VOLUME 30 | ISSUE 3

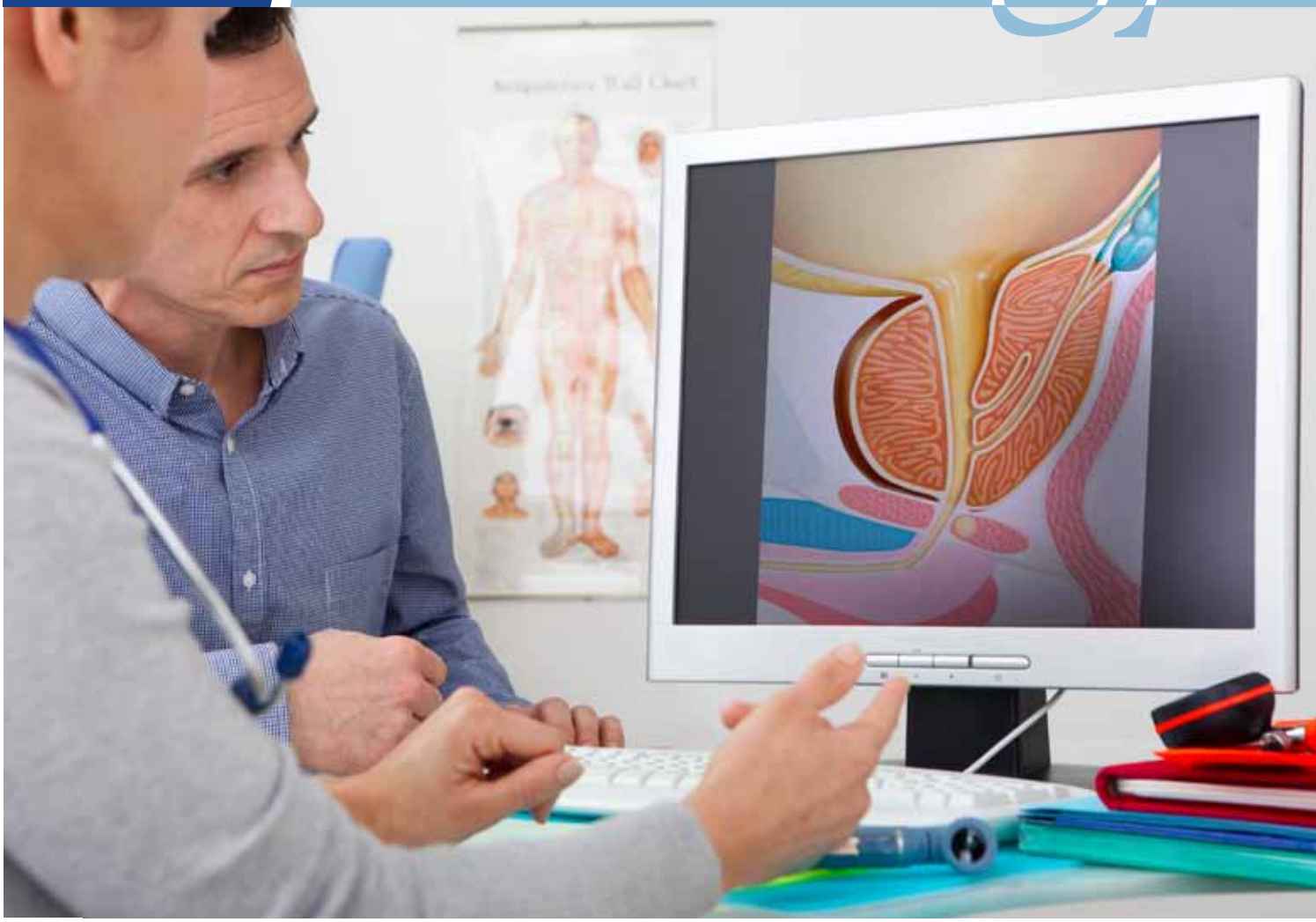
JULY
AUGUST
SEPTEMBER

2018

ISSN 2241 - 9136

Hellenic Urology

Quarterly Publication by the Hellenic Urological Association



Reviews

- Metastatic Renal Cell Carcinoma: The role of surgery in the treatment algorithm
- Urosepsis: How much do we really know?
  How different treatments for clinically localised prostate cancer affect quality of life

Case Reports

- Maximizing success for penile prosthesis revision surgery after glans penis erosion: operative strategies.
- Repair of iatrogenic ureteral injury with a combination of "Boari flap" and "Psoas Hitch" technique

Original Article

- ECIRS (Endoscopic Combined Intrarenal Surgery) Versus Fluoroscopic-guided Renal Access during supine Percutaneous Nephrolithotomy (PCNL): A Comparative Study
- Initial experience with extraperitoneal monopolarless laparoscopic radical prostatectomy in a secondary hospital of Greece

Official Journal
of the Hellenic Urological Association

Official Journal
of the Mediterranean & Gulf Urological Forum

ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC UROLOGICAL ASSOCIATION

ΝΕΑ ΑΝΑΝΕΩΜΕΝΗ ΣΕΛΙΔΑ

ΝΕΑ ON-LINE ΥΠΗΡΕΣΙΑ

Ανανέωση – Πληρωμή Συνδρομής
Τακτικών & Παρέδρων Μελών ΕΟΕ

www.huanet.gr

ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
Ραβινέ 23, 11521 Αθήνα
Τηλ.: 0030 210 7223126
Φαξ: 0030 210 7245959
E-mail: hua@huanet.gr

HELLENIC UROLOGICAL ASSOCIATION (HUA)
23 Ravine Str., 11521Athens-Greece
Tel.: 0030 210 7223126
Fax: 0030 210 7245959
E-mail: hua@huanet.gr

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, εστιάζοντας 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.*

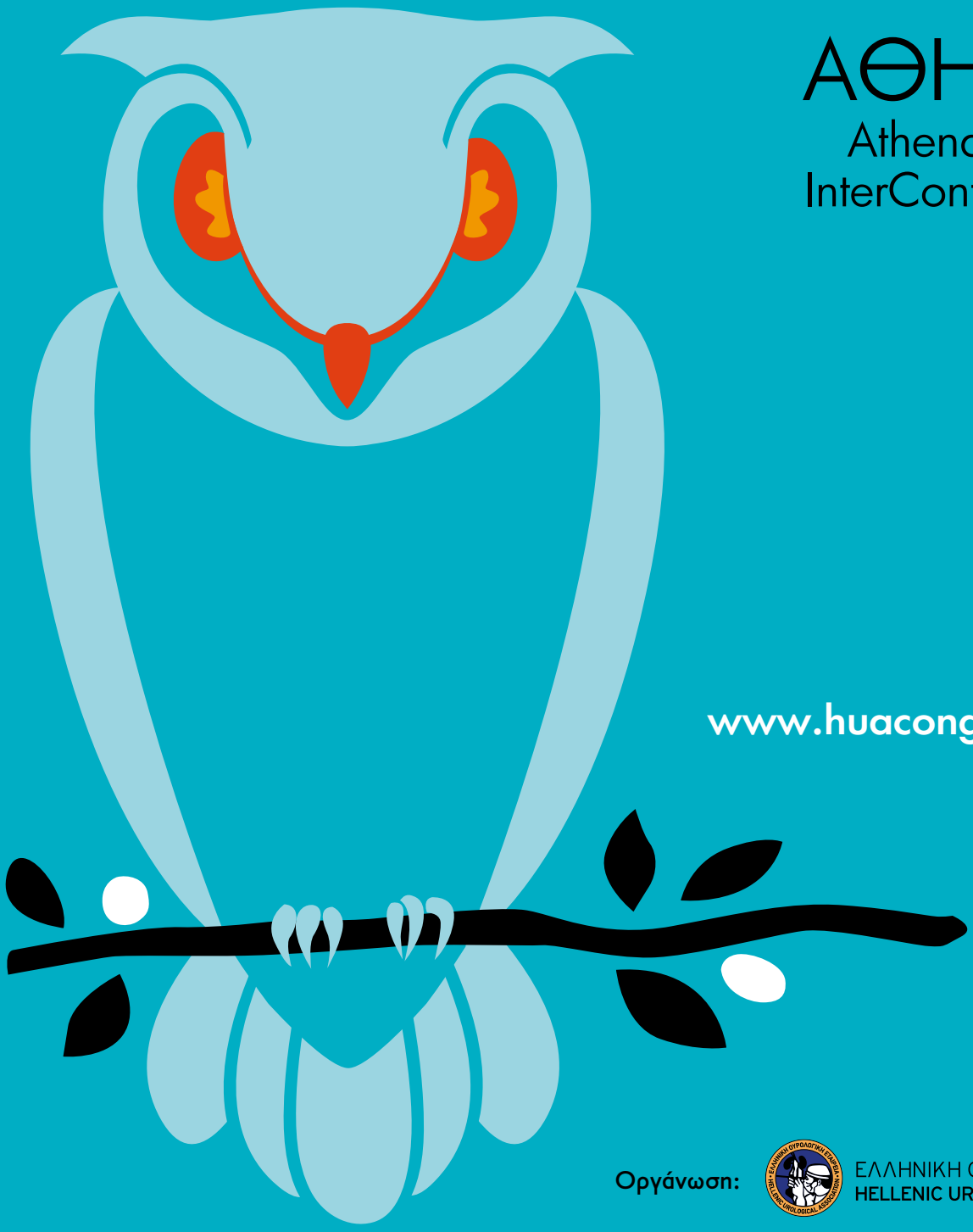
astellas

astellas.gr

ΜΕ ΔΙΕΘΝΗ ΣΥΜΜΕΤΟΧΗ

24ο ΠΑΝΕΛΛΗΝΙΟ ΟΥΡΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ

11-14 ΟΚΤΩΒΡΙΟΥ 2018



ΑΘΗΝΑ

Athenaeum InterContinental

www.huacongress2018.gr

Οργάνωση: ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC UROLOGICAL ASSOCIATION

Με την συνεργασία: ΚΔΕ 1990 CAU · esu · esuo · esut · esgurs · ICS · ILRSA · SIU

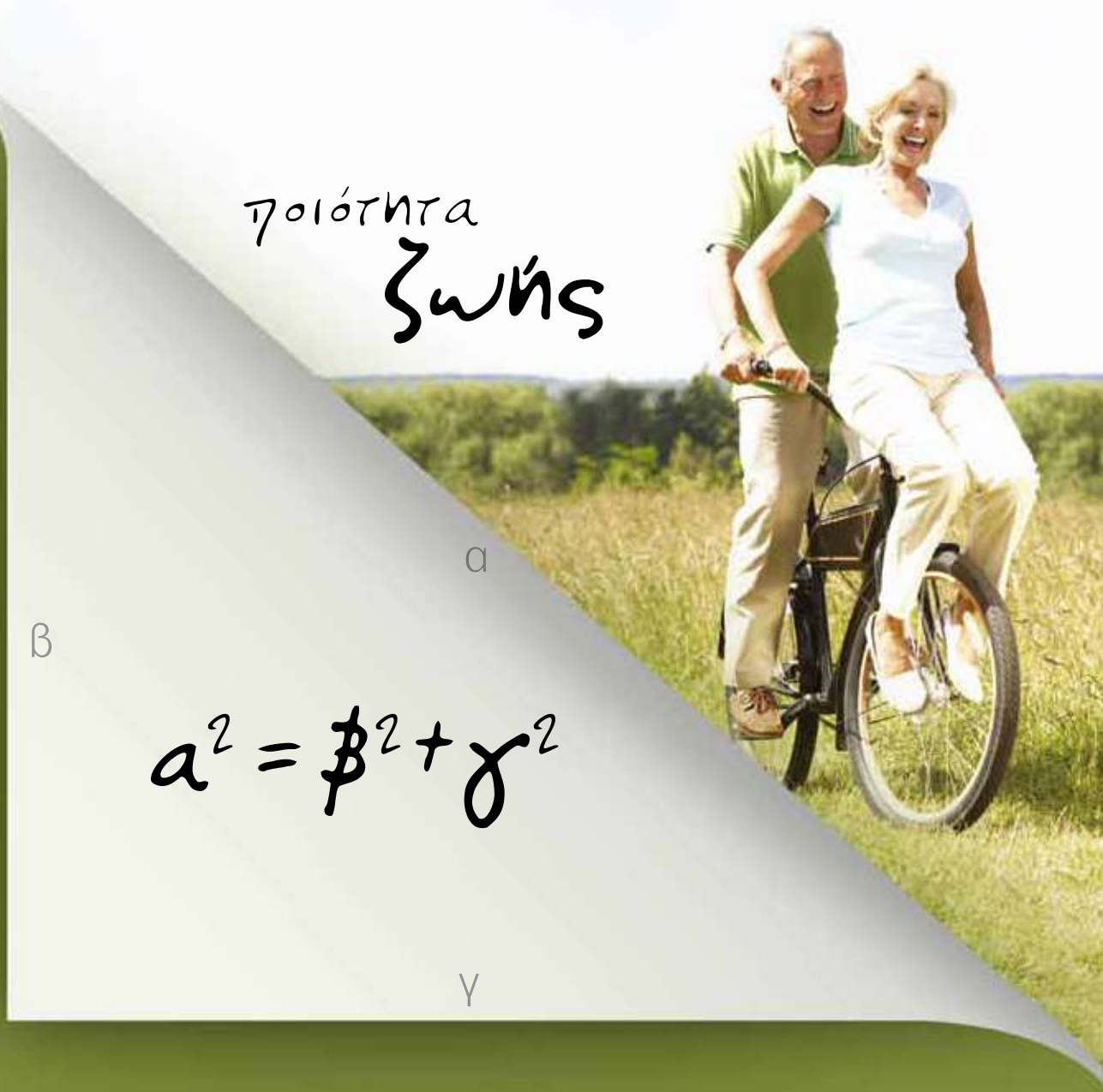
Hellenic
Urology
Quarterly Publication by
the Hellenic Urological Association

Distributed at no charge to all members of the Hellenic Urological Association
Indexed in Iatrotek and the National Documentation Centre
ISSN 2241 - 9136

HELLENIC UROLOGY OFFICIAL JOURNAL OF THE H.U.A.
Address: 23, Ravine St., 115 21 Athens, Greece
Tel.: +30 210 7223 126, Tel. - Fax: +30 210 7245 959, E - mail: hua@huanet.gr, www.huanet.gr

Production by
LYHNIA S.A., 7, Andravidas St., 136 71, Hamomylo - Acharnai, Athens, Greece
Tel.: +30 210 34 10 436, website: www.lyhnia.com

ποιότητα ζωής



$$a^2 = \beta^2 + \gamma^2$$

α

β

γ

Toldesor® PR

Tolterodine L-tartrate

"Θεμελιώδης αξία"

Για συνταγογραφικές πληροφορίες παρακαλώ επικοινωνήστε στα τ/φ της εταιρείας

RAFARM

RAFARM A.E.B.E. ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ
Κορίνθου 12, 154 51, Ν. Ψυχικό, Αθήνα, Τηλ.: 210 6776550 - 1 • Fax: 210 6776552 • e-mail: info@rafarm.gr
www.rafarm.gr

Contents

Instructions to Authors

Hellenic Urology is the official scientific journal of the Hellenic Urological Association. Its main objective is to publish original articles, reviews and case reports on diseases of the genitourinary system. The journal Hellenic Urology is also concerned in the continuous education of the Urologists and aims at promoting the science of Urology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations as well as basic and applied laboratory research; new data and recent developments of urological interest are also welcomed. Papers published in another journal are not accepted.

Submission of Papers

1. General Information: The official language of Hellenic Urology is English. Authors whose native language is not English will have their manuscripts proofread by a professional copyeditor offered by the editorial team. The authors are allowed to submit their manuscript into Greek and translation will be provided.

All the authors are jointly responsible for the contents of the paper and sign together the Authorship Responsibility, Financial Disclosure and Acknowledgment form. The list of authors should not exceed six (6) otherwise the participation of those exceeding the above numbers should be justified accordingly. In case of reports, the authors should not exceed four (4). In review articles the authors should not exceed the number of two. The following should be observed in the case of clinical studies:

a) The authors should state that the research was conducted according to the principles as have set forth by the Helsinki Declaration of 1975.
b) In the Studies that involve human subjects, a statement - approval from the appropriate human ethics committees should be obtained.
c) A statement - approval of the competent scientific committee of the centre in which the research work was carried out, pertaining to the protocol of the perspective studies, should be included.

In the case of the experimental studies on animals a statement should be made that the paper has adhered to the international guidelines for research involving animals, which has been recommended by the WHO, stating that all research on animals was conducted in accordance with guidelines tendered by international law.

2. Copyright Transfer: Papers published in Hellenic Urology constitute copyright ownership of the manuscript to the Hellenic Urological Association (HUA). Thus any reproduction and/or copying of said manuscript is allowed only after consent of the Editorial Board of the Journal.

3. Procedure:

- The corresponding author is informed for receipt of the manuscript and number of registration. The manuscripts are first checked whether they have been written and submitted according to the instructions of the journal (instructions to authors). Manuscripts which do not meet the requirements of correct submission are returned to the corresponding author with instructions for due corrections. The manuscript is double - blind checked by special consultantsreviewers of the journal.
- The revised manuscript with an accompanying letter signed by the corresponding author, in which he declares that all corrections have been done.

The final decision for acceptance of the manuscript lies on the Editorial Board that decides for approval, or return of manuscript for supplementary information, decision for re-approval or to reject the manuscript. As soon as the paper is accepted and has been allotted final publication, a proof is dispatched to the authors for final checking.

Article types

- ***Reviews*** - maximum 4,000 words, 50 references, 6 tables and 10 figures, Abstract 300 words
- ***Original Articles*** - maximum 3,000 words, 30 references, 6 tables and 10 figures, Abstract 200 words
- ***Case Reports*** - maximum 1,500 words, 10 references and 6 figures, Abstract 100 words
- ***Letter to the editor*** - maximum 600 words, 6 references, 1 table and 1 figure

All article types should be accompanied by an abstract in Greek. For authors whose native language is not Greek, a Greek translation will be provided by the Editorial Board.

Article structure

Subdivision: Divide your article into clearly defined sections. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction: State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods: Povide sufficient detail to al-low the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described. Statistical methods should be included in Material and Methods section.

Results: Results should be clear and concise.

Discussion: This should explore the significance of the results of the work, not repeat them. Avoid extensive citations and discussion of published literature.

Conclusions: The main conclusions of the study may be presented in a short conclusions section, which may stand alone or form a subsection of a Discussion section.

Title page information

- ***Title:*** Concise and informative. Titles are often used in information - retrieval systems. Avoid abbreviations and formulae where possible. Author names and affiliations Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual affiliations with a lower - case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- ***Corresponding author:*** Clearly indicate who will handle correspondence at all stages of refereeing and publication. Ensure that phone numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up todate by the corresponding author.

Summary

A concise and factual abstract is required. It should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, references should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract. Abstracts should be structured as to include items of Objectives, Methods, Results and Conclusions.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, "and", "of"). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Instructions to Authors

Abbreviations
In the text, abbreviation should be detailed at their first mention. Ensure their consistency throughout the article.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references. List here those individuals who provided assistance during the research.

Math formulae
Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes
Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article. Do not include footnotes in the reference list.

Table footnotes
Indicate each footnote in a table with a superscript lowercase letter.

Artwork
Image manipulation: Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original.

Electronic artwork
General points:
- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Times New Roman, 12.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the printed version.
- Submit each illustration as a separate file.

Formats: If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format. Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please "Save as" or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below): PDF or JPEG. Keep to a minimum of 300 dpi Vector drawings, embed all used fonts.

Please do not:
- Supply files that are optimized for screen use (e.g.,

GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Figure legends: Ensure that each illustration has a legend. Supply legends separately, not attached to the figure. A legend should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used. Legends should be sent separately.

Tables

Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables above the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

References

Citation in text: Please ensure that every reference cited in the text is also present in the reference list. Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either "Unpublished results" or "Personal communication". Citation of a reference as "inpress" implies that the item has been accepted for publication. Web references: As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Reference style

Text: Indicate Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given. However, for more than 6 authors, only the first three should be listed followed by et al.

List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Examples:

Reference to a journal publication:

1. Van der Geer J, Hanraads JAJ, Lupton RA et al. The art of writing a scientific article. J Sci Commun 2000;163:51 - 9.

Reference to a book:

2. Strunk Jr W, White EB. The elements of style. 3rd ed. New York: Macmillan; 1979.

Reference to a chapter in an edited book:

3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E - Publishing Inc; 1999, p. 281 - 304.

For further details you are referred to Uniform Requirements for Manuscripts submitted to Biomedical Journals (J Am Med Assoc 1997;277:927 - 934) (see also http://www.nlm.nih.gov/bsd/uniform_requirements.html).

Editors' responsibilities

1. Publication decisions
The editor is responsible for deciding which of the articles submitted to the journal should be published.

The decision will be based on the paper's importance, originality and clarity, and the study's validity and its relevance to the journal's scope.

The decision is guided by the policies of the journal's editorial board. The decision is constrained by current legal requirements regarding libel, copyright infringement, and plagiarism. The decision should not be restricted by the authors' race, gender, sex, religious belief, ethnic origin, and citizenship. The editor may confer with other editors or reviewers in making this decision.

2. Confidentiality
The editor and any editorial staff must not disclose any information about a submitted manuscript to anyone other than the corresponding author, reviewers, potential reviewers, other editorial advisers, and the publisher, as appropriate.

3. Disclosure and conflicts of interest
Unpublished materials disclosed in a submitted paper will not be used either in an editor's own project or by the members of the editorial board for their own research purposes without the express written consent of the author.

Duties of Reviewers
1. Contribution to Editorial Decisions
Reviewers' assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper.

2. Promptness
Any selected referee who feels unable or unqualified to review the research reported in a manuscript should notify the editor and exclude himself from the review process.

3. Confidentiality
Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

4. Standards of Objectivity
Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

5. Acknowledgement of Sources
Reviewers should identify relevant published work that has not been cited by the authors. Any statement that an observation, derivation, or argument had been previously reported should be accompanied by the relevant citation.

Reviewers should also call to the editor's attention any substantial similarity or overlap between the manuscript under consideration and any other published paper of which they have personal knowledge.

6. Disclosure and Conflict of Interest
Information or ideas obtained through peer review must be kept confidential and not used for personal advantage. Reviewers should not consider manuscripts in which they have conflicts of interest resulting from competitive, collaborative, or other relationships or connections with any of the authors, companies, or institutions connected to the papers.

Duties of Authors

1. Reporting standards

Authors of original research papers should present accurately the work performed and provide an objective discussion of its significance.

Underlying data should be properly represented in the paper. A paper should contain sufficient detail and references to permit others to replicate the work.

2. Data Access and Retention

Authors are asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data and should in any event be prepared to retain such data for a reasonable time after publication.

3. Originality and Plagiarism

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others that this has been appropriately cited or quoted.

4. Multiple, Redundant or Concurrent Publication

Authors should not publish manuscripts describing essentially the same research in more than one journal or primary publication.

5. Acknowledgement of Sources

Proper acknowledgment of the work of others must always be given. Authors should cite publications that have been influential in determining the nature of the reported work.

6. Authorship of the Paper

Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study.

All those who have made significant contributions should be listed as co-authors while those who have participated in certain substantive aspects of the research should be acknowledged or listed as contributors. The corresponding author should ensure that all appropriate co-authors are included on the paper and that all co-authors have seen and approved the final version of the paper.

7. Hazards and Human or Animal Subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript.

8. Disclosure and Conflicts of Interest

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript.

All sources of financial support for the project should be disclosed.

9. Errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and cooperate with them to correct the paper.

Rafuster®

dutasteride

ΠΕΡΑΙΤΕΡΩ ΠΛΗΡΟΦΟΡΙΕΣ ΔΙΑΤΙΘΕΝΤΑΙ ΑΠΟ ΤΟΝ ΚΑΤΟΧΟ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ

ADV/RAF/02/RAF/04.2018

RAFARM A.E.B.E. ΒΙΟΜΗΧΑΝΙΑ ΦΑΡΜΑΚΩΝ
Κορίνθου 12, 154 51, Ν. Ψυχικό, Αθήνα, Τηλ.: 210 6776550 - 1 • Fax: 210 6776552 • e-mail: info@rafarm.gr
www.rafarm.gr

REVIEW

Metastatic Renal Cell Carcinoma: The role of surgery in the treatment algorithm

Mykoniatis I., Memmos D., Anastasiadis A., Dimitriadis G.
1st Department of Urology, Aristotle University of Thessaloniki, Greece,
41 Ethnikis Aminis Street, Thessaloniki, Greece

Abstract

Renal cell carcinoma (RCC) is a life threatening disease, the most lethal among urinary tract tumors. It accounts for about 2-3% of adult solid malignancies, with a reported worldwide annual increase of 1.5-5.5%. Surgical intervention is the primary treatment for early-stage RCC, however nephrectomy alone offers limited benefit in patients with metastatic disease, except for palliative reasons. The aim of this review is to study the role of surgical intervention in the treatment algorithm of metastatic renal cell carcinoma.

