDPR applies to data concerning health and genetic data. Health data are personal data related to the physical or mental health of a person, including the provision of health care services, which reveal information about his or her health status. Genetic data are defined as personal data relating to the "inherited or acquired genetic characteristics of a person which give unique information about the physiology or the health of that natural person.

Consent

The new regulation explains that consent must be explicit and unambiguous, that is to say, it needs to be given through a clear affirmative act. It has to be freely given, and be an "unambiguous indication of a data subject's agreement to the processing of their personal data". This can be written, electronic or oral. Silence or inactivity (e.g., a pre-ticked box) cannot be considered as consent anymore. For example, a written statement in the patients' file that "he was informed and stated that he agrees to share his personal data" is agreeable, but a disclaimer on the website of the institution that "by making an appointment it is assumed that the patient agrees in sharing his personal data" is not. Moreover, patients should be informed on how to withdraw consent before giving it.

Sharing data

In healthcare, the rules on data protection allow patients' data to be processed as long as the person who does the processing is bound by professional secrecy. This means that healthcare professionals and healthcare institutions do not have an obligation to ask systematically for patients' consent before they can use it. However, they are bound by the principle which ensures the exemption from consent is proportionate and limited to what is necessary for the patients' health and social care.

This greater flexibility in healthcare to use data without consent can be positive and efficient in several respects, as it means that there is more possibility for communication of data within a patients' healthcare team which is important for integrated care. Therefore, the GDPR is less burdensome for healthcare workers. For example, if a patient is presented in a transmural (video)conference, no explicit consent is required. Also, if a general practitioner needs to be informed about the health of the patient, or if a patient is referred to another hospital and the colleague needs to be informed, no consent is required. Even if the urologist needs information from physicians from other institutions who were consulted earlier by the patient, no consent is required. An important safeguard for the patient is that personal data can only be collected, used and shared by a person subject to professional secrecy.

Research

Data protection law only applies to personal data—that is, data that does directly or can indirectly identify an individual. Other data are still fully available for medical research. In the ideal (legal) world, the subjects' data for research need to be anonymized. In practice, this is not feasible, because these patients' data require some kind of reversibility (3). To anonymize the data, the simple deletion of name and address is not sufficient. In fact, truly anonymized data cannot be linked back to an individual, which means that verification of data is not possible by any means. Therefore, some kind of reciprocity is required. This is called pseudonymized data. A third party has identifiers removed and replaced

with a unique key code. The researchers do not possess the requisite key code. This key code, if required, can be used to trace the data back to an individual, enabling any safety concerns to be acted upon and for data to be verified. Pseudonymized data must be treated as precious as personal data. That is because of the increased vulnerability of data these days: if the key code is hacked, then all the data can be linked to an individual once more.

A point of debate is if an exemption should be made from the obligation to always seek consent before using patients' data for research in cases where asking for consent or re-consent is impossible. The European Patients' Forum, an umbrella organization that works with patients' groups across Europe, states that although informed consent is a fundamental right and should be the rule, in some cases exemptions to consent for sharing data are needed to make research possible. In these circumstances, other safeguards need to be in place to ensure patients' rights.

Patients' rights

The right to access the medical record is explicitly mentioned in the new Regulation (4). The institutions' data-controller can charge a fee for administrative cost of providing the data when the request was done "repetitive or unfounded." The patient can request to receive a copy of the health data in order to transfer it to another entity or person. There is also the so-called "right to be forgotten". This is applicable in three circumstances: 1. If patients have withdrawn consent and the data controller has no other grounds for processing their data. 2. If there is no longer a purpose for processing it, in accordance with the principle of limited storage and data minimisation. In practice, there is no fixed period mentioned how long the medical file should be kept and it is still to be defined. 3. If the processing is unlawful in the first place, for example when the data controller has made the information public, e.g. online. He has to take reasonable step to ensure other controllers also remove links etc. in order to implement patients' rights. In case of a data leak ("security breach") the patient needs to be informed and updated if «the rights and freedom are at risk." In research, a derogation of the patients' right to access medical information can be possible in cases where it would render impossible or impair the achievement of the purpose of the research. Providing patients with certain information could for example be a problem in a blind trial, or it could come at an important cost when it concerns a large number of participants. Restriction or objection to processing of one's data can also introduce bias in the sample of data used. It is recommended to make a statement on this issue in the Informed Consent form before entering the research trial.

