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AIMS AND SCOPE

Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

As a surgical journal, the Turkish Journal of Surgery covers all specialties, and its target audience includes scholars, practitioners, specialists and students from all specialties of surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Surgical Society, editors, editorial board, and/or publisher; thus, the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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INSTRUCTIONS TO AUTHORS

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts submitted to another journal for evaluation but rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;
2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for other specific parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Turkish Journal of Surgery requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkjsurg.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all responsibility for authorship during the submission and review stages of the manuscript.

The Turkish Journal of Surgery requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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MANUSCRIPT PREPARATION

Manuscripts should be prepared in accordance with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2017 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkjsurg.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process by the editorial office staff to ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

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- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.turkjsurg.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, which should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7: 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal, and reports on rare cases or conditions constituting challenges in diagnosis and treatment, those offering new therapies or revealing insight not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Surgical Methods: Images of remarkable, striking and rare cases that emphasize the basic mechanisms of diagnosis and treatment of diseases, express discrepancies and extraordinary situations and explain new treatment techniques and options are evaluated for publication. Display items are important in this type of manuscripts, and supporting the manuscript with video (in WMV, AVI or MPEG formats) images can facilitate a faster evaluation process and increase the possibility of publication.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The article being commented on must be properly cited within this manuscript.

Human Subjects Research

All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s) and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. The Journal reserves the right to reject work believed to have not been conducted in a high ethical standard, even when formal approval has been obtained.

Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

Animal Research

All animal research must have approval from the authors' Institutional Animal Care and Use Committee (IACUC) or equivalent ethics committee(s), and the research must have been conducted according to applicable national and international guidelines. Approval must be received prior to beginning the research.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Manuscripts reporting animal research must state in the Methods section: The full name of the relevant ethics committee that approved the work, and the associated permit number(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why. The author should provide any relevant regulations under which the study is exempt from the requirement of approval.

Tables

Tables should be included in the main document, presented after the reference list, and numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA) should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text and numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Only references cited in the text should be included in the reference list. The reference list must be numbered according to the order of mention of the references in the text. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004. pp. 2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp. 1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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CONTENTS

FROM THE EDITOR'S DESK

Dear Readers of the Turkish Journal of Surgery,

You have now in your hand the last issue of 2019. I might say that there are very interesting articles in this issue. I strongly advise you to read these papers and hopefully use as valuable citations in your studies.

One of the current articles is particularly special for us. Dr. Semih Baskan, who is the former President of Turkish Surgical Society, had written a special article entitled "The great leader of Turkish surgery is 90 years old". Dr. Baskan herein summarizes with interesting details the history of the Turkish Surgical Society. I would recommend reading and archiving this outstanding article. To be honest, I have learned a lot of facts that I had not known before.

The beginning of 2019 was a special time for us. Together with my colleagues in the editorial board, we have taken over the editorial work of the journal and tried to establish a better journal throughout the year. I do think that we have overcome some important issues but undoubtedly there is more to do. With this opportunity at hand, I would like to thank my colleagues Dr. Demirkan and Dr. Ulas for their meticulous work as co-editors. Furthermore, I should mention that we are fortunate to work with our partners Bilimsel Tıp Yayınevi and Yazılım Parkı.

As I have previously mentioned, one of our major goals is to be indexed in some prestigious international indexes such as Index Medicus and SCI-expanded. Our preparations are coming now to an end. We are planning to apply in the forthcoming months of the New Year.

Moreover we are also hoping to establish new technology tools in our organization and communication for all parts of the journal in the first half of 2020. Nowadays, the communication tools are dramatically changing. As an emerging journal, we wish to adapt ourselves to these new developments. We will inform you as soon as we establish new communication procedures.

In this respect, we also need your feed-back and support. We always welcome your comments and critics.

On behalf of the editorial team of TJS, I wish a Merry Christmas for our international readers and Happy New Year 2020 for all!

Best wishes,

Kaya SARIBEYOĞLU
Professor of Surgery
Turkish Journal of Surgery
Editor

HISTORY
Turk J Surg 2019; 35 (4): 241-244

The great leader of Turkish surgery is 90 years old

Semih Baskan[1] (İD)

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Istanbul Okan University, Dean of School of Medicine, Istanbul, Turkey

The Great Leader of Turkish Surgery is 90 Years Old

The Turkish Surgical Society, which dates back to the year 1929 when the Turkish Surgical Society was founded, is celebrating its 90th anniversary this year. After the military coup on September 12, 1980, the first seeds of the Turkish Surgical Society were sown in an extraordinary period when all non-governmental organizations were closed down, some of which suspended, and all decisions and accounts scrutinized. Devoted studies in such a difficult period will take their deserved place in the history of Turkish Surgery as admirable services (1).

We believe that it is a historical duty to commemorate our sixty-six colleagues who aren't with us anymore, and in particular, our founding president of the Turkish Surgical Society Professor Dr. Ahmet Yaycıoğlu, our subsequent term presidents Professor Dr. Şadan Eraslan, Professor Dr. Yılmaz Sanaç, and Professor Dr. Sermet Akgün, Professor Dr. Kaya Çilingiroğlu, and Operator Dr. Kemal Altay with respect and gratitude for their outstanding services to Turkish Surgery. Likewise, we feel indebted to wish a healthy and long life to Professor Dr. Erol Düren, Professor Dr. Cemalettin Topuzlu and Operator Dr. Yılmaz Kadıoğlu, who are also among the founding members of our association and still with us.

The Turkish Surgical Society gathering in the offices of our founders during the years of establishment was able to buy an apartment for the first time in 1989 in "Sağlık Sokak" located right behind the Ministry of Health and continued its services there for many years. And on May 8, 2004, it started to operate in a 450 square meter headquarters building built on a 1666 square meters land in Çayyolu neighbourhood in Ankara. In this headquarters building with 2.5 floors, there were conference rooms, offices and meeting rooms. At that time, the number of associations that could have such a headquarters building with its own equity could be counted on the fingers of one hand (2).

Health Manpower and General Surgery Specialty

According to the "General Surgery Manpower in Turkey" Report written by Professor Dr. Cem Terzi and his friends and found among the publications of Turkish Surgical Society in 2009, the 2007 records had shown that there were 3594 general surgeons found to be actively working in Turkey. According to the same data, it was reported that 40% of general surgery specialists were working in Istanbul, Ankara and Izmir (3).

In addition, according to Health Education in Turkey and Health Manpower Status Report (2014), there were 4258 actively working general surgery specialists in Turkey. The number of active general surgeons per 100.000 people was reported as 5.63 (4).

U.E.M.S. Section and Board of Surgery meeting was held on April 5-6 in Istanbul with the participation of the Turkish Surgical Society. In this meeting, the Presi-

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dent of the Turkish Surgical Society, Professor Dr. Seher Demirer, emphasized that there were 5596 general surgeons in Turkey and 282 of these were female. As of today, the number of surgeons who are active members of the Turkish Surgical Society has reached 3903 among the general surgeons actively working in our country. The number of approved site members is 6082. Considering these numbers, it is understood that 69.74% of the active surgeons are registered members of the Turkish Surgical Society (5).

Today, in the 90th year of the Turkish Surgical Society, the number of registered members has reached 3903 (6). It is stated in the 2018 Health Statistics Yearbook of the Turkish Republic Ministry of Health that there are 153.128 doctors available in our country. However, there is no data on how many of these are actively working general surgeons (7).

Proficiency Exams

The Board of Proficiency that began active duty after being elected at the National Surgery Congress in 2000, held its first exam on June 20, 2000 (8). After this date, 35 written and 30 oral exams have been reached in the Board Exams. The Turkish Surgical Society, which plays a pioneering role among the specialist associations in these exams, is thus proud. An analysis of the Board Exams held for 19 years revealed that 2075 specialists took the written exam and there were 635 general surgery specialists who took the exam for the second time or more. Of all the candidates, 817 were successful and were entitled to take the 2nd stage oral exam. 450 of the 474 specialists who took the oral exam were awarded with a passing grade and qualified for the Turkish Surgical Society Board Certificate. Following the written and oral examinations held since 2001, 262 of the 450 general surgery specialists who received the Turkish Surgical Board Certificate, have re-certified their certificates by applying to the Turkish Surgical Society (9).

Accreditation

Accreditation means being audited by an autonomous committee from outside the institution and, if appropriate, being authorized and subsequently being audited periodically. The Turkish Surgical Society, which has pioneered among other associations on this subject as well as many others, started its accreditation activities in 2002. The Co-Authorization Board of the Turkish Surgical Society, which started to work on this date, visits the General Surgery Departments and Clinics that perform surgical training after graduation, and accredits by evaluating the assistant report card, internal and external rotations, opportunities of other clinics, national and international publications in line with objective criteria. In this context, the Turkish Surgical Society published an Assistant Report book in 2006 and determined the criteria junior and senior residents are obliged to meet in terms of knowledge, skill, attitude and behaviour (10).

According to the data from Turkish Republic's Ministry of Health's Health Statistics Yearbook (2018), there are a total of 1534 hospitals in our country, including 889 State Hospitals, 68 University Hospitals and 577 Private Hospitals (11). Based on these data, general surgery speciality training is provided in 957 hospitals. In the 17 years since 2002, only 20 General Surgery Clinics / Departments have been accredited and this is thought-provoking. The ratio of General Surgery Clinics accredited in total is 2.08%. Of the accredited general surgery clinics, only 2 were officially accredited (12).

In our country, accreditation activities in the field of health have been realized much later. In Turkey, the Regulation on the Accreditation in Health System was published on 09.01.2013. Subsequently, with Law No. 6569, Turkey's Health Care Quality and Accreditation Institute was established.

Medical Malpractices

The Turkish Penal Code, which entered into force in 26.09.2004 and Compulsory Financial Insurance on Medical Malpractice introduced in 21.07.2010 have brought some legal obligations and challenges to general surgeons as well as to all other healthcare workers. Insurance of the physicians actively working in the profession is one of them.

General surgery, which was one of the most popular branches in previous years, has begun to be preferred in lower ranks together with other surgical branches. In cases examined at the High Council of Health and the Forensic Medicine Institute, our colleagues are ordered by the court to pay significant indemnifications in actions brought when results arise against general surgeons. In order for us to defend our rights well before the law, we must first know what they are and their limits. The high amount of compensation determined when judicial lawsuits were brought to a conclusion led our colleagues, who are general surgery specialists, to gravitate towards Defensive Medicine practices in Turkey as well as all over the world.

The Turkish Surgical Society, showing awareness on the above-mentioned issues as always, has established the Ethics Committee and the Medicolegal commissions and tried to help our colleagues by publishing examples of our sine qua non Informed Consent on our website.

President of the Turkish Surgical Society, Professor Dr. Seher Demirer, said the following in a statement: "Our association has a law office. When our General Surgeon colleagues apply to us in writing about their complaints and litigation processes, we respond to them through our law office. As an NGO, we cannot intervene in the judiciary process. However, in terms of guiding our colleagues correctly and ensuring that they get out of this process with minimum damage, the Turkish Surgical Society stands behind our general surgeon colleagues." (13).

International Relations

In the European Union, which was initially founded with the participation of Germany, France, Italy, Netherlands, Belgium and Luxembourg in 1958, doctors have established the European Association of Medical Experts (U.E.M.S.) to determine the key quality indicators of postgraduate medical education.

The Turkish Medical Association joined U.E.M.S. as an associate for the first time in 1994. In order to be an active member of this organization, the first criterion was to be a member of the European Union.

In 1996, the Turkish Surgical Society also became a member of the U.E.M.S.'s Section and Board of Surgery at the International Congress organized by Eurosurgery in Rome and our first representative was Professor Dr. Semih Baskan. In the following years, Professor Dr. İskender Sayek, Professor Dr. Sadık Kılıçturgay, Professor Dr. Ethem Geçim and Professor Dr. Cem Terzi took over this task (14).

U.E.M.S. Section and Board of Surgery convened in Istanbul on October 6, 2002 with a large participation, and the Turkish Surgical Society hosted this meeting. This highly successful organization was also appreciated by our foreign colleagues. The Core Training Program Booklet prepared by the Turkish Surgical Society's Proficiency Committee was translated into English and was presented to President Professor Polonius in the meeting held in Graz, Austria in 2018. The report titled "Who Should Perform Thyroidectomy?" prepared by Associate Professor Mahir Özmen was also presented to the President of EBS at the same meeting and sent to the e-mail addresses of the other members. In 2008, Professor Dr. Michael Polonius of U.E.M.S. Section and Board of Surgery was invited to the National Surgery Congress that we organized, and he gave a lecture on two topics: "Subdisciplines in Surgery" and "The Concept of Intensive Care in Surgery" (15).

On May 7-8 of 2010, this time U.E.M.S. Section and Board of Surgery held its General Assembly in Izmir. In this meeting, our country was represented by Professor Dr. Cem Terzi, and important decisions were taken including the curriculum - considered an important part of the examinations - was accepted, the participation of general surgeons of full member states such as Turkey was accepted in line with the proposal of Turkish Surgical Society. At this same general assembly, it was decided to hold the first exam in Turin, Italy. At the end of the meeting, Professor Dr. Michael Polonius was re-elected as the president (16).

After a long break, U.E.M.S. Section and Board of Surgery Spring General Meeting was held on 5-6 April 2019 in Istanbul. Professor, Dr. Seher Demirer, the President of Turkish Surgical Society, Vice President of the Turkish Surgical Society, Dr. Mahir Özmen, Turkish Representative of Surgery Section, Professor Dr. Mehmet Faik Özçelik and Professor Dr. Neşet Köksal gave speeches and informed their visiting colleagues. In the general assembly of the U.E.M.S. Section and Board of Surgery the next day, general surgery training and risk quality assignments were performed with standard data. Professor Dr. Mehmet Faik Özçelik, representative of Turkish Surgical Society, speaking at U.E.M.S. Section and Board of Surgery meeting, announced general surgeons from Turkey that qualified for the European Surgery Board's Proficiency Certificate. According to this data, 63 general surgeon colleagues have been entitled to get their certificates so far. Among these groups, it was determined that the most successful ones who took the exam were from the speciality of Colon-Proctology (23) (17) (Table 1).

Table 1. European Surgical Board Proficiency Certificate Holders

Breast surgery	13
Endocrine surgery	10
Colon-proctology	23
General surgery	9
Surgical oncology	1
Transplantation	2
Hepato-pancreatobiliary	5
Vascular surgery	3
Department unknown	5
Emergency surgery	14
TOTAL	**63**

Continuous Professional Development

At the World Congress held in 1990, the World Medical Association made the following definition: "Medical education is a learning process that begins with the entrance to medical school and ends with retirement". This concept has changed in the 21st century and Lifelong Learning has come to the fore. Turkish Surgical Society performs its duties almost like a post-graduation higher education institution with national congresses, regional congresses, research congresses, courses and panels it has organized especially in recent years. In addition, it has begun to grant awards and scholarships to support young researchers in particular.

The Turkish Surgical Society continues its practices regularly in order to support young researchers. In this context, the following scholarships are given:

1. Turkish Surgical Society Scholarship
2. Turkish Surgical Society Overseas Education Scholarship
3. Dr. Feza Remzi Scholarship
4. Kemal Özden Scholarship
5. Nevin Baykent Scholarship

In the same context, the Turkish Surgical Society grants awards in different branches:

1. Turkish Surgical Society Award & Support,
2. Support to International Surgical Congresses,
3. Promoting Scientific Publications,
4. National Surgical Congress Awards,
5. Overseas Education Support Award,
6. Proficiency Board Support Award,
7. Overseas Project Support Award (18)

The Turkish Surgical Society is proud and honoured to grant 68 Scholarship Awards and 59 Incentive Awards in total to young surgeons (19).

Taking into account the difficulties encountered by young general surgical residents in the operations, the Turkish Surgical Society has prepared 15 sets of drawings for various surgeries to assist them in this regard and offered them to their service. Test Preparation Book for preparing for Board Exams, Board Exam Course notes, preparing a presentation in English - which is an issue young residents have difficulty in in international congresses-, and a medical presentation booklet in English, which would make it easy for them to make presentations, should also be included in the services provided. For the informed consent, nine different Informed Consent Forms explaining different surgical procedures and complications were prepared and explained on the website of the association. Another service that the Turkish Surgical Society has provided to young researchers in recent years is the practice that we define as Virtual Academy. In this practice providing great convenience for young research associates and residents to improve and train themselves when they have free time both in their clinics and at home, modules, manuals and current articles are included. These contemporary practices, which provide easy access to current information, are followed with interest by young surgeons (20).

In addition to scientific activities organized in its new headquarters, the Turkish Surgical Society has also organized public awareness meetings together with non-governmental organizations in the prevention and treatment of different types of cancer for our neighbours living in the neighbourhood, revealing a good example of the public services mentioned in our statute.

In 2009, since it was the 80th anniversary of the Turkish Surgical Society, a comprehensive book was published and broached to our general surgeons. It has been 10 years since then. Now, we are celebrating our 90th anniversary. In the 21st century, there are huge and rapid developments in medical technologies. Particularly, the concepts of Industry 4.0 and Health 4.0, which have been in our agenda since 2013, have begun to introduce brand new concepts and practices into our daily practice each passing day.

We have tried to summarize the activities of our Turkish Surgical Society, the great leader of Turkish Surgery which reached its 90th year, especially for the last 10 years. We hope to share more with our members on our 100th anniversary, which we will celebrate in 10 years, and we pay our respects to you.

The last sentence belongs to our doyen academic member Professor Dr. Erol Düren, one of the founding members of Turkish Surgical Society:

"If We Know Where We Come From, We Can Predict Where We Can Go".

With all respect,

Professor. Dr. Semih Baskan

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ORIGINAL ARTICLE
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Clinicopathologic and prognostic features in appendiceal malignancies: does tumor invasiveness matter?

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ABSTRACT

Objective: To evaluate the survival rates of appendiceal tumors and prognostic factors affecting survival.

Material and Methods: Demographic features, tumor characteristics and pre- and post-operative outcomes of the patients were analyzed retrospectively. The study was performed according to the Helsinki declaration.

Results: Twenty-three of the 2840 specimens were investigated prospectively. Median age of the patients was 28 (range: 1-89) years, with a male (n= 1730, 60.9%) to female (n= 1110, 39.1%) ratio of 1.55. Pediatric group did not present appendiceal malignancy. Carcinoid tumors were reported in 17 (0.59%) and adenocarcinoma was reported in 6 (0.20%) patients. Multivariate analyses of the subtypes showed serosal invasion as an independent risk factor for mucinous and non-mucinous adenocarcinoma (HR: -2.70, 95% CI: 0.006-0.755, p= 0.029). Median follow-up time was 48 months (range: 28-61 months) and disease specific survival rates of carcinoid tumors, mucinous- and non-mucinous adenocarcinomas were 36(95% CI 32-40), 30 (95% CI 13-46), 43 (95% CI 30-55) months, respectively (p= 0.749). Factors affecting survival in the univariate analyses were advanced tumor stage, serosal invasion and tumor invasion depth. In multivariate analyses, tumor invasion depth was the only independent prognostic factor with poor survival rates in all subtypes of appendiceal malignancies (HR= 1.31 (95% CI: 1.01-13.5), p= 0.047).

Conclusion: Tumor subtype and tumor invasiveness are important risk factors for survival. Besides other treatment modalities, appendectomy still remains the survival benefit with better clinical outcomes.

Keywords: Appendectomy, appendicitis, appendiceal malignancies, appendiceal tumors

INTRODUCTION

Acute appendicitis is still the most frequent abdominal pathology requiring emergent surgery worldwide (1,2). Its approximate lifetime prevalence has been reported as 8% (2). The annual incidence of this pathology is about 0.1% in Western countries (2-4).

The most common pathogenesis of acute appendicitis is the luminal obstruction of the appendix by a fecalith (2). However, all causes which may –directly or indirectly– obliterate the appendiceal cavity will lead the patient to an acute appendicitis. Appendiceal tumors are relatively rare but, likely, malignant appendiceal tumors may also obliterate the appendix lumen (5).

Despite extensive usage of antibiotics, appendectomy has been considered the standard treatment of appendiceal acute inflammation for decades (1,2). Nowadays, the primary treatment approach is still surgery. Generally, open or laparoscopic removal of the appendix is the main aim of the surgical procedures. On the other hand, regarding the literature, surgical management still remains unclear in appendiceal malignancy (6).

This study aimed to discuss the management of malignant disease of the appendix in the light of our case series data.

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MATERIAL and METHODS

This retrospective clinical study was conducted in the Department of General Surgery, Bursa Yuksek Ihtisas Training and Research Hospital and Bursa State Hospital. Histopathological examination of 2840 specimens obtained from patients who had undergone appendectomy between January 2012 and December 2015 were investigated retrospectively. Twenty-three of these 2840 specimens were diagnosed as appendiceal malignancies. In total, the data of 23 patients were analyzed in terms of age, gender, preoperative and postoperative clinical parameters. Overall survival rates of the patients and prognostic parameters affecting survival were also evaluated. The study was performed according to the Helsinki Declaration.

Statistical Analysis

In descriptive analyses, mean ± standard deviation was used for data following normal distribution and median and minimum-maximum values for non-parametric data. Non-parametric values were compared using Mann-Whitney U test. Comparison of categorical variables such as data of gender and histopathology was conducted using Fisher's exact and chi-square tests. Factors identified as significant in the univariate analyses were included into the multivariate logistic regression analysis.

Patients were followed up for 5 years after surgery. Death records were completed until January, 2016. Overall survival (OS) was measured until the date of death from any cause. The relationship between clinicopathological characteristics and OS was examined by Kaplan-Meier log-rank survival analyses and univariate Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). Variables statistically significant (p value < 0.20) were entered into a multivariate model using an entered method. The relationship between survival and prognostic parameters was examined using the X^2 method for linear trend. In all statistical tests conducted as part of the study, α value was taken as 0.05 and p< 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences ver. 21.0, SPSS Inc, Chicago, Illinois, USA) computer program.

RESULTS

A total of 2840 patients' demographic, clinical data and pathology reports were analyzed retrospectively. Overall median age of the patients was 28 years (range 1-89 years) with a male (n= 1730, 60.9%) to female (n= 1110, 39.1%) ratio of 1.55. Pediatric group aged between 1-6 years (n= 73, 2.6%), late pediatric group aged between 7-11 years (n= 146, 5.1%) and adolescents aged between 12-17 years (n= 228, 8%) did not present appendix tumors. Carcinoid tumors were reported in 17 (0.59%) patients. Adenocarcinoma of the appendix was reported in 6 (0.20%) patients, in whom 3 (0.1%) of the tumors were with mucinous histology. Median age of the patients was 36 years (range: 19-71 years) in the carcinoid group and 51 years (range: 41-68 years) in the adenocarcinoma group. Patients with carcinoid tumors were significantly younger than patients with adenocarcinoma (p= 0.01). Carcinoid tumors were mostly located on the apex of the appendix in 9 (52.9%) patients while 5 (29.4%) tumors were located at the base and 3 (17.6%) tumors were located at the body of the appendix. Mean tumor size of the carcinoid group (9.47 ± 5.83 mm) was significantly smaller than the adenocarcinoma group (16 ± 3.90 mm, p= 0.02). Histopathology revealed that all of the adenocarcinomas were originated from adenoma. In the adenocarcinoma group, except 1 (16.6%) submucosal mucinous tumor (T1N0M0), 5 (83.3%) patients were presented with serosal invasion (T4N0M0). In the carcinoid group, mucosal and sub-mucosal invasion was present in 2 (11.76%) patients, lamina muscularis propria invasion was present in 5 (29.41%) patients and sub-serosa and serosa invasion was present in 4 (23.52%) patients. Patients with adenocarcinoma were significantly more likely to have tumor extension beyond the appendix, whereas patients with carcinoid tumors tended to be limited to the appendix (p= 0.05). Mucinous/non-mucinous adenocarcinoma histology interpretations also showed significant serosal (p= 0.05) and mesoappendix invasion (p= 0.002). All patients in the adenocarcinoma group and 4 (23.52%) patients in the carcinoid group with mesoappendix invasion underwent right hemicolectomy procedure (p= 0.002). Multivariate analyses of statistically significant factors in the univariate analyses presented serosal invasion as a sole independent risk factor for mucinous and non-mucinous adenocarcinoma group (HR: -2.70, 95% CI: 0.006-0.755, p= 0.029). Tumor characteristics of the patients are summarized in Table 1 and Table 2.