Introduction

Renal cell carcinoma (RCC) is a life threatening disease, the most lethal among urinary tract tumors (1). It accounts for about 2-3% of adult solid malignancies, with a reported worldwide annual increase of 1.5-5.5% (2). This is mainly due to increased availability of cross-sectional imaging leading to earlier detection of small kidney tumors (3). At the time of diagnosis, approximately 20% of patients have locally advanced disease and approximately 30-50% of patients with RCC will either present with or later develop metastatic disease (4). Although 5- year survival for all stages of RCC continues to improve, M1 patients who remain untreated have a 5 year survival of 0-18% (5).

Key words
Metastatic renal cell carcinoma; cytoreductive nephrectomy; metastasectomy; multimodal therapy; immunotherapy

Surgical intervention is the primary treatment for early-stage RCC, however nephrectomy alone offers limited benefit in patients with metastatic disease, except for palliative reasons (6).

Mykoniatis I., Memmos D., Anastasiadis A., Dimitriadis G.
Metastatic Renal Cell Carcinoma: The role of surgery in the treatment algorithm.
Hellenic Urology 2018, 30(3): 13-20

Corresponding author:
Memmos Dimitrios
E-mail: urolauth@med.auth.gr

For advanced or metastatic disease, nephrectomy may only be curative if all metastatic deposits are excised (7). The clinical benefit of cytoreductive nephrectomy (CN) for cases of metastatic RCC (mRCC) was proved in randomized trials in the cytokine era (8, 9). Prior to the advent of antiangiogenic agents, systemic treatment options for mRCC were limited to cytokine therapies (ie, interleukin [IL]-2 and interferon-alpha [IFN-α]). In the past few years, a shift in the treatment algorithm for RCC has occurred with the introduction of receptor tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) antibodies, and mammalian target of rapamycin inhibitors (mTORs). In the past 5 years, several anti VEGF therapies have been approved for use in advanced RCC. These include sorafenib, pazopanib and sunitinib, small molecule inhibitors of VEGF receptors (VEGFRs), c-Kit, platelet-derived growth factor receptors (PDGFRs), and Flt-3. In addition, bevacizumab, an antiVEGF antibody, was approved in combination with IFN-α (10, 11). However, the contribution of molecular-targeted therapies (MTT), which proved to be more effective than cytokine therapy, has recently significantly impacted recurrence-free survival in metastatic patients, challenging in some cases the real interest of nephrectomy (12). Moreover, certain molecular-targeted drugs, particularly TKI, induce tumor shrinkage leading to a critical reevaluation of the surgical management of patients with mRCC.

Surgical treatment in the setting of mRCC may be in the form of palliative nephrectomy, cytoreductive nephrectomy (CN) and metastasectomy.

Palliative Nephrectomy

Although palliative nephrectomy seems to offer a positive effect, regarding the quality of life in selected patients, surgery alone for mRCC without adjuvant therapy is profitless. Taking into concern the frequently displayed poor performance status (PS) of patients in this advanced stage, surgical intervention may be associated with higher morbidity and mortality. Relative indications, in which surgery is an option, are rare cases of major bleeding, intractable pain, uncontrolled hypertension, symptoms due to paraneoplastic syndromes such as erythrocytosis, severe uncontrolled hypercalcemia, and only if usual measures fail.

In a study reported by Walther et al, 12 patients with mRCC and hypercalcemia underwent nephrectomy which resulted in a calcium decrease only in 7 of them, as in 4 persons it increased and in 1 patient calcium measurements were stable. Furthermore, the group of patients in which a reduction was noted did not have a survival benefit as the median survival for all participants was 6 months (13). Maybe the metastatic lesions are the cause of systematic effects and not the primary kidney tumor and therefore palliative nephrectomy may fail to relief the associate problem. In addition, in the era of minimally invasive techniques, such as vessel embolization, which leads to comparable effectiveness, palliative nephrectomy has become a fallback solution.

Cytoreductive Nephrectomy

Biological contribution

Although the reasons for the significant improvement in survival due to CN are still not fully understood, several mechanisms have been proposed. RCC is capable of Influencing and suppressing the host's natural immunity resulting to immunological dysfunction. The primary tumor suppresses the cell-mediated immunity and acting as an 'immunogenic sink' where the circulating macrophages, immunoglobulins and lymphocytes are diverted and kept away from the distant metastases (14). Radical nephrectomy particularly combined with subsequent cytokine therapy may elevate the circulating levels of these immunologic factors, resulting to a more accurate targeting of metastases. In addition, RCC produces high levels of proinflammatory and T-cell inhibitory substances including IL-6, IL-8, IL-10, TGFb-1 and TNF leading to immunologic response suppression (15). Removal of primary tumors may, therefore, eliminate a source of these growth factors leading to limitation of future metastasis.

Significance of Cytoreductive Nephrectomy for mRCC

Nephrectomy alone for mRCC patients is definitively not curative and should not be done indiscriminately. However, when conducted in a frame of a multimodal treatment approach, it does have a beneficial complementary role. The ideal timing of nephrectomy in the multimodal management is still debatable. There are authors who proceed in CN only after systemic therapy and others who prefer an upfront nephrectomy. Both treatments strategies have their own pros and cons.

Nephrectomy before systemic therapy

The advantage of pre-immunotherapy debulking nephrectomy was best supported by two randomized

clinical trials (RCTs) published in 2001, the South West Oncology Group (SWOG) 8949 trial in the USA and the European Organisation of Reasearch and Treatment of Cancer (EORTC) 30947 trial in Europe [7, 8]. Both of them compared a nephrectomy + IFN-a therapy group with an IFN-a monotherapy group.

In the EORTC trial, the overall survival(OS) was 17 and 7 months, in the nephrectomy + IFN-a group and the IFN-a monotherapy group respectively (HR 0.54, 95% CI 0.31–0.94) whereas the time to disease progression was 5 and 3 months, respectively (HR 0.60, 95% CI 0.36–0.97). In the SWOG trial, the OS was 11.1 months in the combination group, and 8.1 months in the IFN-a monotherapy group (P = 0.05). A combination analysis of these two studies carried out by Flanigan and colleagues resulted in a median survival of 13.6 months for the nephrectomy + IFN-a group and 7,8 months for the immunotherapy alone patients. There was a survival advantage of about 6 months for the CN + immunotherapy group (16). One critical point of the SWOG trial which is worth mentioning, is the finding that when a subgroup analysis regarding the PS was done, for the PS 0 patients prognosis was even better in the nephrectomy + IFN-a group compared with the IFN-a monotherapy group (17.4 vs. 11.7 months of survival). However, the difference was reduced in the PS 1 patients, in which survival was 6.9 vs. 4.8 months in the combination group and the IFN-a monotherapy group, respectively. Thus, in the cytokine therapy era, it seems that CN tends to improve prognosis in M1 patients and moreover, in patients showing a favorable general condition the prognosis is prolonged. A review of patients data from the surgical arm of the SWOG 8949 trial demonstrated significantly improved survival in patients who experienced postoperative increase in blood urea nitrogen (BUN) and creatinine compared with those who did not (17 vs. 4-month survival; P = 0.0007), making the provocative hypothesis that the survival advantage could be attributed to the post-operative azothemia resulting from CN and not to tumor excision (17). Additionally, a Cochrane-based analysis concluded that in PS0 M1 patients with minimal symptoms, CN followed by IFN-α offers the best survival strategy for fully validated therapies (18).

The control drug therapy utilized in the aforementioned trials was only IFN-a monotherapy and no RCTs validating the effect of MTT exist, the efficacy of which for mRCC has led some researchers to question the need for CN in this setting. This knowledge gap probably will be bridged by the ongoing CARMENA study in which the primary end-point of OS is assessed in patients with mRCC (ECOG PS 0 or 1), without prior systemic therapy or surgical interventions, who are being randomized to either CN followed by sunitinib or sunitinib alone(19) . In the same direction, at the interesting ongoing since 2010 EORTC-led SURTIME trial, one group of patients underwent immediate CN before sunitinib therapy, similar to the CARMENA study, but there was another group that received three cycles of sunitinib (4 weeks on and 2 weeks off) prior to CN, followed by the resumption of sunitinib therapy. Regrettably, both trials' status is still shown as "This study is currently recruiting participants." keeping us in the dark regarding the importance of CN in mRCC in relation to sunitinib monotherapy.

Other retrospective series report an advantage for patients undergoing CN prior to the systematic drug therapy. Choueiri et al, reported on 314 patients with mRCC, of whom 201 underwent CN followed by MTT (20). They reported that CN was associated with a median overall survival of 19.8 vs. 9.4 months for patients who did not undergo CN ($p < 0.0001$). However, the benefit was marginal in patients in the poor prognostic risk group. Although this was a retrospective study with all the attendant biases, the influence of good prognosis and good PS on patient prognosis after CN was highlighted. Warren et al, reached similar results concerning the improved OS for patients who underwent CN prior to TKI therapy (21). Another retrospective study conducted between 2006 and 2009 included 78 patients (22), dividing patients into two groups: one with 45 patients that underwent CN + MTT and the second one with 33 patients that underwent only MTT. Progression-free survival was 11.7 vs. 9 months, and OS was 21.6 vs 13.9 months, in the CN and the non-CN group, respectively. Sarcomatous change of the tumor, PS and the presence/absence of liver metastasis were relevant with prognosis after multivariate analysis.

A nomogram able to predict the 6- and 12- month survival was published in 2013 by the MD Anderson Cancer Center based on the analysis of the postoperative survival of 601 patients who underwent CN through the period 1991 – 2008 (23). LDH and serum albumin levels were identified as preoperative prognostic factors, whereas the postoperative prognostic factors were N stage, ≥T3 stage and the presence/absence of blood transfusion, additionally to LDH and serum albumin levels. Obviously, the syntax of a nomogram could turn into a useful tool when determining whether or not to proceed to a debulking nephrectomy. Regrettably the

majority of the 601 patients of the study were treated before the MTT era, thus no consideration was given to the induction of postoperative drug therapy in the treatment algorithm. Hence, the nomogram is not immediately applicable to current clinical settings where MTT nearly always follows CN. The development of a nomogram that considers MTT is deemed necessary nowadays.

Potential disadvantages of upfront CN include perioperative morbidity and mortality, and systemic therapy delay. The mortality of CN varies from 6 to 11% and the morbidity is around 20% (24). In the SWOG trial, there was only one death in the perioperative period and only 2% patients were unable to receive IFN-a after surgery (8). Walther et al, compared open nephrectomy, lap-assisted nephrectomy, and lap morcellation regarding the interval needed for the safe immunotherapy induction (13). The median time interval was 67, 60 and 37 days respectively. The patients that benefited the most were those who had morcellation.

Nephrectomy after systemic therapy

With the exception of some case series (24, 25), cytokine therapy (IL-2, IFN) before CN did not produce encouraging results.

Neoadjuvant or presurgical therapy is a novel therapeutic strategy which is currently being investigated in the treatment of mRCC, in conjunction with development of MTT that affects specific angiogenic and growth factor pathways important in RCC biology (26, 27). It has been reported that the tumor progresses after nephrectomy in 22% of patients (28). Loss of angiostatin, an angiogenic inhibitor secreted by the primary tumor, has been proposed as a potential biological mechanism which may partially inhibit the growth of metastases. The concept of neoadjuvant therapy is presented as an attractive treatment paradigm for many reasons. With the primary tumor left in situ during administration of systemic therapy, there is real-time feedback provided on disease response to the selected treatment, which may allow therapy adjustments to ensure maximal response. Downsizing the primary tumor could facilitate resectability, reduce the amount of normal tissue that needs to be removed and decrease operative risk (29). In concert, patients not responding to systemic therapy can avoid highly morbid surgical interventions,which have no hope of offering a better outcome. In addition, presurgical targeted therapy may result in a reduction of cancer-related morbidity prior to surgery. Lastly, tumor tissue, harvested at the time of surgery, can be rigorously interrogated with translational research techniques not only to evaluate the effects of systemic therapy at a molecular level but also to provide clues regarding pathways of resistance and novel therapeutic targets.

The disadvantages of MTT include the possibility of higher surgical morbidity and postoperative complications, mainly due to the inhibition of the VEGF receptors and other related pathways. The proangiogenic pathways hold a major role in tissue integrity and any alteration in these could result to delayed wound healing, incisional hernia and fascial disruption. Additionally, natural regeneration of the microvasculature can be disturbed, resulting in postoperative bleeding and thrombotic events (30).The increased cost of MTT is another serious drawback of this treatment algorithm.

In 2009 Wood et al, published a study in which sunitinib, sorafenib or bevacizumab therapy was administered preoperatively to 44 patients and a control group of 58 patients, who underwent CN only, was used for outcome comparisons. None of the surgery –related complications, which occurred in 33 patients, were more frequent in the preoperative MTT group. Also variables such as median CSS and duration of surgery, was not significantly different between groups. Hence, MTT before CN is unlikely to be linked to decreased survival (31).

In 2011 Powels et al, reported combined data from 2 phase II trials using different protocols (32). In both studies, CN was performed in patients with mRCC 24 hours after the end of 2 cycles of sunitinib in study A, whereas in study B, it took place 14 days after the end of 3 cycles of sunitinib. Thirty-seven patients (70%) were operated, while 16 patients were not, with the reason being, disease progression in 9 of them. Perioperative complications did not differ between study A and B , but cases with Clavien III–V complications (bleeding, renal failure and death) were reported in study B. Interestingly, 13 out of 21 cases (62%) of severe tissue adhesion were all found in study B. Moreover, the crucial finding of this report is the difference in response between primary and metastatic tumors. The primary tumor volume increased in 3 patients, while metastatic tumor volume increased in 10 patients with two patients (both in study B) experiencing an increase of approximately 30%.

Margulis et al, from the MD Anderson cancer center treated 44 patients with neoadjuvant-targeted molecules (group A) while upfront CN was done in 58 patients (group B) (33). Analysis 1 year after revealed that 18.2%

of patients in the group A and 31% patients in the group B died of RCC. Complication rate was 32.4%. Withholding MTT for at least 2 to 3 half lives before and after CN may minimize the adverse effects of these agents on microvasculature and tissue level. Simplified, actually, the authors suggest that a pause of the therapy for 7-10 days before and after CN would probably reduce surgical risks.

Another retrospective study carried out by the same center investigated 70 patients who were treated with MTT before undergoing CN (group A) and outcomes were compared against 103 patients who underwent immediate CN (group B) (34). Although patients who received preoperative MTT had a significantly higher rate of complications, proportions of Clavien ≥III complications did not differ significantly between groups (29.4% vs. 30.2%, P = 0.625). A significant correlation between preoperative drug MTT and all types of complications was not emerged from univariate or multivariate analysis. Thus, the authors proposed preoperative MTT as being a safe treatment option.

Metastasectomy

Despite the advances in MTT treatment for mRCC, surgical resection remains the mainstray of mRCC management. With the exception of brain and possibly bone metastases, metastasectomy remains the most effective local treatment for most sites (35). Retrospective comparative studies, consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, cancer-specific survival (CSS) and delay of systemic therapy (36, 37). A 5-year survival rate of 25-52% is reported after complete resection (36, 38, 39).

Lungs represent the most common site of metastases in RCC patients. Resection of pulmonary metastases is associated with better survival rates compared to other anatomical sites. Predictive factors for a longtime survival postoperatively are: pathological evidence of complete resection, fewer pulmonary metastases, length of the disease-free interval and lack of lymph node involvement (40) According to Assouad et al, the shorter disease-free interval is not an important risk factor for mortality any longer when the resection is complete. Thus, the most crucial predictive factor for a longtime survival is the completeness of resection (41). Repeat metastasectomy for recurrent pulmonary metastases appears to be efficacious in certain patients since the group from the Mayo Clinic reported that the 5-year overall survival in this subgroup was comparable with that in patients without recurrence (42).

Metastases to bones from RCC are seen frequently (30-40%) (43) and are considered to be unique surgical challenges due to the risk of major bleeding and non-response to other forms of treatment. Fit patients with solitary metastases are considered to be the best case scenario for surgery but unfortunately osseous metastases in RCC are commonly combined with poor PS due to pathological fracture and intractable pain. Surgical treatment options in these patients include: cementing and curettage, internal fixation, amputation, en bloc resection and nailing.

Regarding liver metastases, many retrospective studies demonstrated positive results of metastasectomy, especially when the candidates for surgery are carefully selected based on clinical characteristics and patient-defined variables (44, 45). Timing of liver metastases presence, PS, tumor size, negative resection margins, primary tumor characteristics (T-stage, Fuhrman, Grading) and immediate postoperative TKI therapy were prognostic factors regarding OS and recurrence (44-47).

In 2007 Lin et al, published a retrospective review of a series of 295 consecutive patients who had been treated for mRCC at one institution through the period 1974-2004 (48). A total of 368 metastases of renal cell tumors to the extremities and pelvis were treated. The OS rates at 1 and 5 years were 47% and 11%, respectively. The metastatic pattern had a significant effect on the survival rate ($p < 0.0001$): patients with a solitary bone metastasis had the most favorable OS rate. Patients with multiple bone-only metastases had a better survival rate than patients with pulmonary metastases ($p = 0.009$). Moreover clear-cell histological subtype was associated with better survival ($p < 0.0001$). The tumor grade did not predict survival ($p = 0.17$). Toyada et al, have proposed time interval from nephrectomy (< or >2years) to the appearance of the bone metastases and the presence or not of extra-osseous metastases as being two important prognostic factors in the treatment of bone metastases in mRCC patients (49). Based on these 2 factors, they created a bad and a good prognosis group. In the 50 cases they reported, they found that those with poor prognostic factors had a median survival of 5 months while those in the good category had 30 months median survival.

In order to answer whether preoperative MTT is beneficial for patients undergoing metastasectomy, a large-scale retrospective study was carried out in Japan which included 556 patients who underwent metastasectomy between 1988 and 2009(50). MTT

was administered to 128 out of 537 patients (23.8%), but recurrence rate was not proved to depend on the presence/absence of MTT.

In another study published by Tosco et al, outcomes of 109 patients who underwent complete resection of metastases were reviewed (51). Thirty-one patients received MTT as first-line treatment and also 3 patients received VEGF inhibitor therapy as second-line treatment. Multivariate analysis of prognostic factors for CSS showed favorable MTT with a hazard ratio of 0.72, although the effect was not statistically significant (P = 0.38). Taken together, MTT before metastasectomy could be beneficial for some patients, although there is a lack of robust evidence supporting the opinion that this treatment paradigm results in better prognosis.

Regarding postoperative MTT and its results in mRCC patients undergoing metastasectomy, 2 prospective placebo-controlled randomized trials are investigating the use of pazopanib or sorafenib, in M1 patients with clear cell RCC or any subtype, for up to 1 year after complete metastasectomy. Both studies (NCT01575548, NCT 01444807) are still ongoing with disease free survival as the primary end-point.[][]

Conclusion

The recent interest surrounding the multimodal approach of integrating drug therapies combined with nephrectomy for the treatment of mRCC is a direct response to the advent of MTT. The encouraging response data outcomes in both primary tumors and metastases suggest that this is a rational step in the evolution of mRCC treatment. Definitive evidence supporting changes in the current treatment paradigms is not presently available. Selected patients with oligometastatic diseases, long period of interval from radical nephrectomy to the development of metastases and good PS are considered to be the ideal cases regarding the survival rates. In the absence of prospective randomized data, upfront CN followed by systemic therapy still remains the standard treatment algorithm for patients with metastatic disease and good PS with a resectable tumor. In contrast, patients with poor overall health, large tumor burden beyond the kidney, or highly aggressive disease are unlikely to benefit from nephrectomy, and should receive systemic therapy first. The ongoing CARMENA and EORTC trials will go a long way towards defining the role and timing of CN in recipients of targeted anti-VEGF therapy. Until the final results are published, patients with no access to clinical trials should be treated according to guideline recommendations.

Περίληψη

Ο νεφροκυτταρικός καρκίνος είναι μια απειλητική για τη ζωή πάθηση. Για την ακρίβεια αποτελεί τον όγκο του ουροποιητικού με την μεγαλύτερη θνησιμότητα. Αποτελεί περίπου το 2-3% των συμπαγών όγκων στους ενήλικες με ετήσια αύξηση του επιπολασμού κατά 1,5-5,5%. Η χειρουργική αντιμετώπιση αποτελεί την κύρια θεραπεία για τον πρώιμο νεφροκυτταρικό καρκίνο, σε αντίθεση με τον μεταστατικό νεφροκυτταρικό καρκίνο όπου η μονοθεραπεία με χειρουργική αντιμετώπιση αποτελεί παρηγορητική θεραπεία. Σκοπός αυτού του άρθρου είναι να μελετήσει το ρόλο της χειρουργικής αντιμετώπισης στο θεραπευτικό αλγόριθμο του μεταστατικού νεφροκυτταρικού καρκίνου.

Λέξεις ευρετηριασμού

Μεταστατικός νεφροκυτταρικός καρκίνος, Κυτταρομειωτική νεφρεκτομή, Μεταστασεκτομή, συνδυαστική θεραπεία, ανοσοθεραπεία

References

1. Cairns P. Renal cell carcinoma. Cancer Biomark. 2010;9(1-6):461-73.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA: a cancer journal for clinicians. 2013;63(1):11-30.
3. Chow WH, Devesa SS, Warren JL, Fraumeni JF, Jr. Rising incidence of renal cell cancer in the United States. Jama. 1999;281(17):1628-31.
4. Flanigan RC, Campbell SC, Clark JI, Picken MM. Metastatic renal cell carcinoma. Current treatment options in oncology. 2003;4(5):385-90.
5. Hoffmann NE, Gillett MD, Cheville JC, Lohse CM, Leibovich BC, Blute ML. Differences in organ system of distant metastasis by renal cell carcinoma subtype. The Journal of urology. 2008;179(2):474-7.
6. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer treatment reviews. 2008;34(3):193-205.
7. Ljungberg B, Hanbury DC, Kuczyk MA, Merseburger AS, Mulders PF, Patard JJ, et al. Renal cell carcinoma guideline. European urology. 2007;51(6):1502-10.
8. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. The New England journal of medicine. 2001;345(23):1655-9.
9. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for R, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001;358(9286):966-70.
10. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103-11.
11. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(33):5422-8.
12. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(22):3584-90.
13. Walther MM, Lyne JC, Libutti SK, Linehan WM. Laparoscopic cytoreductive nephrectomy as preparation for administration of systemic interleukin-2 in the treatment of metastatic renal cell carcinoma: a pilot study. Urology. 1999;53(3):496-501.
14. Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. Annals of surgery. 1998;228(3):307-19.
15. Flanigan RC, Orris BG. Management of metastatic renal cell cancer: Role of surgery. In: NJ V, PT S, WI S, editors. Genitourinary oncology. 3rd ed: Lippincot: Williams and Wilkinson; 2006.
16. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. The Journal of urology. 2004;171(3):1071-6.
17. Gatenby RA, Gawlinski ET, Tangen CM, Flanigan RC, Crawford ED. The possible role of postoperative azotemia in enhanced survival of patients with metastatic renal cancer after cytoreductive nephrectomy. Cancer research. 2002;62(18):5218-22.
18. Coppin C, Porzsolt F, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. The Cochrane database of systematic reviews. 2000(3):CD001425.
19. Sfoungaristos S, Gofrit ON, Pode D, Landau EH, Duvdevani M. Percutaneous nephrolithotomy for staghorn stones: Which nomogram can better predict postoperative outcomes? World journal of urology. 2016;34(8):1163-8.
20. Choueiri TK, Xie W, Kollmannsberger C, North S, Knox JJ, Lampard JG, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. The Journal of urology. 2011;185(1):60-6.
21. Warren M, Venner PM, North S, Cheng T, Venner C, Ghosh S, et al. A population-based study examining the effect of tyrosine kinase inhibitors on survival in metastatic renal cell carcinoma in Alberta and the role of nephrectomy prior to treatment. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2009;3(4):281-9.
22. You D, Jeong IG, Ahn JH, Lee DH, Lee JL, Hong JH, et al. The value of cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy. The Journal of urology. 2011;185(1):54-9.
23. Margulis V, Shariat SF, Rapoport Y, Rink M, Sjoberg DD, Tannir NM, et al. Development of accurate models for individualized prediction of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. European urology. 2013;63(5):947-52.
24. Walther MM, Alexander RB, Weiss GH, Venzon D, Berman A, Pass HI, et al. Cytoreductive surgery prior to interleukin-2-based therapy in patients with metastatic renal cell carcinoma. Urology. 1993;42(3):250-7; discussion 7-8.
25. Rackley R, Novick A, Klein E, Bukowski R, McLain D, Goldfarb D. The impact of adjuvant nephrectomy on multimodality treatment of metastatic renal cell carcinoma. The Journal of urology. 1994;152(5 Pt 1):1399-403.
26. Jonasch E. Presurgical therapy in metastatic renal cell carcinoma. Expert review of anticancer therapy. 2007;7(1):73-8.
27. Wood CG. Multimodal approaches in the management of locally advanced and metastatic renal cell carcinoma: combining surgery