Registration of implants

Many countries started the unique coding and central registration of medical implants for matters of safety. This, for example, could be relevant in the event of a recall. It should always be clear which implants have been used in which patient. These data need to be pseudonymized as well. A complicating factor is that the implants are typically used in many institutions nationwide or even internationally. Therefore, the pseudonymization of the personal data of the patients could be challenging for all parties. For example, for this purpose, The Dutch National Implants Registry recently became effective in The Netherlands. To meet the GDPR criteria, the data are controlled by the Health Care Inspectorate (HCI) for pseudonymization and registration. In case of a recall, individual medical institutions and patients are approached by the HCI.

Audit

For reasons of quality control, audits are frequently executed in our medical institutions. The GDPR considers audit and health care management are a primary use of health care data, directly relevant to the monitoring and improvement of quality of health care. Therefore, it is seen as a primary use of data and requires no encryption of data or a separate consent. In contrary, as stated above, research is considered secondary use of data. Sometimes an audit could be marked as research. For example, if an audit compares health care systems to discover which is most effective, this can also be categorized as research as the practices are not compared to a gold standard, and there is a hypothesis being generated or even tested by finding associations. Therefore, these kinds of auditory survey require pseudonymization as described above.

The GDPR in Greece

In 2016, there were 196 appeals and complaints regarding Medical Personal Data, according to Hellenic official authority statistics. Two of the opinions issued by the Authority were concerning medical queries such

as the legal obligation of pharmaceutical companies to publish all funding to medical doctors and the operation of an online surgery list of hospitals (5). During 2017, there were 293 appeals out of a total of 1751 concerning health issues. The major health opinion issued was concerning the processing of patients' medical data during in vitro fertilisation procedures (6).

Hellenic major healthcare providers generally operate by implied consent to use patient data for direct care, without breaching confidentiality. A minority of clinicians in Greece find the new regulation confusing and intellectually challenging. The implementation of GDPR requires time and attention to detail; that is the reason why some urologists failed to follow and abandoned the application of the new rules. Urologists ignoring these regulations run the risk, at the very least, of damaging their reputation if anyone cares to notice and ask: "Don't you care about privacy?"

Conclusion

In daily practice the new GDPR is explicit on patient's rights and asks an active approach from the physician, e.g. by the obligations to actively ask for consent and to provide information on patients' request. In research, pseudonymization of personal data requires a third party to be involved and could be demanding on the organization and budget. National implant registration needs political support to be organized properly. On request, the health organization should be able to show what action is taken to comply with the GDPR.

In an age of increasing use of social media, big data analyses and evolving technical possiblities to communicate the hazard is that we may lose control over our privacy. The GDPR has been set up to protect the individual patient against this in a transparent manner. In scientific research and disease or implant registration, the GDRP has big consequences for the health organisations. In daily clinical practice, some simple adjustments usually are sufficient to comply with this new law.

Περίληψη

Με τη θέσπιση του κανονισμού για την προστασία των γενικών δεδομένων, η χρήση των προσωπικών δεδομένων στην ιατρική πρακτική περιορίζεται και προστατεύεται. Τα βασικά στοιχεία του νέου κανονισμού περιλαμβάνουν την ανάγκη σαφούς και θετικής συγκατάθεσης του ενδιαφερόμενου ασθενή, την καταστροφή δεδομένων εάν η διατήρηση δεν είναι πλέον απαραίτητη, το δικαίωμα να λησμονηθεί, το δικαίωμα απόκτησης διορθώσεων προσωπικών δεδομένων, το δικαίωμα του ασθενή να μεταφέρει προσωπικά δεδομένα σε άλλο ίδρυμα και το δικαίωμα του ασθενή να ενημερώνεται όταν τα δεδομένα έχουν παραβιαστεί. Αυτό το άρθρο εξηγεί τις συνέπειες των νέων κανονισμών με πρακτικό τρόπο για τα δημόσια νοσοκομεία, τα πανεπιστημιακά νοσοκομεία και τα ιατρικά ινστιτούτα.

Σε μια εποχή αυξανόμενης χρήσης των κοινωνικών μέσων δικτύωσης, μεγάλης ανάλυσης δεδομένων και εξελισσόμενων τεχνικών δυνατοτήτων επικοινωνίας, ο κίνδυνος είναι η απώλεια ελέγχου της ιδιωτικής μας ζωής. Ο νέος νόμος έχει θεσπιστεί για να προστατεύσει τον κάθε ασθενή με τρόπο διαφανή. Στην επιστημονική έρευνα και την καταγραφή ασθενειών ή εμφυτευμάτων, αυτό έχει σημαντικές συνέπειες για τους οργανισμούς υγείας. Στην καθημερινή κλινική πρακτική, μερικές απλές προσαρμογές συνήθως αρκούν για την συμμόρφωση με αυτόν τον νέο νόμο.