Median follow-up time was 48 months (range: 28-61 months). All patients were alive and disease free since the last follow-up. Estimated median survival rates of the carcinoid tumors, mucinous and non-mucinous adenocarcinomas were 48 (95% CI: 44-52), 55 (95% CI: 42-68), and 42 (95% CI: 26-58) months, respectively. Additionally, disease specific survival rates of carcinoid tumors, mucinous and non-mucinous adenocarcinomas were 36 (95% CI: 32-40), 30 (95% CI: 13-46), and 43 (95% CI: 30-55) months, respectively (p= 0.748).

Univariate analyses demonstrated that serosal invasion (p= 0.129), advanced tumor stage (TNM) (p= 0.108) and tumor invasion depth (p= 0.179) were associated with poor survival rates. In multivariate analyses, tumor invasion depth was the only independent prognostic factor affecting survival (HR= 1.31 (95% CI: 1.01-13.5), p= 0.047). The relationship between clinicopathological characteristics and survival is shown in Table 3.

DISCUSSION

Appendiceal tumors are broadly classified as epithelial and non-epithelial tumors. Epithelial tumors include adenoma, mucinous tumors with uncertain malignant potential and adeno-

Table 1. Patient demographic and tumor characteristics with primary appendiceal malignancies

Case	Gender	Age	Operation	Tumor size (mm)	Localization	Pathology	TNM	Follow up (months)	Recurrence
1	Female	28	CA	5	Apex	Carcinoid tumors	Muscularis	59	None
2	Male	23	CA	10	Distal	Carcinoid tumors	Subserosa	58	None
3	Female	71	CA	11	Apex	Carcinoid tumors	Mucosa	53	None
4	Female	44	CA	7	Apex	Carcinoid tumors	Subserosa	52	None
5	Male	40	CA	2	Apex	Carcinoid tumors	Muscularis	47	None
6	Female	37	RHC	17	Distal	Carcinoid tumors	Subserosa	47	None
7	Female	34	CA	6	Apex	Carcinoid tumors	Subserosa	46	None
8	Male	23	CA	3	Distal	Carcinoid tumors	Submucosa	44	None
9	Male	19	CA	6	Apex	Carcinoid tumors	Submucosa	43	None
10	Female	24	CA	8	Apex	Carcinoid tumors	Muscularis	38	None
11	Male	36	CA	22	Body	Carcinoid tumors	Muscularis	35	None
12	Male	40	CA	4	Apex	Carcinoid tumors	Muscularis	31	None
13	Female	24	CA	3	Apex	Carcinoid tumors	Mucosa	26	None
14	Female	28	CA	12	Body	Carcinoid tumors	Serosa	59	None
15	Male	41	RHC	13	Distal	Carcinoid tumor	Serosa	57	None
16	Male	55	RHC	15	Distal	Carcinoid tumor	Serosa	42	None
17	Female	55	RHC	17	Body	Carcinoid tumor	Serosa	39	None
18	Male	68	RHC	21	Distal	Non-Muscinous AC	Serosa	55	None
19	Male	54	RHC	17	Distal	Non-Muscinous AC	Serosa	53	None
20	Female	48	RHC	13	Distal	Non-Muscinous AC	Serosa	45	None
21	Female	41	RHC	12	Body	Mucinous AC	Submucosa	30	None
22	Female	60	RHC	20	Apex	Mucinous AC	Surrounding tissue	55	None
23	Male	49	RHC	13	Apex	Mucinous AC	Serosa	40	None

CA: Complete appendectomy, RHC: Right hemicolectomy, AC: Adenocarcinom.

carcinoma (7). Appendiceal adenocarcinomas represent 4-6% of the overall appendiceal malignancies and are notably rare tumors (8). Primary appendiceal adenocarcinomas are mostly seen in sixth and seventh decades of life with an equal male-female ratio (9). Presentation of appendiceal adenocarcinomas differs in the clinical setting. The tumor should be presented as an incidental finding following acute appendicitis, as a pelvic mass or as peritoneal carcinomatosis with or without ascites (10). Acute appendicitis is the most common presentation (11). Therefore, there have been difficulties to determine the most appropriate classification system while defining appendiceal adenocarcinomas (12). There is no designated WHO (World Health Organization) and AJCC (America Joint Commission on Cancer) staging systems for all subtypes of primary appendiceal carcinomas regarding to the rarity of the disease (5). Pai and Longacre in 2005 classified appendiceal epithelial tumors into mucinous and non-mucinous (intestinal and signet ring cell) types (13). Mucinous adenocarcinoma represents 60% of all overall primary appendiceal adenocarcinomas, followed by intestinal-type adenocarcinomas and signet ring cell carcinomas (14). Whether the differences in tumor characteristics, tumor progression and overall–disease free survival rates suggest that all subtypes of appendiceal adenocarcinomas are distinct pathologies, to achieve the exact removal of the tumor with clear margins is determined as curative therapy. While simple appendectomy is described as a therapeutic method in local disease, adjunctive right hemicolectomy presented better survival rates (6). In our study, all patients in the adenocarcinoma group underwent right hemicolectomy procedure, but there was no significant survival benefit in between groups even though the median survival rate of the mu-

Table 2. The relationship between clinical parameters and subtypes of appendiceal malignancies

	Carcinoid tumors (n= 17)	Mucinous/Non-mucinous adenocarcinoma (n= 6)	P value, Univariate analyses	P value, Multivariate analyses
Age, years				
Mean (SD)	36.59 (13.94)	53.33 (9.58)	0.01	-
Range	19-71	41-68		
Gender (%)				
Male	8 (34)	3 (13)	0.63	-
Female	9 (39)	3 (13)		
Tumor size, mm (SD)	9.47 (5.83)	16 (3.90)	0.02	-
Tumor Location (%)				-
Distal	5 (21)	3 (13)	0.35	
Body	3 (13)	1 (4)		
Apex	9 (39)	2 (8)		
Type of surgery (%)				
Appendectomy	13 (76)	-	0.002	-
Right hemicolectomy	4 (23)	6 (100)		
Tumor extension (No/Yes, %)				
Limited to appendix	13/4	1/5	0.05	-
Serosa invasion	12/4 (23)	1/5 (83)	0.05	0.029
Mesoppendix invasion	11/4 (23)	1/5 (83)	0.02	-
Vascular invasion	11/6 (35)	2/4 (66)	0.19	-
Perineural invasion	9/6 (35)	2/4 (66)	0.26	-

Table 3. The relationship between prognostic factors and survival of patients with appendiceal malignancies following surgery

Variables	Univariate Analyses, HR (95% CI)	p	Multivariate Analyses, HR (95% CI)	p
Age (15-40 y/40-65 y/> 65 y)	0.54 (0.36-8.05)	0.489	-	-
Gender (Male/Female)	0.21 (0.52-2.92)	0.626	-	-
Tumor type (carcinoid/adenocarcinoma)	0.12 (0.42-2.98)	0.805	-	-
Tumor site (base/body/apex)	0.27 (0.30-1.91)	0.560	-	-
Tumor stage (TNM)	1.96 (0.64-7.86)	0.108	0.23 (0.76-2.11)	0.361
Tumor invasion depth	1.63 (0.47-5.07)	0.179	1.31 (1.01-13.5)	0.047
Meso-appendix invasion (no/yes)	0.26 (0.54-3.10)	0.558	-	-
Vascular invasion (no/yes)	0.33 (0.60-3.21)	0.430	-	-
Perineural invasion(no/yes)	0.33 (0.58-3.31)	0.453	-	-
Serosal invasion (no/yes)	0.70 (0.81-5.04)	0.129	0.45 (0.33-7.36)	0.561
Tumor perforation (no/yes)	0.10 (0.13-9.44)	0.920	-	-

cinous group was higher than the non-mucinous group. Similar to our findings, McCuskey et al. have mentioned in a review of 1061 cases that patients with mucinous and intestinal-type adenocarcinoma histology do not show any significant difference in survival rates (9). In the literature, peritonitis on diagnosis, histologic subtype, tumor grade, extent of surgery and pre-or per-operative peritoneal dissemination and intraperitoneal chemotherapy are well defined prognostic factors affecting survival and tumor recurrence (5,15-17). Besides these prognostic factors, including extended disease and age, aggressive

tumor histology such as poorly differentiated adenocarcinomas and signet ring-cell type carcinomas are associated with 5-year survival rate of only 7% and worst prognosis (14,18).

Non-epithelial tumors of the appendix are endocrine-carcinoid tumors, lymphoma and sarcoma. Unlike appendiceal adenocarcinomas, carcinoid tumors of the appendix are diagnosed at a much younger age of 32-42 years with female predominance (14,19). However, there have been reports regarding a decrease of the overall percentage of appendiceal endocrine neoplasm among all gastrointestinal neuroendocrine tumors, and the prevalence of carcinoid tumors among all primary tumors of the appendix ranges between 43 and 57% (20,21). WHO has classified endocrine tumors according to histological differentiation and graded the tumors as benign and malignant well differentiated tumors and mixed exocrine-endocrine malignant tumors (goblet cell carcinoid) (22). Goblet cell carcinoid (adenocarcinoma) is also a rare tumor containing both epithelial and neuro-endocrine features with progressive clinical course in which 20-40% of the cases presented with early nodal involvement (23). Appendectomy with clear margins is defined as sufficient surgical option for early-stage tumors of primary appendiceal malignancies except goblet cell adenocarcinoma. Locally advanced adenocarcinoma or carcinoid tumors and goblet cell adenocarcinoma have a relative indication for right hemicolectomy with completion of tumor staging. Localization and size of the carcinoid tumors are prognostic factors besides tumor differentiation. AJCC staging system for carcinoid tumors is based on tumor size but does not consider tumor invasion depth and tumor grade. Mitotic activity, mesoappendix and lymphovascular invasion are also independent prognostic factors for carcinoid tumors. Although serosal involvement is not interpreted as a risk factor for carcinoid tumors, meso-appendix invasion is presented with poor prognosis (24). ENETS (European Neuroendocrine Tumor Society) defined a staging system including these important histologic features, tumor grade and meso-appendix invasion (25).

This study showed how the clinicopathological characteristics of the tumor affect survival of the patients undergoing curative resection of appendiceal malignancies. These data support the routine histological sampling of the tumor, preoperative and postoperative clinical outcomes of the patients. In this study, surgical choice between tumor subtypes was not associated with poor clinical outcomes. Statistical analyses between tumor subtypes revealed that patients with adenocarcinoma presented with an advanced age, larger tumor size and more extended disease at diagnosis. Carcinoid tumors were mostly located at the apex of appendix with local disease. As expected, presence of serosal invasion was referred as an independent high-risk factor for patients with adenocarcinoma of the appendix. Although estimated median survival rates between tumor subtypes were in close range, there was no disease related death and recurrence during the follow-up in all subtypes of appendiceal malignancies. Survival rates of the patients between tumor subtypes were not statistically significant. Among all clinical and pathological parameters identified pre- and postoperatively, tumor invasion depth was found as a sole risk factor affecting survival. Increased tumor invasion was found to be associated with the decreased disease specific survival rates.

There are several limitations regarding the multicenter and retrospective nature of the study. Several surgeons and surgery departments participated and provided invaluable clinical and pathological data into the study. Interpretations of the pathological specimens differed among centers and in between pathologists. Unfortunately, there were no reports of signet ring cell carcinoma and goblet cell carcinoid tumors. Therefore, this study could not present the risk factors and survival rates of these group of tumors. Our study also suggests that cooperation between referral clinics in defining the confirmed histological outputs and processing the data prospectively should be more effective to get better clinical outcomes with more reliable data.

In conclusion, tumor subtype and tumor invasiveness is an important risk factor for survival in appendiceal malignancies. Besides that, surgical choice is not presented as an effective factor for improved clinical outcomes and survival rates. Appendectomy alone presents satisfactory results but complete staging of the tumor should always be considered. Further prospective studies are needed to evaluate the proper staging of the tumors.

Ethics Committee Approval: The study is retrospective. The study was performed according to the Helsinki Declaration.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Apendiks tümörlerinin klinikopatolojik ve prognostik özellikleri: tümör invazyon durumu önemli mi?

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ÖZET

Giriş ve Amaç: Apendiks tümörlerinin sağkalım oranlarını ve sağkalımı etkileyen prognostik faktörü değerlendirmektir.

Gereç ve Yöntem: Olguların demografik özellikleri, tümör özellikleri ve ameliyat öncesi ve sonrası sonuçları retrospektif olarak incelendi. Hastaların sağkalımları kaydedildi. Çalışma Helsinki deklerasyonuna uygun olarak yapıldı.

Bulgular: Prospektif olarak 2840 spesmenin 23'ü incelendi. Hastaların medyan yaşı 28 (1-89) erkek (n= 1730, %60,9) ve kadın (n= 1110, %39,1) oranı 1,55 idi. Pediatrik hasta grubunda apandisyel malignite gözlenmedi. On yedi (%0,59) hastada karsinoid tümörler, 6 (%0,20) hastada adenokarsinom tespit edildi. Alt grupların tek değişkenli analizlerinde yaş, tümör boyutu, operasyon tekniği, lokal hastalık, seroza ve mezoapendiks invazyonu gruplar arasında anlamlı derecede farklı bulundu. Subtiplerin çok değişkenli analizinde serozal invazyonun müsinöz ve non-müsinöz adenokarsinom için bağımsız bir risk faktörü olduğu gösterildi (HR: -2,70, %95 GA: 0,006-0,755, p= 0,029). Medikal takip süresi 48 aydı (aralık: 28-61 ay) ve karsinoid tümörler, müsinöz ve non-müsinöz adenokarsinomların hastalıklara özgül sağkalım oranları sırasıyla 36 (%95 GA: 32-40), 30 (%95 GA: 13-46) ve 43 (%95 GA: 30-55) ay arasında değişti (p= 0,749). Tek değişkenli analizlerde sağkalımı etkileyen faktörler ilerlemiş tümör evresi, serozal invazyon ve tümör invazyon derinliği idi. Çok değişkenli analizlerde apandisyel maligniteleri tüm alt tiplerinde yetersiz sağkalım oranları olan tek tümör invazyonu faktörü [HR = 1,31 (%95 GA: 1,01-13,5), p= 0,047] idi.

Sonuç: Tümör alt tipi ve tümör invazyonu sağkalımı belirlemede önemli risk faktörleridir. Diğer tedavi yöntemlerine göre apendektomi, daha iyi klinik sonuçlara ve artmış sağkalım oranlarına sahiptir.

Anahtar Kelimeler: Apendektomi, apendisit, apendiks maligniteleri, apendiks tümörleri

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Validation of prognostic scoring systems for predicting 30-day mortality in perforated peptic ulcer disease

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ABSTRACT

Objective: Perforations in Peptic Ulcer Disease are known to cause considerable morbidity and mortality. The objective of this study was to compare efficacy of known clinical parameters and three existing scoring systems in predicting 30-day mortality and determining mortality risk stratification based on risk factors.

Material and Methods: This was a prospective observational study of 190 patients operated for perforated peptic ulcer over a period of 14 months at a 1500 bed tertiary care university hospital in Western India.

Results: The mortality rate observed was 18.95%. Elderly population, raised serum creatinine, time delay to surgery > 24 hours, preoperative shock and pre-existing medical illness were identified as risk factors for poor postoperative prognosis. The Area under curve for mortality prediction was 0.590 for ASA, 0.745 for Boey and 0.804 for PULP score. Mortality was best anticipated by a combination of raised serum creatinine levels, preoperative shock and delayed surgery by multivariate logistic regression analysis.

Conclusion: Poor outcome was significantly higher in the elderly, patients with raised serum creatinine, preoperative shock, pre-existing medical illness and when the time delay to surgery was > 24 hours. In spite of the Boey score being more practical in application, PULP score proved to be a more precise indicator of mortality. A larger study inclusive of other Mortality Risk Prediction Models would help formulate a more accurate and population specific scoring system.

Keywords: Perforated peptic ulcer, scoring systems, risk factors, 30-day mortality

INTRODUCTION

Perforated peptic ulcer disease (PUD) is potentially fatal unless treated surgically (1). Although the prevalence of peptic ulcer in the general population is not known, American Gastroenterology Association (AGA) has reported a 10-12% prevalence in patients with upper gastrointestinal symptoms (2,3). Among all the complications relating to peptic ulcer disease, perforation is the most dreaded since it has the highest mortality rate (4). Population based studies have reported mortality rates of 25-30% following perforated peptic ulcer (PPU) (5,6).

The pathogenesis of PPU is multifactorial and results from an interaction between environmental, microbiological-*Helicobacter pylori*, pharmacological-Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and steroids and genetic factors (7,8). Recognizing individual clinical parameters indicating higher risk of fatality and classifying patients according to low or high risk pre-operatively can help with optimization of care and resource allocation (9). Various risk prediction models like American Society of Anaesthesiologists (ASA) physical status, Boey and Peptic Ulcer Perforation Score (PULP) have been devised for that. Due to geographic and demographic variations, it becomes prudent to validate each existing model and test its diagnostic efficacy for a particular scenario. An ideal scoring system should be easy to apply, include all pre-operative variables proven to affect outcomes, highly sensitive and specific and should not cause additional fiscal or organizational burden (9). The present study was conducted to compare efficacy of ASA, Boeyand PULP score in predicting 30-day mortality in patients with PPU based on clinical parameters, to determine mortality risk stratification and calculate incidence of 30-day mortality after surgical intervention for PPU at our institution.

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MATERIAL and METHODS

Patients and Setting

A prospective observational study was conducted at the General Surgical Department of a 1500 bed tertiary care Medical Collage Baroda and Sir Sayajirao General Hospital in Western India over a period of 14 months from September 2015 to October 2016, after obtaining prior approval of the institutional ethics committee. Out of the 204 patients operated for PPU, 190 patients were evaluated, 14 were excluded due to incomplete data. Informed consent was obtained from all patients. All consenting patients above the age of 18 years diagnosed and operated for benign gastric or duodenal ulcer were included. Patients with malignant perforated ulcer, those conservatively treated for PPU and patients who expired before any surgical intervention were excluded.

PPU was diagnosed based on clinical features, laboratory tests, plain abdominal skiagram and intraoperative findings. Patients were evaluated for past history of dyspepsia and epigastric pain, long term NSAIDs or steroid ingestion, smoking and alcohol consumption, pre-existing co-morbidities including stroke, diabetes mellitus, tuberculosis, respiratory, cardiovascular, renal or liver disease. All cases were managed by surgical procedure involving open primary closure of perforation by interrupted 2-0 Polyglactin 910 sutures covered with pedicle omentoplasty.

Data Studied

Factors affecting patient outcome like age and gender, long term NSAIDs/steroid intake, renal function, preoperative shock and hydration (systolic blood pressure < 100 mmHg and heart rate >100 beats/min), preoperative co-morbidities and time delay from admission to surgery were recorded. All patients were scored under three PPU scoring systems: ASA, Boey and PULP. Patients were grouped for age ≤ 60 or > 60 years, sex, NSAIDs or steroid intake, serum creatinine ≤ 1.47 or > 1.47 mg/dL, co morbidities present or absent, time delay ≤ 24 hr or > 24 hr, ASA class ≤ 3 or > 3, Boey score ≤ 1 or > 1 and PULP score ≤ 7 or > 7.

Outcome was assessed by mortality within 30-days of surgery for each group. The diagnostic abilitiesof three PPU scoring systems in the form of sensitivity, specificity, positive predictive value and negative predictive valuewere calculated.

Statistical Tests and Statistical Analysis

Data was analyzed using MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Mean and standard deviation for continuous data, and number and percentage for categorical variables were calculated. Pearson's Chi Square or Fisher's exact test was used for categorical data. All tests were 2-tailed with $p< 0.05$ considered significant. Odds ratio for mortality was calculated for age, sex, serum creatinine, use of steroids and NSAIDS, preoperative shock, pre-existing co-morbidities, delay in surgery and individual PPU scores to check for their association.

Univariate analysis was done for pre-operative factors affecting patient outcome, ASA score, Boey score and PULP score to check for their association with the mortality. Results of these analyses were used in Logistic regression analysis for dichotomous outcome like mortality. To assess if the regression models' estimates fit the data, "Goodness of Fit" Chi Square test and Hosmer- Lemeshow test were used. Receiver Operating Characteristics (ROC) Analysis and Area Under Curve (AUC) was calculated for the individual scores and compared. An AUC value > 0.8 was considered good, between 0.60-0.80 was considered as moderate, and < 0.60 was regarded poor.

RESULTS

Of the 190 operated patients, 36 (18.95%) expired within 30-days of surgery.

Patient Profile and Preoperative Clinical Parameters

Patient demographic profiles, pre-operative parameters and their odds ratio for mortality are depicted in Table 1. Mean age of patients was 42.42 ± 16.34 years. Male to female ratio was noted to be 3.63:1. The most commonly observed pre-operative co morbidity was COPD (50%), followed by cirrhosis (26.47%). Five out of 34 patients had multiple coexistent co morbidities.The time delay defined as surgical delay more than 24 hours since admission ranged from 26 to 52 hours.

Risk Assessment Scores and their ROC curves

Majority of the patients belonged to ASA physical class 4 (n= 149, 78.42%), followed by ASA physical class 3 (n= 33, 17.37%) and ASA physical class 5 (n= 8, 4.21%). None of the patients could be classified under class 1 or 2. 157 patients belonged to class 4 or 5. Patients categorized to Boey class 0 were 106 (55.79%), Boey class 1 were 54 (28.42%), Boey class 2 were 28 (14.73%) and 2 (01.05%) belonged to Boey class 3. Maximum number of patients (n= 82, 43.16%) had a PULP score of 5. Patients having PULP score of 6, 7 and 8were 21 (11.05%), 24 (12.63%) and 22 (11.58%) respectively. In PULP score category 3 and 9, 13 (06.84%) and 12 (06.32%) patients were noted. There were none noted with any other score.

The odds ratios (OR) of risk assessment scores for mortality are enlisted in Table 1. Receiver operating characteristic (ROC) curve analysis andArea under curve (AUC) for the three scoring systems are shown in Table 2 and Figure 1.

Regression Analysis

Logistic regression analysis for pre-operative parameters showed significant association of mortality with raised serum creatinine levels, preoperative shock and delayed surgery. Age and preoperative comorbidities were not included in the calculations because of insignificant association with mortality in univariate analysis. Boey and PULP scores when subjected to logistic regression analysis revealed their significant association with mortality (Table 3). ASA score was left out of the regression model

Table 1. Patient characteristics, pre-operative clinical parameters and Odds Ratio for mortality for each univariate factor

Variable	Mean ± SD or Percentage (%)	Number (n)	Odds Ratio for Mortality	p
Age				
≤ 60 years	42.42 ± 16.34 years	162	1	
> 60 years		28	1.914 (0.766-4.782)	0.165
Gender				
Female	21.58%	41	1	
Male	78.42%	149	1.174 (0.473-2.913)	0.729
Steroid intake				
No	95.26%	181	1	
Yes	4.74%	9	1.235 (0.246-6.212)	0.798
NSAIDs intake				
No	91.05%	173	1	
Yes	8.95%	17	0.909 (0.247-3.347)	0.886
Serum creatinine level				
≤ 1.47 mg/dL	68.95%	131	**1**	
> 1.47 mg/dL	31.05%	59	**17.124 (6.847-42.826)**	**< 0.0001**
Preoperative shock				
No	86.32%	164	**1**	
Yes	13.68%	26	**9.286 (3.765-22.904)**	**< 0.0001**
Preoperative comorbidities				
No	82.11%	156	**1**	
Yes	17.89%	34	**3.000 (1.312-6.859)**	**0.009**
Delay in surgery				
No	89.47%	170	**1**	
Yes	10.53%	20	**5.539 (2.098-14.624)**	**0.0005**
ASA score				
≤ 3	17.37%	33	**1**	
> 3	82.63%	157	**9.180 (1.211-69.590)**	**0.032**
Boey score				
≤ 1	84.21%	160	**1**	
> 1	15.79%	30	**18.000 (7.187-45.084)**	**< 0.0001**
PULP score				
≤ 7	74.21%	141	**1**	
> 7	25.79%	49	**18.000 (7.473-43.358)**	**< 0.0001**

SD: Standard deviation, NSAIDs: Non steroidal anti-ınflammatory drugs, ASA: American Society of Anaesthesiologists, PULP: Peptic ulcer perforation score.