and systemic therapies to improve patient outcome. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(2 Pt 2):697s-702s.
28. Krishnamurthi V, Novick AC, Bukowski RM. Efficacy of multimodality therapy in advanced renal cell carcinoma. Urology. 1998;51(6):933-7.
29. Patard JJ, Thuret R, Raffi A, Laguerre B, Bensalah K, Culine S. Treatment with sunitinib enabled complete resection of massive lymphadenopathy not previously amenable to excision in a patient with renal cell carcinoma. European urology. 2009;55(1):237-9; quiz 9.
30. Rini BI, Campbell SC. The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. The Journal of urology. 2007;177(6):1978-84.
31. Wood CG, Margulis V. Neoadjuvant (presurgical) therapy for renal cell carcinoma: a new treatment paradigm for locally advanced and metastatic disease. Cancer. 2009;115(10 Suppl):2355-60.
32. Powles T, Kayani I, Blank C, Chowdhury S, Horenblas S, Peters J, et al. The safety and efficacy of sunitinib before planned nephrectomy in metastatic clear cell renal cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2011;22(5):1041-7.
33. Margulis V, Matin SF, Tannir N, Tamboli P, Swanson DA, Jonasch E, et al. Surgical morbidity associated with administration of targeted molecular therapies before cytoreductive nephrectomy or resection of locally recurrent renal cell carcinoma. The Journal of urology. 2008;180(1):94-8.
34. Chapin BF, Delacroix SE, Jr., Culp SH, Nogueras Gonzalez GM, Tannir NM, Jonasch E, et al. Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. European urology. 2011;60(5):964-71.
35. Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. The Lancet Oncology. 2014;15(12):e549-61.
36. Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer. 2011;117(13):2873-82.
37. Staehler M. The role of metastasectomy in metastatic renal cell carcinoma. Nature reviews Urology. 2011;8(4):180-1.
38. Park YH, Jung JW, Lee BK, Lee S, Jeong SJ, Byun SS, et al. Targeted therapy after complete resection of metastatic lesions in metastatic renal cell carcinoma. International journal of urology : official journal of the Japanese Urological Association. 2015;22(2):153-7.
39. Kim DY, Karam JA, Wood CG. Role of metastasectomy for metastatic renal cell carcinoma in the era of targeted therapy. World journal of urology. 2014;32(3):631-42.
40. Pfannschmidt J, Hoffmann H, Muley T, Krysa S, Trainer C, Dienemann H. Prognostic factors for survival after pulmonary resection of metastatic renal cell carcinoma. The Annals of thoracic surgery. 2002;74(5):1653-7.
41. Assouad J, Petkova B, Berna P, Dujon A, Foucault C, Riquet M. Renal cell carcinoma lung metastases surgery: pathologic findings and prognostic factors. The Annals of thoracic surgery. 2007;84(4):1114-20.
42. Cerfolio RJ, Allen MS, Deschamps C, Daly RC, Wallrichs SL, Trastek VF, et al. Pulmonary resection of metastatic renal cell carcinoma. The Annals of thoracic surgery. 1994;57(2):339-44.
43. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. The New England journal of medicine. 1996;335(12):865-75.
44. Staehler MD, Kruse J, Haseke N, Stadler T, Roosen A, Karl A, et al. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. World journal of urology. 2010;28(4):543-7.
45. Ruys AT, Tanis PJ, Nagtegaal ID, van Duijvendijk P, Verhoef C, Porte RJ, et al. Surgical treatment of renal cell cancer liver metastases: a population-based study. Annals of surgical oncology. 2011;18(7):1932-8.
46. Thelen A, Jonas S, Benckert C, Lopez-Hanninen E, Rudolph B, Neumann U, et al. Liver resection for metastases from renal cell carcinoma. World journal of surgery. 2007;31(4):802-7.
47. Langan RC, Ripley RT, Davis JL, Prieto PA, Datrice N, Steinberg SM, et al. Liver directed therapy for renal cell carcinoma. Journal of Cancer. 2012;3:184-90.
48. Lin PP, Mirza AN, Lewis VO, Cannon CP, Tu SM, Tannir NM, et al. Patient survival after surgery for osseous metastases from renal cell carcinoma. The Journal of bone and joint surgery American volume. 2007;89(8):1794-801.
49. Toyoda Y, Shinohara N, Harabayashi T, Abe T, Akino T, Sazawa A, et al. Survival and prognostic classification of patients with metastatic renal cell carcinoma of bone. European urology. 2007;52(1):163-8.
50. Naito S, Kinoshita H, Kondo T, Shinohara N, Kasahara T, Saito K, et al. Prognostic factors of patients with metastatic renal cell carcinoma with removed metastases: a multicenter study of 556 patients. Urology. 2013;82(4):846-51.
51. Tosco L, Van Poppel H, Frea B, Gregoraci G, Joniau S. Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma. European urology. 2013;63(4):646-52.

REVIEW

Urosepsis: How much do we really know?

Mourmouris P., Markopoulos T., Mperdempes M., Skolarikos A.
2nd Department of Urology, University of Athens, Sismanogleio General Hospital, Athens, Greece

Abstract

Sepsis, a syndrome of physiologic, pathologic and biochemical abnormalities induced by infection, is a major public health concern and its incidence is increasing worldwide. Urosepsis represents an approximately 25% of all sepsis cases and it requires a multi-disciplinary team consisted by urologists, intensive care and infectious diseases specialists. We review the literature for potential changes in the steps of recognition and management of this life-threatening syndrome in an effort to widen our knowledge and minimize the risk of complications of sepsis.

Introduction

Sepsis, a syndrome of physiologic, pathologic and biochemical abnormalities induced by infection, is a major public health concern, accounting for more than $20 billion (5.2%) of total US hospital cost in 2011[1]. The reported incidence of sepsis is increasing worldwide[2,3] making this critical condition a leading cause of mortality[4,5]. Even though some changes have been made since the initial definitions developed from the 1991 consensus conference, the sepsis definition has remained largely unchanged for more than 2 decades[6,7]. Urosepsis is seen in both community-acquired and healthcare associated infections it represents an approximately 25% of all sepsis cases and it requires a multi-disciplinary team consisted by urologists, intensive care and infectious diseases specialists[8]. We review the literature about this critical topic and we summarize all the existing knowledge for the management of this life-threatening entity.

Key words
Sepsis, septic shock, definition, management, complications

Definitions and epidemiology

In coherence with the new recommendations, sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection. This new definition emphasizes the primacy of the non-homeostatic host response to infection, the potential lethality that is considerably in excess of a straightforward infection and the need for urgent recognition. Systemic inflammatory response syndrome (SIRS), which is characterized by two or more of: Temperature >38°C or <36°C, heart rate >90 min, respiratory rate >20/min or $PaCO_2$ <32 mmHg,

Mourmouris P., Markopoulos T., Mperdempes M., Skolarikos A.
Urosepsis: How much do we really know?
Hellenic Urology 2018, 30(3): 21-28

Corresponding author:
Mourmouris Panagiotis
2nd Department of Urology, Athens Medical School Sismanogleio General Hospital
1 Sismanogleiou Str Marousi, Athens, Greece tel.: 00302132058102
e-mail: thodoros13@yahoo.com

Table 1 *SOFA score*

System	Score 0	1	2	3	4
PaO_2/FiO_2 mm Hg (kPa)	≥400(53.3)	<400(53.3)	<300(40)	<200 (26.7) with respiratory support	<100(13.3) with respiratory support
Platelets	≥ 150	<150	<100	<50	<20
Bilirubin mg/dl (μmol/L)	<1.2 (30)	1.2-1.9 (20-32)	20-59 (33-101)	6.0-11.9(102-204)	>12.0 (204)
Cardiovascular	MAP ≥ 70 mmHg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Glasgow Scale	15	13-14	10-12	6-9	<6
Creatinine mg/dl	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥5.0
Urine output ml/d				<500	<200

Table 2 *qSOFA (quick SOFA) Criteria*

RESPIRATORY RATE ≥ 22/MIN
ALTERED MENTATION
SYSTOLIC BLOOD PRESSURE ≤100 MM HG

Table 3 *Goal in early resuscitation*

CENTRAL VENOUS PRESSURE 8-12 MM HG
MEAN ARTERIAL PRESSURE ≥65 MM HG
URINE OUTPUT ≥0.5 MLXKG-1 *HR-1
CENTRAL VENOUS(SUPERIOR VENA CAVA) OR MIXED VENOUS OXYGEN SATURATION ≥70%

White Blood Cell count >12.000 /mm^3 or <4000mm^3 or >10% immature bands[6], is no longer included in the terminology of sepsis[9]. In addition, SOFA (Sepsis related Organ Failure Assessment)[10] score (Table 1) is highly recommended not as a tool for patient management but as means to clinically characterize a septic patient. A higher SOFA score is associated with an increased probability of mortality[11]. Nevertheless, SOFA score contains too much information and it is not very helpful in the rapid assessment of a patient developing sepsis. Furthermore, multivariable logistic regression analysis revealed that any 2 of 3 clinical variables (Glasgow Coma Score of 13 or less, systolic blood pressure of 100 mmHg or less and respiratory rate of 22/min or greater offered predictive validity similar to the full SOFA score[12]. This new measure, termed qSOFA (quick SOFA) (Table 2) incorporating the above-mentioned factors, provides simple bedside criteria to identify adult patients with suspected infection who are like to have poor outcomes.

Sepsis is more common in men than in women[13]. Mortality rates vary depending on the organ source[14] with urinary tract sepsis generally having a lower mortality that that from other sources (in hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000)[15,16]. Gram positive bacteria have become the predominant pathogen overall with gram negative bacteria remaining the predominant pathogen in urosepsis[17]. The basic risk factors for developing sepsis are age, diabetes, immunosuppression, anatomic obstruction, stone presence, neurogenic bladder disorders and endoscopic maneuvers.

Physical course

Patients with sepsis have features consistent with immunosuppression, including a loss of delayed hypersensitivity, an inability to clear infection and a predisposition to nosocomial infections[18-20]. The main reason for the above-mentioned failure may be a change in it's physical course. Initially, sepsis is characterized by an increase in inflammatory mediators whereas later in it's course there is a shift toward an anti-inflammatory immunosuppressive state19-20 via cytokines secretion[21]. Another potential mechanism is the death of immune cells via apoptosis and not via necrosis as the conventional belief implied[21-23]. This apoptosis is more likely due to stress- induced endogenous release of glucocorticoids[24-26]. But the real breakthrough in our understanding of the syndrome was the challenging of Lewis Thomas's theory that the body's primary response to infection is uncontrolled hyperinflammation[27]. Quite the opposite: body's normal stress response is activation of anti-inflammatory mechanisms and these mechanism outside the affected tissues, predominate[28]. This knowledge vastly affects the management of this clinical entity since blocking immune cells and cytok-

ines (who have both pathogenic and protective role) can potentially worsen the outcome[28]. Other factors that may have a potential role in sepsis physical course include genetic factors like genetic polymorphisms of TNF-a and TNF-β[29] and excessive release of oxidants and proteases by neutrophils[30], but further analysis of these factors exceeds the role of this study.

Management

Even though the therapeutic approach of a patient with sepsis must be the case of a multidisciplinary team, a clinical urologist must be aware of the basic steps in treating this potential life-threatening syndrome.

Initial Resuscitation

It is of paramount importance to start the resuscitation as soon as the syndrome is recognized (hypotension or lactic acidosis) and not wait for the admission in the ICU. A quick laboratory exam revealing elevated serum lactate concentration could identify tissue hypoperfusion even in patients who haven't already developed hypotension[31]. The important principles to understand in the management of this complex entity is the need for a thorough and detailed clinical examination and evaluation of patient's physiology that can describe their clinical state. In this goal echocardiography can be a valuable partener[32]. The main goals for the first 6 hours of the initial resuscitation is shown on Table 3. All of the above have been shown to improve survival in septic patients in a randomized, controlled, single-center study[33]. The basic rule in everyday practice is the use of fluids to accomplish the goals of Table 3 even though little data exists about the optimal volume of fluids. Most recent trial suggests approximately 30 ml/kg or 2 lt in sum for the initial resuscitation[34-36]. Nevertheless, many patients will require more fluid than this, so functional dynamic measurements will guide physicians. If central venous oxygen saturation or mixed venous saturation of 70% cannot be achieved with fluid administration to a central venous pressure of 8-12 mm Hg, then transfusion of packed red blood cells must be considered with a limit of ≥30%, or administration of dobutamine can be an alternative. It is important to stress the fact that central venous pressure (CVP) alone cannot guide fluid resuscitation because it's ability to predict a response to fluid challenge when CVP is within a relatively normal range (8-12 mm Hg) is limited[37]. On the other hand, mean arterial pressure (MAP) is considered as the driving pressure of tissue perfusion. A recent pilot trial of 118 septic shock patients suggested that in a controlled group of patients mortality was reduced when MAP was in a range of 60- 65 vs 75-80 mm Hg[38].

Diagnosis

Urologist must be aware that sterilization of cultures can occur within minutes to hours after the first dose of an appropriate antimicrobial[39-40]. Even though it is common in every day practice to obtain culture before antibiotic administration, it is important to stress that this practice increase the yield of cultures, making identification of pathogen more likely. The latter play a significant role in de-escalation of antimicrobial therapy which in fact is the cornerstone of minimizing antimicrobial resistance, side effects and costs[41]. Even more this strategy has been associated with improved survival in several observational studies[42]. Fever and signs of sepsis that develop after an endourological operation is more likely to be of urinary origin so except from blood and urine cultures (2 sets, aerobic and anaerobic) all others must be omitted[44]. Despite the common belief, obtaining blood cultures in temperature spikes has not been proven to improve their efficacy[45-46]. Special consideration for the patients with an intravascular catheter must be acquired, so a culture from this catheter must be obtained along with the blood cultures.

Antimicrobial therapy

There are robust data in the literature, that in patients with sepsis or septic shock, each hour delay in administration of appropriate antimicrobials is associated with a substantial increase in mortality[47-48]. In addition, increased delays can potentially influence nearly all other factors related to sepsis (kidney damage, lung injury, organ injury)[49-51]. From the available data the minimal time target for initiation of antimicrobial therapy is set in one hour. The optimum route of administration is intravenous, even though some agents are available for intra-muscular injection, but urologists must bare in mind that data about the efficacy of this route is not yet proven[52-54].

Of paramount importance, as expected, is not only the initiation of an antimicrobial agent, but also the initiation of the correct regiment. The initial selection must be broad enough to cover all likely pathogens. This selection depends of several and complex factors (concomitant underlying diseases, local epidemiologic

factors, location at the time of infection, type of operation etc). Nevertheless, the basic rule is that the most common pathogens that case sepsis are gram negative bacteria followed by gram positive and mixed bacterial microorganisms. If patient have been hospitalized before the procedure, then methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococci can also be held responsible. Despite the variability of these infections throughout the globe, some general suggestions can be provided. A broad-spectrum carbapenem or extended range penicillin/b-lactamase inhibitor combination can be initially used. Alternatively, several third or higher generation cephalosporin could also be utilized especially as a part of multidrug regimen. Which ever drug is decided to be used it is important to be a part of a multi-drug therapy (of at least two different antimicrobial classes) for optimal management of sepsis. If a multidrug resistant pathogen (eg. Pseudomonas, Acinetobacter) is suspected then a supplemental gram negative agent must be added to the empiric regimen. Especially for urological patients, Candida species could be a potential risk for the patient, and if physicians consider that risk sufficient to justify empiric antifungal therapy, then an appropriate drug must be added to the initial therapy.

After the initiation of the empiric regimen, any modifications must be decided with the aid of local and unit specific antibiograms or after the consultation of an infectious diseases physician[55-59]. The doses of different drugs are an important aspect of the management of the disease since it is well proven that failure to achieve peak plasma targets of initial dosing will eventually result is clinical failure of the antibiotic therapy[60-63]. The further analysis of each drug dose is beyond the scope of this study, however the dosing strategies must be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties. Finally, when the pathogen is identified via acquired cultures, de-escalation starting from the less effective agent should be implemented. Even though data for urinary specific infections are not available, a duration of 7-10 days, of an antimicrobial treatment, is adequate for most serious infections[65-67]. Nevertheless the duration should be tailored to the condition of each patient. There are factors like neutropenia, complicated bacteremia that may require prolonged antibiotic treatments (up to 6 weeks). Measurement of procalcitonin levels can help significantly in decision making of the continuation of the antimicrobial therapy[68-73].

Fluid therapy- Vasoactive Medications-Corticosteroids

Modern management of sepsis without the existence of IV fluid does not exist. Despite this there is little available high level of evidence to support its practice. Furthermore, there are authors that imply that a sustained positive fluid balance not only it is not useful but in the contrary it is harmful[74-78]. The basic idea is to omit fluid administration beyond initial resuscitation, if there is no estimate of likelihood that the patient will respond positively. Likewise, colloid solutions failed to prove beneficial compared to crystalloid solutions and so the latter continue to be the fluid of choice for intravascular volume replacement in patients with sepsis. Additionally, as SAFE study and a meta- analysis of 17 studies succeed to prove albumin administration provides better outcomes in terms of patients mortality when compared to other fluid solutions[79-80].

The benefit from the use of vasopressors and inotrope drugs in septic patients have been extensively outlined in a variety of papers in the past[81-83]. Norepinephrine due to its vasoconstrictive effects increase MAP and produce less side effects than dopamine. Also the former is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. In a recent meta-analysis norepinephrine was found to lower mortality and lower risk of arrythmias compared to dopamine[84]. Based on these data norepinephrine must be the first choice in vasopressor therapy. If MAP target is not reached, then adding vasopressin (up to 0.03 u/min) or epinephrine could potentially raise MAP to target and decrease norepinephrine dosage. Of course, it is imperative that patient requiring vasopressors to have an arterial catheter placed as soon as possible[85].

The use of corticosteroids even in low doses, is a wide spread practice but it doesn't seem to be reinforced by the existing literature. Several systematic reviews analyzed the published data concerning this important issue and despite the fact that their results are contradictive they don't seem to acknowledge any benefit it terms of mortality rate[86-89]. Literature doesn't recommend their use in daily practice but there are exceptions like patients with a history of steroid therapy or adrenal dysfunction and patients that despite all other measures hemodynamic stability could not be reached. In this situation the drug of choice is hydrocortisone 200mg/d.

Conclusions

Throughout the years our perspective of sepsis physiology has done a major shift. Sepsis may not be attributable solely to an exaggerating immune system but may indicate a severely compromised immune system that is unable to eradicate pathogens. Early recognition along with rapid initiation of management may decrease mortality of this potentially life threatening syndrome. A very well structured team involving urologists, intensive care specialists, microbiologists and infectious diseases specialists collaborating with each other is essential.

Περίληψη

Η σήψη, ένα σύνδρομο φυσιολογικών, παθολογικών και βιοχημικών ανωμαλιών που προκαλούνται κυρίως από λοίμωξη από παθογόνο μικροοργανισμό, αποτελεί μείζον πρόβλημα δημόσιας υγείας και η συχνότητά της αυξάνεται παγκοσμίως. Η ουροσήψη αντιπροσωπεύει περίπου το 25% όλων των περιπτώσεων σήψης και απαιτεί μια ομάδα αποτελούμενη από ειδικούς ουρολόγους, εντατικολόγους και λοιμωξιολόγους. Ανασκοπούμε τη βιβλιογραφία για πιθανές αλλαγές στα βήματα αναγνώρισης και διαχείρισης αυτού του απειλητικού για τη ζωή συνδρόμου σε μια προσπάθεια να διευρύνουμε τις γνώσεις μας και να ελαχιστοποιήσουμε τον κίνδυνο επιπλοκών της σήψης.

Λέξεις ευρετηριασμού

Σήψη, Σηπτικό σοκ, ορισμός, αντιμετώπιση, επιπλοκές

References

1. Torio CM, Andrews RM, [Accessed October 31, 2015] National inpatient hospital costs: the most expensive conditions by payer, 2011. Statistical Brief #160. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. 2013 Aug. http://www.ncbi.nlm.nih.gov/books/NBK169005/.
2. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc. 2012; 60(6):1070–1077.
3. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013; 41(5):1167–1174.
4. Vincent J-L, Marshall JC, Namendys-Silva SA, et al. ICON Investigators. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. Lancet Respir Med. 2014; 2(5):380–386. [PubMed: 24740011].
5. Fleischmann C, Scherag A, Adhikari NK, et al. International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med. 2015.
6. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992; 20(6):864–874.
7. Levy MM, Fink MP, Marshall JC, et al. International Sepsis Definitions Conference. 2001 SCCM/ ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530–538. [PubMed: 12664219].
8. Wagenlehner FM1, Pilatz A, Naber KG, Weidner W. Therapeutic challenges of urosepsis Eur J Clin Invest. 2008 Oct;38 Suppl 2:45-9.
9. Singer, M., et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016. 315: 801.
10. Vincent JL, Moreno R, Takala J, et al. Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996; 22(7):707–710.
11. Vincent JL, de Mendonça A, Cantraine F, et al. Working Group on "Sepsis-Related Problems" of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998; 26(11):1793–1800. [PubMed: 9824069].
12. Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet. 2013; 381(9868):774–775.
13. Rosser, C.J., et al. Urinary tract infections in the critically ill patient with a urinary catheter. Am J Surg, 1999. 177: 287.
14. Martin, G.S., et al. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med, 2003. 348: 1546.
15. Hotchkiss, R.S., et al. The pathophysiology and treatment of sepsis. N Engl J Med, 2003. 348: 138.
16. Brun-Buisson, C., et al. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med, 2004. 30: 580.
17. Tandogdu, Z., et al. Antimicrobial resistance in urosepsis: outcomes

from the multinational, multicenter global prevalence of infections in urology (GPIU) study 2003-2013. World J Urol, 2016. 34: 1193.
18. Meakins JL, Pietsch JB, Bubenick O, et al. Delayed hypersensitivity: indicator of acquired failure of host defenses in sepsis and trauma. Ann Surg 1977;186:241-50.
19. Lederer JA, Rodrick ML, Mannick JA. The effects of injury on the adaptive immune response. Shock 1999;11:153-9.
20. Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes: understanding the role of innate and acquired immunity. Shock 2001;16:83-96.
21. O'Sullivan ST, Lederer JA, Horgan AF, Chin DHL, Mannick JA, Rodrick ML. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. Ann Surg 1995;222:482-92.
22. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med 1999;27:1230-51.
23. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. J Immunol 2001; 166:6952-63.
24. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Depletion of dendritic cells, but not macrophages, in patients with sepsis. J Immunol 2002;168:2493-500.
25. Fukuzuka K, Edwards CK III, ClareSalzler M, Copeland EM III, Moldawer LL, Mozingo DW. Glucocorticoid-induced, caspase-dependent organ apoptosis early after burn injury. Am J Physiol Regul Integr Comp Physiol 2000;278:R1005-R1018.
26. Ayala A, Herdon CD, Lehman DL, DeMaso CM, Ayala CA, Chaudry IH. The induction of accelerated thymic programmed cell death during polymicrobial sepsis: control by corticosteroids but not tumor necrosis factor. Shock 1995;3:25967.
27. Thomas L. Germs. N Engl J Med 1972; 287:553-5.
28. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med 2001;163:316-21.
29. 69. Freeman BD, Buchman TG. Gene in a haystack: tumor necrosis factor polymorphisms and outcome in sepsis. Crit Care Med 2000;28:3090-1.
30. Kollef MH, Schuster DP. The acute respiratory distress syndrome. N Engl J Med 1995;332:27-37.
31. Levy B (2006) Lactate and shock state: the metabolic view. Curr Opin Crit Care. 12(4):315–321.
32. Cecconi M, De Backer D, Antonelli M et al (2014) Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 40(12):1795–1815.
33. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368 –1377.
34. Peake SL, Delaney A, Bailey M et al (2014) Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371(16):1496–1506.
35. Yealy DM, Kellum JA, Huang DT et al (2014) A randomized trial of protocol-based care for early septic shock. N Engl J Med 370(18):1683–1693.
36. Mouncey PR, Osborn TM, Power GS et al (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372(14):1301–1311.
37. Eskesen TG, Wetterslev M, Perner A (2016) Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. Intensive Care Med 42(3):324–332.
38. Lamontagne F, Meade MO, Hebert PC et al (2016) Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicenter pilot randomized controlled trial. Intensive Care Med 42(4):542–550.
39. Zadroga R, Williams DN, Gottschall R et al (2013) Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. Clin Infect Dis 56(6):790–797.
40. Kanegaye JT, Soliemanzadeh P, Bradley JS (2001) Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 108(5):1169–1174.
41. Pollack LA, van Santen KL, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A (2016) Antibiotic stewardship programs in U.S. acute care hospitals: findings from the 2014 National Healthcare Safety Network Annual Hospital Survey. Clin Infect Dis. 63(4):443–449.
42. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A et al (2013) De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 40(1):32-40.
43. Weiss CH, Persell SD, Wunderink RG, Baker DW (2012) Empiric antibiotic mechanical ventilation, and central venous catheter duration as potential factors mediating the effect of a checklist prompting intervention on mortality: an exploratory analysis. BMC Health Serv Res. 12(1):1.
44. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA (1983) The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 5(1):35–53.
45. Li J, Plorde JJ, Carlson LG (1994) Effects of volume and periodicity on blood cultures. J Clin Microbiol 32(11):2829–2831.
46. Baron EJ, Miller JM, Weinstein MP et al (2013) A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). Clin Infect Dis 57(4):e22–e121.