Λέξεις ευρετηριασμού

Κανονισμός για την προστασία των γενικών δεδομένων, γενική ουρολογία, προστασία της ιδιωτικής ζωής, συγκατάθεση, εγγραφή, έλεγχος

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TECHNIQUE

A video-guide for fluoroscopic access in PNL

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Abstract

Introduction & objectives: Percutaneous nephrolithotomy (PNL) is the treatment of choice for renal calculi larger than 2cm . Since the first description by Fernstrom and Johansson in the 1980s the technique has been continuously modified and improved in order to minimize the incidence of complications and improve the stone free rate. Many ways of gaining access to the pelvicalyceal system have been described over the years. Fluoroscopy is the most widely used technique (86%) for renal puncture although ultrasound-guided, alone or combined with fluoroscopy, CT-guided and endoscopy combined accesses have been described. The objective of this article is to describe different fluoroscopy-guided techniques for renal puncture in a step-by-step educational video.

Materials and methods: We created a high-resolution video with the most frequently used techniques for fluoroscopic pelvicalyceal access. Each technique is presented both in real cases and animation video as well in order to be fully understood.

Results: Four techniques are described in the video.

Introduction

Percutaneous nephrolithotomy (PNL) is the treatment of choice for renal calculi larger than 2cm[1]. Since the first description by Fernstrom and Johansson in the 1980s[2] the technique has been continuously modified and improved in order to minimize the incidence of complications and improve the stone-free rate. Many ways of gaining access to the pelvicalyceal system have been described over the years. Fluoroscopy is the most widely used technique (86%) for renal puncture[3, 4] although ultrasound-guided, alone or combined with fluoroscopy, CT-guided and endoscopy combined accesses have been described.

Key words
Percutaneous nephrolithotomy, PCNL, nephrolithiasis, renal stones, kidney puncture

The objective of this article is to describe in a step-by-step educational video different fluoroscopy-guided techniques for renal puncture in prone position.

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Monoplanar access

With the mono-planar technique the C-arm remains perpendicular to the patient's body during the entire operation. No rotation is required and the fluoroscopy, coming from the bottom of the operating table, enters always perpendicular to the patient's body. The surgeon orientates the first plane of his puncture by setting the needle on patient's body, in a fashion parallel to the axis of the targeted calyx infundibulum. The surgeon then moves back the tip of the needle at the entry of the targeted calyx at the level of the skin and initially punctures the skin with a 45 degree angle to the horizontal plane. However, at this point it is not known whether a more steep (< 45°) or wide (> 45°) angle is required to correctly locate the calyx as the needle is advanced inside the body. Without rotating the C-arm this is depended on surgeon's experience as he advances the needle towards the kidney. Cephalocaudal adjustments of the needle are required to identify the correct angle. It is crucial to keep the direction of the needle parallel to the axis of the infundibulum of the targeted calyx while the surgeon makes the aforementioned adjustments. Two signs are crucial to identify the correct angle towards the calyx, first the movement of the renal cortex as the needle enters the kidney and the movement of the calyx just prior entering the pelvicalyceal system[5] (**Figure 1**).

Bi-planar Fluoroscopic access by rotating the C-arm in the long axis of the patient's body (cephalocaudal direction)

With the bi-planar techniques the C-arm is rotated into two different positions radiating the patient's body from two different axes. As a consequence two fluoroscopy planes are created. The first one is perpendicular to the patient's body and it is the same plane as the one described for the mono-planar technique. This plane is oriented by positioning the needle on the skin in a fashion parallel to the targeted calyx infundibulum. The second fluoroscopy plane is used to identify the depth of the needle in relation to the targeted calyx. In the current technique the C-Arm is turned towards the head of the patient, in order to estimate the depth of the calyx.