Table 2. Diagnostic ability and performance of ASA, Boey and PULP score for predicting risk of mortality

	AUC*						
Score	Value	SE[a]	95% CI[b]	Sensitivity	Specificity	PPV	NPV
ASA	0.590	0.0215	0.516 to 0.661	97.22	20.78	12	98.5
Boey	0.745	0.0432	0.677 to 0.806	55.56	93.51	48.7	95
PULP	0.804	0.0392	0.740 to 0.858	75	85.71	36.8	96.9

AUC: Area under curve, SE: Standard error, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, ASA: American Society of Anaesthesiologists, PULP: Peptic ulcer perforation score.
[a] Delong et al., 1988.
[b] Binomial exact.
* p value < 0.0001.

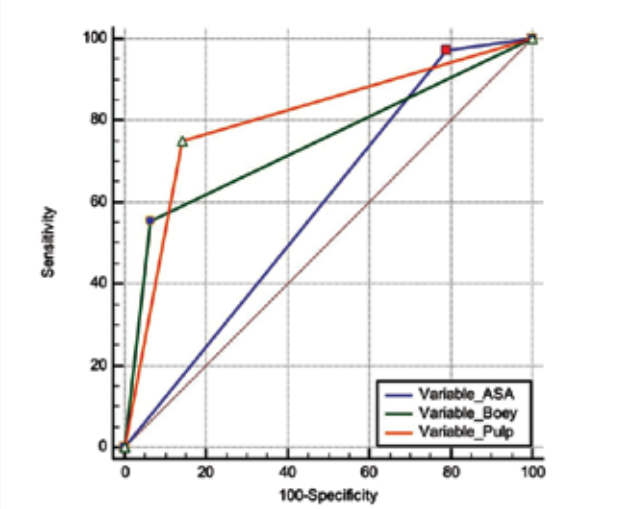

Figure 1. Comparison of ROC curve for ASA, Boey and PULP score.

as including the score in calculations did not change the result significantly.

DISCUSSION

Prevalence of mortality in our study population (18.95%) was less as compared to that noted in previous studies on Western populations (5,6), but higher than studies in other Southeast Asian populations (9,10). This may be because of the advanced age of patients presenting with PPU in Western studies (mean age ~70 years) compared to Asian studies (mean age ~50 years). The elderly, besides suffering from additional pre-operative illnesses such as hypertension and diabetes, have poor physiological reserves to deal with post-operative complications and hence are more prone to fatality.

Demographic Profile and It's Relation to 30-Day Mortality

Higher rate of PPU was observed in males similar to two other studies (9,10). Another Indian study comprising of 50 perforated peptic ulcer patients noted a very high male to female ratio (11.5:1) and attributed it to the habits of smoking and alcohol consumption in young men (11). The current study did not elicit the habits of smoking and alcohol consumption in our patient population. We recorded PPU more commonly in younger age groups unlike four other studies where the mean age of patients was above 50 years (6,9,12,13). Analogous to our data, an Indian study noted a lower mean patient age (38.1 years) (11). The odds of death were 1.91 times more if the age of patient was more than 60 yrs, which confirm the findings that the elderly suffer from more debilitating morbidity and mortality (6,12). No association could be found by us between gender and mortality.

Preoperative Clinical Parameters and Their Relation to 30-Day Mortality

The rates of long term steroid and NSAIDs ingestion were lower (4.74% and 8.95%) in the current study compared to a study by Moller et al (13% and 41%) but higher than those noted by Anbalakan et al. (0.3% and 1.8%) (6,9). None of these studies including ours could find an association between chronic steroid/NSAID ingestion and mortality. At our institution, the significantly higher risk of 30-day mortality (Odds ratio= 17.124) in patients with raised serum creatinine levels was in contrast to another study determining serum creatinine level as an independent risk factor for mortality (12). This could be due to the delayed referral of more critical patients to our tertiary care hospital. Increased creatinine level, which is a well-recognized risk factor for mortality in surgical patients, indicates pre-existing renal failure or acute kidney injury due to dehydration or sepsis caused by PPU (14). The proportion of PPU patients presenting with preoperative shock in our study was lower than that observed by two previous studies, however higherrisk of mortalitywas observed in our patients (6,12). The finding of chronic obstructive pulmonary disease (COPD) in 50% of our cases correlate with the previous studies recording heart disease, COPD and diabetes mellitus as the most common preoperative co-morbidities in patients with PPU (6,9-11). The co-morbidity rate of 17.89% in the present research was comparable to that reported in a study from Singapore (9), but lower than that in a Western study (6) which observed large number of cases with co-morbid heart disease, active malignant disease or AIDS and other co-morbidities like hyperlipidemia. Mortality depends on multiple clinical factors and co-morbidities, thus explaining the higher fatality observed by us (Odds ratio= 3.000).

Table 3. Logistic regression analysis for mortality

Independent Variables		Odds Ratio	95% Confidence Interval		p
			Lower	Upper	
Pre-operative clinical variables	Serum creatinine (> 1.47/≤ 1.47 mg/dL)	12.8599	4.8886	33.8295	< 0.0001
	Pre-operative shock (Yes/No)	4.3294	1.5199	12.3323	0.0061
	Time delay (Yes/No)	3.6957	1.1262	12.1271	0.0311
PPU scores	Boey score (> 1/≤ 1)	5.1473	1.7347	15.2739	0.0032
	PULP score (> 7/≤ 7)	8.5188	3.0861	23.5150	< 0.0001

PPU: Perforated peptic ulcer.

Table 4. Comparison of mortality risk prediction models in different studies

	Study					
Scores	**Present**	**Anbalakan[9]**	**Menekse[13]**	**Thorsen[12]**	**Moller[6]**	**Nichakankitti[10]**
Mortality (%)	18.95	7.2	10.1	16.3	27	3.57
	AUC					
ASA	0.59	0.75	0.914	0.79	0.78	0.776
Boey	0.745	0.72	0.92	0.75	0.7	0.728
PULP	0.804	0.75	0.955	0.79	0.83	0.784
	Sensitivity					
ASA	97.22	83.3	-	85.7	-	-
Boey	55.56	58.3	-	64.3	-	-
PULP	75	62.5	-	92.9	-	-
	Specificity					
ASA	20.78	98.1	-	66	-	-
Boey	93.51	86.3	-	94.4	-	-
PULP	85.71	87.3	-	58.3	-	-
	PPV					
ASA	12	16.4	-	-	-	-
Boey	48.7	25	-	-	-	-
PULP	36.8	27.8	-	-	-	-
	NPV					
ASA	98.5	98.1	-	-	-	-
Boey	95	96.4	-	-	-	-
PULP	96.9	96.8	-	-	-	-

ASA: American Society of Anaesthesiologists, PULP: Peptic ulcer perforation score, AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value.

The Boey score measures 'delay' as the time from perforation to surgery while the PULP score considers it to be the time from perforation to admission based on symptom debut. Alike a previous Norwegian study we defined the time 'delay' as the time interval from admission to surgery, because it would be a better prognosticator as time of hospital admission and surgery are always accurately noted in the case records (12). This would eliminate the recall bias by patient or record bias by hospital. We observed around 10% cases with delay of > 24 h while Thorsen et alrecorded around 18% (12). Research by Buck et al. has shown that it is crucial to reduce the time interval between perforation and operation since each hour adds to the poor prognosis (15). Since there are long travelling distances between our hospital and the rural primary care centres the actual delay would be significantly more than that noted, thus explaining the higher risk of mortality in our patients in contrast to that reported by Thorsen et al. (12).

Logistic regression analysis revealed strong correlation between preoperative clinical variables (raised serum creatinine, preoperative shock and time delay in surgery) and mortality as proven in previous studies (5,6).

Comparison of Risk Assessment Scores and Their Relation to 30-Day Mortality

We evaluated three commonly used scoring systems for predicting mortality in PPU patients. Comparison of Mortality Risk Prediction Models in different studies is illustrated in Table 4. The risk of mortality in patients with higher ASA (> 3), Boey (> 1) and PULP (> 7) scores when individually calculated was greater alike a previous study (12). Logistic regression analysis indicated positive relationship between higher Boey/PULP scores and mortality.

In our study, PULP score achieved the highest OR and AUC values, followed by Boey and ASA scores which can be explained by the inclusion of multiple objective predictors related to patients' current health status and acute disease severity in PULP score as compared to the other two. Thorsen et al. included acute state of patient in ASA scoring, therefore observed equal performance of the ASA and PULP score (12). Unlike their analysis, our ASA grading was based only on pre-existing illnesseshence we noted a poor performance by the ASA score. The efficiency of Boey score predicted by us was analogous to most other studies because of the same three variable system employed by all (6,9,10,12).

Though ASA score is the easiest to calculate, it was not designed for PPU studies. Prior studies have concluded that ASA Physical Status is an objective scoring system having inter-observer variability and hence prone to observer bias (12,16). If the acute state of the patient is not taken into consideration, it may affect the outcome in terms of mortality (17). Boey scoring system includes only three parameters: co-morbidity, preoperative shock and time from onset of abdominal pain. Therefore it is simpler for clinical application (12). Boey score does not take into consideration other well-established prognostic factors like age, sex, concomitant drug intake or renal impairment and that leads to its questionable accuracy in predicting mortality risk (9,18). The original Boey score defines shock as blood pressure < 90 mmHg whereas shock by routine definition is systolic blood pressure of < 100 mmHg and pulse ≥ 100/minute. Hence the score may vary if the data collected donot strictly adhere to the original definitions (14). PULP score incorporates parameters of both ASA and Boey score and can be evaluated preoperatively (14). It includes age which is a recognized risk factor for mortality, therefore is more predictive (13). The shortcoming of PULP score is that it ismore clinically complex andrequires exact time of symptom origin and admission for time delay, so not easy to use.

Variations in patient demographic profiles and study inclusion criteria may bias comparison of the AUC values between different studies. Therefore it is preferable to compare ROC curve analysis and AUC values of studies carried out in similar group of patients (14). The PPU scoring systems found in the literature were validated at different times in different countries on different populations with varied ages. So, further validation is recommended before any particular scoring system can be applied to any one population (14).

Strengths and Limitations of Study

The sample size was relatively small but adequately powered to show association between pre-operative clinical variables and 30-day mortality. In the present study, time'delay' was considered as the time interval from admission to surgery, which is clinical feasible to monitor thus avoiding bias and hence a more accurate prognosticator. Due to a small sample sizeno significant association was found between use of steroids or NSAIDS and mortality. Individual factors which have demonstrated proven association with PPU and mortality like smoking, alcohol, *H. pylori* infection, hypoalbumineamia and hyperbilirubinemia were not studied. Preoperative co-morbidities were not independently evaluated for their relation with mortality.

Meaning of This Study and Implications for Clinicians

The use of a near-ideal and validated mortality risk prediction score would help clinicians find out the prognosis of a patient postoperatively, optimize perioperative care including intensive care and counsel the family appropriately. The role of a surgeon in identifying and modifying the preoperative risk factors is crucial, which can lead to a better outcome in cases of PPU. A study validating and determining diagnostic effectiveness of other Mortality Risk Prediction Models (MRPMs) like Hacettepe score, Jabalpur score, Charlson co-morbidity index, Sepsis score, Mannheim Peritonitis Index (MPI), Acute physiology and chronic health evaluation II (APACHE II), Simplified acute physiology score II (SAPS II), Mortality probability models II (MPM II) and Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity physical sub-score (POSSUM-phys score) would guide selection of a comprehensive and suitable scoring system for the Indian population.

CONCLUSION

In conclusion, this study evaluated a limited number of mortality risk assessment tools used frequently in day to day practice to confirm the importance of mortality risk stratification models in evaluating the prognosis of postoperative patients of PPU. The PULP score, although more complex, predicted mortality risk better than the ASA score and the Boey score. Elderly population, raised serum creatinine, time delay to surgery > 24 hours, preoperative shock and pre-existing medical illness predicted-poor prognosis. Gender and NSAIDS or steroids intake had no role in mortality risk prediction. A number of scoring systems have been reported yet none prove to be superior and most are tested in isolation on geographically and demographically different study populations. This study confirmed the importance of mortality risk prediction models in assessing the patients of perforated peptic ulcer in Asian-Indian population. A larger study comparing more Mortality Risk Prediction Models would help to identify the risk factors in a wide variety of patients and aid in the improved risk estimation.

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Informed Consent: Obtained from all patients.

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ORİJİNAL ÇALIŞMA-ÖZET
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Perfore peptik ülser hastalığında 30 günlük mortaliteyi öngören prognostik skorlama sistemlerinin geçerliliği

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ÖZET

Giriş ve Amaç: Peptik ülser hastalığında perforasyonların önemli ölçüde morbiditeye ve mortaliteye sebep olduğu bilinmektedir. Bu çalışmanın amacı, 30 günlük mortaliteyi öngörmede ve risk faktörleri temelinde mortalite risk stratifikasyonunu belirlemede bilinen klinik parametrelerin ve var olan üç skorlama sisteminin etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: Bu çalışma, Batı Hindistan'da 1500 yataklı üçüncü basamak üniversite hastanesinde 14 aylık bir süreç içerisinde perfore peptik ülser sebebiyle opere edilen 190 hastanın prospektif gözlemsel bir çalışmasıdır.

Bulgular: Gözlemlenen mortalite oranı %18,95 idi. Postoperatif prognozu kötü etkileyen risk faktörleri arasında yaş, yükselmiş serum kreatin seviyesi, ameliyatın 24 saatten daha fazla gecikmesi, preoperatif şok ve var olan tıbbi rahatsızlıklardı. Mortalite öngörmesi için eğri altındaki alan ASA için 0,590, Boey için 0,745 ve PULP skoru için 0,804 idi. Çok değişkenli regresyon analizi sonucunda mortaliteyi öngören faktörlerin yükselmiş serum kreatin seviyesi, preoperatif şok ve geciken ameliyatlar olduğu belirlendi.

Sonuç: Kötü sonuçlar, yaşlı popülasyonda ve yükselmiş serum kreatin seviyesi olan, peroperatif şok geçiren, önceden tıbbi hastalığı olan ve ameliyata alınmaları 24 saatten daha çok geciken hastalarda belirgin derecede yüksekti. Boey skorlamasının uygulanması daha pratik olsa da PULP skorlama sistemi mortalitenin daha keskin bir göstergesi olarak kanıtlandı. Mortalite Riski Öngörü Modelleri içeren daha geniş bir çalışma daha doğru ve popülasyon spesifik bir skorlama sistemi oluşturmada yardımcı olacaktır.

Anahtar Kelimeler: Perfore peptik ülser, skorlama sistemi, 30 günlük mortalite

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ORIGINAL ARTICLE
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Is intraoperative nerve monitoring useful for surgical training in thyroid surgery?

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ABSTRACT

Objective: Parathyroid glands and recurrent laryngeal nerves (RLNs) are at risk during thyroid surgery. However, the identification of the nerves has reduced these risks. Intraoperative nerve monitoring (IONM) during thyroid surgery has gained widespread acceptance as an aid to the gold standard of visually identifying the RLN. The aim of the present study was to evaluate the effect of the identification of the RLN during thyroidectomy by using IONM.

Material and Methods: Seven hundred forty-eight patients were included in our prospectively designed study. Of these 748 patients, 1496 nerves at risk were studied. Group 1 consisted of 736 nerves that were identified using IONM, whereas Group 2 consisted of 760 visually identified nerves.

Results: In the non-IONM group, the rate of temporary nerve palsy was lower in patients operated by experienced surgeons than in patients operated by residents (p= 0.001). In the IONM group, RLN injury rates were similar between experienced surgeons and residents.

Conclusion: In spite of the fact that the duration of the operation was lower with IONM, the abbreviated duration may not appear to have clinical significance. The main advantage is for less experienced surgeons. IONM significantly decreases RLN palsy rates of the surgeons with limited experience in thyroid surgery.

Keywords: Thyroidectomy, nerve injury, nerve monitoring

INTRODUCTION

Thyroidectomy is performed very frequently in regions with iodine deficiency. The most serious complications of thyroidectomy are recurrent laryngeal nerve (RLN) palsy and hypoparathyroidism, which can considerably worsen the patients' quality of life. In spite of the fact that the rate of nerve paralysis is small, when it happens, it may be life-long in capacity (1,2). The incidence of nerve paralysis is reported to be 0%-14% (1-4). Conditions, such as retrosternal goiter, redo surgeries, or surgeries for malignant thyroid disorders, put the nerves at highest risks, and even experienced surgeons may accidentally damage the recurrent nerve, resulting in nerve paralysis in approximately 1%-2%. Since the early 1930's, routine visualization of RLN rather than avoiding it has become the standard of care (5-7).

Intraoperative nerve monitoring (IONM) during thyroid surgery has gained widespread acceptance as an aid to the gold standard of visually identifying the RLN (8-10). Different techniques to monitor the nerve include palpation of the cricothyroid muscle while stimulating the nerve; observation of the glottis for vocal cord movement while stimulating the recurrent nerve, which can be performed by either laryngoscopy or fiberoptic nasopharyngoscopy; monitoring the pressure of the glottis on the endotracheal tube and finally, through surface electrodes placed on the endotracheal tube, which are in contact with the vocal cords (8,9,11-14). Currently, the most common type of IONM is made by an endotracheal tube with electrodes secured on its wall, and those electrodes record the activities of the vocal cords as stimulated.

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Many studies have shown that routine intraoperative RLN monitoring decreases permanent paralysis rates (12,15-18). Nevertheless, its role in foreseeing postoperative nerve function and decreasing RLN injury is an ongoing debate (19-22). The aim of the present study was to assess the effect of intraoperative RLN identification by using IONM during thyroidectomy.

MATERIAL and METHODS

Patients

This was a prospectively designed study. Eight hundred fifteen consecutive patients with benign euthyroid thyroid disorders (multinodular goiter) (fine needle aspiration biopsy with suspicion of malignancy, aesthetic concerns, and pressure symptoms) who underwent thyroidectomy at the Department of General Surgery, Istanbul University, Istanbul Medical Faculty between April 2008 and April 2016 were intended to be included into the study.

Exclusion criteria were vocal cord dysfunction on preoperative evaluation, monitoring malfunction, and patient's refusal to participate in the study. Sixty-seven patients were excluded from the study, with 36 patients for vocal cord paralysis, 11 patients for signal loss, and 20 patients refused to participate in the study. Overall, 748 patients and 1496 nerves at risk were included (Figure 1).

Patients were randomized to have RLNs recognized by visualization or neuronal monitoring throughout the surgery. Randomization of the cases was provided by the resident not working in the study using coins (heads or tails method). Group 1 (n= 736) consisted of nerves, which were recognized with IONM, whereas Group 2 (n= 760) without IONM. Both groups were further divided into subgroups A and B. Groups 1A and 2A consisted of patients whose surgeries were performed by a qualified endocrine surgeon (n= 3), and groups 1B and 2B consisted of patients who were operated by 4th year residents (n= 4). Ethics committee approval was received for this study from the institutional Ethics Committee of Istanbul University, Istanbul Medical Faculty (762/2007). Informed consent was obtained from all patients.

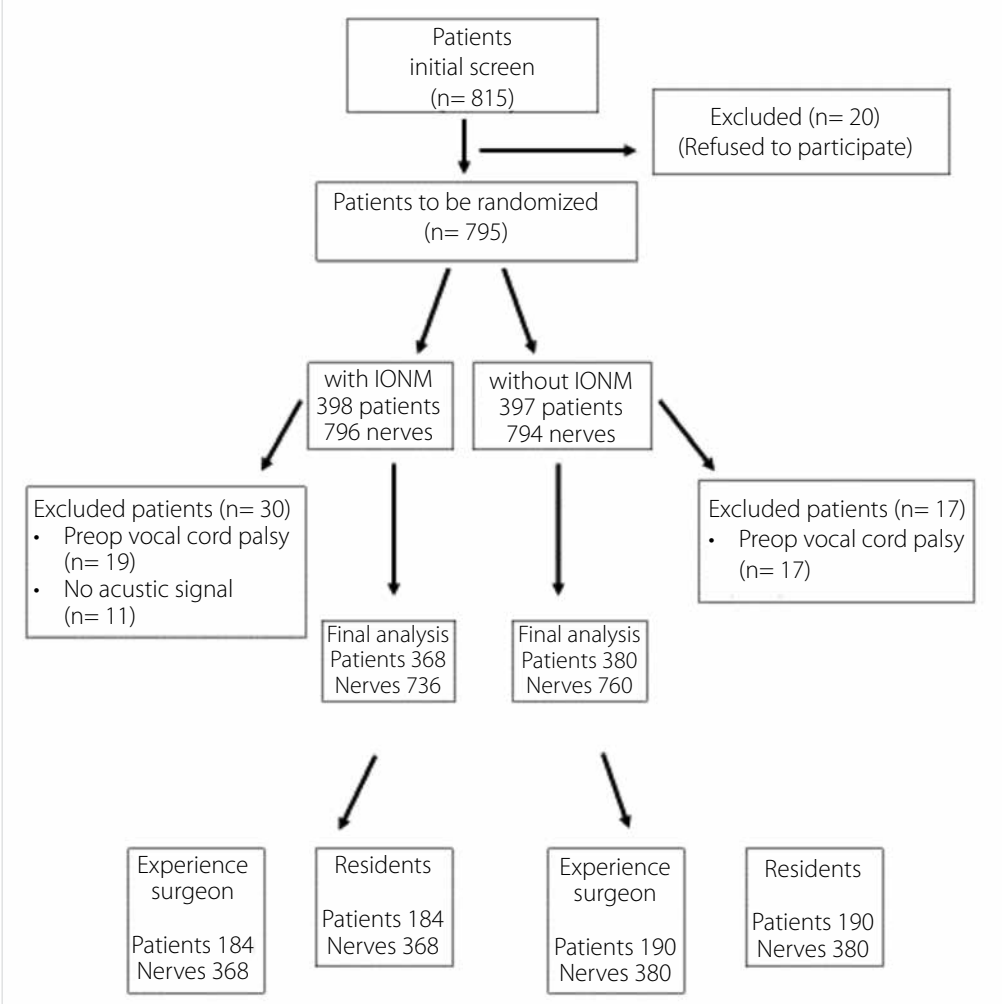

Figure 1. Flowchart of enrolled and randomized patients. IONM: Intraoperative nerve monitoring.

Technique

An experienced endocrine surgeon performed thyroidectomies in groups 1A and 2A, and 4th year residents performed surgeries in groups 1B and 2B.

The patient was in supine position under general anesthesia with the neck extended. Following a low collar incision, the superior and inferior subplatysmal flaps were prepared. After the strap muscles were separated and lateralized, the thyroid lobe was freed from its investing fascia and retracted medially. When present, the middle thyroid vein was sealed and cut. The superior thyroid artery and vein were ligated close to the thyroid tissue. The tracheoesophageal groove was prepared and dissected to identify the recurrent nerve. When found, the RLN was delicately freed from the adjacent tissues. As soon as the RLN and parathyroid glands were secured, the ligament of Berry was divided, and the thyroid lobe was detached from its attachments to the trachea.