47. Kumar A, Roberts D, Wood KE et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34(6):1589–1596.
48. Ferrer R, Martin-Loeches I, Phillips G et al (2014) Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 42(8):1749–1755.
49. Bagshaw SM, Lapinsky S, Dial S et al (2009) Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. Intensive Care Med 35(5):871–881.
50. Iscimen R, Cartin-Ceba R, Yilmaz M et al (2008) Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. Crit Care Med 36(5):1518–1522.
51. Garnacho-Montero J, Aldabo-Pallas Garnacho-Montero C et al (2006) Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis Crit Care 10(4):R111.
52. Romanelli G, Cravarezza P, Group IIMS (1995) Intramuscular meropenem in the treatment of bacterial infections of the urinary and lower respiratory tracts. J Antimicrob Chemother 36(suppl A):109–119.
53. Cormio L, Berardi B, Callea A et al (2002) Antimicrobial prophylaxis for transrectal prostatic biopsy: a prospective study of ciprofloxacin vs piperacillin/tazobactam. BJU Int 90(7):700–702.
54. Barbhaiya RH, Knupp CA, Tenney J, Martin RR, Weidler DJ, Pittman KA (1990) Safety, tolerance, and pharmacokinetics of cefepime administered intramuscularly to healthy subjects. J Clin Pharmacol 30(10):900–910.
55. Green DL (2005) Selection of an empiric antibiotic regimen for hospital-acquired pneumonia using a unit and culture-type specific antibiogram. J Intensive Care Med. 20(5):296–301.
56. Kaufman D, Haas CE, Edinger R, Hollick G (1998) Antibiotic susceptibility in the surgical intensive care unit compared with the hospital-wide antibiogram. Arch Surg 133(10):1041–1045.
57. Kerremans JJ, Verbrugh HA, Vos MC (2012) Frequency of microbiologically correct antibiotic therapy increased by infectious disease consultations and microbiological results. J Clin Microbiol 50(6):2066–2068.
58. Raineri E, Pan A, Mondello P, Acquarolo A, Candiani A, Crema L (2008) Role of the infectious diseases specialist consultant on the appropriateness of antimicrobial therapy prescription in an intensive care unit. Am J Infect Control 36(4):283–290.
59. Bai AD, Showler A, Burry L et al (2015) Impact of infectious disease consultation on quality of care, mortality, and length of stay in Staphylococcus aureus bacteremia: results from a large multicenter cohort study. Clin Infect Dis 60(10):1451–1461.
60. Moore RD, Smith CR, Lietman PS (1984) Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. Am J Med 77(4):657–662.
61. Men P, Li HB, Zhai SD, Zhao RS (2016) Association between the AUC0-24/MIC ratio of vancomycin and its clinical effectiveness: a systematic review and meta-analysis. PLoS One 11(1):e0146224.
62. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ (2004) Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 43(13):925–942.
63. Zelenitsky S, Rubinstein E, Ariano R et al (2013) Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus associated septic shock. Int J Antimicrob Agents 41(3):255–260.
64. Kalil AC, Metersky ML, Klompas M et al (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clin ical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63(5):e61–e111.
65. Chastre J, Wolff M, Fagon JY et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290(19):2588–2598.
66. Choudhury G, Mandal P, Singanayagam A, Akram AR, Chalmers JD, Hill AT (2011) Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia-a propensity-adjusted analysis. Clin Microbiol Infect 17(12):1852–1858.
67. Pugh R, Grant C, Cooke RP, Dempsey G (2015) Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev 8:CD007577.
68. Schuetz P, Briel M, Christ-Crain M et al (2012) Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis 55(5):651–662.
69. Matthaiou DK, Ntani G, Kontogiorgi M, Poulakou G, Armaganidis A, Dimopoulos G (2012) An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. Intensive Care Med 38(6):940–949.
70. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P (2013) Procalcitonin guided therapy in intensive care unit patients with severe sepsis and septic shock–a systematic review and meta-analysis. Crit Care 17(6):R291.
71. Westwood M, Ramaekers B, Whiting P et al (2015) Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis. Health Technol Assess 19(96):v–xxv, 1–236.
72. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P (2013) Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 13(5):426–435.
73. Soni NJ, Samson DJ, Galaydick JL et al (2013) Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. J Hosp Med. 8(9):530–540.

74. Acheampong A, Vincent JL (2015) A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care 19:251.
75. Brotfain E, Koyfman L, Toledano R et al (2016) Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. Am J Emerg Med 34(11):2122–2126.
76. Mitchell KH, Carlbom D, Caldwell E, Leary PJ, Himmelfarb J, Hough CL (2015) Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. Ann Am Thorac Soc. 12(12):1837–1844.
77. De Oliveira FS, Freitas FG, Ferreira EM et al (2015) Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock. J Crit Care 30(1):97–101.
78. Malbrain ML, Marik PE, Witters I et al (2014) Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 46(5):361–380.
79. Finfer S, Norton R, Bellomo R, Boyce N, French J, Myburgh J (2004) The SAFE study: saline vs. albumin for fluid resuscitation in the critically ill. Vox Sang 87(Suppl 2):123–131.
80. Delaney AP, Dan A, McCaffrey J, Finfer S (2011) The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 39(2):386–391.
81. Day NP, Phu NH, Bethell DP et al (1996) The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. Lancet 348(9022):219–223.
82. De Backer D, Creteur J, Silva E, Vincent JL (2003) Effects of dopamine norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 31(6):1659–1667.
83. Yamazaki T, Shimada Y, Taenaka N, Oshumi H, Takezawa J, Yoshiya I (1982) Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. Crit Care Med 10(7):432–435.
84. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A (2015) Vasopressors for the treatment of septic shock: systematic review and meta- analysis. PLoS One 10(8):e0129305.
85. Cohn JN (1967) Blood pressure measurement in shock. Mechanism of inaccuracy in ausculatory and palpatory methods. JAMA 199(13):118–122.
86. Sprung CL, Annane D, Keh D et al (2008) Hydrocortisone therapy for patients with septic shock. N Engl J Med 358(2):111–124.
87. Sligl WI, Milner DA Jr, Sundar S, Mphatswe W, Majumdar SR (2009) Safety and efficacy of corticosteroids for the treatment of septic shock a systematic review and meta-analysis. Clin Infect Dis 49(1):93–101.
88. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y (2015) Corticosteroids for treating sepsis. Cochrane Database Syst Rev 12:CD002243.
89. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F (2015) Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 41(7):1220–1234.

REVIEW

How different treatments for clinically localised prostate cancer affect quality of life

Lardas Michael [1], Papachristou Christos [1], Chrysafis Emmanouil [1], Skolarikos Andreas [2]
[1] Urology Department, LETO Obstetrics, Gynaecology & Surgery Centre, Athens, Greece
[2] 2nd Department of Urology, University of Athens, Sismanogleio General Hospital, Greece

Abstract

Introduction: Patients with clinically localised prostate cancer have a favourable long-term overall and cancer-specific survival regardless of treatment choice. These options differ in terms of side effects. Knowledge of the side effects of different management options is crucial for making treatment decisions, as they can negatively impact on patient's quality of life.

Methods: We conducted a literature review for articles concerning treatment and quality of life for clinically localised prostate cancer to access the impact of different treatments on patient's quality of life.

Results: We identified 5 prospective randomised comparative studies reporting QoL outcomes, recruiting a total of 2933 patients.

Conclusion: Surgery seems to produce sexual and urinary incontinence deterioration, while external beam radiotherapy can cause bowel dysfunction and bother. Men managed with active surveillance have good overall quality of life scores, which seem to be better than those of patients undergoing radical treatments.

Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer among men in Europe[1]. Since the introduction of PSA testing, there has been a substantial shift to a more favourable stage at presentation of newly diagnosed disease, with approximately 81% of cases being diagnosed at a clinically localised stage[2]. Currently, evidence-based management for clinically localised PCa includes active surveillance (AS), surgery, external beam radiotherapy (EBRT) and brachytherapy (BT)[3].

Key words
Localised Prostate Cancer, Quality of life, Radical Prostatectomy; Radiotherapy, Active surveillance, Brachytherapy

While patients with clinically localised prostate cancer have a favourable long-term overall and cancer-specific survival regardless of treatment choice[4], these options differ in terms of side effects. Knowledge of the adverse events of different management options is crucial for making treatment decisions, as they can negatively impact on patient's

Lardas M., Papachristou C., Chrysafis E., Skolarikos A.
How different treatments for clinically localised prostate cancer affect quality of life.
Hellenic Urology 2018, 30(3): 29-32

Corresponding author:
Michael Lardas
E-mail: lardamk@gmail.com

quality of life (QoL). The objective of this review is to determine how different treatments for clinically localised PCa can influence the QoL of patients.

Material and Methods

We conducted a literature review for articles concerning treatment and QoL for clinically localised PCa. The search was limited to studies published from the year 2000 onwards in English language and indexed in PubMed. Only prospective randomised comparative studies (RCTs) reporting QoL outcomes with at least 12 months of follow up, were eligible for inclusion. The study population was adult men (≥18 years of age) diagnosed with clinically localised PCa that had not undergone any previous treatment for PCa. The following interventions were eligible for inclusion: AS, watchful waiting, radical prostatectomy (RP) (Open or Laparoscopic or Robot-Assisted), EBRT (any type) and BT.

Results

A total of 5 RCTs[5-9] were included, recruiting 2933 patients. Four studies[5-8] used specific questionnaires, otherwise called Patient Reported Outcome Measures (PROMs). These questionnaires have been developed and validated to assess common issues that affect men after PCa diagnosis and treatment and generate scores, which reflect the impact on perceptions of QoL.

The most noteworthy RCT, was the Prostate Testing for Cancer and Treatment (ProtecT) trial[6] where 1643 men aged 50-69 years, were randomised to active monitoring, RP or EBRT. It must be noted though, that approximately 50% (291) of men who initially underwent active monitoring had either surgery or radiotherapy by the completion of the trial. The study reported no difference in QoL of these patients for up to 5 years of follow-up, when using the EORTC QLQ-C30 questionnaire. However, when using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, the authors found that urinary summary, urinary incontinence and sexual summary, function and bother scores were worse in men treated with RP compared to active monitoring or EBRT. On the other hand, the authors also reported that bowel function, bother and summary scores were poorer for men receiving radiotherapy when compared to RP or active monitoring.

Similar observations have been reported for patients undergoing RP and watchful waiting in the most recent publication of the Scandinavian Prostate Cancer Group-4 (SPCG-4) trial[8] for a median follow up of 12.2 years. In this RCT, 695 men younger than 75 years with clinically localised prostate cancer and a life expectancy of more than 10 years were randomly assigned to radical prostatectomy or watchful waiting. The authors used a study-specific questionnaire and found that men who underwent surgery reported an inability to satisfy sexual partner. Notably, in both groups high occurrence of erectile dysfunction was present. Urinary leakage was more common after radical prostatectomy than with watchful waiting and an increased occurrence of urinary emptying symptoms was noted in men allocated watchful waiting, but average levels of self-assessed QoL were similar in the two SPCG-4 groups.

Two other RCTs[5, 7] compared QoL after RP vs BT using PROMs. The Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT)[5] enrolled 168 men with low-risk PCa (Gleason score ≤ 6, PSA < 10 ng/mL, stage T1 to T2a) who received either RP (66) or BT (102). This RCT has a high selection bias, as only 19% of patients were randomly assigned to treatment arms and was closed prematurely, due to poor accrual. The investigators using the EPIC questionnaire, found a statistically significant difference in the urinary and sexual domain, favouring men treated with BT at a mean follow up of 5.2 years.

Gilberti et al[7] recruited 200 patients and had the same inclusion criteria as SPIRIT trial. The authors used 2 different questionnaires: the EORTC-QLQ-C30 and the EORTC-QLQ- PR25 and compared pre-treatment and post-treatment scores in men undergoing BT and in men undergoing RP. It is notable that only within group scores were reported in this trial (there was no direct comparison of scores in patients undergoing BT vs scores in patients undergoing RP). The authors found that there were no statistically significant differences in both questionnaire scores at 5 years of follow up and concluded that these 2 treatment options produce similar long-term functional outcomes.

Finally, the Prostate Cancer Intervention versus Observation Trial (PIVOT)[9] included 731 men younger than 75, with localized prostate cancer, who were randomly assigned to either RP or observation. The investigators of this trial did not use a PROM questionnaire and only assessed the prevalence of urinary incontinence and erectile and bowel dysfunction at 2 years of follow-up, which was based on self-reported dysfunction that was at least moderate in severity. The authors reported that at 2 years, urinary incontinence

and erectile dysfunction but not bowel dysfunction, were significantly more common among men who were assigned to RP when compared to men managed with observation.

Discussion

As QoL considerations largely rely on an individual's values and preferences, it may be that the different interventions for localised PCa are not equally acceptable from a personal point of view. Therefore, given the number of choices available and their potential side effects, newly diagnosed PCa patients may experience difficulty in deciding which treatment is best suited for them. The EAU Prostate Cancer Guidelines Panel recommends shared decision-making[3]. However, when involving patients in decision making, it is important that they have an accurate understanding of the differences amongst the treatment options. That is why, from the early 2000's, there is a growing interest in the use of PROMs, which has led to the development of instruments designed specifically for localized prostate cancer patients[10, 11].

The ProtecT trial[6] using two of these PROMs, provided level 1 evidence for what was already known. The trial confirmed that surgery had a negative effect on urinary continence and sexual function, EBRT was associated with a negative effect in bowel function which was more intense the first year after treatment, while active monitoring had the lowest impact on QoL. Similar results have been previously reported by several other observational studies. A notable observational study[12] compared men undergoing RP vs EBRT vs BT using the University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) questionnaire and authors reported that there was a significant bowel function decline for men treated with EBRT and in bowel bother score for men treated with BT or EBRT. Men treated with RP had a significant urinary and sexual function decline at 2 years of follow-up.

In a large study including 1201 patients Sanda et al[13] using the EPIC tool, compared clinically relevant differences within treatment groups in QoL scores (a difference that exceeded half a standard deviation of the baseline value) from baseline to 2 years post treatment. Patients in the RP group reported significant decline in urinary continence and sexual function as compared with baseline, however urinary irritation/obstruction scores significantly improved after surgery. EBRT was also associated with improvement in urinary irritation/obstruction scores but with reduced QoL related to bowel function. Surprisingly, in that study patients in the BT group reported significant reduction in all QoL scores.

The most important observational study was The Prostate Cancer Outcomes Study (PCOS)[14] that used a cohort of 1655 men, of whom 1164 had undergone RP and 491 EBRT. The study reported that at 5 years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and erectile dysfunction, while men treated with radiotherapy had a higher prevalence of bowel dysfunction. However, despite these differences detected at 5 years, there were no significant differences of urinary incontinence, bowel dysfunction or erectile dysfunction between RP and radiotherapy at 15 years[15]. Recently, Barocas et al[16] using the EPIC questionnaire in a cohort of 2,121 men, reported that RP was associated with a greater decrease in sexual function and urinary incontinence than EBRT at 3 years of follow up. No clinically meaningful differences existed in bowel function beyond 12 months between RP and EBRT.

Conclusion

In conclusion, RP seems to produce sexual and urinary incontinence deterioration, while EBRT can cause bowel dysfunction and bother. Men managed with AS have good overall QoL scores, which seem to be better than those of patients undergoing radical treatments. Data for BT are scarce, but based on what is available, brachytherapy seems to have a negative impact on urinary function at 1 year, but there are no significant differences in QoL 5 years after treatment. Clinicians and patients with localised PCa should be informed of these different adverse events and their impact on QoL, before making treatment decisions.

Conflicts of interest

The authors declared no conflicts of interest.

Περίληψη

Σκοπός: Οι επιλογές θεραπείας σε ασθενείς με κλινικά εντοπισμένο καρκίνο προστάτη περιλαμβάνουν την ενεργή παρακολούθηση, τη ριζική προστατεκτομή, την εξωτερική ακτινοθεραπεία και τη βραχυθεραπεία. Οι θεραπείες αυτές έχουν διαφορετικές επιπτώσεις στην ποιότητα ζωής των ασθενών.

Μέθοδος: Πραγματοποιήσαμε μια ανασκόπηση της βιβλιογραφίας για τυχαιοποιημένες μελέτες, οι οποίες πραγματεύονται τη θεραπεία των ασθενών με τοπικά εντοπισμένο καρκίνο προστάτη και την επίπτωση των θεραπειών αυτών στην ποιότητα ζωής.

Λέξεις ευρετηριασμού

Τοπικά εντοπισμένος καρκίνος προστάτη, ποιότητα ζωής, ριζική προστατεκτομή, ακτινοθεραπεία, βραχυθεραπεία, ενεργός παρακολούθηση

Αποτελέσματα: Αναγνωρίσαμε 5 τυχαιοποιημένες μελέτες, οι οποίες περιλαμβάνουν συνολικά 2.933 ασθενείς

Συμπεράσματα: Η ριζική προστατεκτομή φαίνεται να έχει αρνητική επίπτωση στην εγκράτεια ούρων και στην σεξουαλική λειτουργία, ενώ η εξωτερική ακτινοθεραπεία επηρεάζει αρνητικά την εντερική λειτουργία. Οι ασθενείς που ακολουθούν ενεργό παρακολούθηση έχουν τις λιγότερες επιπτώσεις στην ποιότητα ζωής τους.

References

1. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer. 2015;51:1164-87.
2. Newcomer LM, Stanford JL, Blumenstein BA, Brawer MK. Temporal trends in rates of prostate cancer: declining incidence of advanced stage disease, 1974 to 1994. J Urol. 1997;158:1427-30.
3. N. Mottet JB, E. Briers, R.C.N. van den Bergh, M. Bolla, N.J. van Casteren, P. Cornford, S. Culine, S. Joniau, T. Lam, M.D. Mason, V. Matveev, H. van der Poel, T.H. van der Kwast, O. Rouvière, T. Wiegel. Guidelines on Prostate Cancer. Accessed 12/07/16 at https://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf 2015.
4. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375:1415-24.
5. Crook JM, Gomez-Iturriaga A, Wallace K, Ma C, Fung S, Alibhai S, et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. J Clin Oncol. 2011;29:362-8.
6. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375:1425-37.
7. Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. World J Urol. 2009;27:607-12.
8. Johansson E, Steineck G, Holmberg L, Johansson J-E, Nyberg T, Ruutu M, et al. Long-term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian Prostate Cancer Group-4 randomised trial. The Lancet Oncology. 2011;12:891-9.
9. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203-13.
10. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the Expanded Prostate Cancer Index Composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56:899–905.
11. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998;36:1002-12.
12. Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol. 2015;68:600-8.
13. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008;358:1250-61.
14. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst. 2004;96:1358-67.
15. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368:436-45.
16. Barocas DA, Alvarez J, Resnick MJ, Koyama T, Hoffman KE, Tyson MD, et al. Association Between Radiation Therapy, Surgery, or Observation for Localized Prostate Cancer and Patient-Reported Outcomes After 3 Years. JAMA. 2017;317:1126-40.

CASE REPORT

Maximizing success for penile prosthesis revision surgery after glans penis erosion: operative strategies.

Kousournas Georgios [1,2], Drettas Petros [1], Levis Panagiotis [2], Spanos[2] Nikolaos
[1]Andrology Piraeus
[2]1st University Urology Clinic, National and Kapodistrian University of Athens, "Laiko" General Hospital

Abstract

We present the case of a 68-year-old male who presented with an inflatable penile prosthesis protruding through the glans penis. A thorough preoperative investigation was conducted, in order to perform an evidence-based surgical approach, aiming to remove the prosthetic materials and reconstruct all compromised penile structures in order to maximize the chance for a future prosthesis reimplantation. Although the insertion of a penile prosthesis has become a routine procedure, managing complications has always been one of the most challenging aspects of prosthetic urology.

INTRODUCTION

Alongside infection, erosion constitutes one of the most feared and potentially catastrophic inflatable penile prosthesis' complications [1]. Although the insertion of a penile prosthesis in uncomplicated cases has become a relatively straightforward and standardized procedure, knowing how to manage complications in any way or at any time point they may present, distinguishes between novice and serious implanters. In such complex cases, managing complications with precise preoperative planning, in a timely and structured manner, maximizes the chances for a successful resolve and future reimplantation. We present a case of a penile prosthesis erosion, giving emphasis to the preoperative planning and the operative techniques used to set the foundation for a successful reimplantation.

Key words
penile prosthesis, IPP, reconstructive urology, complications, prosthesis protrusion

CASE PRESENTATION

A 68-year-old male presented with a cylinder protruding from the glans penis since the last couple of months. No signs of infection were macroscop-

Kousournas G., Drettas P., Levis P., Spanos N.
Maximizing success for penile prosthesis revision surgery after glans penis erosion: operative strategies. *Hellenic Urology* 2018, 30(3): 33-37

Corresponding author:
Georgios Kousournas, Andrology Piraeus/1st University Urology Clinic, National and Kapodistrian University of Athens, "Laiko" General Hospital, E-mail: giorgoskousournas@gmail.com, Tel: 00306970097117

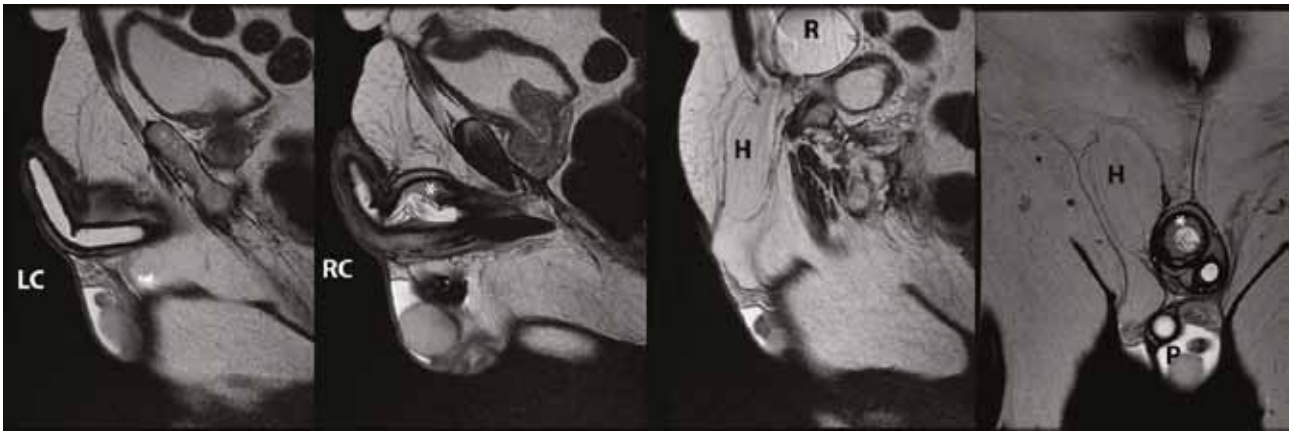


Figure 1. *RC: Right cylinder, LC: Left cylinder, H: Hernia sac, P: Pump, *: Peri-prosthetic fluid*

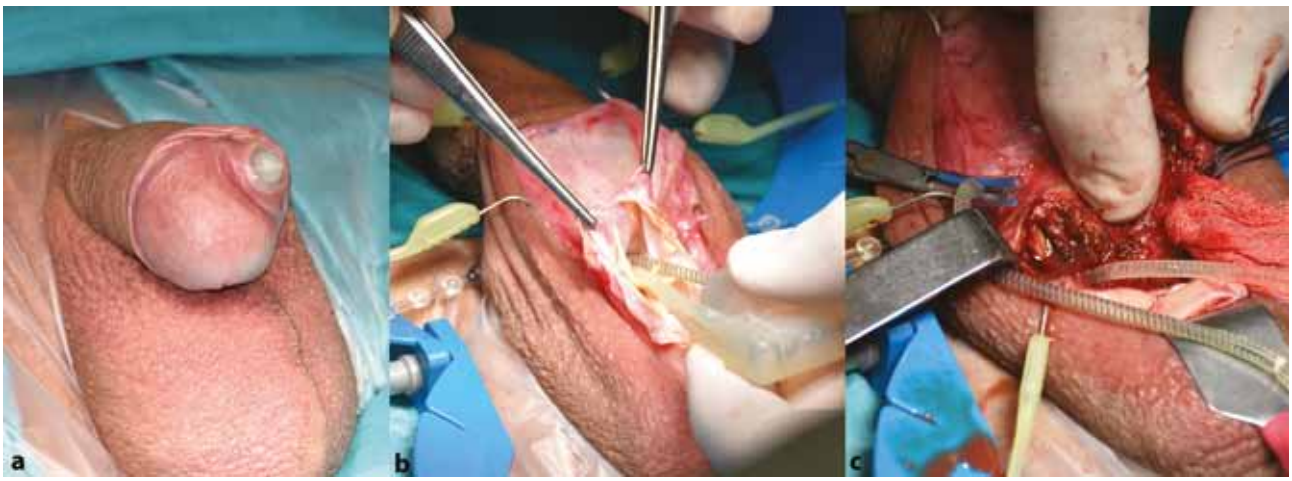


Figure 2. *a: Cylinder extrusion b: Pump removal c: Right corpus cavernosum, brownish peri- prosthetic fluid.*

ically and clinically evident at the time of presentation. The 3-piece penile prosthesis was implanted 13 years ago, after a work accident that resulted among others in multiple fractures of the pelvic region, involving the sacrum and the 3 lower lumbar vertebrae. At the time of the accident, a posterior urethral disruption injury was identified and treated with primary endoscopic realignment. Alongside erectile dysfunction, the patient developed a neurogenic bladder, for which he is treated with antimuscarinics and clean intermittent self-catheterization. According to the patient, since the last 5 years, the timing of the catheterizations was erratic, due to the discomfort that his enlarged prostate was causing.