To better understand the technique a mosquito forceps is attached to the skin at the level of the targeted calyx. As the mosquito is superficial to the targeted calyx its position in relation to the needle will help the surgeon to identify the correct depth. In detail, initially the needle punctures the skin in a 45-degree to the horizontal plane and is advanced approximately 5cm into the patient's body, or depended on surgeon's experience, directly to the desired calyx. Then, the C-arm is rotated 30 degrees towards the patient's head. If the needle is located at the level of the calyx both in the perpendicular and the lateral position of the C-arm then the needle is into the calyx. If the needle and the mosquito move to the same direction (patient's feet) in the fluoroscopy image, it means that the needle is more superficial to the desired calyx and the surgeon needs to readjust it by slightly withdrawing the needle shaft and re-advancing the tip in a more steep (deep) direction. If the needle moves in the opposite to the mosquito direction (mosquito to the patient feet and needle to the patient head) in the fluoroscopy image, it means that the needle is deeper to the desired calyx and the surgeon has to readjust it by slightly withdrawing the needle shaft and re-advancing the tip in a more wide (superficial) angle[6] (**Figure 2**).

Figure 1. *The surgeon orientate the needle parallel to the axis of the calyx's infundibulum. The depth of the puncture is estimated by surgeon's experience*

Figure 2. *Bi-planar Fluoroscopic access in the long axis of the patient's body*

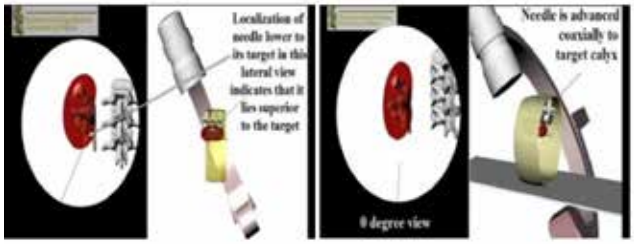
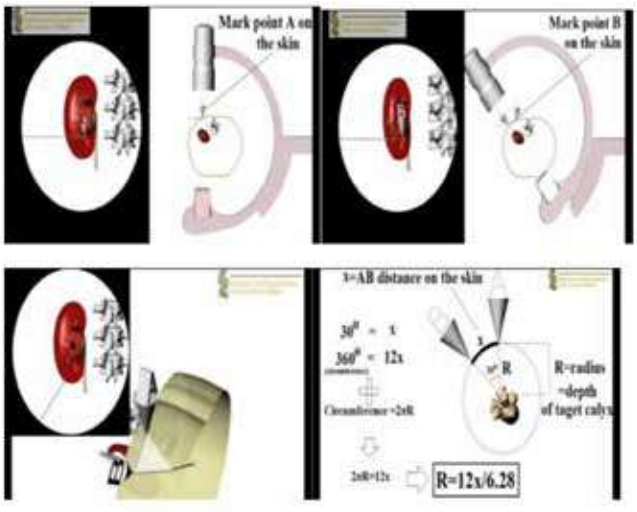


Figure 3. *Bi-planar Fluoroscopic Access Perpendicular to the Long Axis of the patient's body – "Bull's Eye" Technique*

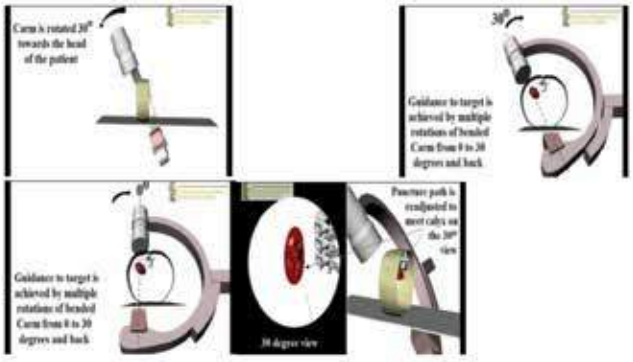
Figure 4. *Triangulation Technique*



Bi-planar Fluoroscopic Access by rotating the C-arm Perpendicular to the Long Axis of the patient's body – "Bull's Eye" Technique

The first step of this bi-planar technique is exactly the same to the first plane described in the two previous techniques. With the C-arm in the perpendicular position the surgeon puts the needle on the patient's skin in a fashion parallel to the longitudinal axis of the desired calyx infundibulum. The correct angle of the puncture line related to the horizontal skin plane, in order to appropriately target the calyx, is determined by rotating the C-arm 30 degrees towards the surgeon site. This lateral fluoroscopy plane determines the correct skin-puncture angle when the calyx, the needle tip, the needle shaft and the needle hub are shown as a single dot at the fluoroscopy screen (Bull's eye). This means that the calyx and the needle are in-line. Next, the surgeon advances the needle towards the desired calyx with the fluoroscopy remaining at 30 degrees