No neuromuscular blocking agents were utilized during intubation in the IONM group. Endotracheal tube monitoring systems (Medtronic; Nerve Integrity Monitor (NIM), Jacksonville, FL, USA) were used to screen the thyroarytenoid muscles for electromyographic (EMG) activity. Intermittent nerve monitoring was used. The stimulation current was set at 1.5 mA, and a disposable probe was used. First, an EMG signal from the vagus nerve was aimed. Dissection of the RLN was started after the EMG signal was obtained from the vagus nerve, which confirmed the accuracy of the tube placement. The event threshold was set at 100 mV. Then signal from the RLN was obtained in the tracheoesophageal groove, which was totally dissected from the ligament of Berry. If a signal loss occurred at a level of 2 mA, equipment failure was assumed. After hemostasis was performed and the operative field was free of any fluids, the final test of the vagus was performed. Duration of the operation was measured from skin preparation until the end of wound closure.

Both pre- and postoperative laryngoscopic examinations of the patients were performed by an otolaryngologist to assess vocal cord functions. If vocal cord palsy occured, presented with dysphonia, laryngoscopic examinations were repeated on postoperative months 1 and 6. If clinical dysphonia and dysfunction of the vocal cords lasted > 12 months, it was considered as persistent nerve palsy.

Data regarding age, sex, body mass index (BMI), weight of the resected thyroid tissue, duration of the operation, and postoperative complications (RLN paralysis and hypoparathyroidism) were recorded.

Statistical Analysis

Statistical analysis was made using the Statistical Packages for the Social Sciences (SPSS) version 21.0 for Windows (IBM Corp.; Armonk, NY, USA). Results were expressed as mean ± SD. Chi-square test, Wilcoxon signed-rank test, and logistic regression analysis were used for the comparison of data. A p value< 0.05 was considered as statistically significant.

RESULTS

Patients

Male/female ratio, BMI, mean age, mean duration of operation, and mean weight of the thyroid gland were 130/665, 27.4 ± 3 kg/m^2, 47.8 ± 13 years, 83.9 ± 36 min, and 71.2 ± 38 g, respectively. There was no operative mortality. Transient vocal cord palsy rate was 2.6% (20 patients), and temporary hypoparathyroidism rate was 4.4% (33 patients). There were no persistent vocal cord paralysis and hypoparathyroidism in our series.

Assessment of Patients According to the Presence or Absence of IONM

Age, gender, and BMI were similar in both groups. There was also no difference between postoperative complication rates and resected weight of the thyroid gland (p> 0.05) (Table 1).

Mean duration of the operation was significantly longer in Group 2 (83.1 ± 28 min) than in Group 1 (69.7 ± 31 min) (p= 0.001). Duration of operation of surgeries performed by experienced surgeons (63.7 ± 27 min) was significantly lower than that of surgeries performed by residents (89.3 ± 18 min) (p= 0.001).

In the non-IONM group, the rate of transient vocal cord palsy was significantly lower in patients who were operated by ex-

Table 1. Comparison of patient demographics in the groups

Parameters	Group 1 (n= 398) with IONM	Group 2 (n= 397) without IONM	p
Age (year)	47.2 ± 14	48.3 ± 12	NS
Female/Male ratio	330/68	335/62	NS
BMI (kg/m^2)	27.1 ± 3	27.6 ± 3	NS
Thyroid gland weight (g)	72.6 ± 41	69.8 ± 37	NS
Complications (n) • Nerve palsy • Hypoparathyroidism	 9 17	 11 16	NS

Table 2. Evaluation of the patients according to the experience level of the surgeon

		RLN injury	p	Hypocalcemia	p
With IONM (n= 368)	Experienced surgeon (n= 184)	4	NS	8	NS
	Resident surgeon (n= 184)	5		9	
Without IONM (n= 380)	Experienced surgeon (n= 190)	3	0.001	7	NS
	Resident surgeon (n= 190)	8		9	

perienced surgeons than in patients who were operated by residents (p= 0.001). In the IONM group, RLN injury rates were similar between experienced surgeons and residents. Transient hypoparathyroidism rates were similar between experienced surgeons and residents in both IONM and non-IONM groups (Table 2).

DISCUSSION

Nerve palsy and hypoparathyroidism are the most common surgical complications of thyroidectomy. There are many factors affecting the risk of possible nerve injury. Amount of resection, nature of thyroid disease, such as Graves' disease, retrosternal goiter, and malignant diseases, and surgeon experience are among them (1-3). Experienced surgeons also report RLN injury and paralysis in approximately 1%-2% of cases (1-4,8). Paralysis may be caused by too much skeletonization of the nerve, disruption of anatomic integrity, thermal injury, excessive traction of the nerve causing axonal injury, hematoma due to bleeding, edema, and forced intubation. The rates of nerve injury have declined over the last couple of decades owing to nerve identification during operation. Currently, this is the most applied approach by endocrine surgeons (1-4,8,9).

Between 1882 and 1898, Theodor Kocher decreased his operative mortality down to 0.18%, which was as high as 14.8% before. He even managed to decrease his recurrent nerve injury rates to the levels of today's surgeons with his meticulous dissection technique (23). In 1938, Lahey dissected and visualized the RLN in practically every case he operated on. He reported that careful dissection and visualization of the RLN reduced the amount of injuries (24).

In the literature, nerve palsy rates vary from < 1% to 20% despite meticulous dissection techniques (1-3). In some operations, identification of the nerve can be challenging. Redo surgeries, surgery for malignant diseases, anatomical variations, such as non-recurrent nerve, large retrosternal goiters, and inflammation, or radiation history may cause difficulties in the identification of the nerve (1-4).

Identification of the RLN and monitoring its functions during surgery has been made possible through various medical devices developed during the last 20 years (9). Several methods, such as cricoarytenoid muscle palpation while stimulating the nerve, direct or fiber optic laryngoscopy observation of the vocal cords, or vocal cord electrodes, have been described (12-14). However, the most commonly used method among all is the NIM (17,18). In the NIM system, vocal cord electrodes are fixed on the endotracheal tube itself. Thus, there is no need for specific skills or surgical experience; on the other hand, there is a need for skilled anesthesiologist to place the electrodes correctly in regard with the vocal cords (9,11,17,18).

There is recent evidence in the literature stating that neuromonitoring can help dissection and visualization of the RLN (11,12,15-19). However, it is still debatable how effectively NIM can reduce RLN injury rates and predict postoperative nerve function (20-22). In a multicentric large study (16.448 patients with 29.998 nerves at risk), Dralle et al. (11) have revealed no significant difference between visual identification of the nerve and visualization with RLN neuromonitoring. Nonetheless, when the subgroups were evaluated in detail, it revealed a significant decrease in the incidence of permanent RLN palsy in low-volume surgeons who use IONM (11). In addition, being able to identify the nerve before visualization may cause a significant reduction in transient RLN palsy rates (6).

Some researchers have shown that neuromonitoring can be helpful in resident training by means of anatomical identification of the nerve (12-16). In our series, there was a clear benefit of RLN monitoring in surgeries performed by residents. In the non-IONM group, there was a statistically significant difference in RLN palsy rates between residents and experienced surgeons (p= 0.001), but in the IONM group, the rates were similar. The RLN palsy rates decreased to the levels comparable with experienced endocrine surgeons when neuromonitoring is used by residents. There was no difference between hypoparathyroidism rates in both groups.

Similar results were also presented by Alesina et al. (25) who analyzed 1116 thyroid procedures performed by residents in their center in the years 2005-2012. In the first group, operations without neuromonitoring were performed by residents assisted by an experienced surgeon, and the percentage of transient RLN injuries was 2.6%. In the second group, procedures with neuromonitoring were performed by residents assisted by specialists with limited experience in thyroid surgery, and the

percentage of transient RLN injuries was 2.7%. They concluded that although neuromonitoring could not replace standard RLN identification, yet in the case of surgeons with limited experience in thyroid surgery, it allowed for achieving results that were comparable to the results obtained by more experienced surgeons.

The major disadvantage of this system is that it is very costly. It is clearly more expensive than the conventional technique. In addition, in our study, duration of the operation is significantly lower with IONM, but this shortening might not have great clinical impact.

The limitation in our study is, that the operations performed by four resident and three experienced surgeons. Therefore, one-to-one matching could not be performed.

CONCLUSION

As most surgeons try to protect the nerves during surgery, we do not think that IONM is an alternative to visual nerve identification, but it may find itself a role as an adjunct to visual identification. Although it may seem to reduce the duration of operation in our series, the major benefit is for less experienced surgeons. IONM significantly decreases RLN palsy rates of surgeons with limited experience in thyroid surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional Ethics Committee of İstanbul University, İstanbul Medical Faculty (762/2007).

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ORİJİNAL ÇALIŞMA-ÖZET
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Tiroid cerrahisinde intraoperatif sinir monitörizasyonu cerrahi eğitiminde yararlı mı?

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ÖZET

Giriş ve Amaç: Paratiroid bezler ve rekürren laringeal sinirler (RLS) tiroid cerrahisi sırasında risk altındadır. Ancak sinirlerin tanımlanması bu riskleri azaltmaktadır. Tiroid cerrahisi sırasında intraoperatif sinir monitörizasyonu (İOSM) kullanımı, RLS'nin görsel olarak tanımlanmasının altın standardına bir yardımcı olarak yaygın olarak kabul görmektedir. Bu nedenle, bu prospektif çalışma ile tiroidektomi sırasında RLS tanımlamasında İOSM kullanımının etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Yedi yüz kırk sekiz hasta bu prospektif çalışmaya dahil edildi. Bu 748 hastanın risk altındaki 1496 siniri incelemeye alındı. 736 sinirin olduğu grup 1'de sinirler İOSM ile tanımlanırken, 760 sinirin olduğu grup 2'de sinir görsel olarak tanımlandı.

Bulgular: İOSM kullanılmayan gruptaki hastalarda, geçici sinir felci oranı deneyimli cerrahlar tarafından ameliyat edilenlerde kıdemli asistanlara göre daha düşük olarak saptandı (p=0.001). İOSM kullanılan grupta ise RLS yaralanma oranları deneyimli cerrahlar ve kıdemli asistanlar arasında benzerdi.

Sonuç: Ameliyat süresinin İOSM kullanılan grupta daha düşük olduğu gerçeğine rağmen, kısalmış olan ameliyat süresi klinik bir öneme sahip görünmeyebilir. Asıl avantaj, daha az deneyimli cerrahlar içindir. Tiroid cerrahisinde kısıtlı deneyime sahip olan cerrahlarda, İOSM kullanımı RLS felç oranlarını önemli ölçüde azaltmaktadır.

Anahtar Kelimeler: Tiroidektomi, sinir yaralanması, sinir monitörizasyonu

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ORIGINAL ARTICLE
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Value of tomography in detecting breast masses and discriminating malign and benign lesions

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ABSTRACT

Objective: The main purpose of the present study was to determine the effectivity of computerized tomography (CT) in detecting breast masses and discriminating masses as malignant or benign.

Material and Methods: After having received the institutional local ethics committee approval, an experienced radiologist who did not participate in the study created a patient pool by searching our health center's Pathology department database between 2010 and 2018. The group created consisted of dense and non-dense breast types equally and included approximately similar percentages of benign and malignant breast mass sizes. Finally, 70 subjects were included: 30 females with definite malign, 20 with definite benign breast masses, and 20 without any breast pathology based on mammography and ultrasonography results, who were considered as the control group. Three experienced Radiologists (R1, R2, R3) who were not aware of the final diagnosis evaluated all images independently. Radiologist performance was assessed by calculating the area under the receiver operating characteristic curve (AUC) and interobserver reliability values were estimated by intraclass correlation coefficient (ICC) analysis.

Results: The diagnostic accuracy suitability of CT according to BI-RADS scores for R1, R2 and R3 were found as $p< 0.001$, $p< 0.001$ and $p< 0.001$, respectively. There were significant interobserver reliability rates between all investigators ($p= 0.0001$).

Conclusion: CT may be used as a valuable diagnostic tool in discriminating breast masses with further training in widely varying appearances of normal breast tissues leading to false positive findings.

Keywords: Computerized tomography, thorax, breast cancer, breast tomography

INTRODUCTION

Breast cancer, which is the most commonly seen cancer type in women, is the second most important leading cause of cancer deaths in women. Majority of breast cancer detection is made by breast cancer screening programs in routine clinical examinations or during body image screening for other disorders. Mammography, sonography and magnetic resonance imaging (MRI) are standard imaging modalities used to evaluate breast cancer worldwide (1). However, computerized tomography (CT) may occasionally be the first imaging modality to reveal a new primary breast cancer (2).

Over the past 10 years, the use of cross-sectional imaging has increased significantly.

A recent study has shown a stunning 226% increase in thoracic CT assessment in emergency departments (3).

Even thoracic CT is used to performed for evaluating lung, mediastinum, pleura, diaphragm and chest wall pathologies, breast tissue is usually contained in the area of thoracal CT sections.

CT is mainly valuable to determine breast masses with dense breast pattern in women (4,5). However, for lesions that are close to the chest wall or masses located in the axillary regions, CT may be superior to other imaging modalities.

There are studies about incidentally detected breast lesions by tomography (2,6-15).

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CT imaging features of breast cancer have been investigated in some studies (16,17).

The purpose of present study was to determine the effectivity of CT in detecting breast masses and discriminating malign and benign masses.

To the best of our knowledge, there is no reader study investigating the diagnostic value of thoracic CT in detecting breast cancer and its role in discriminating malign and benign lesions.

In this context, our study is the first in the current literature.

MATERIAL and METHODS

Study Population

After having received institutional local ethics committee approval (2017/61), an experienced radiologist, who had no knowledge of clinical data and did not participate in the reader study, created a patient pool among 1000 patients by searching our health center's Pathology department database between 2010 and 2018. All of the selected patients were correlated with our radiology breast department database, and results of the breast sonography and mammography examinations before sonographically guided core needle biopsy and/or surgery was collected.

Patients without available CT images within one month after mammographic and sonographic examination were excluded from the study.

Gold standard in this study was determined as histopathologic data for suspected malignant lesions or radiological stability for the lesions in the follow-up examinations for at least 24 months (18).

The researcher ensured that the breast types were equally present in the selected patient pool.

While forming the benign and malignant breast mass groups, the researcher was careful that the mass sizes in both groups were close to each other. Lesion measurements and breast density classifications (18) were determined by the same researcher.

Thirty female patients with histopathologically definitive malignant breast masses confirmed by thoracic CT and 20 benign breast masses, whose definitive diagnosis was made histopathologically in ten cases and whose lesion stability was confirmed at a period of 2-year-follow-up in ten cases, were selected.

In total, seventy cases were included into the study, of whom 30 female patients had definitive malignant, 20 had definitive benign breast masses, and the rest of the 20 female patients without any breast pathology according to breast screening programs were included as the control group.

The created pool was evaluated by three experienced radiologists (R1, R2, R3) independently, one of whom was a specialist who had worked on breast for over 18 years (R1). One of the other researchers had twelve years (R2) and the other had eight years (R3) experience in thoracic radiology.

The reviewers were not informed whether there was a lesion or not and of the patients' final diagnoses and mass locations, but were only aware that they had to evaluate the breasts meticulously. The accuracy of the localization of the masses identified during blind evaluation was confirmed subsequently by ultrasound and mammography. Focuses and non-mass lesions were excluded from the study.

This retrospective, single-institution reader study was conducted in compliance with the Helsinki Declaration and good clinical practice guidelines of the Ministry of Health of our country. Secondary to retrospective nature of the study, written informed consent was not acquired.

CT Technique

Thoracic CT was performed using a 64-detector Multidetector Computerized Tomography (MDCT scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Tochigi, Japan) in supine position. Contrast-enhanced scans were performed. Standard protocol at our hospital is a pitch of 0.828, 0.5 s scanner rotation, 120 kV, 150 mAs, 38 cm field of view and 1 mm slice thickness. Subsequently, a contrast-enhanced helical CT was performed with intravenous administration of non-ionic contrast material (Ultravist; Iopromide, Bayer Health Care Pharmaceuticals, Berlin, Germany), 300 mg/mL, which was injected as 2 mL/kg dose at a speed of 4-6 mL/min using an automatic injector system. Scanning was performed 50 seconds after injection of the contrast medium.

CT Image Analysis

The created CT images, consisting of a total of 70 lesions, were randomly evaluated by the radiologists on a workstation (Leonardo; Siemens Healthcare, Erlangen, Germany) in our radiology department.

All of the reviewers were blinded to each other's findings and decisions.

Evaluation was performed first independently, later in consensus for the presence of masses and for the determination whether these masses were malignant or benign. The accuracy of the localization of the masses identified in blind evaluation was confirmed subsequently by ultrasound and mammography.

CT images were classified into two groups according to whether there were any radiological findings in the breasts within the CT sections or not.

Lesion visibility was classified into four groups as 0: no, 1: poor, 2: moderate, and 3: high visibility.

The ratio of malignancy suspicion was classified into five main groups as 1 ≤ 2%, 2= 2-10%, 3= 10-50%, 4= 50-90%, 5 ≥ 95% (Figure 1).

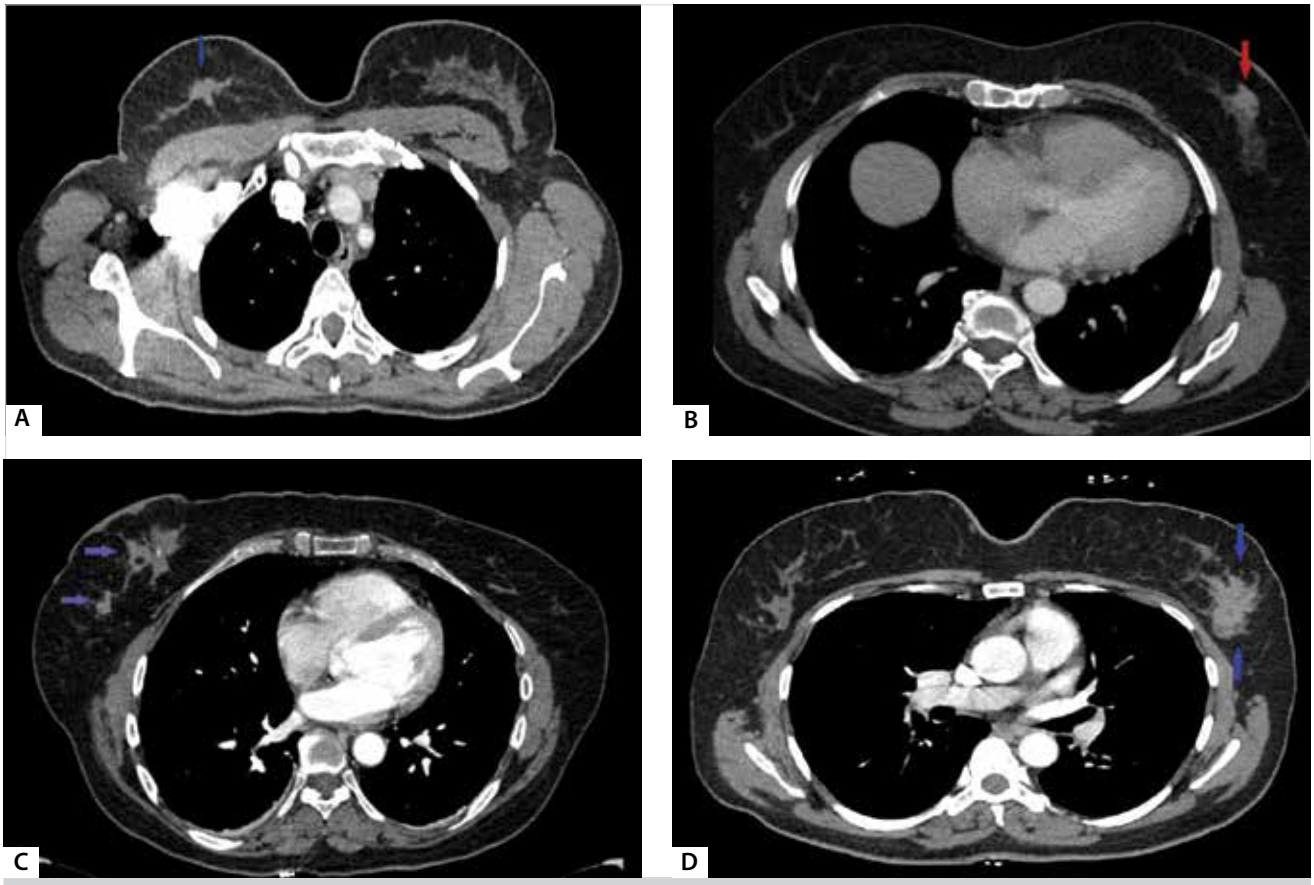

Figure 1. Axial CT image is shown **(A)** a speculated lesion (blue arrow) with moderate enhancement in the upper middle quadrant of right breast with moderate malignancy suspicion ratio (x= 10-50%, BI-RADS 3), **(B)** well defined mass appearance (red arrow) with homogeneous enhancement in the upper middle quadrant of left breast with moderate malignancy suspicion ratio (x= 50-90%, BI-RADS 4), **(C)** two speculated neighboring lesions (purple arrows) with calcifications in the lower inner quadrant of right breast with high malignancy suspicion ratio (x > 95%: BI-RADS 5) and increased skin thickness was also demonstrated in the image, **(D)** a well-defined, speculated countered mass appearance (blue arrows) with high enhancement pattern in the upper outer quadrant of left breast. This lesion reflects a high-grade malignancy suspicion ratio (x > 95% : BI-RADS 5).

Finally, lesions were classified according to the American College of Radiology Classification, Breast Imaging Reporting and Data System 5th edition (BI-RADS) (19).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed in percentages.

Sensitivity was calculated as the ratio of true-positive readings among true-positive and false-negative readings. Specificity was calculated as the ratio of true-negative readings among true-negative and false-positive readings.

For evaluating sensitivity and specifity, BI-RADS scores were divided into two groups. BI-RADS 1, 2 and 3 scores were considered as negative findings and BI-RADS 4 a-c and 5 scores were considered as positive findings.

Interobserver correlation coefficient (ICC) was used to determine the degree of compromise on BI-RADS scoring between all observers (20). In this study, an ICC less than 40% was considered as poor, 40-59% as fair, 60-74% as good and 75-100% as excellent.

For the assessment of diagnostic test accuracy, test sensitivity, specificity and AUC [the area under the receiver-operating characteristic (ROC) curve] were calculated separately for each radiologist.

Discordances in mass visibility were analyzed by using the Wilcoxon matched-pairs signed-ranks test.

For evaluating radiologist performance according to breast density, BI-RADS breast density scores were divided into two groups. BI-RADS 1, 2 scores were determined as not-dense breast and BI-RADS 3 and 4 scores were determined as dense breast types. Radiologist performance was evaluated by calculating the area

under the receiver operating characteristic curve (AUC) and partial area index above a sensitivity threshold of 0.90 by using malignancy suspect ratings. Significance of the difference between the areas under two Independent ROC curves among all radiologists were calculated by a special statistical analysis program, MedCalc for Windows, version 16.2.1 (MedCalc Software, Ostend, Belgium).

Interobserver reliability values and radiologist agreement for lesion visibility was estimated statistically by ICC analysis.

Statistical analysis was conducted using SPSS 22.0 statistical software (21).

RESULTS

Characteristics in Subjects

In order to demonstrate the homogeneity of the created study group, sizes of breast lesions and breast types are shown in Figure 2.

Mean age was 53 years (range, 32-81 years). Mean lesion size was 2.06 cm (range, 0.5-4.5 cm).

Breast density of the patients according to the BI-RADS classification system and pathologic results of the lesions are summarized in Table 1.

Box plot of each radiologist's visibility scores is shown in Figure 3.

Malignancy Suspicion Ratios

For R1, R2 and R3, respectively, p values comparing the ratio of malignancy suspect respect to pathology; diagnostic accuracy (AUC) for CT was p< 0.001, p< 0.001 and p< 0.001.

ROC curve analysis of lesion malignancy suspect ratios is shown in Figure 4.

In the control group without any masses, R1 reported masses in 5 patients (7.15%) (two of which were malignant); R2 reported masses in 7 patients (10%) (5 of which were malign); and R3 reported masses in 6 patients (8.6%) (3 of which were malignant). All of these diagnoses were regarded false positive.