Imaging was planned and a magnetic resonance imaging (MRI) tomography **(Figure 1)** of the pelvic region was performed. The examination revealed a full reservoir in the right retropubic space, next to the urinary bladder which presented with many small diverticula. A large inguinal hernia sac, involving a considerable portion of the omentum and the reservoir tube was present at the right side. The right cylinder of the prosthesis presented with a considerable amount of peri-prosthetic fluid, compatible with cylinder leakage, as the cylinder itself was not inflated. The left cylinder, was semi-inflated and protruding from the glans penis. The place and condition of the pump were unremarkable.

The patient was given antibiotics (fluoroquinolone for 10 days) and a surgical removal was planned. Preoperatively, a thorough scrubbing was performed, as if in a virgin penile prosthesis insertion case. All operative strategies were followed, in order to minimize the risk of infection (limitation of people in the operating room, lower temperature in the operating theater, having all possible surgical instruments available). Broad spectrum antibiotics were administered intravenously **(Figure 2a)**. A longitudinal low penoscrotal incision was per-

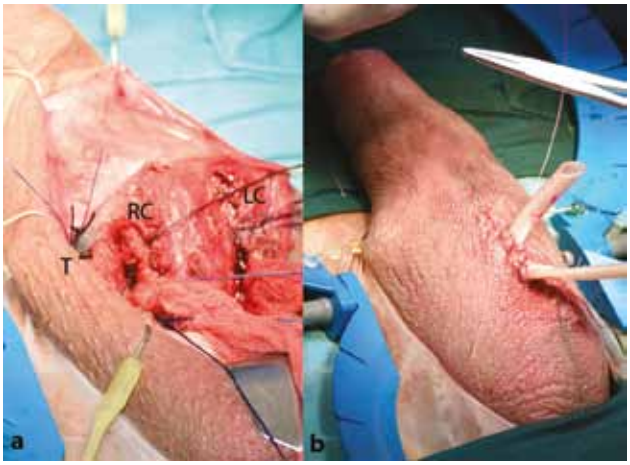


Figure 3. *RC: Right corporotomy, LC: Left corporotomy, T: watertight-sealed tube towards the reservoir.*

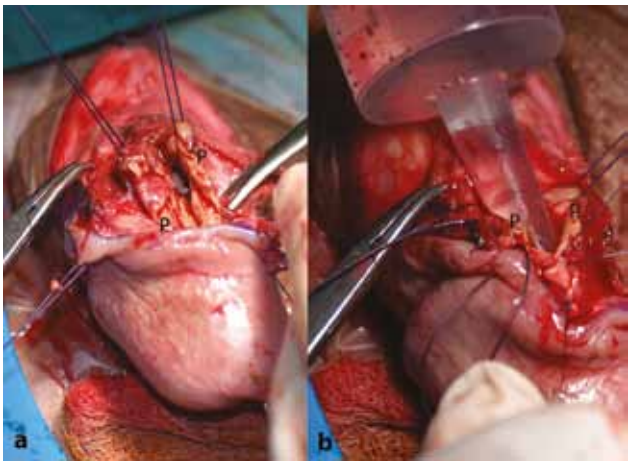


Figure 4. *Pseudocapsule release and corporoplasty procedure (P: Pseudocapsule).*

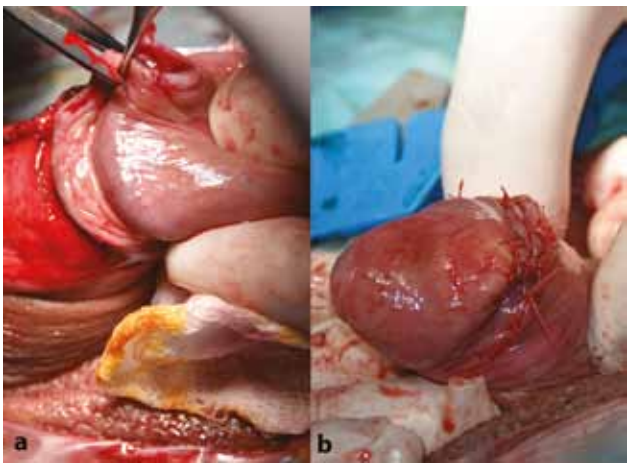


Figure 5. *Glans penis reconstruction.*

Figure 6. *Final result, postoperative day 5.*

formed and the pump was released from the scrotal pouch **(Figure 2b)**. Following the tubing, the left corpus cavernosum was identified and incised as low towards the crus as possible, in order to remove the left cylinder. Special attention was given in order to remove the rear tip extenders (RTE). The same approach was used on the right side, where a brownish liquid was identified and collected for cultures **(Figure 2c)**. The right cylinder presented eroded and perforated. Following the tube to the reservoir, the connection point was found and the tube of the reservoir was cut after a tubing-shod hemostat was placed to prevent leakage. A silk suture was used to perform a watertight closure of the tube and facilitate identification in a future time **(Figure 3a)**. A thorough lavage with an antibiotic solution was used in all cavities and two Penrose drains were passed through the cavernosal incisions through the whole corpora cavernosa lengths. The corporotomies were closed, as well as the penoscrotal incision, leaving small openings for the drains **(Figure 3b)**.

In order to facilitate access to the erosion site, a half sub coronal incision towards the right side was performed and Buck's fascia was identified and incised parallel to the urethra. Underneath Buck's fascia, the left corpus cavernosum was identified and incised. The incision was extended to the lower limit of the glanular defect. The pseudocapsule of the cylinder was identified and meticulously divided from the surrounding tissues **(Figure 4a)**. The tip of a 60cc syringe was used primarily as a scaffold, but also as a guide towards the correct longitudinal axis of the corpus cavernosum and the pseudocapsule was used to close the cavernosal defect

(Figure 4b). The reconstruction was reinforced with the overlying layer of Buck's fascia and an extra layer of subcutaneous and dartos tissue. The water tightness of the reconstruction was tested. A thorough debridement of the glanular defect edges was performed. The defect was trimmed, rotated and stitched as in a form of z-plasty, in order to ensure healthy tissue on top of the reconstructed corporal tip **(Figure 5)**. The sub coronal incision was closed and the penile shaft was dressed with a gauge bandage roll.

The postoperative period was unremarkable and the patient exited the hospital on the same day. Both Penrose drains were removed after 24 hours and the mummy-wrap was removed after 48 hours. The surgical and aesthetic result was excellent **(Figure 6)**.

DISCUSSION

Infection is a most feared complication of prosthetic surgery [2]. It has been well prescribed that most prosthetic materials develop a bacterial biofilm, even without presenting with a clinical infection. It has also been suggested that a critical threshold of the biofilm extent might exist, beyond which an infection might occur [3]. Therefore, proper use of antibiotics must be a routine [4].

Before each complex case, a careful preoperative planning is of outmost importance. The MRI computed tomography has proven its superiority compared to the conventional ultrasound scan in revealing penile prosthesis' complications [5].

In our case, the urinary bladder diverticula and the inguinal hernia on the same side as the reservoir, rendered its removal a true riddle [6]. Either we would proceed with a potentially difficult removal of the reservoir, or we could leave it in situ and use it in a future reimplantation surgery, revisioning only the cylinders and the pump. What should be also noted, is the suggestion that replacing a single and not all prosthetic parts, results in higher infection rates and lower overall device survival rates [7,8]. With all of this information in mind, we opted for a third solution. Since the reservoir was full and with no signs of leakage, we opted to leave it in place, in order to be used as a guide primarily for future surgery, in order to enter Retzius' space without compromising the bladder and secondarily as a means to have a dedicated expanded space for the new reservoir.

During the removal of the cylinders, we performed the corporotomies as low towards the crura as possible, in order not to compromise the corpora cavernosa of the penile shaft. The rationale behind this decision is that the point where the tubes exit the cylinders should be as low as possible and that generally, potential crural complications are easier to manage [9]. The right corpus cavernosum tip was reconstructed using the pseudocapsule that was formed around the protruding cylinder [10]. This method is also proposed in cases of impending erosion. It is our opinion, that the usage of synthetic materials such as dacron or grafts such as SIS (small intestine submucosa) or Epiflex (acellular human dermis), should be kept in the armament of the prosthetic urologist for extreme cases, in lack of native tissue.

Last but not least, the glans penis presented with a defect. The reconstruction is not only cosmetically compelled, but it is also of great importance for the coitus and the survival of the new prosthesis. It has been suggested that the glans penis restricts the increase in intracavernosal pressure during coitus and plays a protective role for both the corpora cavernosa and the female genitalia [11]. This suggestion is even more important in our case, where the glans penis remains flaccid during intercourse, the right corpus cavernosum has been compromised and reconstructed and the mechanics, rigidity and elasticity of the penile prosthesis are different from those of a naturally engorged corpus cavernosum.

In conclusion, special attention was given to every aspect of the operation, in an effort to achieve both an aesthetically correct and functional result, in order to facilitate the replacement of the penile prosthesis in a future operation.

CONCLUSION

Prosthetic and reconstructive urology is a challenging field. Many urologists are capable of performing a textbook placement of a penile prosthesis, but not all are capable of managing complications. Even fewer are skilled to perform a reconstruction focused on the replacement of the prosthetic parts, in order to achieve both cosmesis and function. In every case, familiarization with all available techniques, continuous education and training and respect of basic and advanced surgical principles, are keys to a successful outcome.

Περίληψη

Η τοποθέτηση πεϊκής πρόθεσης έχει γίνει μια επέμβαση ρουτίνας σε παρθένα περιστατικά. Τα πράγματα όμως περιπλέκονται σε περιπτώσεις επιπλοκών, όπου η αντιμετώπιση παίζει σημαντικό ρόλο στο τελικό λειτουργικό και αισθητικό αποτέλεσμα. Στο περιστατικό που παρουσιάζεται, η πεϊκή πρόθεση, τοποθετημένη αρχικά προ 13 ετών, εξήλθε του σηραγγώδους σώματος μέσω της βαλάνου. Απεικονιστικά, αναδείχθηκε συλλογή υγρού περιξ του έτερου κυλίνδρου καθώς και ευμεγέθης βουβωνοκήλη συστοίχως του ρεζερβουάρ. Κατά την επέμβαση, διενεργήθηκε αφαίρεση των κυλίνδρων, επιμελής ανακατασκευή του διαβρωμένου σηραγγώδους και ανακατασκευή της βαλάνου. Η μετεγχειρητική πορεία ήταν ανεπίπλεκτη και το τελικό αποτέλεσμα άριστο. Η επανατοποθέτηση των υλικών προγραμματίστηκε σε δεύτερο χρόνο.

Λέξεις ευρετηριασμού

πεϊκή πρόθεση, επιπλοκή πρόθεσης, ανακατασκευή, επανορθωτική ουρολογία

References

1. Stember DS, Kohler TS, Morey AF et al. Management of Perforation Injuries During and Following Penile Prosthesis Surgery. J Sex Med 2015;12(suppl 7):456–461.
2. Wilson SK. The complicated implant J Sex Med 2006;3(suppl 2):87–89.
3. Silverstein AD, Henry GD, Evans B et al. Biofilm formation on clinically noninfected penile prostheses J Urol 2006, 176(3):1008-1011.
4. Henry GD, Wilson SK, Delk JR II et al. Revision washout reduces penile prosthesis infection in revision surgery: A multicenter study. J Urol 2005; 173:89-92.
5. Moncada I, Jara J, Cabello R et al. Radiological assessment of penile prosthesis: the role of magnetic resonance imaging. World J Urol 2004;22(5):371-377.
6. Henry GD, Laborde E. A review of surgical techniques for impending distal erosion and intraoperative penile implant complications: Part 2 of a three-part review series on penile prosthetic surgery. J Sex Med 2012; 9:927-936.
7. Henry GD, Wilson SK, Donatucci C et al. Single component exchange during penile prosthesis revision appears to have higher infection rates and lower overall device survival rates than complete component replacement: a multicenter analysis. J Urol 2012;187(4), Suppl: e752-e753.
8. Morey AF, Cefalu CA, Hudak SJ. High submuscular placement of prosthetic balloons and reservoirs via transscrotal approach. J Sex Med 2013; 10:603-610
9. Mulcahy JJ. Crural perforation during penile prosthetic surgery. JSex Med 2006;3(1):177-180.
10. Carson CC, Noh CH. Distal penile prosthesis extrusion: treatment with distal corporoplasty or Gortex windsock reinforcement. Int J Impot Res 2002;14(2):81-84.
11. Hatzichristou DG, Tzortzis V, Hatzimouratidis K et al. Protective role of the glans penis during coitus. Int J Impot Res 2003; 14:337-342.

CASE REPORT

Repair of iatrogenic ureteral injury with a combination of "Boari flap" and "Psoas Hitch" technique

Tzelves Lazaros, Berdempes Marinos, Markopoulos Titos, Lazarou Lazaros, Zerva Maria, Pinitas Alexandros, Xatzikraxtis Nikolaos, Mitsogiannis Iraklis, Karagiotis Euaggelos, Skolarikos Andreas

[1] *2nd Department of Urology, Sismanogleion Hospital, National and Kapodistrian University of Athens, Athens, Greece*

Abstract

A common cause of ureter trauma is iatrogenic, especially during gynecologic and obstetric procedures. Early diagnosis is of vital importance for the successful management of these patients and depends on the type, anatomic location and length of ureteral deficit. Preoperative placement of ureteral stent does not seem to reduce incidence of these cases. For extended length traumas, surgical techniques like Boari flap and Psoas hitch have been reported, in order to reconstruct ureter and accomplish ureteroneocystostomy. We describe the case of a patient, who presented with a deficit of 13 cm after sigmoidectomy. We performed a combination of Boari flap and Psoas hitch successfully and restored the continuity of urinary tract.

Key words

Boari flap, Psoas hitch, iatrogenic ureteral trauma, ureteroneocystostomy, ureteric stricture, ureteral injury

Introduction:

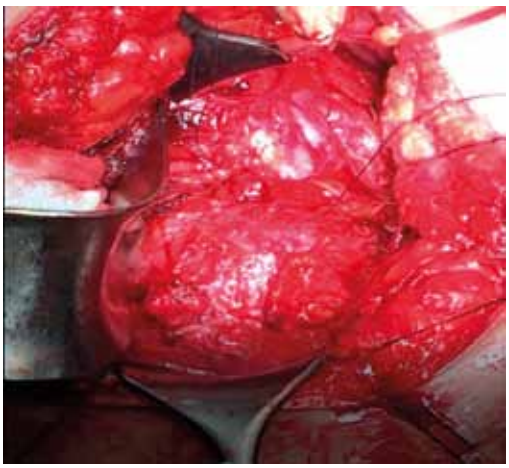
Ureteral injury may occur during abdominal or pelvic surgery at 0.5-1.5% of cases (2-9). The leading cause is obstetric/gynecologic surgeries with reported incidence of 0.07-1.70%(10-20) followed by general surgery operations with incidence ranging from 0.24 to 1.95%(2,11,21,22,23,24). Urological procedures, especially endoscopic such as ureteroscopy and ureterolithotripsy constitute the third most common cause. Halabi et al (25) in a long term study conducted in the US, involving 2.165.848 colon and rectal surgical procedures with 6027(0.28%)cases of ureteric injury, concluded that it occurs more often in women, especially if major comorbidities such as hypertension, diabetes mellitus, congestive heart failure, obstructive lung disease, renal failure and metastatic cancer are present(25). Rectal surgery was most often associated with injury compared with other types of cancer (25). Unfortunately preoperative ureteral catheterization, proposed to show a prophylactic effect for such events, was not proved to lower the rate of their appearance during a randomized trial (12). The distal ureter is the most susceptible part with 91% of cases, followed by middle third (7%) and upper third (2%).(2)

Surgeons should ideally identify injury intraoperatively since delayed diagnosis can lead to sepsis, uri-

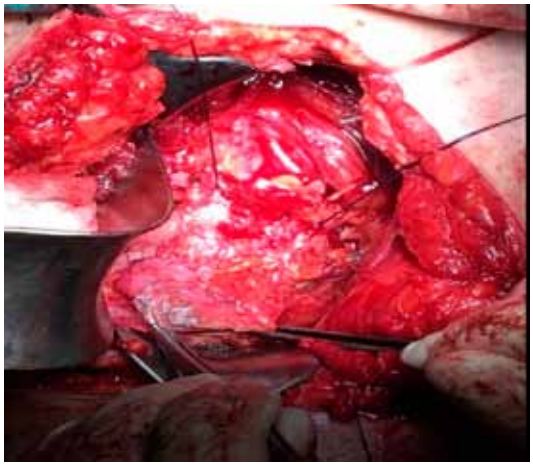
Tzelves L., Berdempes M., Markopoulos T., Lazarou L., Zerva M., Pinitas A., Xatzikraxtis N., Mitsogiannis I., Karagiotis E., Skolarikos A. Repair of iatrogenic ureteral injury with a combination of "Boari flap" and "Psoas Hitch" technique. *Hellenic Urology* 2018, 30(3): 38-42

Tzelves Lazaros, Berdempes Marinos, Markopoulos Titos, Lazaros Lazarou, Zerva Maria, Pinitas Alexandros, Xatzikraxtis Nikolaos, Mitsogiannis Iraklis, Karagiotis Euaggelos, Skolarikos Andreas

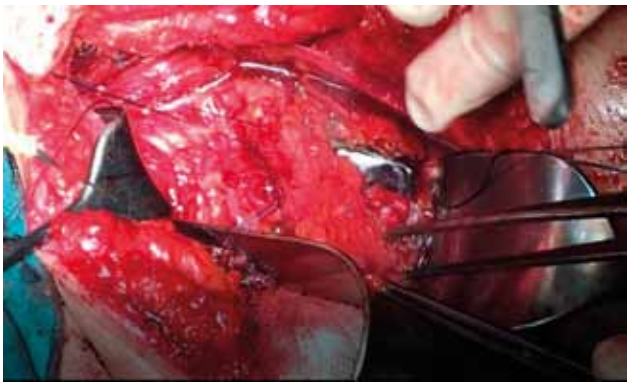
2nd Department of Urology, Sismanogleion Hospital, National and Kapodistrian University of Athens, Athens, Greece



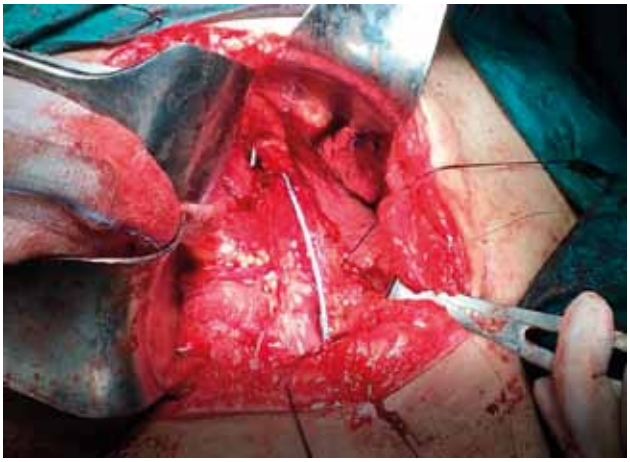
Pic 1. *Stay sutures of the bladder*



Pic 2. *Bladder dissection and preparation of Boari flap*



Pic 3. *Boari flap preparation*



Pic 4. *Creation of ureteroneocystostomy*

nomas, urinary fistulas, nephrectomy, abscesses, renal failure and death (26).

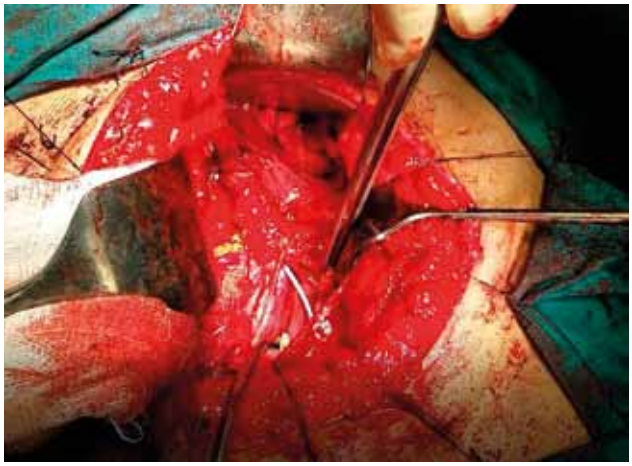
Several techniques are proposed for management of ureteric injuries depending on degree and location of the defect. Turner-Warnick and Worth combined principles developed by Dolff, Paquin and Zimmerman et al(27,28,29,30) to establish "Psoas Bladder-Hitch procedure" for ureteroneocystostomy. For defects larger than 6-8 cm a Boari flap can be also performed to achieve a tension-free anastomosis (27). We present here the case of a combined Psoas-hitch and Boari-flap repair of a ureter defect of 13 cm in a 63 year old male after sigmoidectomy for complicated diverticulosis.

Patient-Methods

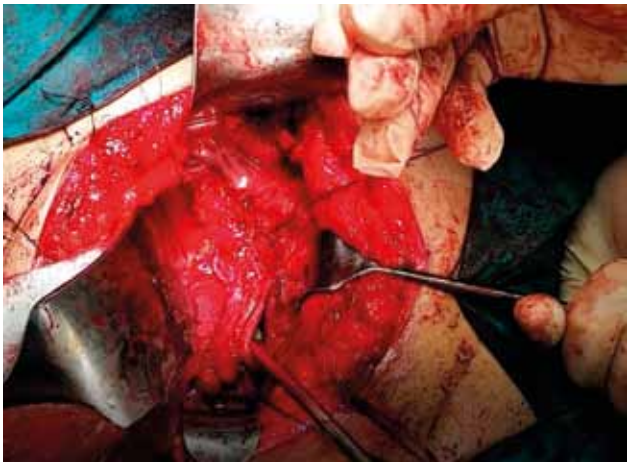
A 63 year old male with a history of sigmoidectomy 2.5 months before admission, presented to our clinic with fever and flank pain. Ultrasound revealed hydronephrosis of the left side, while CT confirmed this finding along with a distended ureter up to insertion to the pelvis. We relieved distention after placing percutaneous nephrostomy guided by ultrasound and X-ray. Attempts to forward a ureteral-stent both in antegrade and retrograde manner failed. Ureteroscopy was performed and complete blockage was noted. The combination of intraoperative and imaging findings suggested the necessity of a ureteroneocystostomy.

Results

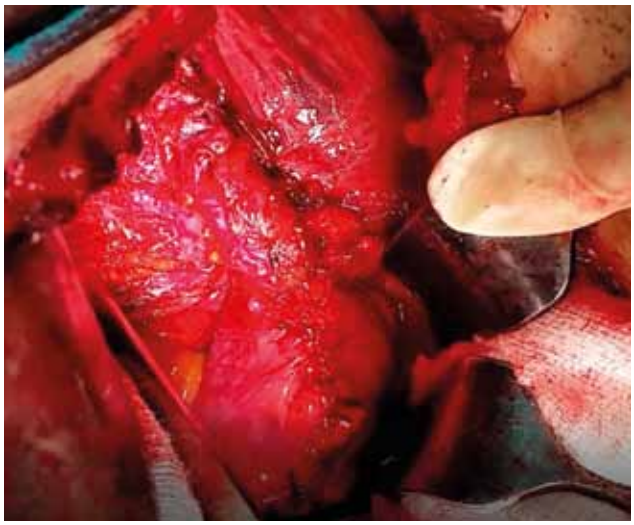
Patient was put in supine position under general anesthesia and a Foley catheter was inserted. We used a



Pic 5. *Ureteral tunnel into bladder*



Pic 6. *Closure of the first bladder layer*



Pic 7. *Closure of second bladder layer*

left extended supra-inguinal hockey stick incision. After dissecting the external oblique, internal oblique and transversus abdominis muscles and their aponeuroses, we accessed the retroperitoneum. After division of the inferior epigastric vessels we recognized iliac vessels, spermatic cord and vessels, which we ligated.

We identified the ureter after anatomically dissecting the lower kidney pole and observed the site of injury about 2 cm above crossing the iliac vessels. Anatomic preparation was not possible due to strong adhesions with right colon. Obliterated site of the ureter was removed and a stay suture was put at 6 o'clock to the proximal stump while distal was ligated.

We filled with 300 cc of normal saline and then mobilized urinary bladder, after ligating superior vesical artery and median umbilical ligament. We passed stay sutures and performed an oblique incision to the bladder. Due to the extended length of ureteral deficit a Boari flap was also created to assist a loose ureteral-bladder anastomosis. Then we put three nylon 3-0 sutures between psoas and detrusor muscles, after securing common iliac artery and femoral branch of genitofemoral nerve. A submucosal layer through bladder wall was created and ureter was pulled across it' s length. Psoas-bladder sutures were tied and ureter entrance to the bladder was checked for kinking. Ureter orifice was tied at bladder wall with 4-0 monocryl sutures and ureter adventitia was anchored at the entrance of submucosal tunnel. A utereteric stent S-S-6/28 was placed and sutured to bladder mucosa and detrusor muscle. Bladder was sutured at two layers and two drain tubes were left in place. Finally the incision was closed according to anatomic order.

Post-operative course:

Patient did not suffer any major complication during the post-operative days. An ultrasound revealed no dilation. Antibiotics were administered for 15 days, drain tubes removed at day 2, Foley catheter was left in place for 15 days and ureteric stent for 94 days.