Figure 5. *Triangulation Technique in clinical practice*



and keeping the angle and the "dot" stable. What it is not known during this step is the exact depth that the needle should be advanced in order to enter the calyx. To identify the depth, the C-arm is rotated back to the perpendicular position or minus 10 degrees to the perpendicular position. Fluoroscopy at this position identifies the location of the tip of the needle. When the tip is at the center of the calyx then the needle is in the pelvicalyceal calyx. When the needle has not reached the tip of the calyx the surgeon has to advance its tip until it is into the calyx. When the tip of the needle is advanced beyond the wall of calyx the surgeon has to withdraw under fluoroscopy the tip of the needle until it is located inside the calyx. During this technique the surgeon may radiate his/her hands. In order to avoid radiation exposure the fluoroscopy field may be coned or the surgeon may use mosquito forceps or specifically designed plates to guide the needle[7] (**Figure 3**).

Triangulation Technique

This technique is based on the fact that if you have the location of a target in two fluoroscopic planes you can calculate the exact target's location through the puncture site.

With the C-Arm at 0° the aimed calyx is marked as point "A". Then the C-Arm is turned at 30° towards the surgeon and the aimed calyx is marked as point "B". The distance between "A" and "B" (x) can be measured. The two marked points and the calyx form a theoretical circle. The radius of the circle (R) is the depth of the aimed calyx. So, the circumference of the circle equals with 12 × x. Then the radius can be calculated; circumference = 2πR → R = 12x/6.28. An equilateral trigone can be

defined using "A" and "B"; the third corner of the trigone (point "C") is the site of puncture. The calyx is expected after R cm of insertion of the needle[8] (**Figure 4**).

In clinical practice, for the triangulation technique, the C-arm is initially angled away from the site of the puncture, with the image intensifier pointing towards the head of the patient (when the lower calyx is punctured). This decreases radiation exposure to the surgeon. The C-arm is moved back and forth between two positions; one that is parallel and one that is oblique to the line of the puncture. With the C-arm at the parallel position, adjustments are made to the mediolateral direction; right to left. With the C-arm in the oblique position, adjustments are made at the cephalad-caudal direction; up to down. It is crucial to only make adjustments in one direction at a time and to respect the different orientations as they pertain to the C-arm position. As soon as the proper orientation is obtained, the needle is advanced towards the targeted calyx. With the C-arm at the oblique position, before the renal capsule is penetrated, the position of the needle is checked with the C-arm in the parallel position. After proper position is confirmed, the needle is advanced into the renal collecting system with the C-arm back to the oblique position[9] (**Figure 5**).

Conclusion

PNL is less often employed than ESWL/ RIRS and has a short but most difficult first step. Sometimes percutaneous access takes less than one minute in a PNL operation. Thus, learning of this step may be difficult for residents or beginners. In this step, surgeon tries to enter a 3-dimensional organ blindly with the aid of 2-dimensional imaging modalities.