Even though patients had benign masses confirmed pathologically, 4 (5.75%), 13 (18.6%), and 10 (14.3%) patients were repor-

Table 1. Types of breast density according to BI-RADS classification system and pathologic results of the lesions

Breast density	Number (%)
Not dense	36 (51.4)
Type 1. Entirely fatty	8 (11.4)
Type 2. Scattered areas of fibroglandular density	28 (40.0)
Dense	34 (48.5)
Type 3. Heterogeneously dense	29 (41.4)
Type 4. Extremely dense	5 (7.1)
Pathology	
IDC	25 (35.7)
ILC	2 (2.9)
DCIS	1 (1.4)
MIX CA	1 (1.4)
IPC	1 (1.4)
Fibrocystic disease	1 (1.4)
Stable lesion during 24 months	8 (11.4)
Fibroadenoid hyperplasia	6 (8.6)
Adenosis	1 (1.4)
Benign papiller lesions	1 (1.4)
Minimal epitelial hyperplasia	1 (1.4)
Non necrotizan granuloma	1 (1.4)
Lymphoid tissue	1 (1.4)
Control group	20 (28.6)

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; DCIS: Ductal carcinoma in situ; MIX CA: Mixed type carcinoma; IPC: Intraductal papillary carcinoma.

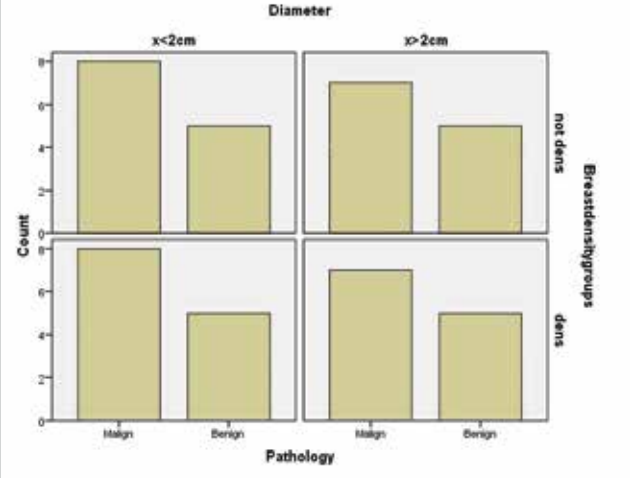

Figure 2. Homogeneity of the study group.

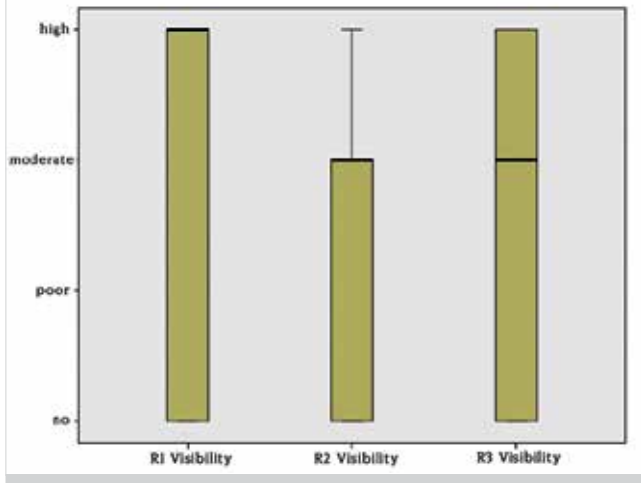

Figure 3. Box plot of the visibility scores of each radiologist.

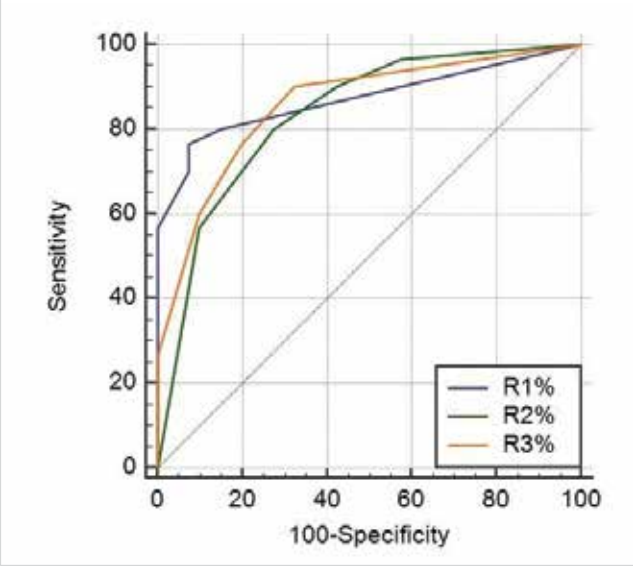

Figure 4. ROC curves of malignancy suspicion ratios with respect to pathology.

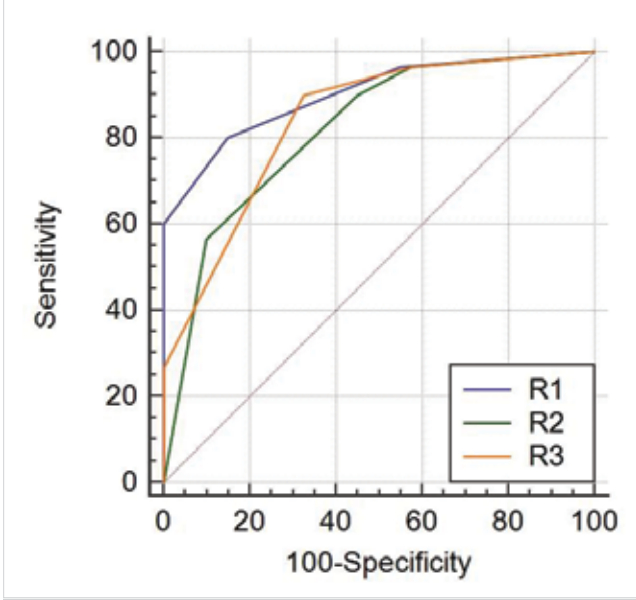

Figure 5. BIRADS ROC curves with respect to pathology.

Table 2. Summary of Observer's performance for discriminating malignancy (n= 70 patient)

Study population n (%)	**R1**		**R2**		**R3**		**p value between R1, R2, R3**
	Benign + Normal	Malign	Benign + Normal	Malign	Benign + Normal	Malign	
Malign 30 (42.9)	6 (8.6)	24 (34.3)	3 (4.3)	27 (38.6)	3 (4.3)	27 (38.6)	0.0001
Benign + Normal 40 (57.1)	34 (48.6)	6 (8.6)	22 (31.4)	18 (25.7)	27 (38.6)	13 (18.6)	
R1: Radiologist 1; R2: Radiologist 2; R3: Radiologist 3.							

ted mistakenly having malignant masses by the radiologists R1, R2 and R3, respectively.

Summary of radiologist performance for discriminating malignancy is shown in Table 2.

BI-RADS Classification Results

For R1, R2 and R3, respectively, p values comparing the BI-RADS classification of lesions respect to pathology; diagnostic accuracy (AUC) for CT was p< 0.001, p< 0.001 and p< 0.001.

For R1, diagnostic accuracy (AUC) was found numerically higher when compared to other radiologists: however, it was not statistically significant.

ROC curve analysis of BI-RADS scores of all lesions by the radiologists were shown in Figure 5.

Interobserver Reliability Results

Interobserver agreement analyses ICC results are shown on Table 3.

Table 3. Interobserver reliability among all radiologist

Parameters	**CI**
Mass detection	0.75 (0.63-0.84)*
Lesion Visibility	0.83 (0.73-0.88)*
Suspect of malignancy	0.82 (0.68-0.87)*
BI-RADS classification	0.81 (0.72-0.88)*

CI: Confidence intervals.
In this study, an ICC less than 40% was considered as poor, 40-59% as fair, 60-74% as good and 75-100% as excellent " * ".
BI-RADS: Breast Imaging Reporting and Data System.

Interobserver reliability of mass detection, lesion visibility, malignancy suspicion and BI-RADS classification for all radiologists were found within the ranges of 0.75 (95% CI 0.63-0.84), 0.83 (95% CI 0.73-0.88), 0.82 (95% CI 0.68-0.87) and 0.81 (95% CI 0.72-0.88), respectively.

There were significant interobserver reliability rates between all researchers (p= 0.0001).

DISCUSSION

In this reader study, high sensitivity and low specificity rates for breast cancer diagnostic accuracy of CT were shown. Interobserver diagnostic capability rates were statistically similar and significant. For breast specific radiologists, even though the diagnostic accuracy of R1 (AUC) was found numerically higher when compared to other radiologists, it was not statistically significant.

Breast cancer is a major health problem worldwide.

While there are many randomized controlled trials of screening mammography to reduce mortality, mammography has many limitations (22,23).

Especially in women with increased risk for breast cancer, dynamic contrast enhanced MRI is much more sensitive than ultrasound and mammography scans (24,25).

Though not considered as a screening method, breast masses are caught incidentally in patients who undergo tomography examination for other reasons. Tomography rates have increased significantly in recent years in clinical practice.

Tomography is a faster, less noisy, comfortable imaging modality and offers more comfortable examination ambience for claustrophobic patients, as well (26).

CT is a real 3D high-resolution imaging modality that enhances mass visibility by reducing overlapping of breast tissues and can be considered as an alternative imaging method in patients with MR contraindications, especially in dense breast types.

Our results are comparable to previous studies although they were all prospective incidental study concepts and did not focus on CT diagnostic capability in patients with established diagnosis of cancer.

Hussein et al. have found incidental masses in 33 out of 432 patients. Only 8 of them have been diagnosed with primary cancer. In addition, there is no data regarding the presence of breast mass and no mention of false negative evaluation of the patients (6).

Lin et al. have incidentally detected 23 masses with contrast staining. Sixteen of them have been confirmed as malignant. However, there is no mention of other types of masses such as non-contrast staining. Furthermore, the authors have not given any details related to false negative patients. Therefore, patients with no-contrast staining masses cannot be evaluated in terms of diagnosis (7).

Our study has a different protocol when compared to the previous studies mentioned above. Our study consisted of patients with pathologically confirmed masses and a control group to whom all screening methods were applied and in whom no masses were seen. Therefore, we assume that our study protocol may be more reliable for investigating the role of CT in discriminating breast masses.

Study Limitations

Our study had some limitations. First, the study group of the enrolled patients to our study and the number of the radiologists were relatively small. Second, non-mass enhancement lesions, calcifications and focuses were excluded from the research group. Finally, because of the nature of the study, CT examinations were performed independent from the menstrual cycle.

Further studies are required to enrich the findings of the present study.

To the best of our knowledge, our study is the first to evaluate the diagnostic validity of thoracic CT by evaluating the histopathologically confirmed malignant enriched patient population.

CONCLUSION

Though not considered as a screening method due to adverse effect of radiation, CT may be used in terms of diagnosis of breast cancer with high sensitivity rates.

Our study may reveal that in order to avoid confusion of the normal structures and benign masses as malignant lesions, radiologists should need further training for not only in the appearance of different abnormalities but also in the widely varying appearances of normal tissues leading to positive findings.

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ORİJİNAL ÇALIŞMA-ÖZET
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Meme kütlelerinin saptanmasında ve iyi-kötü huylu ayrımında tomografinin yeri

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ÖZET

Giriş ve Amaç: Bu çalışmanın temel amacı bilgisayarlı tomografi (BT)'nin meme kütlelerini saptamadaki yerini ve lezyonların iyi ya da kötü huylu ayrımını yapabilirliğini değerlendirmektir.

Gereç ve Yöntem: Etik kurul onayı sonrası, alanında tecrübeli ve çalışmaya araştırmacı olarak katılmayacak bir radyolog tarafından 2010-2018 yılları arasında, hastanemizin Patoloji Bölümü veritabanı taranarak bir hasta havuzu oluşturulmuştur. Oluşturulan hasta havuzunda yoğun ve yoğun olmayan meme tiplerinin, iyi ve kötü huylu lezyon sayılarının ve lezyon boyutlarının eşit oranlarda olmasına özen gösterilmiştir. Sonuç olarak her meme tipinde eşit oranda olmak üzere kötü huylu tümör tanısı almış 30, iyi huylu tümör tanısı almış 20 ve taramalarda herhangi bir meme lezyonu bulunmayan 20 kontrol grubu hasta olmak üzere toplamda 70 hasta çalışmaya dahil edilmiştir. Meme Radyolojisi konusunda deneyimli üç radyolog (R1, R2, R3) tarafından tüm BT görüntüleri nihai tanıya kör olarak ayrı ayrı değerlendirilmiştir. Okuyucu performansları, eğri altındaki alanın (AUC) hesaplanmasıyla değerlendirilmiş ve araştırmacılar arası güvenilirlik, sınıf içi korelasyon katsayısı (ICC) analizi ile hesaplanmıştır.

Bulgular: R1, R2 ve R3 için sırasıyla BT'nin BI-RADS skorlama sistemine göre doğru tanı koyma yeterliliği; $p< 0.001$, $p< 0.001$ ve $p< 0.001$ olarak belirlenmiştir. Araştırmacıların tümü arasında anlamlı bir okuyucu güvenilirliği saptanmıştır ($p= 0.0001$).

Sonuç: BT, meme kütlelerinin saptanmasında ve iyi-kötü huylu ayrımının yapılmasında, yalancı pozitifliğe yol açabilecek normal meme dokularının BT görüntüleri hakkında ileri eğitim alınması halinde oldukça faydalı bir görüntüleme yöntemi olarak kullanılabilir.

Anahtar Kelimeler: Bilgisayarlı tomografi, toraks, meme kanseri, meme tomografisi

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Laparoscopic splenectomy: clip ligation or en-bloc stapling?

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ABSTRACT

Objective: Various techniques are used in the management of splenic hilum during laparoscopic splenectomy. Among them, the most used ones are polymer clips, en-bloc stapling and ultrasonic devices. To the best of our knowledge, there is no study in the literature comparing the results of clip and stapler techniques. This study was aimed to compare our results of clip ligation and en-bloc stapling of the splenic hilum.

Material and Methods: The records of 67 patients undergoing laparoscopic splenectomy between December 2012 and October 2017 were reviewed. Patients were divided into two groups according to surgical method (stapler group: 26 patients and clip group: 41 patients). Patient age, sex, diagnosis, surgical technique, operation time, spleen dimensions, perioperative complications, postoperative hospital stay, blood transfusions, postoperative thrombocyte and hemoglobin levels were recorded.

Results: Operating time was median 115 min (75-230) in the stapler group and 120 min (60-210) in the clip group, and there was no significant difference between the groups (p= 0.2593). There were no significant difference between the groups in terms of the postoperative complications (p= 0.59). Postoperative hospital stay was median 3.5 (2-8) days in the stapler group and 3 (2-6) days in the clip group with no significant difference (p= 0.0733).

Conclusion: Clip ligation and en-bloc stapling techniques have no superiority over each other. Our results also showed that both techniques are safe and feasible. We suggest opting for the method according to the surgeon's experience and hospital facilities.

Keywords: Laparoscopic splenectomy, clip ligation, en-bloc stapling

INTRODUCTION

Splenectomy is indicated in a large number of benign and malignant conditions. In total, the most common indication for splenectomy is spleen injury, and open surgery is performed in most of them. On the other hand, the most common indication for elective splenectomy is hematologic diseases, the most common being immune thrombocytopenic purpura (ITP). Laparoscopic splenectomy (LS) is recommended as the gold standard surgical approach for elective splenectomy (1). In experienced hands, LS provides many benefits, including less intraoperative blood loss, shorter hospital stay and lower morbidity when compared to open splenectomy (2).

During LS, splenic vessels can be clipped after separating them one by one via careful dissection of the splenic hilum, or the splenic hilum can be managed by en-bloc stapling. There are also some surgeons who use energy devices alone to divide the splenic vessels. All methods have various advantages and disadvantages, some of which are compared in the literature. However, to the best of our knowledge, there is no study in the literature comparing the results of clip ligating and en-bloc stapling techniques. In stapler usage, there are some concerns about possible rare complications such as arteriovenous fistula formation, bleeding from the transection line and pancreas or vascular injuries because of improper positioning of the stapler. In addition, cost of the stapler devices is more than that of the clips. In clip usage, on the other hand, splenic vessels need to be dissected one by one and isolated, which may entail a risk of bleeding and requires experience (3,4). Hence, this study was aimed to compare our results of clip ligation and en-bloc stapling of the splenic hilum.

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MATERIAL and METHODS

The records of 67 patients undergoing laparoscopic splenectomy between December 2012 and October 2017 were retrospectively reviewed. Patients were divided into two groups according to surgical method (stapler group, 26 patients with endoscopic stapler; clip group, polymer clips, 41 patients). Converted cases (one in the stapler group and two in the clip group) were excluded from the study. Patient age, sex, indications for LS, surgical technique, operation time, spleen dimensions, perioperative complications, postoperative hospital stay, blood transfusions, postoperative thrombocyte and hemoglobin levels were recorded. Spleen sizes were obtained from preoperative ultrasonography or computerized tomography recordings. Although we considered ultrasonography adequate for preoperative accessory spleen research in previous years, computerized tomography has been started to be used routinely for the last three years.

For preoperative preparation; methyl-prednisolone or intravenous immunoglobulin was given to the patients with ITP and erythrocyte suspension to the patients with hereditary spherocytosis if needed. ITP patients were taken to surgery after raising their platelet levels to the appropriate levels for surgery. For this purpose, thrombocyte suspension was applied to the patients preoperatively and/or perioperatively, and those whose platelet levels could not be elevated preoperatively, were given steroid therapy. All the patients received an anti-pneumonia vaccine 10 days before the surgery.

The study was designed in accordance with the principles of the Helsinki Declaration.

Surgical Technique

Patients were placed in right semi-decubitus and approximately 15° reverse Trendelenburg position in general anesthesia for laparoscopic splenectomy. In most of the cases, a 30° optic and 4 trocars were used. After exploration of the abdominal cavity and removal of the accessory spleen, if present, the splenocolic, gastrosplenic, splenorenal and splenophrenic ligaments attached to the splenic tissue were divided with energy dissection. Splenectomy was completed after the splenic hilus was divided by endoscopic stapler (Ethicon Endo-Surgery, LLC, Puerto Rico, USA) or splenic vessels were isolated and clipped (Changzhou Lookmed Medical Instrument Co., Jiangsu, China). The spleen was placed in a sterile plastic bag and removed from the 15 mm trocar site after fractionated by overclamp to enable piecemeal removal. A negative pressure drain was placed in the left subphrenic area, if necessary. The removed spleen was sent for histopathological examination. 10 and 15 trocar sites were closed with number 1 vicryl.

Response to splenectomy was evaluated within the first month after surgery. American Hematology Association 2011 criteria were used in evaluating the response to splenectomy in ITP patients (5). These criteria are; 1- Complete response; The platelet levels of at least 100.000/mm^3 without splenectomy treatment, 2- Partial response; Platelet levels between 30.000/mm^3 and 100.000/mm^3, or at least twice the basal level, 3-Complete unresponsiveness; Platelet levels below 30.000/mm^3 or 2-fold below basal level.

Statistical Analysis

The data collected were analyzed using SPSS Statistics for Windows version 20.0 (SPSS Inc). The Kolmogorov–Smirnov test was used to test the normality of the variables. For the comparison of continuous variables, Mann-Whitney U test was used. Categorical variables were compared using a Pearson Chi-square test or Fisher's exact test. A p value < 0.05 was considered statistically significant.

RESULTS

Totally, twenty-one (31.3%) of the patients were male and 46 (68.7%) of them were female. Median age of the patients was 35 (14-62) years. Median age was 36.0 (16-62) in the stapler group and 31.0 (14-39) in the clip group, with no significant difference (p= 0.2547). Median size of the spleen was 13 (11-20) in the stapler group and 13 (10-23) in the clip group with no significant difference (p= 0.3084).

In the stapler group, indications for the operations were ITP in twenty-one patients, hereditary spherocytosis in two patients, and thalassemia, splenic cyst and splenic infarct one in each case (Table 1). In this group, accessory spleen was detected in five patients (19.2%) and removed during operation.

In the clip group, indications for the operations were ITP in 33 cases, hereditary spherocytosis in two cases, splenic cysts in five cases and lymphoma in one case (Table 1). Thrombocytosis de-

Table 1. Indications for laparoscopic splenectomy

	Stapler group	Clip group	p
ITP	21	33	
Hereditary spherocytosis	2		
Thalassemia	1	-	0.3553
Splenic cyst	1	5	
Lymphoma	-	1	
Splenic infarct	1	-	

ITP: Idiopathic thrombocytopenic purpura.

veloped in one (3.8%) case with no need for anticoagulant treatment. Accessory spleens were detected and removed in four patients (9.8%) during operation in this group.

Operating time was median 115 min (75-230) in the stapler group and 120 min (60-210) in the clip group, and there was no significant difference between the groups (p= 0.2593).

There were three cases converted to open, one in the stapler group and two in the clip group. The case in the stapler group bled after firing the stapler and we converted to open and ligated the vessels. Two cases in the clip group were converted due to the spleen sizes of more than 25 cm and difficulty in exposure.

Totally, postoperative complications developed in five (7.4%) cases. Atelectasis developed in one (3.8%) case in the stapler group and in two (4.8%) cases in the clip group. Wound dehiscence developed in one case in each group. There was no significant difference between the groups in terms of postoperative complications (p= 0.59). In the stapler group, thrombocytosis developed in two (7.6%) cases but anticoagulant treatment was needed in only one due to over 1 million platelet level. Thrombocytosis developed in onw (3.8%) case in the clip group with no need for anticoagulant treatment. Postoperative hospital stay was median 3.5 (2-8) days in the stapler group and 3 (2-6) days in the clip group with no significant difference (p = 0.0733) (Table 2).

Hematologic treatment continued because of persistent refractory thrombocytopenia in two patients, and temporary thrombocytopenia in five patients with ITP. In a patient with persistent refractory thrombocytopenia, an accessory/ectopic spleen was detected within the pancreas in a spleen scintigraphy performed postoperatively, and the patient continued to take hematologic treatment.

There were two patients (one in each group) who underwent concurrent cholecystectomy, and one umbilical hernia repair in the clip group. No deaths were recorded in both groups.

DISCUSSION

Since the first LS performed in 1991, this technique has been used increasingly and become the gold standard for elective surgery for splenic disorders (6,7). In this technique, several methods have been used for division and management of the splenic hilus; such as endoscopic vascular staplers, polymer clips and energy devices (8). Although several papers have recently been reported on safety and feasibility of energy devices for the division of splenic vessels in adults, we use energy devices only for cutting splenic attachments. In the division of hilar vessels, we routinely use polymer clips or vascular staplers.

Endoscopic stapler is a safe and effective alternative instrument, especially for the first cases of training surgeons due to its relatively easy feasibility. Complications are rare when performed properly. However, it requires proper positioning as close as possible to the splenic hilum after sufficient separation of the attachments of the spleen. Inserting the device blindly on the hilar structures or removing it without firing is dangerous and may cause tearing of the thin-wall veins. Moreover, there are some concerns about the usage of endoscopic stapler such as bleeding from the transection line, injury to the pancreatic tail due to improper positioning of the device that results in pancreatitis or pancreatic fistula, metallosis or migration of the staples, and its costliness (9-12). AVF of the splenic vessels is a quite rare complication of LS. Due to the very close approximation of the splenic artery and vein, en bloc ligation of the splenic hilum may rarely cause AVF via injury to the vessel walls from the ligating staples. However, there is no risk of AVF in individual clipping of

Table 2. Patients' characteristics and results of surgery

	Stapler group	Clip group	p
Sex distribution			
Female	19	27	0.5376
Male	7	14	
Median age	36.0 (16-62)	31.0 (14-39)	0.2547
Median length of the spleen (cm)	13 (11-20)	13 (10-23)	0.3084
Median operating time (min)	115 (75-230)	120 (60-210)	0.2593
Median postoperative hospital stay (days)	3.5 (2-8)	3 (2-6)	0.0733
Postoperative complications			
Atelectasis	1 (3.8%)	2 (4.8%)	0.59
Wound dehiscence	1 (3.8%)	1 (2.4%)	
Refractory thrombocytopenia			
Persistent	1 (3.8%)	1 (2.4%)	0.9445
Temporary	2 (7.6%)	3 (7.3%)	

the splenic vessels (4,11). In our case series, we did not encounter AVF or pancreatic injury but we converted to open due to bleeding from the transection line of the stapler in one case.