We followed patient for 15 months with regular ultrasounds and blood tests per month initially and then every 3 months and we observed no dilation of the urinary tract or any other major complication.

Discussion

Ureteral injury after major surgeries especially of oncological nature is a common culprit. The ideal management includes intraoperative recognition and correction but this is not the rule.

We describe a patient with a large ureteral stricture of 12-13 cm after a sigmoidectomy which was not recognized early, thus patient presented with a long stricture months after primary surgery. A combination of "Psoas hitch and Boari flap" technique was used with both short and long-term success and low incidence of complications. Therefore we believe that this technique should be considered in such cases.

Περίληψη

Μία συχνή αιτία κάκωσης του ουρητήρα είναι η ιατρογενής, κυρίως σε γυναικολογικές επεμβάσεις. Η έγκαιρη διάγνωση, ιδανικά διεγχειρητικά, είναι ζωτικής σημασίας για την αποτελεσματική αντιμετώπιση των περιστατικών αυτών και εξαρτάται από το είδος, την ανατομική εντόπιση και την έκταση-μήκος της βλάβης. Η προεγχειρητική τοποθέτηση ουρητηρικού stent δεν έχει αποδειχθεί πως μειώνει την επίπτωση του τραύματος στους ουρητήρες. Σε ασθενείς με εκτεταμένου μήκους κακώσεις, έχουν περιγραφεί χειρουργικές τεχνικές για την ανακατασκευή του ουρητηρικού ελλείμματος και τη διενέργεια ουρητηρονεοκυστοστομίας, όπως η παρασκευή κρημνού από το τοίχωμα της ουροδόχου κύστεως(Boari flap) και η καθήλωση της κύστεως στον ψοίτη μυ(Psoas hitch). Περιγράφουμε ασθενή με κάκωση του ουρητήρα μετά από σιγμοειδεκτομή, μήκους 13 εκατοστών, στον οποίο διενεργήθηκε συνδυασμός Boari flap και Psoas hitch με επιτυχία για την αποκατάσταση της συνέχειας του ουρητήρα.

Λέξεις ευρετηριασμού

Κρημνός Boari, καθήλωση ουροδόχου κύστεως στον ψοίτη μυ, ουρητηρονεοκυστοστομία, ιατρογενές τραύμα ουρητήρα, στένωση ουρητήρα

References

1. Marcelissen TA, Den Hollander PP, Tuytten TR, Sosef MN. Incidence of Iatrogenic Ureteral Injury During Open and Laparoscopic Colorectal Surgery: A Single Center Experience and Review of the Literature. Surg Laparosc Endosc Percutan Tech. 2016 Dec;26(6):513-515.
2. Selzman AA, Spirnak JP. Iatrogenic ureteral injuries: a 20-year experience in treating 165 injuries. J Urol. 1996 Mar;155(3):878-81.
3. Higgins CC. Ureteral injuries during surgery. A review of 87 cases. JAMA. 1967 Jan 9;199(2):82-8.
4. Smith AM. Injuries of the pelvic ureter. Surg Gynecol Obstet. 1975 May;140(5):761-4.
5. Gangai MP, Agee RE, Spence CR. Surgical injury to ureter. Urology. 1976 Jul;8(1):22-7.
6. Bright TC 3rd, Peters PC. Ureteral injuries secondary to operative procedures. Report of 24 cases. Urology. 1977 Jan;9(1):22-6.
7. O'Brien WM, Maxted WC, Pahira JJ. Ureteral stricture: experience with 31 cases. J Urol. 1988 Oct;140(4):737-40.
8. Neuman M, Eidelman A, Langer R, Golan A, Bukovsky I, Caspi E . Iatrogenic injuries to the ureter during gynecologic and obstetric operations. Surg Gynecol Obstet. 1991 Oct;173(4):268-72. Review.
9. Zinman LM, Libertino JA, Roth RA. Management of operative ureteral injury. Urology. 1978 Sep;12(3):290-303.
10. Mahendran HA1, Praveen S, Ho C, Goh EH, Tan GH, Zuklifli M. Iatrogenic ureter injuries: eleven years experience in a tertiary hospital. Med J Malaysia. 2012 Apr;67(2):169-72.
11. Al-Awadi K1, Kehinde EO, Al-Hunayan A, Al-Khayat A. Iatrogenic ureteric injuries: incidence, aetiological factors and the effect of early management on subsequent outcome. Int Urol Nephrol. 2005;37(2):235-41.
12. Chou MT, Wang CJ, Lien RC. Prophylactic ureteral catheterization in gynecologic surgery: a 12-year randomized trial in a community hospital. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jun;20(6):689-93.
13. Kuno K, Menzin A, Kauder HH, Sison C, Gal D. Prophylactic ureteral catheterization in gynecologic surgery. Urology. 1998 Dec;52(6):1004-8.
14. Tanaka Y1, Asada H, Kuji N, Yoshimura Y. Ureteral catheter placement for prevention of ureteral injury during laparoscopic hysterectomy. J Obstet Gynaecol Res. 2008 Feb;34(1):67-72.
15. Léonard F1, Fotso A, Borghese B, Chopin N, Foulot H, Chapron C. Ureteral complications from laparoscopic hysterectomy indicated for benign uterinepathologies: a 13-year experience in a continuous series of 1300 patients. Hum Reprod. 2007 Jul;22(7):2006-11.
16. Oboro VO, Dare FO, Fadiora SO, Aderounmu AO, Adeoti ML, Ajadi

AM. Ureteric injuries following pelvic operations. East Afr Med J. 2002 Nov;79(11):611-3.
17. Jung SK1, Huh CY. Ureteral injuries during classic intrafascial supracervical hysterectomy: an 11-year experience in 1163 patients. J Minim Invasive Gynecol. 2008 Jul-Aug;15(4):440-5.
18. Ozdemir E, Ozturk U, Celen S, Sucak A, Gunel M, Guney G, et al. Urinary complications of gynecologic surgery: iatrogenic urinary tract system injuries in obstetrics and gynecology operations. Clin Exp Obstet Gynecol. 2011;38(3):217-20.
19. Rao D1, Yu H, Zhu H, Duan P. The diagnosis and treatment of iatrogenic ureteral and bladder injury caused by traditional gynaecology and obstetrics operation. Arch Gynecol Obstet. 2012 Mar;285(3):763-5.
20. Vakili B, Chesson RR, Kyle BL, Shobeiri SA, Echols KT, Gist R, et al. The incidence of urinary tract injury during hysterectomy: a prospective analysis based on universal cystoscopy. Am J Obstet Gynecol. 2005 May;192(5):1599- 604.
21. Palaniappa NC, Telem DA, Ranasinghe NE, Divino CM. Incidence of iatrogenic ureteral injury after laparoscopic colectomy. Arch Surg. 2012 Mar;147(3):267-71.
22. Aghaji AE, Odoemene C. Ureteric injuries in Enugu, Nigeria. East Afr Med J. 1999 Apr;76(4):184-8.
23. Wilhelm TJ, Refeidi A, Palma P, Neufang T, Post S. Hand-assisted laparoscopic sigmoid resection for diverticular disease: 100 consecutive cases. Surg Endosc. 2006 Mar;20(3):477-81.
24. Lawrence DM, Pasquale MD, Wasser TE. Laparoscopic versus open sigmoid colectomy for diverticulitis. Am Surg. 2003 Jun;69(6):499-503; discussion 503- 4.
25. Halabi WJ1, Jafari MD, Nguyen VQ, Carmichael JC, Mills S, Pigazzi A, et al. Ureteral injuries in colorectal surgery: an analysis of trends, outcomes, and risk factors over a 10-year period in the United States. Dis Colon Rectum. 2014 Feb;57(2):179-86.
26. Abboudi H1, Ahmed K, Royle J, Khan MS, Dasgupta P, N'Dow J. Ureteric injury: a challenging condition to diagnose and manage. Dis Colon Rectum. 2014 Feb;57(2):179-86.
27. Stein R, Rubenwolf P, Ziesel C, Kamal MM, Thüroff JW. Psoas hitch and Boari flap ureteroneocystostomy. BJU Int. 2013 Jul;112(1):137-55.
28. DOLFF C. Improved results of ureterocystanastomosis by flexible bladder fixation. Zentralbl Gynakol. 1952;74(45):1777-87
29. PAQUIN AJ Jr. Ureterovesical anastomosis: the description and evaluation of a technique. J Urol. 1959 Nov;82:573-83.
30. ZIMMERMAN IJ, PRECOURT WE, THOMPSON CC. Direct ureterocysto- neostomy with the short ureter in the cure of ureterovaginal fistula. J Urol. 1960 Feb;83:113-5.

ORIGINAL ARTICLE

ECIRS (Endoscopic Combined Intrarenal Surgery) Versus Fluoroscopic-guided Renal Access during supine Percutaneous Nephrolithotomy (PCNL): A Comparative Study

Stylianos Kontos[1,3], Athanasios Papatsoris[2], Sarath K Nalagatla[1]
1.Department of Urology, Monklands District General Hospital, Airdrie. United Kingdom.
2.University Department of Urology, Sismanoglio Hospital, Athens,Greece
3. Private Practise, Peiraeus, Greece

Abstract

Objective: To evaluate the intra- and post-operative outcomes of percutaneous renal access using either ECIRS (Endoscopic Combined Intrarenal Surgery) or fluoroscopic-guided renal access for supine percutaneous nephrolithotomy (PCNL).
Methods: In our institute, over a 24-month period (April 2012 to March 2014), two surgeons performed a total of 68 PCNLs (not consecutive staghorn stone cases); 33 ECIRS and 35 fluoroscopically-guided access (FGA). All patient and calculi demographics were recorded, as well as intra-operative parameters and complication/secondary procedure rates.
Results: We demonstrate that ECIRS offers rapid operating time (total procedure time 113 vs. 142 min, $p<0.05$), low complication rates (sepsis (0% vs. 5.8%), transfusion (0% vs. 8.6%) or bowel injury (0%)), with reduced in-patient stay (2 vs. 4 days, $p<0.05$) and high rates of stone clearance/residual fragments <4mm (3% vs. 25.7%, $p<0.05$) and low rate of secondary procedure (6.1% vs. 31.4%, $p<0.05$).
Conclusion: ECIRS offers shorter operating times, with low complication rates, higher rates of stone clearance and a reduced requirement for secondary procedures in comparison to purely FGA. We envisage that this is due to a combination of quicker and more accurate needle placement, as well as the ability to perform concomitant FURS and laser stone fragmentation.

Kontos S., Papatsoris A., Nalagatla K. S.
ECIRS (Endoscopic Combined Intrarenal Surgery) Versus Fluoroscopic-guided Renal Access during supine Percutaneous Nephrolithotomy (PCNL): A Comparative Study. *Hellenic Urology* 2018, 30(3): 43-48

Corresponding author:
Mr Stylianos Kontos,
Kritseli 19, Kallipoli, Peiraias
ATHENS, GREECE
Email: kontostylianos@gmail.com

Introduction

Since being first described in 1976, percutaneous nephrolithotomy (PCNL) has become a mainstay for treatment of large renal calculi 1. PCNL is generally a safe technique, with complications rarely associated with the initial puncture to gain access to the renal collecting system, resulting in injury to surrounding organs (e.g. spleen, liver, pleura/lung and colon)[1]. In this paper we describe our experiences with ECIRS versus fluoroscopic-guided access (FGA) for PCNL.

Key words
combined nephrolithotomy, renal puncture, learning curve

Materials and Methods

In our institute, over a 24 months period (April 2012 to March 2014), 68 PCNLs were performed by two surgeons. 1 practicing ECIRS and the other practicing FGA. Patient demographics, baseline characteristics, and operative and post-operative outcomes were compared using univariate and multivariate analysis. Patients were assigned to be performed either by ECIRS (n=33) or FGA (n=35), based on the most suitable technique for each case, which is a limitation of the paper. Information was collected retrospectively. Baseline information included patient sex, age, side, stone size (in millimetres), number and stone configuration (staghorn vs. calyceal) number of calyces involved, and Hounsfield units (HU). All patients has been reviewed with CTKUB 3months post-op.

Recorded operative and postoperative parameters included total operative time, stone clearance, as well as whether a nephrostomy/ureteric stent was required. We recorded all complications as per Clavian grading as well as the need for any secondary procedures.

Continuous variables are described as means, and ranges. Categorical measures are summarised using frequencies and percentages. The two-tailed t test, or the Mann Whitney test, as appropriate, was used to evaluate the relationship between variables of interest. All statistics were performed on GraphPad Prism v5.0 (La Jolla, CA).

Surgical Techniques

ECIRS (Endoscopic Combined Intrarenal Surgery)

Under general anaesthetic the patient is positioned in the supine (with a gel cushion beneath the ipsilateral flank to elevate & expose the loin for percutaneous access and to reduce the possibility of pleural damage) split leg position to allow simultaneous percutaneous and perineal access[2]. Both areas are prepared and draped. A flexible cystoscope is used for both males and females. The ipsilateral ureteric orifice is cannulated with Sensor guidewire with a hydrophilic tip (Boston Scientific), and the guidewire is advanced up the ureter and its position is confirmed fluoroscopically. Then a 9/11 Fr ureteral access sheath (Cook) is advanced over the guidewire where possible. Next a 7.5Fr Storz Flex-X2 flexible ureteroscope is passed into the renal pelvis through the access sheath. Contrast (50:50) is then injected to allow calyceal system mapping and identification a suitable posterior calyx for puncture. An 18-gauge nephrostomy needle is advanced towards the tip of the flexible ureteroscope, which is in the desired calyx close to the renal papilla, which provides the radiopaque target. The advancement of the needle is monitored fluoroscopically, with the needle initially advanced 4 to 6 cm into the flank to fix its trajectory. The insertion of the nephrostomy needle into the collecting system is monitored under both direct ureteroscopic vision and fluoroscopy. Once the needle is visualised ureteroscopically, the needle's obturator is removed and a super-stiff guidewire is passed into the collecting system. An 8 Fr, and then a 10 Fr dilator is passed over the guidewire, just into the collecting system to facilitate passage of NephroMax (Boston Scientific) balloon dilator. The NephroMax balloon is advanced over the Superstiff guide wire until the tip of the balloon is ureteroscopically and fluroscopically seen to enter the calyx. The nephrostomy tract is then dilated by inflating the balloon under direct ureteroscopic and fluoroscopic control. Next, a 30F Amplatz sheath is advanced over the balloon until it is visualised ureteroscopically. The balloon dilator is deflated and withdrawn. The guidewire is fixed in place and a rigid nephroscope (Richard Wolf, 20.8 Fr) is introduced through the Amplatz sheath. Stone fragmentation is then performed using the lithoclast Master (EMS). Meticulous examination of the collecting system at the end of the procedure is carried out to ensure no residual fragments remain. **Fig 1**.

A 4.8 Fr ureteric stent is then placed retrogradely with the position confirmed by fluoroscopic and direct endoscopic visualisation. A Foley catheter is inserted into the bladder. The evening of surgery, a haemoglobin is obtained, as well as urine for culture. The patient is

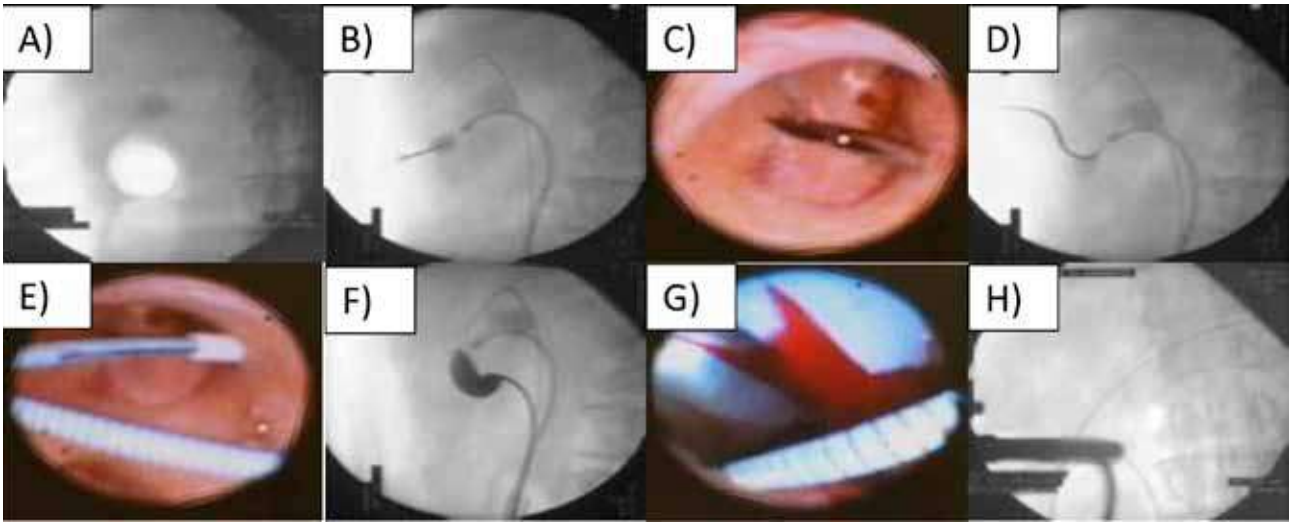


Figure 1. *Endoscopic and Fluoroscopic images of the procedure. A) Demonstrates the renal calculi fluoroscopically, subsequently with the FURS in place. B) The nephrostomy needle is inserted into the calyx of choice C) and D), and the guidewire is subsequently inserted E-G) and pulled down into the ureter. H) Demonstration of insertion of the 30F balloon catheter.*

Table 1	*Patient Demographics. Continuous variables presented as median (with range) where appropriate. NS – Non-significant*		
Variable	Endoscopic-guided Access (n=33)	Fluoroscopic-guided Access (n=35)	P value
Age (years)	67 (39-83)	64 (36-79)	NS
Male: Female	18:15	20:15	NS
Laterality - Right: Left	14:19	18:17	NS
Single: Multiple	20:13	25:10	NS
Staghorn	8	10	NS
Upper: Middle: Lower Calyx	6:4:23	5:5:25	NS
Stone Size (cm)	2.3 (1.4-5.4)	2.1 (1.3-4.4)	NS
Hounsfield Units (HU)	980 (670-1268)	879 (689-1245)	NS
Body Mass Index (BMI)	28 (18-43)	25 (19-42)	NS

on bed rest for 24 hours, and then allowed to mobilise. A trial of voiding is performed the next morning and the patient is discharged.

FGA-Renal Puncture

Again, under general anaesthetic the patient is in the same supine position, as described above. A flexible cystoscope is used to cannulate the ipsilateral ureteric orifice with Sensor guidewire (Boston Scientific), which is advanced up the ureter with fluoroscopic confirmation of position. Once the access sheath is placed as above, we perform retrograde pyelography (50:50 contrast). A 21-gauge needle is introduced to the calyx of interest under fluoroscopic guidance. Contrast is injected though the needle to confirm proper positioning and access to the stone. Subsequently, tract dilatation and stone fragmentation proceeds as above.

Results

All patient and stone characteristics are shown in Table 1. Both groups were comparable, with no significant difference in terms of patient or stone variables. Operative times were significantly reduced in the ECIRS group (113 vs. 142 min, p<0.05) **(Table 1)**. There was

Table 2 *Endoscopic-guided vs. fluoroscopic-guided access patient complications. Continuous variables presented as median (with range), categorical variables presented as number. Clavian grade, where appropriate in []. Hb – haemoglobin, NS – Non-significant.*

Variable	Endoscopic-guided Access (n=33)	Fluoroscopic-guided Access (n=35)	P value
Operative Time (min)	113 (70-155)	142 (110-219)	< 0.05
Pyrexia >38oC	5 [II]	8 [II]	NS
Septicaemia	0	2 [II]	NS
Acute Kidney Injury	0	2 [I]	NS
Nephrostomy	0	2	NS
Hb change (mg/dL)	-1.1 (+0.3 to -2.1)	-2.2 (+0.1 to –5.4)	< 0.05
Transfusion	0	3 [II]	NS
Bowel Injury	0	0	NS
Hospital Stay (days)	2 (1-6)	4 (1-11)	< 0.05

Table 3 *Outcomes from Endoscopic-guided vs. fluoroscopic-guided access. Variables are presented as number (with percentage in brackets). NS – Non-significant.*

Variable	Endoscopic-guided Access (n=33)	Fluoroscopic-guided Access (n=35)	P value
Residual Fragments (<4mm)	1 (3.0%)	9 (25.7%)	<0.05
Residual Fragments (>4mm)	1 (3.0%)	3 (8.6%)	NS
Secondary Procedure	2 (6.1%)	11 (31.4%)	< 0.05
ESWL	1 (3.05%)	4 (11.4%)	NS
FURS and Laser Lithotripsy	1 (3.05%)	7 (20.0%)	< 0.05

a non-significant trend towards increases in the incidence of pyrexia, septicaemia, acute kidney injury and requirement for nephrostomy in the FGA group **(Table 2)**. However there was a statistically significant drop in haemoglobin (Hb) in the immediate post-operative values in the FGA group when compared to those who had ECIRS (drop of 2.2 vs. 1.1 mg/dL, p<0.05) **(Table 2)**. This resulted in 3 patients in the ECIRS group being transfused when their Hb was <80g/l (when compared to none in the EGA group (8.6% vs. 0%). Overall hospital stay was lower in the ECIRS group (2 vs. 4 days, p<0.05) **(Table 2)**. This is due to patients that require blood transfusions, so they had to remain inpatients for longer.

Incidence of residual fragments <4mm (as determined by CT-KUB) was significantly less in the ECIRS group (3% vs. 25.7%, p<0.05), with no statistically significant difference in fragments >4mm **(Table 3)**. Again, secondary procedures were higher in the FGA groups (31.4% vs. 6.1%, p<0.05), with the majority of these cases being treated with FURS and laser lithotripsy (20.0% vs. 3.05%, p<0.05) **(Table 3)**.

Discussion

PCNL continues to be the gold standard for management of large renal calculi. Often, the process of gaining renal access is the most critical step, and the stage at which the most serious complications can occur. In this study we describe our experiences with ECIRS for supine PCNL.

Grasso et al first described successful FURS guided renal access in 7 patients with renal disease or body habitus that made percutaneous access difficult3. Kidd

et al described the technique in 3 challenging patients (body habitus, ptotic kidney and complete staghorn), demonstrating its value in these select cases[4]. Khan et al reported excellent surgical outcomes with the elective FURS guided renal access procedure in 12 patients[5]. Sountoulides et al demonstrated in their retrospective analysis the benefits of ECIRS (n=51) over standard PCNL (n=70), with lower rates of blood loss and transfusion, with similar rates of stone clearance[6]. Recently Isac et al reported their unit's retrospective results, comparing 159 patients who either underwent ECIRS (n=62) or FGA (n=96) by 2 surgeons for PCNL. They demonstrated decreased fluoroscopic time, reduced multiple puncture attempts, and reduced need for secondary procedures[7].

In our study of 68 patients we demonstrate that ECIRS enables safe and precise placement of the nephrostomy needle in the desired calyx, allowing controlled and safe tract dilatation, and subsequent Amplatz sheath placement. This reduces the risk of calyceal wall perforation and bleeding. Indeed, where a large stone occupies the required calyx, one can carry out laser fragmentation of the stone to clear that calyx, allowing needle placement, and reducing the need for multiple tracts. We also observed a shorter operating time, which is due to the combination of improved needle placement and the ability to fragment the stone using FURS.

Renal access is the stage of PCNL at which the most complications arise, with the number of tracts correlating with a higher risk of parenchymal injury, blood loss and transfusion[8]. A recent case report by Borin et al demonstrated how FURS and laser could reduce the number of tracts used for PCNL, reducing morbidity and transfusion rates[9].

As well as ensuring safe renal access, the use of FURS allowed increased rates of stone clearance, because access to almost all renal calyxes can be achieved with current FURS. Similarly the use of a ureteral access sheath allows the extraction of residual stone fragments.

The access sheath also allowed FURS at the end of the procedure to both identify and removed any missed ureteral fragments. The cost of using a flexible scope and an access sheath is much higher but not higher than the cost of a second or third operation to clear all the reaming fragments.

We have observed that ECIRS may address the issue of the steep learning curve of PCNL, with up to 60 cases required to reach competence[10]. This is further emphasized by the fact that only 11% of American urologists obtain their own renal access, with higher rates of access-related complications when radiologists were obtaining the percutaneous tract[11].

Thus, this technique of FURS guided renal access may address this issue of the steep learning curve[12], allowing the surgeon to feel more comfortable with the procedure.

Conclusion

We demonstrate that ECIRS for PCNL facilitates rapid operating times, with low complication rates, higher rates of stone clearance and a reduced requirement for secondary procedures in comparison to purely FGA. We envisage that this is due to a combination of quicker and more accurate needle placement, as well as the ability to perform concomitant FURS and laser stone fragmentation.

Περίληψη

ΕΙΣΑΓΩΓΗ

Είναι πλέον κοινά αποδεκτό ότι η διαδερμική νεφρολιθοτομή (PCNL) σε ύπτια θέση είναι η μέθοδος εκλογής για την αντιμετώπιση ευμεγέθους νεφρολιθίασης. Την τελευταία δεκαετία έχουν προταθεί διάφορες μέθοδοι παρακέντησης (puncture) του νεφρού. Ο στόχος της παρούσας εργασίας είναι η αξιολόγηση των δια- και μετεγχειρητικών αποτελεσμάτων της διαδερμικής νεφρικής πρόσβασης χρησιμοποιώντας είτε ενδοσκοπική καθοδηγούμενη ή φθοροσκοπική καθοδηγούμενη νεφρική πρόσβαση για διαδερμική νεφρολιθοτομή υπό ύπτια θέση (PCNL).