Περίληψη

Εισαγωγή/Σκοπός: Η διαδερμική νεφρολιθορθυσία (PNL) αποτελεί την επέμβαση εκλογής για την αντιμετώπιση νεφρικών λίθων >2cm και καραλλοειδούς λιθίασης. Από την πρώτη περιγραφή της τη δεκαετία του '80 από τους Fernstrom και Johansson, εξελίσσεται συνεχώς, με σκοπό να ελαχιστοποιηθούν οι επιπλοκές και να αυξηθεί το stone-free rate. Η ακτινοσκοπική παρακέντηση του πυελοκαλυκικού συστήματος είναι η πιο συχνά χρησιμοποιούμενη μέθοδος παγκοσμίως, με τις περισσότερες PNLs να εκτελούνται στην κλασσική πρηνή θέση.
Σκοπός του άρθρου είναι να παρουσιάσει τις διάφορες τεχνικές ακτινοσκοπικής παρακέντησης.
Υλικό/Μέθοδος: Παρουσιάζουμε τις συχνότερα χρησιμοποιούμενες ακτινοσκοπικές τεχνικές παρακέντησης του πυελοκαλυκικού συστήματος στη διαδερμική νεφρολιθοθρυψία. Η κάθε τεχνική παρουσιάζεται σε πραγματικά περιστατικά, αλλά και σε animation video, ώστε να γίνει πιο εύκολα κατανοητή.
Αποτελέσματα: Παρακέντηση σε ένα επίπεδο. Με το C-Arm στις 0°, ο χειρουργός τοποθετεί τη βελόνα παράλληλα με τον αυχένα του κάλυκα. Το βάθος διείσδυσης προσδιορίζεται εμπειρικά και με συνεχείς διορθώσεις, είτε επιφανιακότερα, είτε βαθύτερα.
Παρακέντηση σε δύο επίπεδα, παράλληλα στο κορμό του ασθενούς. Ομοίως όπως και στη πρώτη τεχνική, η βελόνα τοποθετείται παράλληλα με τον αυχένα του κάλυκα στις 0°. Έπειτα, το C-Arm στρέφεται είτε προς το κεφάλι ή τα πόδια του ασθενούς για να προσδιοριστεί το βάθος εισόδου της βελόνας.
Παρακέντηση σε δύο επίπεδα, κάθετα κορμό του ασθενούς (Bull's eye). Το C-Arm στρέφεται στις 30°προς το χειρουργό και η άκρη της βελόνας τοποθετείται στο κάλυκα. Η βελόνα φέρεται παράλληλα στον άξονα του C-Arm, ώστε βελόνα και κάλυκας να σχηματίζουν μία κουκίδα. Το βάθος εισόδου προσδιορίζεται με το C-Arm στις 0°.
Τεχνική τριγωνισμού. Όταν ένα σημείο απεικονίζεται σε δύο πλάνα στην ακτινοσκόπηση, μπορεί να υπολογιστεί η ακριβής θέση του στο χώρο με μαθηματικούς υπολογισμούς. Στις 0° ορίζεται ο κάλυκας σαν σημείο «Α» και στις 30° σαν σημείο «Β». Ο κάλυκας και τα σημεία «Α» και «Β» σχηματίζουν ένα νοητό κύκλο που μπορεί να υπολογιστεί η ακτίνα του, δηλαδή το επιθυμητό βάθος παρακέντησης. Το σημείο παρακέντησης είναι η κορυφή ενός ισόπλευρου τριγώνου που σχηματίζουν τα σημεία «Α» και «Β».
Συμπέρασμα: Η ακτινοσκοπική παρακέντηση είναι η πιο συχνά χρησιμοποιούμενη τεχνική στη PNL. Ο χειρουργός θα πρέπει να γνωρίζει όλες τις παραλλαγές για την επιτυχή παρακέντηση οποιοδήποτε κάλυκα.

Λέξεις ευρετηριασμού
διαδερμική νεφρολιθοθρυψία, PCNL, νεφρολιθίαση, τεχνικές διαδερμικής παρακέντησης

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NOTES

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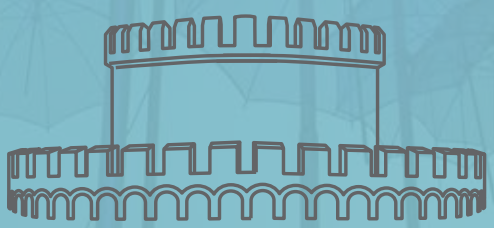

ΘΕΣΣΑΛΟΝΙΚΗ

Οργάνωση:

ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC UROLOGICAL ASSOCIATION

Η Astellas είναι αφοσιωμένη στο να μετατρέπει την επιστημονική καινοτομία σε ιατρικές λύσεις που αποφέρουν αξία και ελπίδα στους ασθενείς παγκοσμίως.

Κάθε μέρα εργαζόμαστε ώστε να καλύψουμε ανικανοποίητες ιατρικές ανάγκες εστιάζοντας πρωτίστως στις θεραπευτικές κατηγορίες της ογκολογίας, της ουρολογίας, των λοιμώξεων και της μεταμόσχευσης εξελίσσοντας παράλληλα νέες θεραπευτικές κατηγορίες και αξιοποιώντας νέες τεχνολογίες έρευνας. Παραμένουμε αφιερωμένοι στο να ικανοποιούμε τις ανάγκες των ασθενών και η υποστήριξή μας προς αυτούς δεν θα πάψει ποτέ να υφίσταται.

Μέσω της αφοσίωσής μας να προσφέρουμε στους ασθενείς ελπίδα για ένα λαμπρότερο μέλλον, επιδιώκουμε να ηγηθούμε στις θεραπευτικές κατηγορίες που εξειδικευόμαστε, εστιάζοντάς στις κατηγορίες όπου υπάρχουν ιατρικές ανάγκες που παραμένουν ανικανοποίητες. Μέσω της καινοτομίας, θα συνεχίσουμε να αναγνωρίζουμε και να αναπτύσσουμε νέους τρόπους για να καλυτερεύσουμε την υγεία των ασθενών.

Στην Astellas, εστιάζουμε στο να κάνουμε πραγματικότητα το *αλλάζοντας το αύριο.*

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