Various types of surgical clips are also used in LS to ligate the splenic vessels. Dissection of the splenic hilum and isolation of the splenic vessels are needed to place the clips, thus it necessitates advanced laparoscopic skill. In our study, in 26 of the cases splenic hilus was managed by endoscopic stapler and in 41 of the cases by clips. There was no difference in terms of operating time, hospital stay, intra-operative and post-operative complications. Within our knowledge, there is no study in the literature comparing clip and stapler techniques. We suggest that surgeons can choose anyone of these two techniques according to their own experience. Shabahang et al. have reported on 40 cases of LS to compare clip ligation with ligature during LS (3). They have suggested that both clip and ligature can be used for the ligation of the splenic hilum, but the risk of bleeding may be higher in clip ligation because dissection of the splenic hilum is usually needed in this method. Splenic hilar dissection necessitates advanced laparoscopic experience and as experience increases, complications decrease. Since an average of 3 or 4 clips are used during LS, we think clip ligation is more cost effective than stapler usage. Despite many reports on safety and feasibility of energy devices in splenic hilar management, a lot of surgeons still prefer using clips or stapler because of various concerns about ligature usage alone (2-4,7-12). The major concern is about bleeding because of cutting the vessels halfway without dissecting the splenic hilum and separating splenic artery and vein. On the other hand, in cases of separating the splenic vessels, why not use one or two clips to be safer about bleeding? We think the debate about the methods will continue and more prospective randomized studies are needed.

Another point of challenge for splenectomy is splenomegaly. Is spleen size important in choosing surgery technique? Excessive size of the spleen may necessitate conversion to an open approach. Various definitions of splenomegaly have been used based on length and weight. An accurate cut-off point for the length doesn't exist for indication of open surgery. Many authors define splenomegaly as the length of the spleen being more than 15 cm. In our study, median size of the spleens were similar in both groups. There were 4 cases which sized more than 15 cm in the stapler group and 3 in the clip group. The largest spleen size was 23 cm in our laparoscopically completed 67 cases. In two of the cases converted, conversion was due to the spleen sizes of more than 25 cm. We did not find an importance of the spleen size in choosing the surgery technique. Independently of the aforementioned surgical techniques, early ligation of the splenic artery is proposed as a useful alternative method in cases with splenomegaly to reduce blood loss (13,14). We use this approach not only in laparoscopic cases, but also in open cases with excessive spleen sizes with minimal blood loss.

In conclusion, according to our results, clip ligation and en-bloc stapling of the splenic hilum techniques have no superiority over each other. Our results also show that both techniques are safe and feasible. We suggest opting for the method according to the surgeon's experience and hospital facilities.

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Laparoskopik splenektomi: klip ligasyon mu, enblok stapler mi?

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ÖZET

Giriş ve Amaç: Laparoskopik splenektomi esnasında splenik hilus yönetiminde çeşitli teknikler kullanılmaktadır. Bunların arasında en sık kullanılanlar; polimer klipler, enblok stapler ve ultrasonik araçlar. Bildiğimiz kadarıyla, literatürde klip ve stapler tekniklerinin sonuçlarını karşılaştıran çalışma yoktur. Bu çalışmanın amacı, splenik hilus yönetiminde klip ligasyon ve enblok stapler yöntemlerinin sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Aralık 2012 ve Ekim 2017 arasında laparoskopik splenektomi geçiren 67 hastanın kayıtları incelendi. Hastalar cerrahi yönteme göre 2 gruba ayrıldı (stapler grubu 26 hasta ve klip grubu 41 hasta). Hasta yaşı, cinsiyet, tanı, cerrahi teknik, operasyon süresi, dalak boyutu, perioperatif komplikasyonlar, postoperatif hastanede kalış süresi, kan transfüzyonu, postoperatif trombosit ve hemoglobin düzeyleri kaydedildi.

Bulgular: Operasyon süresi stapler grubunda ortalama 115 dakika (75-230) ve klip grubunda 120 dakika (60-210) idi ve gruplar arasında anlamlı fark saptanmadı (p= 0,2593). Postoperatif komplikasyonlar ve hastanede kalış süreleri açısından gruplar arasında anlamlı fark saptanmadı (p= 0,59).

Sonuç: Klip ligasyon ve enblok stapler tekniklerinin birbirlerine göre üstünlüğü yoktur. Bizim sonuçlarımız gösteriyor ki iki teknik de güvenli ve uygulanabilirdir. Biz, yöntem seçimini cerrahın tecrübesine ve hastane imkanlarına göre seçilmesini öneriyoruz.

Anahtar Kelimeler: Laparoskopik splenektomi, klip ligasyon, enblok stapler

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Excision and tension-free primary closure of pilonidal disease

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ABSTRACT

Objective: This study aimed to estimate simple excision and tension free primary closure and to study its effectiveness in terms of operating and healing time, duration of hospital stay, degree of post operation complications, and rate of recurrence.

Material and Methods: This is study included 78 patients, of whom 71 were (91%) males and 7 (9%) females, who underwent excision and tension free closure. The procedure was based on bilateral side flaps, which were released and dissected 2-3 cm from the edge of the wound. Patient's age, gender, body mass index, wound healing, operation, drain removal, length of hospital stay, and complications and recurrence were analysed.

Results: The study involved 78 patients, 71 (91%) males and 7 (9%) females. Median age of the patients was 28.5 years. Mean operation time was 44.6 minutes . Sixty-one patients (78.2%) had full primary healing without any complication. No one had hematoma or seroma, but five (6.4%) cases had a minor wound infection and three (3.8%) obese patients developed recurrence. Mean length of hospital stay was 2.5 days , most patients went back to their work within 3 weeks. Median follow-up period was in a 26.2 weak range (1-51.4 weak). Five (6.41%) cases had wound infection and three (3.85%) developed recurrence.

Conclusion: Excision and tension free primary closure were found to be simple procedures associated with lower rates of wound infection, shorter hospital stay, lower recurrence, early wound recovery and short period of being absent from work. Surgery can be easily performed and preferred for cases of non-recurrent pilonidal sinus and cyst.

Keywords: Pilonidal, primary closure, natal cleft sinus, cyst

INTRODUCTION

Pilonidal sinus (PNS) is a chronic inflammatory disease associated with excessive hair growth around the infected area and can cause anxiety, perplexity and absence from work. It was first described by Hodges in 1880 (1). It mostly exists in the natal spilt of the sacrococcygeal region and it manifests like inflammation, pus discharge and sinus formation (2,3).

Onset of PNS is scarce both before adulthood and after the age of forties. Males are influenced more by this disease than females, which may be due to their more hairy nature than females (4).

Even though the progress in medical research and study, the tactic to control the pilonidal sinus illness is not well defined yet. However, the therapy regimen must perfectly decrease soreness, provide a shorter hospital stay, reduce complications and rate of recurrence, and show quick healing and return to normal life (5).

A lot of surgical procedures have been used in the caring of the pilonidal sinus disease. Incision and drainage, excision and recovery by second intention are the most commonly used practical methods (6,7), whereas, there are procedures like excision and tension free primary closure, excision with reconstructive flap techniques (8), and other less prevalently used technical methods include phenol injection, cryosurgery and electro cauterization (9,10). Our aim in this study was to estimate the technique, the excision of the pilonidal sinus or cyst, and examine its efficiency to reduce operating period, time of healing, and the duration of hospital stay, the degree of postoperative complications and recurrence rate.

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MATERIAL and METHODS

Seventy-eight patients suffering from un-complicated pilonidal sinus or cyst with an age ranging between 18 to 39 years participated in this prospective study. The patients were admitted to hospital from January 2013 to May 2016. Before starting our study, approval from the ethics committee of our hospital was obtained, and informed consent was taken from each patient, and their parents or partner were informed about the aim and the nature of the study, and written consent was obtained. Patient age, gender, body mass index, wound healing time, operation times, length of hospital stay, drain removal time, complications, and recurrence rates were analyzed.

Surgical Procedure

Simple excision and tension- free primary closure were performed and involved the following steps:

- Antibiotics in the form of Metronidazole (Flagyl, Sanofi-Aventis, Paris, France,) or clindamycin (Vanconex-Cp, Venus Remedies Limited, Baddi.H.P., India) And ceftriaxone (Forsef, Bilim pharmaceuticals, Maslak -Istanbul Turkey) were given to the patient half an hour before the operation.

- When the patient was placed under full anesthesia, he/she was put in the Jack-Knife position to expose the inter gluteal cleft, which was the main site of the operation. The gluteus muscles on both sides were abducted by adhesive strips of plaster stuck to the sides of the operation table. Probing and methylene blue (methylene blue, Navi Mumbai, Maharashtra, India) injection through the opening of the sinus to delineate the main tract and its side branches if present were done (Figure 1).

- Through the elliptical vertical wide incision, excision of the sinus tracts or cyst was performed and the dissection was continued down to the posterior sacral fascia (Figure 2).

- To avoid closure of the defect under tension, bilateral side flaps including skin layers and subcutaneous tissues were dissected and cut 2-3 cm from the edge of the elliptical wound down to the posterior sacral fascia and gluteus maximus muscle fibers with meticulous hemostasis (Figure 3).

Figure 1. Probing and methylene blue injection through the opening of the sinus to delineate the main tract and its side branches if present.

Figure 2. Excision of the sinus tracts or cyst and dissection was continued down to the posterior sacral fascial.

Figure 3. Bilateral side flaps including the skin and subcutaneous tissues were dissected, elliptical intradermal incision.

- The residual cavity was obliterated by 1-Prolene sutures (POlYGLYCOLIC ACID, Yancheng Huida Medical Instrument Co., Ltd, China) which were taken through the skin, subcutaneous tissue and post sacral fascia (Figure 4).

- A second vertical mattress suture 2-0 silk (silk braided, Yancheng Huida Medical Instrument Co., Ltd, China) was taken to close the gap between the Prolene stitches. Closure must be tension free to prevent dehiscence of the wound and be flat as much as possible to avoid the development of intergluteal cleft, which is the site of sinus recurrence (Figure 5).

Our practice is to put a small suction drain in the depth of the residual cavity to tighten the long threads of the Prolene sutures rolled above. Povidone -iodine (Umod, ine YMCO, Medical Indus-

Figure 4. The residual cavity was obliterated by 1-Prolene sutures.

Figure 5. Closing the gap. Closure must be tension free to prevent dehiscence of the wound.

tries, Yemen) soaked gauze dressing was placed over the closed wound to provide some external pressure in an attempt to obliterate the potential space and to prevent the formation of seroma or hematoma. Post-operatively, the patients nursed were advised to sleep on one side and encouraged to mobilize early.

The suction drains were removed after 24-72 hours postoperatively depending on the amount of drainage, which must be less than 10 ml during the last 24 hours. Antibiotics were given pre and postoperatively for 5 days in the form of Metronidazole (Flagyl, Sanofi-Aventis, Paris, France,) or vancomycin (vancomycin, Boisar, Dist-Thane, India), and Ceftriaxone (Forsef, Blim pharmaceuticals, Maslak -Istanbul, Turkey) for 24 hours and replaced by amoxicillin-clavulinate (MAGMA, ALPHA-Aleppo pharmaceutical industries, Syria) and metronidazole for 4 days. All patients were discharged after two to three days of the operation, the sutures and rolled-in compressive gauze packing were removed 2 weeks after the operation. (Figure 6).

Figure 6. Postoperative picture.

Table 1. Operative data

	Range
Operative time*	44.6 (42-57) minutes
Hospital stay*	2.5 (2-3) days
Drain removal **	48 (24-72) hours
Suture removal	2 weeks
Flow up time**	26.2 weeks (1 week -12 months)

* Mean (range), ** Median (range).

Postoperative follow-up was once per week for the first 4 weeks and then at three, 6 and 12 months from the date of the operation (Table 1).

Analytical Statistic Data

Statistical Package for the Social Sciences program (SPSS) ver. 20 (SPSS Inc., Chicago, IL, United State of America) for Windows 7.0 computer software was used for statistical analysis. Data were described in the form of frequency, mean, median, percentage (%) and average.

RESULTS

This study included 78 Patients, 71 (91%) males and 7 (9%) females. Median age of the patients was 28.5 years, ranging between 18-39 years. Thirty-one (39.7%) of the patients was overweight with a BMI between 25-30 kg/m^2, and 19 (24.3%) patients were obese with a body mass index of over 30 kg/m^2 according to the classification of the World Health Organization of Obesity (11). Fourteen (17.9%) were males and 5 (6.4%) were females. Thirty-eight (48.7%) males had excessive hair (Table 2). The occupation of the patients mainly involved accounting and computer technologies working for more than 8 hours daily in 37 (47.4%) cases and long-distance driver more than 8 hours dai-

Table 2. Preoperative patient characteristic		
Clinical presentation	**Number of patients (%)**	
Age*	28.5 (18-39)	
Gender	Male	71 (91%)
	Female	7 (9%)
Obesity	Overweight	19 (24.3%)
	Obese	14 (17.9%)
	Non-obese	45 (57.8%)
Hair density in the area	Excessive hair	38 (48.7%)
	Non-excessive	40 (51.3%)
* Median (range), (%) percentage.		

Table 3. Modes of presentation	
Clinical presentation	**Number of patients (%)**
Pain	16 (20.5%)
Discharge	53 (67.95%)
Abscess	9 (11.5%)

Figure 7. 38-year-old male patient with a case of perianal sinus tract at the level of. 4 o'clock.

ly in 13 cases (16.66%). Fifty-three patients (67.95%) presented with chronic discharge, 16 (20.5%) patients presented with dull aching pain of the distended non-infected cyst and 9 (11.5%) patients had an acute abscess for which incision and drainage was performed followed by excision and primary closure 3 months later (Table 3).

All of the chronic cases except the one presented with perianal pilonidal sinus underwent excision and tension free primary closure. Mean time of the operation was 44.6 minutes, ranging between 42-57 minutes.

Table 4. Postoperative complications	
	Number of patients (%)
No -complication	61 (78.2%)
Wound infection	5 (6.46%)
Recurrence	3(3.8%)
Patient Disappear not follow up	9 (11.54%)
Hematoma	0 (0%)
Seroma	0 (0%)

One of our cases, a 38-year-old male patient, was referred to us and described as a case of sinus in ano, and during the operation, we found perianal sinus tract at the level of 4 o'clock which was completely excised and proven by histopathology as pilonidal sinus (Figure 7).

Mean length of hospital stay was 2.5 days (range, 2-3 days). Postoperatively, sixty-one (78.2%) cases were without intraoperative, early or late postoperative complications, 5 (6.41%) cases had minor wound infection and 3 (3.85%) obese hairy patients developed recurrence, and 9 (11.54%) cases could not be reached during follow-up, which was conducted even by phone for cases living in far governorates (Table 4).

DISCUSSION

Intergluteal pilonidal disease is an infection disease affecting the skin and subcutaneous tissue in the midline of the upper part of the natal cleft of the buttocks (12). If the depth of the intergluteal sulcus increases, it will blead to the increase in anaerobic bacteria and form a good media for growth in this area (13).

In addition, the development of pilonidal disease is thought to be a result of a vacuum effect created between heavy buttocks. The vacuum effect sucks the anaerobic bacteria, hair, and debris into the subcutaneous fat tissue. If these factors responsible for the development of the disease are not eliminated, they will play important roles in the development and recurrence of the disease (14,15).

The mainstay of operative management for chronic or persistent disease is eradication of all pilonidal sinus tracts. En bloc eradication of the entire pilonidal sinus and epithelialized tracts was performed down to the sacrococcygeal fascial level, keeping normal tissue intact as much as possible (16,17).

There are several surgical methods used in the treatment and control of sacrococcygeal pilonidal sinus, however postoperative morbidity could not be reduced by those methods and there is no agreement on the best gold standard method of

surgical treatment (18). Any procedure should stress well on other parameters than postoperative morbidity and recurrence, such as simple technique, length of hospital stay, and length of absence from work (17,19). Many studies comparing various procedures have documented the relative superiority of one over the other. For simple, non-recurrent pilonidal sinus, less invasive surgery with excision and primary closure could be enough (18).

Primary closure technique is associated with earlier wound healing (complete epithelialization) and a faster return to daily work, but a delayed (open) closure is associated with a lower likelihood of pilonidal disease recurrence (12,20) .

The results of our study in which primary closure was tension free boosted these proposal. Patients walked freely without significant pain, but minor wound infection was noted in only 5 cases.

Low morbidity rate of certain surgery techniques is also naturally reflected by hospitalization time and time off work. In some papers reported for tension free primary closure, hospital stay is short and less than 5.5 days as reported by Rossi et al. (1993) for Limberg flap (21) and 5.7 days as reported by Singh et al. (2005) for adipose fasciocutaneus flap (22,23). Hospital stay in this study was shorter than 4 days and time off work was not more than three weeks. A total of 11 trial studies (n= 1729 patients) have included data for work return time, where nine studies have reported a faster return time to work following primary closure (24). The largest study including 144 patients has found that patients undergoing a primary repair have a significantly faster rate of return to work as compared to those with open wounds (11.9 versus 17.5 days, respectively) (24). Some authors say that primary closure is better and comfortable, especially in small defects. Excision surgery alone, or Excision and Primary closure of the wound, has been compared in a previous study (25). In addition, post-operative wound importance in this study was considered. Any exercise or sitting down on the wound was avoided for 3 weeks, and the patient was advised to return as slowly as possible to his/her normal activities. Hair-shaving from the edges of the wound is necessary (26,27). Shaving has to be continued for a long time or until complete healing of the wound (27). In this study, during follow-up of 12 months, only three recurrences (%4.6) in obese, hairy male patients were seen in a total of 65 (83.3%) patients at 1 year after surgery, which is in agreement with the study by Akinci et al. (1999) stating that pilonidal sinus is an acquired disease, penetration of hair is the main cause, and understanding the causes help prevent the disease (28). Time of healing was shorter after excision and closure, but recurrences occurred more as compared with excision alone. In addition, primary closure has been reported to result in a higher initial primary rate of healing with shorter and a reduced duration of hospital stay (19). For more comparisons with other studies, see Table 5.

Study Limitations

The limitation to our study includes losing contact with some patients after surgery.

Table 5. Comparison with other studies

Patients (no.)	Surgical procedure	Hospital stay (days)	Complication (%)	Recurrence (%)	First author, Year (Reference)
110	Excision and Limberg flap	3.7	5.88	4.9	(Urhan et al. 2002) (29)
312	Excision and primary closure	2	4	3	(Ciccolo et al. 2004) (30)
238	Excision with a Limberg transposition flap	2.1 (1-3)*	0.8	1.26	(Mentes et al. 2004) (31)
25	Limberg technique	4**	16	4	(Katsoulis, Hibberts, and Carapeti 2006) (32)
411	Excision and Limberg flap	3.2 (1-10)***	16.78	2.91	(Akin et al. 2008) (33)
229	Excision and primary closure	2.1 (2-5)*	9.1	4.4	(Toccaceli et al. 2008) (34)
110	Limberg technique	3	5.5	4.9	(Aslam, Shoaib, and Choudhry 2009) (35)
60	Rhomboid flap closure	6 (5-11)*	15	10	(el-Khadrawy et al. 2009) (36)
78	Excision and tension-free primary closure	2.5 (2-3)*	5 cases (6.4%)	3 cases (3.84%)	Current study

* Mean(range), ** Median, ***Average, (%) percentage.

CONCLUSION

Excision and tension-free primary closure of the pilonidal disease is effective with low complication rates, short hospitalization, low recurrence rates, earlier healing and shorter time off work. The surgery can be easily performed. It is now clearly shown that there is better patient satisfaction with primary wound closure rather than leaving it open.

Ethics Committee Approval: Approval from the ethics committee of our hospital was obtained.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Pilonidal hastalıkta eksizyon ve gerilimsiz primer kapanma

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, basit eksizyon ve gerilimsiz primer kapamayı değerlendirmek ve operasyon ve iyileşme süresi, hastanede kalış süresi, postoperatif komplikasyon derecesi ve tekrarlama oranındaki etkisini incelemekti.

Gereç ve Yöntem: Çalışmaya 71'i erkek (%91) ve 7'si kadın olmak üzere eksizyon ve gerilimsiz primer kapama cerrahi işlemi geçiren toplam 78 hasta dahil edildi. Cerrahi işlem, yara kenarından salınıp 2-3 cm kadar diseke edilen bilateral taraflı flepler ile gerçekleştirildi. Hastaların yaşı, cinsiyeti, vücut kitle indeksi, yara iyileşmesi, operasyon, drenin çıkarılması, hastanede kalış süresi, komplikasyonlar ve rekürrans analiz edildi.

Bulgular: Çalışmaya 71'i erkek (%91) ve 7'si kadın (%9) olmak üzere toplam 78 hasta dahil edildi. Hastaların ortanca yaşı 28,5 yıldı. Ortalama operasyon süresi 44,6 dakika idi. Altmış bir hastada (%78,2) herhangi bir komplikasyon olmaksızın tam primer iyileşme gözlemlendi. Hiçbir hastada hematom veya seroma gelişmedi, ancak beş olguda (%6,4) hafif yara enfeksiyonu ve üç obez hastada (%3,8) rekürrens oluştu. Ortalama hastanede kalış süresi 2,5 gündü ve çoğu hasta 3 hafta içerisinde çalışma hayatlarına geri döndü. Ortanca takip süresi 26,2 haftalık bir aralık içerisindeydi (1-51,4 hafta). Beş hastada (%6,41) yara enfeksiyonu, üç hastada da (%3,85) rekürrens vardı.

Sonuç: Eksizyon ve gerilimsiz primer kapama, daha düşük yara enfeksiyonu oranı, daha kısa hastanede kalış süresi, daha düşük rekürrens, erken yara iyileşmesi ve iş hayatından kısa süreli uzaklaşma ile ilişkili basit operasyonlardır. Cerrahi müdahale kolaylıkla yapılabildiği gibi nüks olmayan pilonidal sinüs ve kist olgularında tercih edilen cerrahi işlem olabilir.

Anahtar Kelimeler: Pilonidal, primer kapama, natal kleft sinüs, kist

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Protective effects of spironolactone against hepatic ischemia/reperfusion injury in rats

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ABSTRACT

Objective: In the present study, it was aimed to study the antioxidant effects of spironolactone (SPL) to determine its possible protective effects in hepatic ischemia reperfusion injury.

Material and Methods: Hepatic artery, portal vein, and bile duct of Wistar albino rats were clamped for 45 minutes under anesthesia to form an ischemia period. Then reperfusion was allowed and the rats were decapitated 60 minutes later. SPL (20 mg/kg, p.o.) or SF was orally administered for 30 minutes before ischemia. Rats in the control arm underwent sham surgery and were administered isotonic saline. Liver function was studied by measuring aspartate aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor-alpha (TNF-α), and interleukin 1beta (IL-1β) levels. Malondialdehyde (MDA), glutathione (GSH), luminol, and lucigenin levels, myeloperoxidase (MPO) and Na^+-K^+-ATPase enzyme activities were analyzed to study tissue injury under light microscope.

Results: While IR increased AST, ALT, TNF-α, and IL-1β levels and MDA, luminol, and lusigenin levels and MPO activities, it caused a decrease in GSH levels and Na^+K^+-ATPase activity. Spironolactone administration significantly improved these values.

Conclusion: Protective effects of SPL against ischemia/reperfusion injury via various mechanisms suggest that this agent may become a novel treatment agent in clinical practice.