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ

Σε διάστημα 24 μηνών (Απρίλιος 2012 - Μάρτιος 2014), δυο χειρουργοί πραγματοποίησαν συνολικά 68 PCNL. 33 ενδοσκοπική-καθοδηγούμενη πρόσβαση ECIRS και 35 φθοριοσκοπική καθοδηγούμενη πρόσβαση (FGA). Όλα τα δημογραφικά στοιχεία των ασθενών και τα χαρακτηριστικά των νεφρικών λίθων καταγράφηκαν, καθώς και οι ενδο-μετα-εγχειρητικές επιπλοκές.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Η εμπειρία μας έδειξε ότι η παρακέντηση του νεφρού με τη βοήθεια εύκαμπτου ουρητηροσκοπίου-υπό όραση υπερτερεί στατιστικά, στην ακρίβεια της τοποθέτησης της βελόνας, έναντι της καθαρά ακτινοσκοπικής τεχνικής διευκολύνοντας τους ταχείς χειρουργικούς χρόνους, με χαμηλά ποσοστά επιπλοκών, υψηλότερα ποσοστά εκκαθάρισης από πέτρα και ελάττωση της ανάγκης για επαναφορά του ασθενούς στο χειρουργείο για αντιμετώπιση υπολειμματικής λιθίασης. Η καμπύλη εκμάθησης, σύμφωνα με παρόμοιες μελέτες αλλά και σύμφωνα με τη δική μας εμπειρία, είναι πιο σύντομη, επιτρέποντας στο νέο εκπαιδευόμενο ενδοουρολόγο να αισθάνεται πιο άνετα με την διαδερμική νεφρολιθοτριψία.

ΣΥΜΠΕΡΑΣΜΑ

Η ECIRS προσφέρει ταχύτερους χειρουργικούς χρόνους, με χαμηλά ποσοστά επιπλοκών, υψηλότερα ποσοστά εκκαθάρισης από πέτρα και μειωμένη απαίτηση για επανεπέμβαση σε σύγκριση με καθαρά FGA. Αυτό οφείλεται στον συνδυασμό ταχύτερης και ακριβέστερης τοποθέτησης βελόνων, αλλά καθώς και στην δυνατότητα προσέγγισης του νεφρικού λίθου διαδερμικά και ανάδρομα με τη χρήση του εύκαμπτου ουρητηροσκοπίου.

Λέξεις ευρετηριασμού

συνδυασμένη διαδερμική νεφρολιθοτριψία, νεφρική προσπέλαση, καμπύλη εκμάθησης

References

1. Fernstrom I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scandinavian journal of urology and nephrology. 1976;10(3):257-259.
2. Papatsoris AG1, Zaman F, Panah A, Masood J, El-Husseiny T, Buchholz N. Simultaneous anterograde and retrograde endourologic access: "the Barts technique".J Endourol. 2008 Dec;22(12):2665-6
3. Grasso M, Lang G, Taylor FC. Flexible ureteroscopically assisted percutaneous renal access. Techniques in urology. Spring 1995;1(1):39-43.
4. Kidd CF, Conlin MJ. Ureteroscopically assisted percutaneous renal access. Urology. Jun 2003;61(6):1244-1245.
5. Khan F, Borin JF, Pearle MS, McDougall EM, Clayman RV. Endoscopically guided percutaneous renal access: "seeing is believing". Journal of endourology / Endourological Society. Jul 2006;20(7):451-455; discussion 455.
6. Sountoulides PG, Kaufmann OG, Louie MK, et al. Endoscopy-guided percutaneous nephrostolithotomy: benefits of ureteroscopic access and therapy. Journal of endourology / Endourological Society. Oct 2009;23(10):1649-1654.
7. Isac W, Rizkala E, Liu X, Noble M, Monga M. Endoscopic-guided versus fluoroscopic-guided renal access for percutaneous nephrolithotomy: a comparative analysis. Urology. Feb 2013;81(2):251-256.
8. Stoller ML, Wolf JS, Jr., St Lezin MA. Estimated blood loss and transfusion rates associated with percutaneous nephrolithotomy. The Journal of urology. Dec 1994;152(6 Pt 1):1977-1981.
9. Borin JF. Prone retrograde laser lithotripsy facilitates endoscope-guided percutaneous renal access for staghorn calculi: two scopes are better than one. Journal of endourology / Endourological Society. Sep 2008;22(9):1881-1883.
10. de la Rosette JJ, Laguna MP, Rassweiler JJ, Conort P. Training in percutaneous nephrolithotomy--a critical review. European urology. Nov 2008;54(5):994-1001.
11. Watterson JD, Soon S, Jana K. Access related complications during percutaneous nephrolithotomy: urology versus radiology at a single academic institution. The Journal of urology. Jul 2006;176(1):142-145.
12. Papatsoris AG , Shaikh T, Patel D, Bourdoumis A, Bach C, Buchholz N, Masood J, Junaid I. Use of a virtual reality simulator to improve percutaneous renal access skills: a prospective study in urology trainees. Urol Int. 2012;89(2):185-90

ORIGINAL ARTICLE

Initial experience with extraperitoneal monopolarless laparoscopic radical prostatectomy in a secondary hospital of Greece

Kyriazis Iason[1,2], Dimitriou Dimitrios[1], Karavitakis Markos[3], Liatsikos Evangelos[2], Thanos Anastasios[1]

[1] Department of Urology, Ygeias Melathron Hospital, Athens, Greece
[2]Department of Urology, University Hospital of Patras, Patras, Greece
[3] Laparoscopic Urology Unit, Athinaiki Mediclinic, Athens, Greece

Abstract

Aim of the study: To report the prospectively collected outcomes of our initial experience with laparoscopic radical prostatectomy in a secondary hospital of Greece.

Materials and methods: In total 15 cases with localized prostate cancer (3x low risk, 5x intermediate risk and 7x high risk) and a mean age of 70 years (range 58-79) were operated during a 9 month period in our department. All operations were performed by a single laparoscopic surgeon under the supervision of two senior experienced open surgeons and the assistance of an assistant experienced in laparoscopic prostatectomy.

Results: No case was converted into open surgery. Mean operating time (OT) dropped gradually from 5.5 hours in the beginning of our experience to up to 2 hours with a mean OT of 3.2 hours including 6 cases where a pelvic lymph node dissection was deemed necessary. Blood loss was minimum in all cases and no transfusion was required. All but 3 cases (80%) were discharged on the first postoperative day and catheter was removed 5 days later under cystographic verification of anastomotic water tightness in the vast majority of cases. Positive surgical margins (PSMs) were present in 5 patients (33%). Immediate continence after catheter removal was evident in 53% of our cases and early continence (continent within 2weeks from catheter removal) in 60%. Out of 10 patients having completed a 3month follow-up, 80% (8/10) were pad free. Both two incontinent patients still use 1 pad per day and include one case with immediate continence which started leaking after salvage radiotherapy initiation. PSA failure (>0.2ng/dL) at 3 months was evident in 3 (30%) of patients including one patient operated with a PSA of 136ng/dL and two patients without PSMs. All these cases were included in the first 6 operated cases and were scheduled for salvage radiation treatment. At a mean of 56 days post prostatectomy, potency was restored in 3 patients following a penile rehabilitation protocol after surgery while none of the rest of patients requested further treatment for impotency.

Conclusions: In the hands of a well-trained surgical group, perioperative morbidity of laparoscopic radical prostatectomy during the initial phases of learning curve is minimum. Early continence outcomes can reach comparative levels with the high volume center literature after the very first cases. Initial oncological outcomes were inferior to the published literature yet they were most likely due to case selection (older patients with adverse pathology) than due to limitations of the operative technique.

Kyriazis I., Dimitriou D., Karavitakis M., Liatsikos E., Thanos A.
Initial experience with extraperitoneal monopolarless laparoscopic radical prostatectomy in a secondary hospital of Greece. *Hellenic Urology* 2018, 30(3): 49-54

Corresponding author:
Iason D. Kyriazis, MD, PhD, MSc, FEBU
Aristotelous 1, Cholargos, Athens, Greece
E-mail: www.modernurology.gr

Introduction

Radical prostatectomy represents the gold standard treatment option in the management of localized and locally advanced prostate cancer in fit men with a significant life expectancy [1]. The procedure was first introduced and traditionally is still being performed via an open access which remains the approach of choice for the majority of surgeons worldwide. Nevertheless, significant perioperative morbidity has been associated with the technique including prolonged hospitalization, increased blood loss and postoperative pain. In an attempt to decreased the former morbidity, endoscopic approaches, namely the conventional laparoscopic and the robotic assisted radical prostatectomy were introduced [2,3]. According to European Association of Urology Guidelines both techniques are able to provide similar oncological and functional outcomes to the traditional open technique [4].

Key words
Prostate Cancer; Laparoscopic; Radical Prostatectomy; Learning curve

During the last year, laparoscopic radical prostatectomy was introduced in our department (Ygeias Melathron Hospital, TYPET) and replaced open approach. In this work we present our initial experience with the procedure aiming to document the oncological and functional outcomes during the beginning of learning curve and question whether lack of previous experience affected negatively the outcomes of initial cases.

Material and Methods

In total 15 cases with localized prostate cancer (3x low risk, 5x intermediate risk and 7x high risk) and a mean age of 70 years (range 58-79) were operated during a 9 month period in our department. Patient demographics, preoperative oncological characteristics, perioperative data including operative time, need for transfusion, hospitalization and catheterization data as well as functional and oncological follow-up data were prospectively collected and analyzed.

Operating group characteristics

All operations were performed by a single operating surgeon (IK) who had attended an official fellowship program in laparoscopic and robotic assisted surgery and had previously assisted as first or second assistant in more than 300 laparoscopic or robotic assisted radical prostatectomies. An experienced first assistant with prior experience on endoscopic radical prostatectomy as a first surgeon also joined each operation (MK) and the operating group was supervised via two senior open surgeons with a wide experience in open radical prostatectomy (AT, DD) who served as camera holders. A designated proctor (EL) had prior performed a laparoscopic prostatectomy in our department to setup operating theater coordination and assessed the video of each case guiding necessary changes in practice.

Surgical technique

Through a paramedial 2cm subumbilical incision an access to the extraperitoneal space was created under the anterior sheath of rectus abdominis muscle and a balloon dilation of the extraperitoneal space followed. Under direct vision 5 trocars were inserted to the extraperitoneal space (1x Hasson trocar, 1x12mm and 3x5mm trocars). Ultrasonic scissors, a bipolar grasper and cold scissors were used for dissection throughout the procedure. The periprostatic fat was dissected free and the endopelvic fascia was blindly opened bilaterally. The exact location of bladder neck was then identified through traction of urethral catheter. Bladder neck was incised and urethral catheter was retrieved through the opening. The posterior bladder neck was incised at a safe distance from ureteral orifices accessing the space between the posterior prostatic capsule and the bladder. Bilateral ligation of vas deference followed and both seminal vesicles were dissected from denonvilliers fascia. Denonvilliers fascia was opened and based on preoperative risk stratification an intrafascial (for low risk disease) or an extrafascial (for high risk disease) dissection plane was followed. Extrafascial plane was evident by the presence of perirectal fat at the posterior aspect of dissection template. A nerve sparing dissection of prostatic pedicles followed employing an athermal technique using hem-o-lock clips and cold scissors. In case of high risk disease a wide excision of pedicles was performed with the use of ultrasonic scalpel. A ligation suture was then placed at the Santorini venous plexus and an apical dissection followed using constant cephalad traction of the prostate to ensure a maximum urethral length preservation. Urethra was finally divided under the level of verumontanum and prostate was placed in a retrieval bag upon its release from the urethra. In the case of high risk disease a bilateral pelvic lymph node dissection followed. Finally, a continuous urethrovesical anastomosis was created over an 18Fr urethral catheter using a double needle PDS 2-0 suture running from 6

Figure 1. *Operative time in our series. *: Cases subjected to a concomitant pelvic lymph node dissection.*

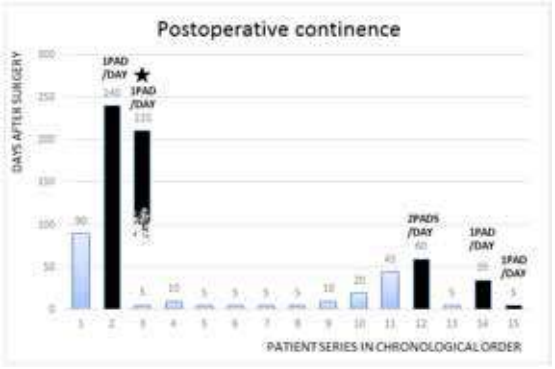


Figure 2. *Postoperative continence outcomes in our series. Blue: pad free patients. Black: Incontinent patients (last follow-up date reported). *: patient with immediate continence started leaking after salvage radiotherapy initiation.*

to 12 o'clock of the anastomosis from both sides. After replacing the urinary catheter with a silicon 18Fr catheter the watertightness of suture line was verified via inflating 120cc of saline into the bladder. A drain was inserted through one of the lateral 5mm ports and placed over the bladder, keeping a minimum safety distance from the anastomosis. Specimen bag was retrieved through the camera port and all port sites were sutured.

Postoperative care and follow up

Drain was removed on the same night or the morning after surgery and patient was discharged after restoration of bowel movements on the first postoperative day. Urethral catheter was removed after cystographic verification of anastomotic watertightness on the 5th postoperative day. A telephone assessment 2 days and one week later followed and patients were scheduled a follow up visit to access PSA levels, continence and potency outcomes at 3months after surgery.

Results

No case was converted into open surgery. Mean operating time (OT) dropped gradually from 5.5 hours in the beginning of our experience to up to 2 hours with a mean OT of 3.2 hours including 6 cases where a pelvic lymph node dissection was deemed necessary **(Figure 1)**. Blood loss was minimum in all cases and no transfusion was required. All but 3 cases (80%) were discharged on the first postoperative day and catheter was removed 5 days later under cystographic verification in the vast majority of cases. Drain was removed on the same night of the operation in all but two cases where an anastomotic leak was evident. In both cases leak was managed conservatively by placing mild traction to the catheter and retrieving drain few cms away from its initial position. Both cases followed an uneventful course apart from being discharged on the second postoperative day and having a cystography for catheter removal set on day 10 postponing catheterization for 5 additional days.

Immediate continence after catheter removal was evident in 53% of our cases and early continence (continent within 2 weeks from catheter removal) in 60%. Out of 10 patients having completed a 3month follow-up, 80% (8/10) were pad free **(Figure 2)**. Both two incontinent patients still use 1 pad per day and include one case with immediate continence which started leaking after salvage radiotherapy initiation. Positive surgical margins (PSMs) were present in 5 patients (33%). PSA failure (>0.2ng/ml) at 3 months was evident in 3 (30%) of patients including one patient operated with a PSA of 136 ng/ml and two patients without PSMs. All these cases were included in the first 6 operated cases and were scheduled for salvage radiation treatment. At a mean of 56 days post prostatectomy, potency was restored in 3 patients following a penile rehabilitation protocol after surgery (tadanafil 5mg p.os every second day) while none of the rest of patients requested further treatment for impotency.

Discussion

The minimum number of cases required for a surgeon to become proficient in laparoscopic radical prostatectomy remain unclear as due to significant heterogeneity between performed studies, reported outcomes range from 38 to 250 or even 1000 cases [5-7]. In this work we provide evidence based on our experience that in the hands of a well-trained and properly prepared operative team laparoscopic radical prostatectomy can provide optimum outcomes even from the first cases of learning curve.

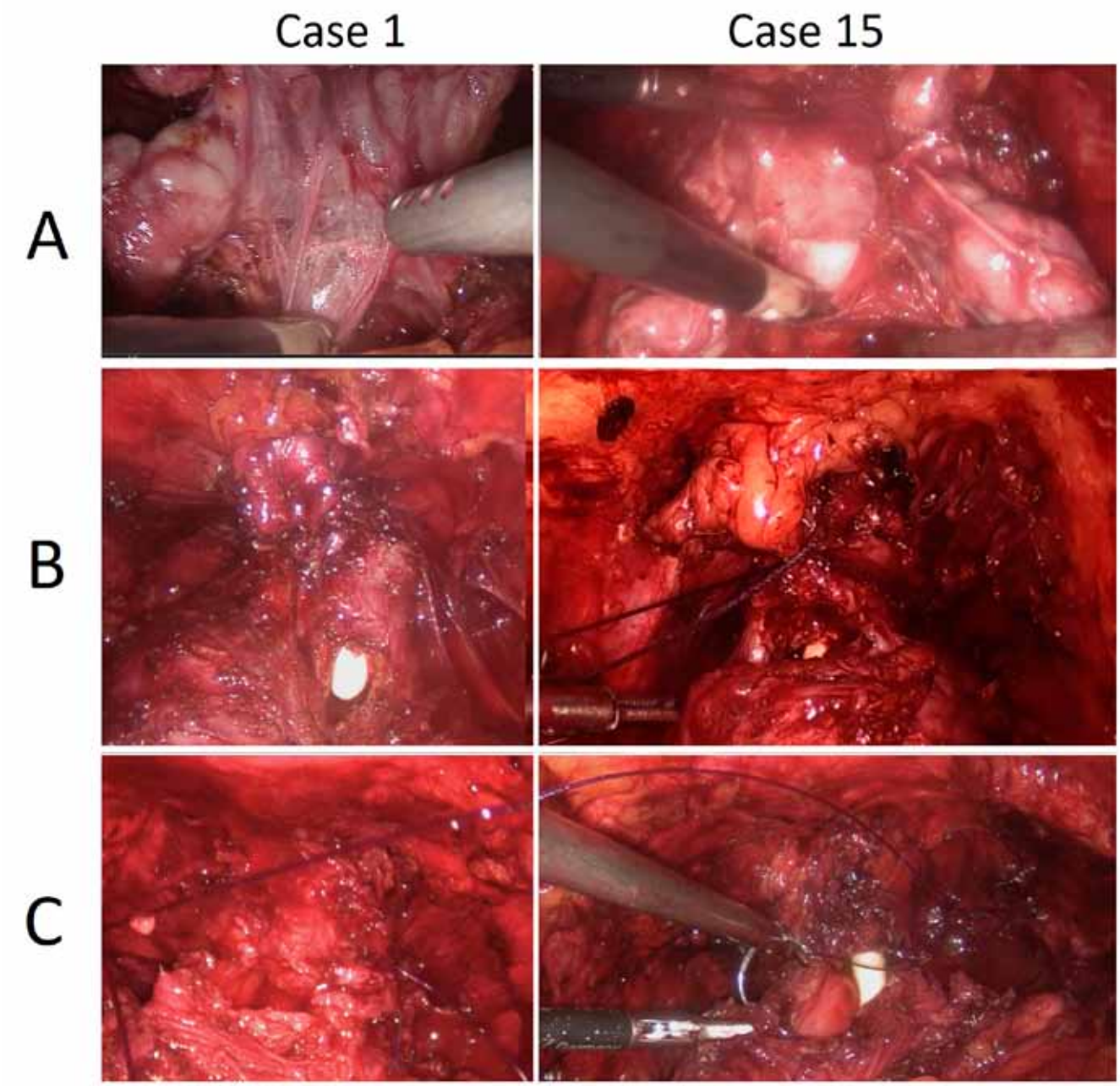


Figure 3. *Operative steps demonstrating the difference in fine tissue dissection between the first and the last case. A. Pulling down denonvilliers fascia to enter intrafascial plane of dissection after mobilization of seminal vesicles. B. Apical dissection immediately after entering the urethra accessing urinary catheter, C. Urethrovesical anastomosis creation.*

No serious complication such as rectal injury or major bleeding was noted on our first 15 cases. Still, the presence of a well experienced open surgeon ready to convert the case and resolve every potential hazard was a safety measure that we undertook to ensure patients safety during our initial experience. Blood loss was minimum in all cases and none of our patients required blood transfusion. High blood's CO_2 levels were evident perioperatively on our first cases which was restored by prolongation of ventilation during recovery. Reducing operative times and lowering intraabdominal pressures after trocar placement as well as adaptation of our anesthesiology team to the specific demands of extraperitoneal insufflation in a steep Trendelenburg position (requiring higher ventilation pressures since the beginning of the procedure to keep CO_2 levels low), prevented following

cases from this effect.

Within our initial experience we faced several technical difficulties. It took two consecutive cases with big prostates and a large medial lobe to learn how to easily retrieve medial lobe through bladder neck opening and enter the right plane of posterior dissection since in the first two cases we initially followed an enucleation plane during posterior bladder neck opening. In addition, even in the last cases of our experience (cases 12 and 14) we faced major gas leak from trocar sites in two cases of obese patients with a thick fat layer in the abdominal wall, which led to suboptimum operative field exposure throughout both operations and prolonged operative times. We intent to use extra-long obesity trocars in the following cases to resolve such a problem. Finally, the last part of the procedure that we gained confidence at was the management of prostatic apex. While we were able to preserve a long urethral stump from the first case of our experience, on our first cases we were entering into the prostatic tissue several times during dissection leading to a potential higher risk for positive surgical margins **[Figure 3]**. Based on our experience, the best cases for a surgeon to start his learning curve would be in thin patients with medium to small prostate sizes. In addition, given that the clarity of apical dissection was gained last in our series, patients with evidence of disease in prostatic apex should be avoided in the initial cases as the risk for positive surgical margins would be higher.

It is of notice that early continence outcomes in our series was surprisingly good with the majority of our cases being continent or almost continent since catheter removal on postoperative day 5 or 10. In a prospective, controlled, nonrandomised trial of patients undergoing prostatectomy in 14 centers in Sweeden via either a robotic assisted or an open approach, incontinence rates at 12 months were 21,3% and 20.2% for robotic assisted and open approach accordingly [8]. We speculate that the lack of monopolar energy in our monopolarless technique might play some role to the superior continence outcomes herein documented. During the apical dissection, periurethral tissue and sphincter remain the only anchor of prostate to the abdominal wall and as such every monopolar energy employed during robotic assisted apical dissection is expected to pass through these vulnerable structures. Accordingly, athermal division of dorsal vein complex has been associated with major effects in early continence during robotic procedures [9]. The use of harmonic scalpel in the presented laparoscopic approach deploy only local effects to the dissected tissue and as a result can combine the hemostatic benefits of energy usage, skipping any deleterious effects to distal structures. In addition, the meticulous apical dissection aiming to ensure maximum urethral length preservation as well as the presence of a continuous watertight anastomosis carefully created under the magnified view of the laparoscope also assisted in the reported optimum continence results as opposed to the gross interrupted anastomosis of open surgery.

Relatively high positive surgical margins were evident in this cohort (5/15 cases). As previously reported, a PSM rate around 30% is expected in the initial learning curve of laparoscopic radical prostatectomy and is anticipated to drop slowly over the following 1000 cases [7]. Still, our high PSMs could also have be affected by the small sample size of this cohort including cases with really high risk disease. Four out of these 5 cases had pT3 disease including a case with preoperative PSA of 137ng/ml, a case with Gleason score 5+4 and a case with Gleason score 4+3 in all (12/12) samples of transrectal biopsy. Preoperative PSA, Gleason score and T stage are well-defined risk factors for the presence of positive margins in radical prostatectomy and as a result, attribution bias might be somewhat responsible for the high rate of of disease presence at the margins of our surgical specimens [10].

Limitations of this study include the relative small sample size and the short follow up to access the oncological outcomes of our experience. Still we aim to keep tracing our outcomes in a prospective manner aiming to provide higher quality evidence in the future on the safety of the approach during the initial learning curve of surgical team. In addition, reported outcomes in this study represent the outcomes of a single operating surgeon. Given that previous surgical experience and training of any operating surgeon might affect significantly the required learning of a new procedure, data derived from other centers are necessary to generalize the conclusions drawn from this study.

Conclusions:

In the hands of a well-trained surgical group, perioperative morbidity of laparoscopic radical prostatectomy during the initial phases of learning curve is minimum. Early continence outcomes can reach comparative levels with the high volume center literature after the very first cases. Initial oncological outcomes were inferior to the published literature yet they were most likely due to case selection (older patients with adverse pathology) than due to limitations of the operative technique.

Περίληψη

Σκοπός της μελέτης: Η καταγραφή των πρώιμων αποτελεσμάτων από την εισαγωγή της εξωπεριτοναικής λαπαροσκοπικής ριζικής προστατεκτομής στην κλινική μας και η εκτίμηση του αν η καμπύλη εκμάθησης επηρέασε αρνητικά τα ογκολογικά και λειτουργικά αποτελέσματα των αρχικών ασθενών.

Υλικά και μέθοδος: Στο σύνολο 15 ασθενείς με εντοπισμένο καρκίνο προστάτη (3x χαμηλού, 5x ενδιάμεσου, 7x υψηλού κινδύνου) και μέση ηλικία τα 70 έτη (58-79) χειρουργήθηκαν μέσα σε μια περίοδο 9 μηνών. Όλες οι επεμβάσεις έγιναν από ένα χειρουργό υπό την επίβλεψη δύο πολύπειρων ανοικτών χειρουργών και τη βοήθεια ενός 1ου βοηθού με εμπειρία στη λαπαροσκοπική προστατεκτομή.

Αποτελέσματα: Όλες οι επεμβάσεις ολοκληρώθηκαν λαπαροσκοπικά. Ο μέσος χειρουργικός χρόνος μειώθηκε σταδιακά από 5.5 ώρες στην αρχή της εμπειρίας μας σε έως και 2 ώρες με μέσο χειρουργικό χρόνο για όλες τις επεμβάσεις τις 3.2 ώρες, συμπεριλαμβανομένων 6 περιστατικών όπου ακολούθησε πυελικός λεμφαδενικός καθαρισμός. Σε κανένα περιστατικό δεν απαιτήθηκε μετάγγιση αίματος. Εκτός από 3 περιπτώσεις, όλοι οι ασθενείς έλαβαν εξιτήριο την 1η MTX ημέρα και ο καθετήρας αφαιρέθηκε υπό κυστεογραφικό έλεγχο την 5η MTX ημέρα. Θετικά χειρουργικά όρια παρατηρήθηκαν σε 5 ασθενείς (33%). Άμεση εγκράτεια με την αφαίρεση του καθετήρα παρατηρήθηκε στο 53% των ασθενών και πρώιμη εγκράτεια (εντός 2 εβδομάδων από την αφαίρεση του καθετήρα) στο 60% των περιπτώσεων. Από τους 10 ασθενείς που έχουν ολοκληρώσει 3 μήνες παρακολούθησης, 80% (8/10) δεν φέρουν κανένα βοήθημα για την εγκράτεια. Οι δύο ακρατείς ασθενείς χρησιμοποιούν 1 πάνα/μέρα και περιλαμβάνουν έναν ασθενή με άμεση εγκράτεια μετά το χειρουργείο που έγινε ακρατής μετά την έναρξη ακτινοθεραπείας διάσωσης. Αποτυχία ελέγχου του PSA (>0.02ng/dL) στους 3 μήνες παρατηρήθηκε σε 3 ασθενείς (30%), συμπεριλαμβάνοντας έναν ασθενή με προεγχειρητικό PSA 136ng/ml και δύο ασθενείς με αρνητικά χειρουργικά όρια. Και οι τρεις αυτές περιπτώσεις εντοπίζονται στα 6 πρώτα περιστατικά της σειράς μας και έχουν προγραμματιστεί για ακτινοθεραπεία διάσωσης. Σε μέσο χρόνο 56 ημερών από την επέμβαση η στυτική λειτουργία επανήλθε σε 3 ασθενείς που ακολούθησαν MTX θεραπεία αποκατάστασης ενώ κανείς από τους υπόλοιπους ασθενείς δεν έχει αναζητήσει περεταίρω βοήθεια για την στύση του.

Συμπεράσματα: Η περιεγχειρητική νοσηρότητα της λαπαροσκοπικής ριζικής προστατεκτομής κατά την αρχική καμπύλη εκμάθησης είναι αμελητέα. Τα ποσοστά πρώιμης εγκράτειας μπορούν να φτάσουν τα επίπεδα των κέντρων μεγάλου όγκου επεμβάσεων μετά από πολύ μικρό αριθμό περιστατικών. Τα πρώιμα ογκολογικά αποτελέσματα φάνηκαν υποδεέστερα από την βιβλιογραφία εντούτοις φαίνεται αυτό να αποδίδεται στην επιλογή των αρχικών μας περιστατικών (ασθενείς μεγαλύτερης ηλικίας υψηλότατου κινδύνου) και όχι σε περιορισμούς της εφαρμοζόμενης χειρουργικής τεχνικής.

Λέξεις ευρετηριασμού

Καρκίνος Προστάτη, Λαπαροσκοπική Ριζική Προστατεκτομή, Καμπύλη εκμάθησης

References

1. Catalona WJ, Ramos CG, Carvalhal GF. Contemporary results of anatomic radical prostatectomy. CA Cancer J Clin. 1999 Sep-Oct;49(5):282-96.
2. Ficarra V, Novara G, Artibani W, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009 May;55(5):1037-63.
3. Caras RJ, Lustik MB, Kern SQ, et al. Laparoscopic radical prostatectomy demonstrates less morbidity than open radicalprostatectomy: an analysis of the American College of Surgeons-National Surgical Quality Improvement Program database with a focus on surgical trainee involvement. J Endourol. 2014 Mar;28(3):298-305.
4. Mottet N, Bellmunt J2, Bolla M3, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017 Apr;71(4):618-629.
5. Stolzenburg JU, Rabenalt R, Do M, et al. Modular training for residents with no prior experience with open pelvic surgery in endoscopicextraperitoneal radical prostatectomy. Eur Urol. 2006 Mar;49(3):491-8.
6. Vallancien G, Cathelineau X, Baumert H, et al. Complications of transperitoneal laparoscopic surgery in urology: review of 1,311 procedures at a single center. J Urol. 2002 Jul;168(1):23-6.
7. Secin FP, Savage C, Abbou C, et al. The learning curve for laparoscopic radical prostatectomy: an international multicenter study. J Urol. 2010 Dec;184(6):2291-6.
8. Haglind E, Carlsson S, Stranne J, et al. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol. 2015 Aug;68(2):216-25.
9. Lei Y, Alemozaffar M, Williams SB, et al. Athermal division and selective suture ligation of the dorsal vein complex during robot-assisted laparoscopic radical prostatectomy: description of technique and outcomes. Eur Urol. 2011 Feb;59(2):235-43.
10. Li K, Li H, Yang Y, et al. Risk factors of positive surgical margin and biochemical recurrence of patients treated with radical prostatectomy: a single-center 10-year report. Chin Med J (Engl). 2011 Apr;124(7):1001-5.

ΠΡΟΣΕΧΕΙΣ ΕΠΙΣΤΗΜΟΝΙΚΕΣ ΕΚΔΗΛΩΣΕΙΣ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΟΥΡΟΛΟΓΙΚΗΣ ΕΤΑΙΡΕΙΑΣ

ΓΙΑ ΠΕΡΙΣΣΟΤΕΡΕΣ ΠΛΗΡΟΦΟΡΙΕΣ ΕΠΙΣΚΕΥΘΕΙΤΕ ΤΗΝ ΙΣΤΟΣΕΛΙΔΑ ΤΗΣ Ε.Ο.Ε **www.huanet.gr**

NOTES

ONLINE ΠΡΟΣΒΑΣΗ ΣΕ ΟΛΕΣ ΤΙΣ ΕΚΔΟΣΕΙΣ ΤΗΣ EAU, ΣΤΟ EUROPEAN UROLOGY ΚΑΙ EUROPEAN UROLOGY FOCUS

ΕΤΗΣΙΑ ΣΥΝΔΡΟΜΗ ΜΕΛΟΥΣ ΣΤΗΝ ΕΟΕ ΚΑΙ ΣΤΗΝ EAU

ΠΡΟΤΕΡΑΙΟΤΗΤΑ ΣΤΑ ΑΙΤΗΜΑΤΑ ΥΠΟΤΡΟΦΙΩΝ ΚΑΙ ΥΠΟΣΤΗΡΙΞΗΣ ΔΙΑΤΡΙΒΩΝ ΤΗΣ ΕΟΕ

ΔΥΝΑΤΟΤΗΤΑ ΥΠΟΨΗΦΙΟΤΗΤΑΣ ΓΙΑ GRANTS Η AWARDS

ΜΙΑ ΕΓΓΡΑΦΗ

ΟΛΑ ΤΑ ΠΡΟΝΟΜΙΑ

ΜΕΙΩΜΕΝΕΣ ΤΙΜΕΣ ΕΓΓΡΑΦΗΣ ΣΤΙΣ ΕΚΔΗΛΩΣΕΙΣ ΤΗΣ EAU ΚΑΙ ΤΗΣ ΕΟΕ

ΕΝΤΥΠΗ ΚΑΙ ΗΛΕΚΤΡΟΝΙΚΗ ΠΡΟΣΒΑΣΗ ΣΤΟ ΠΕΡΙΟΔΙΚΟ ΤΗΣ ΕΟΕ "HELLENIC UROLOGY"

ΠΡΟΣΒΑΣΗ ΣΤΙΣ MEMBER PAGES ΤΗΣ ΙΣΤΟΣΕΛΙΔΑΣ UROWEB: MYEAU

ΠΡΟΧΩΡΗΜΕΝΗ ΠΡΟΣΒΑΣΗ ΣΤΟ UROSOURCE: GUIDELINES, E-COURSE, ΠΕΡΙΕΧΟΜΕΝΟ

SCIENTIFIC MEETINGS CME CREDITS

EAU ID CARD

NEO

Επιλέγοντας την κοινή συνδρομή EAU-ΕΟΕ, προσφέρεται **ΔΩΡΕΑΝ ΕΓΓΡΑΦΗ** στη Société Internationale D'Urologie
Περισσότερες πληροφορίες στο site της ΕΟΕ: www.huanet.gr

ΓΙΝΕ ΜΕΛΟΣ ΤΩΡΑ

Toviaz®
fesoterodine fumarate

Θεραπεία των συμπτωμάτων Ισυχνουρία ή/και έπειξη για ούρηση ή/και επιτακτικού τύπου ακράτειαΙ τα οποία μπορεί να παρουσιαστούν σε ενήλικες ασθενείς με σύνδρομο υπερδραστήριας ουροδόχου κύστης.[1]

ΑΝΑΚΤΗΣΤΕ ΤΟΝ ΕΛΕΓΧΟ[1]

1. Περίληψη Χαρακτηριστικών του Προϊόντος, 09/2017

TOVIAZ (φουμαρική φεσοτεροδίνη) **ΔΙΣΚΙΑ ΠΑΡΑΤΕΤΑΜΕΝΗΣ ΑΠΟΔΕΣΜΕΥΣΗΣ 4 & 8 mg/Tab ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΝΔΕΙΞΕΙΣ:** Το TOVIAZ ενδείκνυται για χρήση σε ενήλικες στη θεραπεία των συμπτωμάτων (συχνουρία ή/και έπειξη για ούρηση ή/και επιτακτικού τύπου ακράτεια) τα οποία μπορεί να παρουσιαστούν με σύνδρομο υπερδραστήριας ουροδόχου κύστης. **ΑΝΤΕΝΔΕΙΞΕΙΣ:** Υπερευαισθησία στη δραστική ουσία ή στο φυστίκι ή στη σόγια ή σε οποιοδήποτε από τα έκδοχα, επίσχεση ούρων, γαστρική κατακράτηση, μη ελεγχόμενο γλαύκωμα κλειστής γωνίας, βαριά μυασθένεια, σοβαρή ηπατική δυσλειτουργία (Child- Pugh C), ταυτόχρονη χορήγηση ισχυρών αναστολέων του CYP3A4 σε άτομα με μέτρια έως σοβαρή ηπατική ή νεφρική δυσλειτουργία, σοβαρή ελκώδης κολίτιδα, τοξικό μεγάκολο. **ΕΙΔΙΚΕΣ ΠΡΟΕΙΔΟΠΟΙΗΣΕΙΣ ΚΑΙ ΠΡΟΦΥΛΑΞΕΙΣ ΚΑΤΑ ΤΗ ΧΡΗΣΗ:** Το TOVIAZ πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με: Κλινικά σημαντική απόφραξη της κυστικής εξόδου με επαπειλούμενη επίσχεση ούρων, (π.χ. κλινικά σημαντική διόγκωση του προστάτη λόγω καλοήθους υπερπλασίας του προστάτη), αποφρακτικές βλάβες του γαστρεντερικού σωλήνα, π.χ. στένωση του πυλωρού, γαστροοισοφαγική παλινδρόμηση ή/και ασθενείς που παίρνουν ταυτόχρονα φαρμακευτικά προϊόντα (όπως διφωσφονικά από το στόμα), τα οποία μπορεί να προκαλέσουν ή να παροξύνουν υπάρχουσα οισοφαγίτιδα, μειωμένη γαστρεντερική κινητικότητα, αυτόνομη νευροπάθεια, ελεγχόμενο γλαύκωμα κλειστής γωνίας. Συνιστάται προσοχή κατά τη συνταγογράφηση ή την αύξηση της δόσης της φεσοτεροδίνης σε ασθενείς στους οποίους αναμένεται αυξημένη έκθεση στον ενεργό μεταβολίτη: Ηπατική δυσλειτουργία, νεφρική δυσλειτουργία, ταυτόχρονη χορήγηση ισχυρών ή μέτριας ισχύος αναστολέων του CYP3A4, ταυτόχρονη χορήγηση ισχυρού αναστολέα του CYP2D6. Αυξήσεις της δοσολογίας: Σε ασθενείς με συνδυασμό αυτών των παραγόντων, αναμένονται επιπρόσθετες αυξήσεις της έκθεσης. Αντιμουσκαρινικές δοσοεξαρτώμενες ανεπιθύμητες ενέργειες είναι πιθανόν να εμφανισθούν. Σε πληθυσμούς όπου η δόση μπορεί να αυξηθεί στα 8 mg μία φορά την ημέρα, η εκτίμηση της ανταπόκρισης και ανοχής του κάθε ασθενή ξεχωριστά θα πρέπει να προηγηθεί της αύξησης της δόσης. Πρέπει να αποκλειστούν όλα τα οργανικά αίτια προτού εξεταστεί οποιαδήποτε θεραπεία με αντιμουσκαρινικά. Η ασφάλεια και η αποτελεσματικότητα δεν έχουν ακόμα τεκμηριωθεί σε ασθενείς με νευρογενή αίτια για την υπερδραστηριότητα του εξωστήρα μυός. Άλλα αίτια της συχνουρίας (θεραπεία της καρδιακής ανεπάρκειας ή νεφροπάθεια) πρέπει να αξιολογούνται πριν τη θεραπεία με φεσοτεροδίνη. Εάν είναι παρούσα λοίμωξη των ουροφόρων οδών, πρέπει να ληφθεί μια κατάλληλη ιατρική προσέγγιση/ να ξεκινήσει αντιμικροβιακή θεραπεία. Αγγειοοίδημα: Έχει αναφερθεί αγγειοοίδημα με φεσοτεροδίνη και έχει εκδηλωθεί μετά την πρώτη δόση σε κάποιες περιπτώσεις. Εάν εκδηλωθεί αγγειοοίδημα, η φεσοτεροδίνη θα πρέπει να διακοπεί και θα πρέπει να παρασχεθεί η κατάλληλη θεραπεία. Ισχυροί επαγωγείς του CYP3A4: Η ταυτόχρονη χρήση της φεσοτεροδίνης με έναν ισχυρό επαγωγέα του CYP3A4 (δηλ. καρβαμαζεπίνη, ριφαμπικίνη, φαινοβαρβιτάλη, φαινυτοΐνη, υπερικό) δεν συνιστάται. Παράταση του διαστήματος QT: Το TOVIAZ πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με κίνδυνο παράτασης του διαστήματος QT (π.χ. υποκαλιαιμία, βραδυκαρδία και ταυτόχρονη χορήγηση φαρμάκων για τα οποία είναι γνωστό ότι παρατείνουν το διάστημα QT) και σχετικές προϋπάρχουσες καρδιακές ασθένειες (π.χ. ισχαιμία του μυοκαρδίου, αρρυθμία, συμφορητική καρδιακή ανεπάρκεια). Αυτά ισχύει ιδιαίτερα κατά τη λήψη ισχυρών αναστολέων του CYP3A4. Λακτόζη: Τα TOVIAZ δισκία παρατεταμένης αποδέσμευσης περιέχουν λακτόζη. Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, ανεπάρκειας λακτάσης του Lapp ή δυσαπορρόφησης γλυκόζης-γαλακτόζης δεν πρέπει να λαμβάνουν αυτό το φάρμακο. **ΕΠΙΔΡΑΣΕΙΣ ΣΤΗΝ ΙΚΑΝΟΤΗΤΑ ΟΔΗΓΗΣΗΣ ΚΑΙ ΧΕΙΡΙΣΜΟΥ ΜΗΧΑΝΩΝ:** Το TOVIAZ έχει ελάχιστη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανών. Απαιτείται προσοχή κατά την οδήγηση ή χειρισμό μηχανών, λόγω της πιθανής εμφάνισης ανεπιθύμητων ενεργειών όπως θαμπή όραση, ζάλη και υπνηλία. **ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ:** Περίληψη του προφίλ ασφαλείας: Η ασφάλεια της φεσοτεροδίνης, αξιολογήθηκε σε ελεγχόμενες με εικονικό φάρμακο κλινικές μελέτες σε ένα σύνολο 2.859 ασθενών με υπερδραστήρια ουροδόχο κύστη, από τους οποίους 780 έλαβαν εικονικό φάρμακο. Λόγω των φαρμακολογικών ιδιοτήτων της φεσοτεροδίνης, η θεραπεία ενδέχεται να προκαλέσει ήπιες έως μέτριες αντιμουσκαρινικές δράσεις, όπως ξηροστομία, ξηροφθαλμία, δυσπεψία και δυσκοιλιότητα. Επίσχεση ούρων μπορεί να εκδηλωθεί σπάνια. Η ξηροστομία, η μόνη πολύ συχνή ανεπιθύμητη ενέργεια, εμφανίστηκε με συχνότητα 28,8% στην ομάδα φεσοτεροδίνης σε σύγκριση με 8,5% στην ομάδα του εικονικού φαρμάκου. Η πλειονότητα των ανεπιθύμητων ενεργειών παρατηρήθηκαν κατά τη διάρκεια του πρώτου μήνα θεραπείας με εξαίρεση περιστατικά που κατηγοριοποιήθηκαν ως επίσχεση ούρων ή υπόλειμμα ούρων μετά την ούρηση μεγαλύτερο από 200 ml, το οποίο μπορεί να συμβεί μετά από μακροχρόνια θεραπεία και ήταν πιο συχνό στους άντρες απ' ότι στις γυναίκες. Παρακάτω παρουσιάζεται η συχνότητα των ανεπιθύμητων ενεργειών που παρουσιάστηκαν κατά τη θεραπεία, από τις ελεγχόμενες με εικονικό φάρμακο κλινικές δοκιμές και από την εμπειρία μετά την κυκλοφορία του φαρμάκου στην αγορά. Οι ανεπιθύμητες ενέργειες αναφέρονται με την ακόλουθη συνθήκη συχνότητας: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥1/10.000 σε <1/1.000). Πολύ συχνές: Ξηροστομία, Συχνές: Αϋπνία, ζάλη, κεφαλαλγία, ξηροφθαλμία, ξηρότητα του φάρυγγα, κοιλιακός άλγος, διάρροια, δυσπεψία, δυσκοιλιότητα, ναυτία, δυσουρία,. Όχι συχνές: Θυρεολοίμωξη, δυσγευσία, υπνηλία, θαμπή όραση, ίλιγγος, ταχυκαρδία, αίσθημα παλμών, φαρυγγολαρυγγικό άλγος, βήχας, Ξηρότητα του ρινικού βλεννογόνου, κοιλιακή δυσφορία, μετεωρισμός, γαστροοισοφαγική παλινδρόμηση, αυξημένη ALT, αυξημένη GGT, εξάνθημα, ξηροδερμία, κνησμός, επίσχεση ούρων (συμπεριλαμβανομένου του αισθήματος υπολειπόμενων ούρων και της διαταραχής της ούρησης), δυσκολία στην ούρηση, κόπωση. Σπάνιες: Κατάσταση σύγχυσης, αγγειοοίδημα, κνίδωση. Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών: Στις κλινικές δοκιμές της φεσοτεροδίνης, αναφέρθηκαν περιπτώσεις σημαντικά αυξημένων ηπατικών ενζύμων με συχνότητα εμφάνισης όμοια με εκείνη της ομάδας του εικονικού φαρμάκου. Η συσχέτιση με τη θεραπεία φεσοτεροδίνης δεν έχει διευκρινιστεί. Ελήφθησαν ηλεκτροκαρδιογραφήματα 782 ασθενών υπό θεραπεία με 4 mg, 785 ασθενών υπό θεραπεία με 8 mg, 222 ασθενών υπό θεραπεία με 12 mg φεσοτεροδίνης και 780 ασθενών που λάμβαναν εικονικό φάρμακο. Το διορθωμένο για τον καρδιακό ρυθμό διάστημα QT στους ασθενείς υπό θεραπεία με φεσοτεροδίνη δεν διέφερε από εκείνο των ασθενών που λάμβαναν εικονικό φάρμακο. Τα ποσοστά εμφάνισης QTc ≥ 500 ms μετά την αρχική αξιολόγηση ή εμφάνισης αύξησης QTc ≥ 60 ms είναι 1,9%, 1,3%, 1,4% και 1,5%, για φεσοτεροδίνη 4 mg, 8 mg, 12 mg και εικονικό φάρμακο, αντίστοιχα. Η κλινική σημασία αυτών των ευρημάτων θα εξαρτηθεί από τους παράγοντες κινδύνου και τους προδιαθεσικούς παράγοντες του κάθε ασθενούς ξεχωριστά (βλ. παράγραφο Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση). Περιστατικά επίσχεσης ούρων μετά την κυκλοφορία του φαρμάκου στην αγορά, τα οποία απαιτούσαν καθετηριασμό, έχουν περιγραφεί γενικά μέσα στην πρώτη εβδομάδα θεραπείας με φεσοτεροδίνη. Σε αυτά συμπεριλαμβάνονταν κυρίως ηλικιωμένοι άντρες ασθενείς (≥65 ετών) με ιστορικό σχετιζόμενο με καλοήθη υπερπλασία του προστάτη (βλ. παράγραφο Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση). Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω: **Ελλάδα:** Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 21 32040380/337 Φαξ: + 30 21 06549585 Ιστότοπος: http://www.eof.gr **Κύπρος:** Φαρμακευτικές Υπηρεσίες, Υπουργείο Υγείας, CY-1475 Λευκωσία Φαξ: + 357 22608649 **ΥΠΕΡΔΟΣΟΛΟΓΙΑ:** Η υπερδοσολογία με αντιμουσκαρινικά, συμπεριλαμβανομένης της φεσοτεροδίνης, μπορεί να έχει ως αποτέλεσμα σοβαρές αντιχολινεργικές επιδράσεις. Η αντιμετώπιση πρέπει να είναι συμπτωματική και υποστηρικτική. Σε περίπτωση υπερδοσολογίας, συνιστάται παρακολούθηση του ΗΚΓ και λήψη τυποποιημένων υποστηρικτικών μέτρων για την αντιμετώπιση της παράτασης του QT. Η φεσοτεροδίνη χορηγήθηκε με ασφάλεια σε κλινικές μελέτες σε δόσεις μέχρι 28 mg/ημέρα. Σε περίπτωση υπερδοσολογίας φεσοτεροδίνης, οι ασθενείς πρέπει να υποβάλλονται σε πλύση στομάχου και χορήγηση ενεργού άνθρακα. Τα συμπτώματα πρέπει να αντιμετωπίζονται ως εξής: Σοβαρές κεντρικές αντιχολινεργικές επιδράσεις (π.χ. ψευδαισθήσεις, σοβαρή διέγερση): αντιμετώπιση με φυσοστιγμίνη. Σπασμοί ή έντονη διέγερση: αντιμετώπιση με βενζοδιαζεπίνες. Αναπνευστική ανεπάρκεια: αντιμετώπιση με μηχανική αναπνοή. Ταχυκαρδία: αντιμετώπιση με βήτα-αποκλειστές. Επίσχεση ούρων: αντιμετώπιση με καθετηριασμό. Μυδρίαση: αντιμετώπιση με οφθαλμικές σταγόνες πιλοκαρπίνης ή/και ο ασθενής πρέπει να παραμείνει σε σκοτεινό θάλαμο. **ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Ηνωμένο Βασίλειο. **ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** EU/1/07/386/001-020 **ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ:** 09/2017. **ΛΙΑΝΙΚΗ ΤΙΜΗ:** 4 mg δισκία παρατεταμένης αποδέσμευσης BT x 30, Λ.Τ.: 31,17 €, 8 mg δισκία παρατεταμένης αποδέσμευσης BT x 30, Λ.Τ.: 31,57 €

ΦΑΡΜΑΚΕΥΤΙΚΟ ΠΡΟΪΟΝ ΓΙΑ ΤΟ ΟΠΟΙΟ ΑΠΑΙΤΕΙΤΑΙ ΙΑΤΡΙΚΗ ΣΥΝΤΑΓΗ
ΓΙΑ ΠΛΗΡΕΙΣ ΣΥΝΤΑΓΟΓΡΑΦΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ ΠΑΡΑΚΑΛΕΙΣΘΕ ΝΑ ΑΠΕΥΘΥΝΘΕΙΤΕ ΣΤΗΝ ΕΤΑΙΡΙΑ.

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την «ΚΙΤΡΙΝΗ ΚΑΡΤΑ»

PFIZER HELLAS A.E.
Λ. ΜΕΣΟΓΕΙΩΝ 243 · 15451 Ν. ΨΥΧΙΚΟ,
ΤΗΛ: 210 6785 800

Pierre Fabre FARMAKA A.E.
Λ. Μεσογείων 350, 15341, Αγία Παρασκευή
Τηλ. 210 7234 582

PP-TOV-GRC-0013-MAR18