Keywords: Hepatic ischemia reperfusion, spironolactone, malondialdehyde, glutathione, cytokines

INTRODUCTION

Ischemia/reperfusion injury takes place in various clinical settings such as hepatic trauma, hemorrhagic shock, resection of large intrahepatic tumors, and liver transplantation (1,2). The pathophysiology of hepatic ischemia reperfusion injury involves many mechanisms. It consists of several major steps including Kuppfer cell activation, formation of reactive oxygen derivatives, cytokine release, activation of polymorphonuclear leukocytes, altered mitochondrial permeability, and activation of endothelial cells and complement systems, among several other cellular and molecular mechanisms (3,4). These events lead to the activation of local and systemic inflammatory responses, causing injury to local organs.

Aldosterone is secreted by zona glomerulosa in the adrenal cortex. Sprinolactone is a specific aldosterone antagonist. It acts by binding to aldosterone receptors, sparing potassium ions while removing sodium and water in distal tubuli. Its impact on renal ischemia/reperfusion injury was demonstrated in a study conducted by Meija-Vilet et al (5). To date, however, no researcher has studied the effects of sprinolactone on hepatic ischamia/reperfusion. We therefore consider that our work will have an important place in the literature by being the first study that investigates this subject.

Under the light of the above mentioned information, this study aimed to investigate the effects of sprinolactone on liver injury resulting from ischemia/reperfusion

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applied at the level of middle and left hepatic artery, portal vein, and bile ducts.

MATERIAL and METHODS

This experiment was performed after obtaining the approval of the Local Ethics Committee at Marmara University Laboratory Animals Research Center with the protocol code numbered 80.2012.mar, dated 08.11.2012. The rats were obtained from and the experiment was conducted at the same laboratory.

The study used 32 ten-week-old female Norvegian rats of the Wistar albino strain weighing between 200 and 250 grams. The rats were randomly grouped into 4 groups containing 8 rats each and they were kept in wire cages containing 4 rats each under standard laboratory conditions (20-24°C, 50-60% humidity; 12-hour cycles of light and darkness); the rats were fed ad libitum with standard rat feed and tap water during the whole study period. No enteral or parenteral antibiotics were administered throughout the study.

Each rat was kept in a jar containing ether for 40-60 seconds for anesthesia induction. Following anesthesia induction, ketamin at 100 mg/kg and chlorpromazine at 1 mg/kg were administered intraperitoneally (ip) for anesthesia maintenance.

The rats were then laid supine under anesthesia. The anterior abdominal wall was shaved with a scalpel and the shaved area was sterilized with povidone iodine solution. Then, the abdominal cavity was entered via midline incision. Hepatic artery, portal vein, and bile duct were explored and clamped for 45 minutes to create ischemia. At the end of this period, reperfusion was established, and the rats were decapitated 60 minutes later. Spironolactone (20 mg/kg, p.o) or isotonic saline were applied via oral route for 30 minutes before ischemia. The rats in the control group were applied sham operation and isotonic saline infusion.

1. Sham group: Following the completion of the standard operation, a 2-cc blood sample and a hepatic tissue sample were taken without clamping the hepatic artery, portal vein, and bile ducts.

2. Spironolactone (SPL) group: The rats were orally administered SPL at a dose of 20 mg/kg for 30 minutes before the time of the sham operation. Then a 2-cc blood sample and a hepatic tissue sample were taken.

3. Ischemia reperfusion (I/R) group: The rats were orally administered isotonic for 30 minutes before the time of the sham operation. Following the completion of the standard operation, hepatic artery, portal vein, and bile ducts were clamped to create ischemia. The rats were subjected to ischemia for only 45 minutes, followed by 60 minutes of reperfusion. At the end of the reperfusion period, a 2-cc blood sample was obtained from the heart and a tissue sample was taken from liver.

4. The Spironolactone administered ischemia/reperfusion (I/R-SPL) group: The rats were orally administered sprinolactone at a dose of 20 mg/kg for 30 minutes before the time of the hepatic ischemia procedure. The rats were subjected to ischemia for only 45 minutes, followed by 60 minutes of reperfusion. At the end of the reperfusion period a 2-cc blood sample was obtained from the heart and a tissue sample was taken from the liver. The resected hepatic tissues were washed with cold 0.9% NaCl, wrapped in aluminium foils and stored at -80°C for biochemical studies. After thawing the frozen samples at room temperature, malondialdehyde (MDA), myeloperoxidase (MPO), and glutathione (GSH) levels, Na-K ATPase activity were studied. The samples put into formol were examined for structural damage. The blood samples were centrifuged at 3000 rpm for 15 minutes, and the separated plasma was stored at -70°C. The frozen samples were thawed at room temperature for the study of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), tumor necrosis factor-alpha (TNF-α), and interleukin-1beta (IL-1β) levels.

Serum Studies

Determination of serum AST (Biolabo Europe S.A. Catalog No: REF 92025, 02160 Maizy, France) and ALT (Biolabo Europe S.A. Catalog No: REF 80027, 02160 Maizy, France) is a kinetic spectrophotometric method which was perfomed in the Opera Technican Bayer Autoanalyser (Germany) device. TNF-α (BioSource Europe S.A. Catalog No.KRC 3014, Nivelles, Belgium) and IL-1β (ELISA, BioSource Catalog No.KRC0011, Nivelles, Belgium) levels were determined with the ELISA method using specific rat kits.

Tissue Studies

Determination of free oxygen radicals in tissue was performed by the Chemiluminescence Method (6,7). Tissue samples were put into 2 ml PBS-Hepes buffer, and 4 ml luminol (0.2 mM) and 4 ml lusigenin (0.2 mM) were added to 2 separate tubes containing samples of the same tissue. Photonic activity occurring as a result of the reaction of reactive oxygen species and luminol and lusigenin were recorded by a luminometer for 10 minutes and the "area under curve" (AUC) formed by the count was calculated.

To determine MDA and GSH levels, samples of the tissue were homogenized with ice-cold 150 mM KCl. As described by Beuge et al. in 1978 (8) for products of lipid peroxidation, MDA levels were assayed by monitoring thiobarbituric acid reactive substance formation. Lipid peroxidation was expressed in terms of MDA equivalents using an extinction coefficient of 1.56×10^5 M^{-1} cm^{-1} and results were expressed as nmol MDA/g tissue. GSH measurements were performed with the modification of the Ellman procedure (9). After centrifugation at 1077 x g for 10 min, 0.5 mL of supernatant was added to 2 ml of 0.3 mol/L $Na_2HPO4.2H_2O$ solution. A 0.2 ml solution of dithiobisnitrobenzoate (0.4 mg/ml 1% sodium citrate) was added, and the absorbance at 412 nm was measured immediately after mixing. GSH levels were calculated using an extinction coefficient of 1.36×10^4 M^{-1} cm^{-1}. Results were expressed in μmol GSH/g tissue.

Tissue MPO was measured with the Hillegeas method (10). Tissue samples taken immediately after decapitation were washed with isotonic saline to remove any blood clots and debris, dried with a filter paper, and weighed. The liver sample was homogenized with 50 mM K_2HPO_4 (pH: 6) to prepare a 10% homogenate, and it was centrifuged at 41400 g for 10 minutes at 4°C. The supernatant was discarded; and the samples that were re-homogenized by adding 0.5% HETAB (Hexadesyltrimethyl-ammonium bromide) to the precipitate were frozen, thawed, and sonicated for three times. Then the samples were centrifuged at 41400 g for 10 minutes at 4°C. The supernatant was discarded and the precipitate was added 50 mM K_2HPO_4 (pH: 6), 20 mM H_2O_2, and o-Dianizidine-2 HCl. It was incubated in a 37°C water bath for 3 minutes, and added 2% sodium azide to stop color reaction. The samples were then centrifuged at 41400 g for 10 minutes at 4°C, the supernatant was discarded, and the absorbance level of the final color was read at 460 nm in spectrophotometry.

Determination of tissue Na^+/K^+-ATPase activity was done with the Reading and İsbir method (11). The liver tissue sample was homogenized in a 10% sucrose solution and centrifuged at 3000 rpm for 10 minutes. Zero point one milliliter of the supernatant was discarded and the homogenates were incubated in a suitable medium containing 3 mM ATP. $Mg2^+$ -ATPase activity was determined in the presence of 1mM ouabain while total ATPase activity was determined in the presence of 100 mM NaCl, 5 mM KCl, 6 mM $MgCl_2$, 0.1 mM EDTA, and 30 mM Tris HCl (pH 7.4). The difference between total ATPase activity and Mg^{2+} -ATPase activity was considered Na^+/K^+-ATPase activity, and the specific activity of the enzyme was expressed as nmol Pi mg-1 $proteinh^{-1}$. The protein concentration of the supernatant was measured with the Lowry method (12).

The Method of Histopathological Examination

Light microscope: The tissue samples were put into 10% formol, washed with tap water for at least 3 hours or overnight, dehydrated with increasing alcohol concentrations (70% alcohol for 15 minutes, 90% alcohol for 15 minutes, 96% alcohol for 30 minutes, 100% alcohol twice for 30 minutes, 100% toluen twice for 30 minutes), and waited in paraffin at 60°C overnight, and embedded in parafin blocks on the next day. Following the blocking procedure, 5-6 mm sections were obtained from the samples and put on slides, waited in toluene for 2 hours for dewaxing, subjected to reduction to water (treated with 100% alcohol for 2 minutes, 90% alcohol for 2minutes, 70% alcohol for 2 minutes), and put in distilled water. Following treatment with hematoxylin for 15 minutes, the samples were put in tap water for empurpling process. After adding eosin and distilled water for 5 minutes, dehydration procedure was repeated with increasing concentrations of alcohol (70% alcohol for 2 minutes, 90% alcohol for 2 minutes, 96% alcohol for 2 minutes, 100% alcohol for 10 minutes). Then the samples were washed with Toluene twice (first bath for 5 minutes, second bath for 10 minutes), covered with Entellan, and examined under light microscope.

Statistical Analysis

Serum ALT, AST, TNF-α, and IL-1β levels and hepatic GSH, MDA, luminol, lucigenin levels, Bcl-2/Bax ratio, and MPO, Na^+, K^+-ATPase, caspase 3 and caspase 9 activities were compared with one-way analysis of variance (ANOVA) test, with paired comparisons being performed with Tukey's test.

A p value of less than 0.05 was considered statistically significant.

RESULTS

In our study ALT, AST, TNF-α, IL-1β levels in serum, and GSH, MDA, luminol, lucigenin levels, MPO, Na^+, K^+-ATPase activities in liver tissue were compared between the groups with one-way analysis of variance (ANOVA) test, with paired comparisons being performed with Tukey's test.

In the group applied with hepatic IR serum, AST, ALT, TNF-α, and IL-1β levels were significantly higher than the sham group. On the other hand, these parameters approximated to the control levels with SPL administration (Table 1).

Hepatic GSH level was lower in the IR group than the sham group. This decrease was largely prevented after the SPL administration in the IR group (Figure 1A). MDA levels were significantly higher in the IR group than the sham group. SPL administration significantly blunted this increase in the MDA levels (Figure 1B).

Table 1. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), tumor necrosis factor-alpha (TNF-α) and interleukin 1-beta (IL-1β) levels of the study groups in hepatic ischemia/reperfusion (I/R) model in rats.

	Sham	SPL	I/R	I/R-SPL
AST (U/L)	56.5 ± 7.5	61.1 ± 5.5	139.2 ± 15.1***	62.3 ± 8.8+++
ALT (U/L)	53.1 ± 4.9	59.7 ± 5.6	142.5 ± 14.8***	90.8 ± 12.6+
TNF-α (pg/ml)	51.2 ± 2.96	44.5 ± 3.1	78.70 ± 4.2***	51.90 ± 2.2+++
IL-1β (pg/ml)	359 ± 22	319 ± 16	466 ± 28**	371 ± 11+

Mean ± standard error.
** p< 0.01, ***p< 0.001 vs. sham group.
+ p< 0.05, +++ p< 0.001 vs. I/R group.
SPL: Spironolactone.

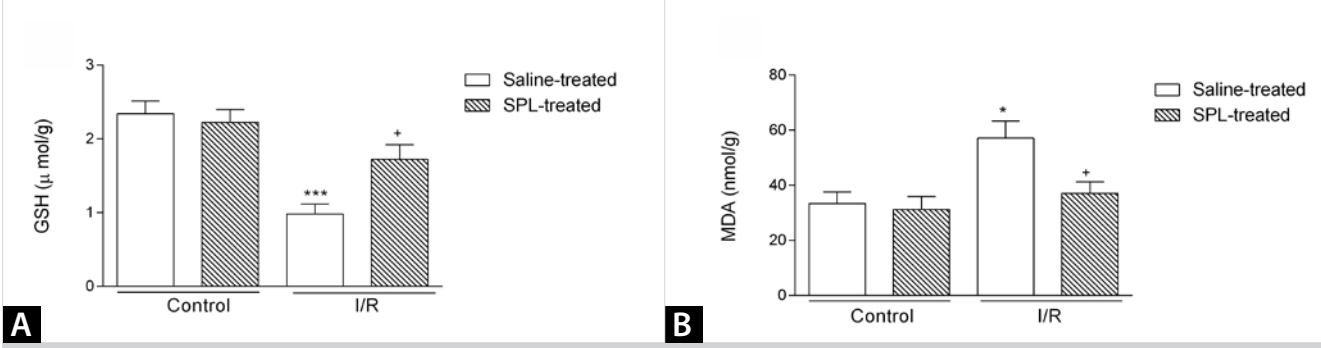

Figure 1. A. Tissue GSH, level of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. ***p< 0.001 vs. sham group, + p< 0.05 vs. I/R group. **B.** Tissue MDA, level of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. * p< 0.05 vs. sham group, + p< 0.05 vs. I/R group.

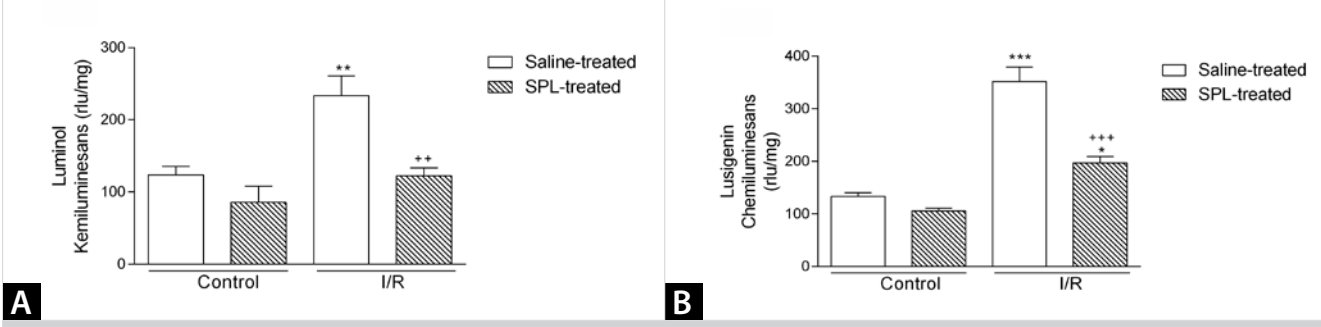

Figure 2. A. Tissue Luminol level of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. **p< 0.01 vs. sham group; ++ p< 0.01 vs. I/R group. **B.** Tissue Lucigenin level of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. * p< 0.01, ***p< 0.001 vs. sham group; +++ p< 0.001 vs. I/R group.

Figure 3. A. Tissue MPO, levels of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. ***p< 0.001 vs. sham group; + p< 0.05 vs. I/R group. **B.** Tissue Na^+-K^+ATPase levels of the study groups in the hepatic ischemia/reperfusion model (I/R) in rats. SPL: Spironolactone. **p<0.01 vs. sham group; + p< 0.05 vs. I/R group.

Hepatic luminol and lucigenin levels were significantly higher in the IR group than the sham group. This increase was observed to be significantly inhibited by SPL in the IR group (Figure 2A, B).

While hepatic ischemia led to a significantly increased neutrophil infiltration and thus MPO levels in the hepatic tissue compared to the sham group, MPO activity was significantly reduced in the SPL administered group and approached the MPO levels of the sham group (Figure 3A). Na^+-K^+-ATPase activity was lower in the IR group than the sham group. This reduction was largely prevented in the SPL administered group (Figure 3B).

The histopathological examination of the sham group showed that sinusoids and hepatocytes were intact and liver parenchyma preserved its normal morphology (Figure 4A), SPL administered group revealed intact sinusoids and hepatocytes with preserved morphology of the liver parenchyma (Figure 4B), IR group demonstrated extensive congestion and hepatocyte

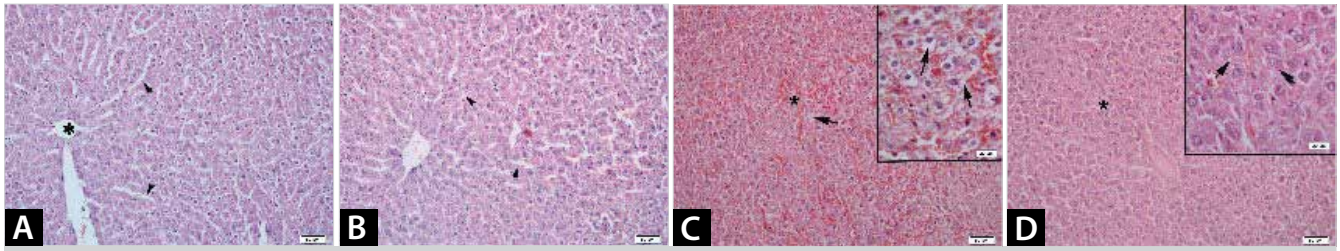

Figure 4. A. Sham group, central vein (*) and sinusoids (►) with smooth contours, **B.** SPL group, sinusoids with smooth contours (►). **C.** Hepatic ischemia group, extensive congestion in sinusoids (arrows) and central vein (*). **D.** Hepatic ischemia and SPL group, reduced congestion in sinusoids (arrows) and central vein (*).

degeneration caused by ischemia (Figure 4C) and SPL administered IR group demonstrated low-intensity sinusoidal and hepatocyte degeneration despite mild congestion (Figure 4D).

DISCUSSION

Ischemia, defined as oxygen deprivation of any tissue or organ as a result of insufficient perfusion secondary to the cessation of blood flow, and subsequent reperfusion together trigger a series of pathological reactions resulting in cell death and organ dysfunction. During the process of ischemia, cell death ensues as a result of the depletion of cellular energy stores and the accumulation of toxic metabolites. Restoration of blood flow is essential for both cellular regeneration and clearance of toxic metabolites. Nevertheless, a number of studies have indicated that tissue reperfusion paradoxically gives rise to a substantially more severe injury in ischemic tissue compared to that inflicted by ischemia per se (13).

Although dysfunction following reperfusion injury shows variability depending on structural alterations of an organ, oxygen radicals have been determined to be responsible for this injury in every organ (14).

In hepatic tissue, it was first observed in an experimental liver transplantation carried out by Toledo-Pereyra et al. in 1975 (15). It resulted in graft necrosis in the transplanted liver, which culminated into congestion, progressive thrombosis, and organ failure (16). Since blood loss during major liver surgery is closely related to mortality and morbidity, it should be kept at minimum through vascular isolation of the liver. Maneuvers performed to limit afferent blood flow of the liver primarily result in hepatic ischemia. Once the obstacle to hepatic blood flow is removed, the reperfusion process begins. IR injury is the leading cause of post-transplant dysfunction (17).

In an experimental study in rats, we biochemically and immunohistochemically evaluated pathological alterations in the liver tissue secondary to hepatic IR which was formed by clamping the middle and left hepatic arteries, portal vein, and bile duct. We aimed to assess the antioxidant and antiapoptotic actions of SPL, a mineralocorticoid receptor antagonist, in an attempt to investigate its protective effects against IR injury.

Although there exist various different methods to assess liver function after ischemia reperfusion injury, determination of the activities of AST, ALT is currently the most accepted method. The activities of these enzymes are known to increase in hepatic injury (18). Various studies have shown the antioxidant protective effects of mineralocorticoid receptor antagonists (19,20).

In our study, serum AST and ALT levels were significantly higher in the hepatic IR group compared to the control group. In contrast, the levels approached to the control levels upon the administration of SPL. These results suggest that tissue injury was less intense in the SPL administered group.

TNF-α is a cytokine released from monocytes, macrophages, and T cells that are abundant in the peritoneum and splanchnic tissues. It is also found in Kuppfer cells, the largest macrophage aggregate in the human body. TNF-α has some significant roles in muscle catabolism during stress and cachexia (1). In an experimental renal IR model, Kabasakal et al. have shown that IR injury can be reduced by inhibiting the formation of TNF-α (21). The result that we found is parallel to the literature. We found significantly higher TNF-α levels in the hepatic IR group when compared with the control group. In contrast, the SPL administered IR group showed a significantly blunted increase in TNF-α level, which approached that of the control group.

IL-1 is released from KCs in response to inflammatory stimuli. It is also synthesized by neutrophils, epithelial cells, and endothelial cells. Kato et al. have reported that IL-1β level is one of the major indicators of hepatic IR injury (22). In our study, the hepatic IR group had significantly higher serum IL-1β levels than the control group. On the other hand, SPL administered group enjoyed a significantly reduced increase, and IL-1β levels approached the control levels. Mineralocorticoid receptor antagonist Spironolactone has been shown to inhibit proinflammatory cytokines in previously conducted inflammation studies (23,24). The results that we found in our study are parallel to the literature. Because of the hepatic ischemia/reperfusion, increased values were near to normal values with spironolactone application.

Lipids are among the main targets of free radicals that are formed during ischemia reperfusion. Lipid peroxidation is considered by some researchers a key factor in IR injury (25).

Reactive oxygen species take one hydrogen atom from polyunsaturates fatty acids and initiates lipid peroxidation to form hydroperoxides. These reactions cause cell membrane to lose its liquidity and integrity, which ultimately leads to the release of cellular fractions to the surrounding medium, and cell death. These subcellular structures trigger inflammatory events and further aggravate injury (26). Different methods are used to detect tissue lipid peroxidation. One of the most widely used among them is the determination of the levels of MDA, a conjugated diene. Our study showed that MDA levels were significantly higher in the liver IR group compared to the controls. SPL administration substantially reduced the increase in MDA level.

All aerobic living beings are subjected to oxidative stress during cellular metabolism. Free radicals such as H_2O_2, O_2, which are formed in an organism, are transformed into more toxic metabolites and attack various targets including DNA, lipids, and proteins, disrupting metabolic processes. However, organisms possess many defensive mechanisms to neutralize these reactive agents. Referred to as the "antioxidant defense system", this system has glutathion as the most important component. GSH reacts with free radicals and peroxides to protect cells against oxidative injury. GSH concentration has been shown to be reduced rapidly during hepatic IR injury as a result of being used to neutralize reactive oxygen molecules. Many studies have shown that exogenously administered GSH increases intracellular GSH levels and prevents oxidative injury. Therefore, GSH has a major protective effect against oxidative injuries (27). Our study indicated lower hepatic GSH levels in the IR group than the sham group. This reduction in GSH levels was prevented by SPL in the IR group.

Studies have shown that agents used as antioxidants prevent the increase in MDA levels by increasing GSH levels (28,29). In this study, Spironolactone, which we used as a protective agent, increased the levels of decreased glutathione in the liver and significantly decreased the levels of MDA.

Neutrophils activated by ischemia reperfusion release myeloperoxidase into the medium and induce the formation of hypochloric acid (HOCl) from H_2O_2 and chloride ions. HOCl exerts cytotoxic effects by oxidizing sulphides, inactivating cytochrome and heme proteins, and degrading amino acids and proteins (30). Tissue MPO activity is considered an indicator of neutrophil accumulation. Our study demonstrated that while the induction of hepatic ischemia caused neutrophil infiltration and an associated significant increase in MPO activity compared to the control group, MPO activity was significantly lowered in the SPL administered group, approaching to that in the sham group. Considering the positive effects of Spironolactone on blood parameters used in our study, the fact that these agents significantly suppressed myeloperoxidase enzyme in the tissues supports that this enzyme plays an important role in HI. Thus, the presence of inhibitor properties on the MPO activity of the agents used in HI therapy will ensure that the tissue is protected against oxidation and will increase the success of treatment. Spironolactone has been reported to reduce increased myeloperoxidase activity during inflammatory events by the effect of free radical scavenging (31). When all these studies are taken into consideration, it is understood that our findings are in conformity with the literature.

Na^+-K^+-ATPase is an important membrane enzyme playing a key role in hepatocyte structure and physiology by maintaining sodium-potassium gradient on cellular membrane. It is an important indicator of maintenance of tissue viability and liver function. Studies have shown a reduction in Na^+-K^+-ATPase level after hepatic ischemia reperfusion (32,33). Our study revealed that Na^+-K^+-ATPase activity in the liver tissue was lower in the IR group when compared to the control group. This reduction was largely prevented by treatment with SPL.

Luminol hydroxyl radical is an indicator of the formation of reactive oxygen metabolites such as hydrogen peroxide and hypochloric acid. Lusigenin marks the formation of superoxide anion radical (33). They indirectly indicate the level of ROM-mediated tissue injury. In our study, luminol levels were higher in the IR group than the control group, and the increase was prevented by SPL administration. Lucigenin levels were significantly higher in the hepatic IR group compared to the controls. SPL administration, however, reduced this elevation to a significant extent. Spironolactone suggests that this effect is probably accomplished by inhibiting neutrophil infiltration.

Hepatic IR injury is known to induce hepatocellular necrosis and sinusoidal congestion. In our study, the histopathological examination of the control and SPL groups revealed that sinusoids and hepatocytes were intact, and liver parenchyma preserved its normal morphology; the histopathological examination of the IR group showed that hepatic ischemia caused extensive congestion and hepatocyte degeneration; and the histopathological examination of the IR group treated with SPL indicated low-grade sinusoidal and hepatocellular degeneration despite mild congestion.

In conclusion, it was observed that GSH level and Na^+-K^+-ATPase activity intensity decreased, lumiol, lucigenin, MDA level and MPO activity increased, and accordingly, hepatic dysfunction occurred in the liver after IR of the hepatic tissue. SPL provided protection against IR by largely reducing IR-induced injury. These results suggest that SPL treatment can lower the morbidity and mortality of hepatic IR to a considerable extent by preventing IR-induced free radical-mediated organ injury and dysfunction.

Ethics Committee Approval: This experiment was performed after obtaining the approval of the Local Ethics Committee at Marmara University Laboratory Animals Research Center with the protocol code numbered 80.2012.mar, dated 08.11.2012.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.A., B.S., A.Ö.Ş.; Design - S.A., A.Ö.Ş.; Supervision - S.A., A.Ö.Ş.; Resource - S.A., A.A., A.V.Ö., S.Ç., N.M., C.E.; Materials - S.A., B.S., A.Ö.Ş.; Data Collection and/or Processing - S.A., B.S., A.Ö.Ş.; Analysis and/or Interpretation - S.A., A.Ö.Ş.; Literature Search - S.A., B.S., A.Ö.Ş.; Writing Manuscript - All of authors; Critical Reviews - S.A., A.Ö.Ş.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
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Sıçanlarda hepatik iskemi/reperfüzyon hasarına karşı spironolaktonun koruyucu etkisi

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ÖZET

Giriş ve Amaç: Bu çalışmada, hepatik iskemi reperfüzyon hasarında olası koruyucu etkilerini saptamak için spironolaktonun (SPL) antioksidan etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Wistar albino sıçanların hepatik arter, portal ven ve safra kanalı, bir iskemi dönemi oluşturmak için anestezi altında 45 dakika boyunca klemplendi. 60 dakikalık reperfüzyonun sonunda sıçanlar dekapite edilmiştir. SPL (20 mg/kg, p.o.) veya SF, iskemiden 30 dakika boyunca oral yolla uygulandı. Kontrol grubundaki sıçanlara sham cerrahisi yapıldı ve izotonik salin verildi. Serumda aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), tümör nekrozis faktör-alfa (TNF-α) ve interlökin-1beta (IL-1β) düzeyleri ölçüldü. Malondialdehid, glutatyon, luminol ve lucigenin seviyeleri, miyeloperoksidaz ve Na^+-K^+-ATPase enzim aktiviteleri ve ışık mikroskobu altında doku hasarını incelemek üzere analiz edilmiştir.

Bulgular: IR,; AST, ALT, TNF-α ve IL-1β seviyelerini ve MDA, luminol ve lusigenin seviyelerini ve MPO aktivitelerini artırırken, GSH düzeylerinde, Na^+K^+ -ATPase aktivitesinde azalmaya neden olmuştur. Spironolakton uygulaması bu değerleri önemli ölçüde iyileştirmiştir.

Sonuç: SPL'nin iskemi/reperfüzyon hasarına karşı çeşitli mekanizmalarla koruyucu etkileri, bu ajanın klinik uygulamada yeni bir tedavi ajanı olabileceğini düşündürmektedir.

Anahtar Kelimeler: Hepatik iskemi reperfüzyon, spironolakton, malondialdehit, glutatyon, sitokinler

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Erectile dysfunction after surgery for rectal cancer: a prospective study

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ABSTRACT

Objective: Erectile dysfunction may occur as a complication of surgical treatment of rectal cancer in male patients. We compared the rates of postoperative erectile dysfunction and response to medical treatment after low anterior resection (LAR) and Miles' procedures.

Material and Methods: Fifty patients who underwent the Miles' procedure or LAR were prospectively assessed. This study includes fifty patients with stages 1 and stage 2 rectal cancer based on clinical and radiologic assessments, who underwent Miles' (25 out of 50 patients underwent the Miles'procedure and) or LAR (25 patients underwent LAR) procedures were prospectively assessed. The International Index of Erectile Function (IIEF) form was, used in the assessment to assess erectile dysfunction. This questionnaire, was administered preoperatively and 6 months postoperatively. For the patients with IIEF scores ≤ 25 at postoperative 6th months, tadalafil 5 mg is was given for 12 weeks and IIEF is was repeated after then.

Results: No significant differences were found in mean IIEF scores preoperatively (p= 0.695). In both groups, IIEF scores were significantly lower postoperatively compared with preoperatively (p= 0.00001, LAR; p= 0.00001, Miles'). Mean postoperative IIEF scores were significantly lower in patients who underwent Miles' compared with the LAR procedures (p= 0.0001). For patients with IIEF scores ≤ 25 at 6 months, tadalafil 5 mg was given for 12 weeks and IIEF scores were better in both groups (p= 0.00001).

Conclusion: The erectile dysfunction rate after Miles' procedure was significantly higher than the rate of patients who developed erectile dysfunction after LAR surgery. We tried to emphasize that in after LAR surgery. We should not be concerned only with cancer treatment surgically in rectal tumour patients, but remember that situations affecting their social life, such as postoperative erectile dysfunction, have medical and psychologic importance.

Keywords: Erectile dysfunction, rectal cancer, rectal tumors, colorectal surgery

INTRODUCTION

Rectal cancer surgery was performed by William Ernest Miles in 1908, who described abdominoperineal resection for the first time, called Miles' procedure. In the 1950s, sphincter-sparing procedures (low anterior resection [LAR]) came to the forefront. The main goals in rectal cancer surgery include low recurrence rates along with autonomic nerve preservation.

In 1970, Tsuchiya and Ohki first described autonomic nerve-sparing surgery that reduces urogenital complications, which were reported to occur in 39% to 76% of cases of rectal cancer surgery (1). Currently, total mesolectal excision (TME) is the standard of care for rectal cancer surgery. This procedure also aims at preserving sphincter function, if appropriate. In the TME procedure, the parietal layer of the endopelvic fascia should be spared, if possible. Special consideration should be given to the superior hypogastric and parasympathetic nerves (pelvic splanchnic nerves, pelvic plexus and its branches) lying beneath the parietal layer. Any damage to these nerves may have a central role in the development of erectile dysfunction (2). Erectile dysfunction also depends on psychologic factors, such as alcohol use, hormonal pathologies, low testosterone levels, ageing and especially chronic diseases, such as diabetes. Erectile dysfunction may occur in patients with diabetes mellitus due to vascular and neural damage (3,4).

Erectile dysfunction following rectal cancer surgery is not uncommon. However, studies are limited on the development of erectile dysfunction following rectal can-

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cer surgery. Several studies have compared open, laparoscopic, transanal and robotic surgery in terms of erectile dysfunction. Erectile dysfunction has been reported by all of these studies, although at varying rates.

We determined the rates of postoperative erectile dysfunction in patients undergoing LAR and Miles' procedures for treatment of rectal cancer. We compared these procedures in terms of their impact on erectile function and investigated potential benefits of medical treatment in this patient population.

MATERIAL and METHODS

Patients

Ethics approval for this study was obtained from the ethics committee (KAEK-50-1345). Patients diagnosed with low rectal cancer (in the region between 0 and 6 cm from the anal verge) at our clinic were prospectively included. Patient age, comorbidities (diabetes mellitus and hypertension) and smoking status were recorded at baseline. All patients underwent colonoscopy, and rectal cancer was histologically diagnosed in obtained biopsy specimens. Screening for metastasis included chest computed tomography (CT) and whole abdomen CT scans and/or magnetic resonance imaging scans. On the basis of clinical and radiologic assessments, patients with stage 1 or 2 disease were included in the study, while they should be American Society of Anesthesiologists (ASA) Class 1 or 2, based on the anaesthesiology assessment. Tumour stages were determined according to the Union for International Cancer Control classifications. Study subjects received detailed information about the study, and informed written consent was provided.

Exclusion criteria included unwillingness to participate in the study, prior pelvic or urologic surgery, ASA 3 and 4 class patients, homosexual tendencies, polyposis or synchronous tumour in a different part of the large intestine detected on preoperative studies, radiologic or clinical stage 3 or 4 cancer, metastatic disease detected during surgery, non-R0 resections or major complications postoperatively.

Study subjects underwent either Miles' or LAR procedure. All surgical procedures were performed via open techniques. Frozen section tissue was examined in all patients in the LAR group and if the tissue was positive for tumour or surgical margins were inadequate, then resection was repeated, if appropriate. If re-resection was not appropriate, Miles' procedure was performed. All procedures were performed by the same surgical team.

The International Index of Erectile Function (IIEF) form was used to assess erectile dysfunction in all patients preoperatively and 6 months postoperatively. This form contained six questions evaluating erectile dysfunction by scores of 0-10 (severe), 11-16 (moderate), 17-21 (mild-to-moderate), 22-25 (mild) and 26-30 (no erectile dysfunction). For patients with an IIEF score ≤ 25 after 6 months postoperatively, tadalafil 5 mg was begun daily for 12 weeks and then IIEF was repeated and erectile function was re-evaluated.

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences software (Version 9.0; SPSS, Inc., Chicago, IL, USA). In addition to descriptive statistics (mean and standard deviation), the paired t-test was used in the repeated measures analysis of the groups, the independent t-test was used in two-group comparisons and the χ^2 test was used to compare qualitative data. $p< 0.05$ was considered significant.

RESULTS

A total of 97 patients had low rectal cancer based on physical examination and colonoscopy. Histologic examination demonstrated adenocarcinoma in every patient. Of the 97 patients, 47 were excluded because they did not fulfil the study criteria. Mean age was 51.80 ± 7.50 years in the LAR group and 50.56 ± 8.92 years in Miles' procedure group (not statistically significant; p= 0.614). No statistically significant differences were found in the rates of patients with diabetes mellitus, hypertension or smoking status (p= 0.420, p= 0.275, p= 0.915, respectively; Table 1).

Mean preoperative IIEF score was 28.32 ± 1.60 and 28.48 ± 1.36 in the LAR and Miles' procedure groups, respectively (not statistically significant; p= 0.695). The 6 month postoperative scores were 18.92 ± 2.79 and 8.84 ± 1.93, respectively. When comparing mean preoperative and postoperative IIEF scores, the postoperative scores were significantly lower (p= 0.00001, LAR group;

Table 1. The mean age, the prevalences of diabetes mellitus and hypertension and smoking status in study groups

	The LAR group (n= 25)	The Miles group (n= 25)	
Age	51.80 ± 7.50	50.56 ± 8.92	t= 0.511; p= 0.614
DM	3 (12%)	4 (16%)	χ^2= 0.649; p= 0.420
HT	5 (20%)	4 (16%)	χ^2= 1.190; p= 0.275
Smoking status	8 (32%)	9 (36%)	χ^2= 0.011; p= 0.915

LAR: Low anterior resection; DM: Diabetes mellitus; HT: Hypertension.

Table 2. Intergroup comparisons of preoperative and postoperative IIEF scores

IIEF	The LAR group (n= 25)	The Miles group (n= 25)	t	p
Before the surgery	28.32 ± 1.60	28.48 ± 1.36	-0.397	0.695
After the surgery	18.92 ± 2.79	8.84 ± 1.93	18.727	**0.00001**
After medical treatment	24.92 ± 1.75	15.20 ± 2.44	15.335	**0.00001**
t	46.96	17.91		
p	0.00001	0.00001		

IIEF: International Index of Erectile Function.

Table 3. Intergroup comparisons of reductions IIEF scores

	The LAR group (n= 25)	The Miles group (n= 25)	t	p
Reduction in IIEF scores -comparison between preoperative and postoperative scores	9.40 ± 2.86	19.64 ± 2.04	-22.122	**0.0001**
Change %	33.12 ± 9.65	68.97 ± 6.57	-21.718	**0.0001**
Increases in IIEF scores-comparisons betwen postoperative scores and scores after medical treatment	6 ± 2.97	6.36 ± 3.44	0.423	**0.676**
Change %	34.31 ± 20.61	81.34 ± 54.76	4.332	**0.0001**
Reduction in IIEF scores-comparisons between preoperative scores and scores after medical medical treatment	3.40 ± 2.25	13.28 ± 2.73	-12.213	**0.0001**
Change %	11.76 ± 7.68	46.53 ± 8.77	-12.993	**0.0001**

IIEF: International Index of Erectile Function.

p= 0.00001 Miles' procedure group). At 6 months postoperatively, all of our patients received 5 mg tadalafil because of IIEF scores < 25. After 12 months of medical treatment, IIEF scores were 24.92 ± 1.75 in the LAR group and 15.20 ± 2.44 in Miles' procedure group. After medical treatment, mean preoperative IIEF scores were significantly higher than postoperative scores (p= 0.00001, LAR group; p= 0.00001 Miles' procedure group; Table 2).

The decrease in mean IIEF scores was statistically significantly higher in Miles' procedure group than in the LAR group (p= 0.0001). The percentage reduction in mean IIEF scores was 68.97% ± 6.57% in Miles' procedure group and 33.12 ± 9.65% in the LAR group (statistically significant, p= 0.0001) and the reduction in Miles' procedure group was far more remarkable. The comparison between the mean scores postoperatively and after medical treatment indicated significant improvements in both groups, which were reflected as a mean change of 6 ± 2.97 and 6.36 ± 3.44 points in the LAR and Miles' procedure groups, respectively. Intergroup comparisons did not reveal any significant difference in the rates of improvement with medical treatment. Comparisons between IIEF scores preoperatively and after medical treatment indicated significant decreases in both groups (p= 0.676, p= 0.0001; Table 3).

DISCUSSION

In rectal cancer surgery, postoperative erectile dysfunction index was reported to vary from 40% to 60% before introduction of TME. Even after introduction of nerve-sparing techniques in TME, erectile dysfunction still remains a common surgical complication with rates of 10% to 35%. Several causes underlie erectile dysfunction postoperatively for rectal cancer. The most common and important cause is intraoperative injury of the pelvic autonomic nerves (5-7).

Normal sexual function in men is controlled by sympathetic branches of the superior hypogastric plexus and parasympathetic branches of the pelvic splanchnic nerves. Injuries to sympathetic nerves may result in ejaculatory problems, whereas injuries to parasympathetic nerves may result in erectile dysfunction. Injuries to these nerves are common as they are located close to the mesorectum. Meticulous dissection is of paramount importance in the TME (8).

Open, transanal and laparoscopic rectal surgeries were compared in several studies on erectile dysfunction, and different rates of erectile dysfunction have been reported. The differences between our study and previous studies include the following: (1) in other studies, the mean age of study subjects was ≥ 60 years, compared with < 60 years in our study subjects

(51.80 ± 7.50 and 50.56 ± 8.92 years in the LAR and Miles' procedure groups, respectively). (2) Patients with all stages of disease were included in the previous studies. Our study was conducted in a more homogeneous patient group (stage 1 or 2 based on clinical or radiologic assessments). (3) Several other studies included ASA 3 class patients. Our study included ASA 1 and 2 class patients with less comorbidity.

In a study comparing transanal surgery to laparoscopic surgery in patients with low rectal cancer, the mean age was 62 years. Patients with advanced disease and lymph node involvement were included in that study. In the IEFF assessment performed at least 1 year after colostomy closure and the end of chemotherapy and/or radiotherapy, the mean IIEF score was 7 in the laparoscopy group and 17.5 in the transanal surgery group; however, the difference was not statistically significant (8).

Another study assessed only patients who underwent open surgery. Similar to the aforementioned study, that study also included predominantly patients > 60 years, and patients with stages 1 to 3 disease or who had received neoadjuvant chemotherapy and/or radiotherapy also were eligible. The investigators reported that age (> 60 years) and low rectal cancer had no negative impact on erectile function. The average IIEF domain scores were significantly decreased postoperatively. Erectile function decreased from 14.4 ± 10.8 to 9.14 ± 9.9 ($p< 0.05$). In parallel with our study, follow-up assessment with IIEF was performed at 6 months postoperatively and revealed the negative impact of surgery on erectile function. This negative impact was more prominent particularly in those who underwent Miles' procedure (9).

In another study of patients with similar demographic characteristics, IIEF assessments were performed preoperatively and at 3, 6 and 12 months postoperatively in patients who underwent open or robotic surgery for rectal cancer. In line with our results, the negative impact on erectile function was more prominent in those who underwent Miles' procedure in that study. No significant differences were found between open and robotic surgery in terms of erectile dysfunction rates. Unlike other studies, age, lymph node involvement and tumour stage had no demonstrable effect on erectile dysfunction. Tumours in the lower rectum, neoadjuvant chemotherapy and postoperative complications reportedly have a significant negative impact on erectile function (10).

Stamopoulos et al. compared open and laparoscopic rectal surgery and found no statistically significant differences in IIEF scores. The impact on IIEF scores was lower in the LAR than in Miles' procedure groups, in agreement with our study. This study concluded that the negative impact on erectile function was more significant in stages T3 and T4 tumours compared with stages T1 and T2 tumours in patients who had received neoadjuvant chemo- and/or radiation therapy preoperatively compared with those who did not and in elderly compared with younger patients (5).

No statistically significant differences were found between the patient groups in terms of commodities (diabetes mellitus and hypertension) and smoking status. A literature search did not reveal any studies specifically focused on the impact of comorbidities; however, it is well known that comorbidities and smoking have a negative impact on erectile function.

Normal sexual function is controlled by the sympathetic system. However, dysfunction may result from damage to the parasympathetic system. Superior hypogastric plexus and parasympathetic nerves (pelvic splanchnic nerves, pelvic plexus and its branches) should be preserved during TME procedures. Preservation of the pudendal nerves during dissection of the rectum may reduce the risk of erectile dysfunction. Therefore, perirectal and perineal muscles should be avoided during dissection as long as possible, as the pudendal nerves pass through these muscles. Even partial preservation of pelvic nerves was reported to maintain sexual function (11,12). However, as seen in the study of Ameda and Hendren, erectile dysfunction remains a serious complication of rectal cancer surgery, even in nerve-sparing procedures (13). Dong Kil Li reported a 61% reduction in late IIEF scores following nerve-sparing surgery (14). There studies report significant improvement in postoperative erectile dysfunction following treatment with udenafil given orally (15). In a study performed by Yavascaoglu et al., Sildenafil citrate treatment, which is a citrate-selective phosphodiesterase-5 inhibitor in erectile dysfunction caused by chronic diseases, reached a treatment level of 66.6% (16). Our patients at least partially benefited from tadalafil daily 5 mg given for erectile dysfunction.

Psychologic factors are considered to have a role in erectile dysfunction in these patients. Being aware of their cancer, feeling helpless and worrying about staying alive are important factors. In addition, psychologic impact was related to treatment with chemotherapy or radiotherapy, and the impact of colostomy/ileostomy on patients' mood further contributed to the development of erectile dysfunction. Postoperative erectile dysfunction should be assessed by urologists in collaboration with psychiatrists to bring these patients back to their usual life. Gradual decrease in the age at occurrence of rectal cancer further emphasises the importance of the resolution of this complication.

The number of patients in our study was limited. In addition, we cannot say that we do not evaluate psychologic (depression and anxiety) parameters, which may be effective on erectile dysfunction in patients with cancer who have had major surgery.

CONCLUSION

Regardless of the surgical technique used for rectal cancer, erectile dysfunction may occur as a serious, prevalent complication. This complication is more common in patients who undergo

Miles' procedure. We believe that, in addition to adequate preoperative psychologic support, careful surgical dissection and postoperative psychologic support when required, urologic support also is necessary in these patients.

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ORİJİNAL ÇALIŞMA-ÖZET
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Rektum kanser cerrahisi sonrası erektil disfonksiyon; prospektif bir çalışma

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ÖZET

Giriş ve Amaç: Rektum kanseri cerrahi tedavisi sonrası erkek hastalarda erektil disfonksiyon görülebilen bir komplikasyondur. Bu çalışmada amacımız rektum kanseri sebebiyle low anterior rezeksiyon (LAR) veya Miles prosedürü uygulanan hastaların postoperatif erektil disfonksiyon gelişim oranını ve medikal tedaviye cevabı karşılaştırmaktır.

Gereç ve Yöntem: Kliniğimizde rektum kanseri nedeniyle Miles prosedürü veya LAR uygulanan 50 hasta prospektif olarak değerlendirildi. Çalışmaya klinik ve radyolojik olarak evre 1 ve 2 kategorisinde olan hastalar alındı. Yirmi beş hastaya Miles prosedürü 25 hastaya ise LAR ameliyatı uygulandı. Postoperatif erektil disfonksiyon değerlendirilmesinde, ereksiyon işlevi uluslararası değerlendirme formu (IIEF) kullanıldı. Bu form ameliyat öncesi ve postoperatif altıncı ayda uygulandı. Postoperatif altıncı ayda yapılan IIEF formunda 25'in altı değeri olan olgulara her gün 5 mg tadalafil tedavisine başlandı ve 12 hafta sonra tekrar IIEF formu uygulandı ve medikal tedavi cevabı değerlendirildi.

Bulgular: LAR ve Miles gruplarının ameliyat öncesi IIEF ortalamaları arasında istatistiksel farklılık yoktu (p= 0.695). Her iki grupta ameliyat sonrası IIEF düzeyi ameliyat öncesine göre belirgin düşük olarak saptandı (LAR grubu p= 0.00001, Miles grubu p= 0.00001). Miles ameliyatı olan hastaların ameliyat sonrası IIEF ortalamaları, LAR ameliyatı olan hastalardan istatistiksel olarak anlamlı derecede düşük bulundu (p= 0.0001). Postoperatif altıncı ay sonunda IIEF skoru 25 altı olan olguların 12 hafta günlük tadalafil kullanımı sonrası her iki grupta da IIEF skorlamasında yükselme saptandı (p= 0.00001).

Sonuç: Miles prosedürü uygulanan hastalarda postoperatif gelişen erektil disfonksiyon oranı LAR yapılan hastalardan daha yüksektir. Rektum kanseri olan olgularda sadece kansere yönelik cerrahi veya medikal tedaviyle ilgilenmememiz, postoperatif erektil disfonksiyon gibi sosyal yaşamlarını etkileyen durumları hatırlamamız gerektiğini ve bu durumlarlada medikal, psikolojik desteği sağlamamız gerektiğini vurgulamak istedik.

Anahtar Kelimeler: Erektil disfonksiyon, rektum kanseri, rektal tümörler, kolorektal cerrahi

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ORIGINAL ARTICLE
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Posterior rectus canal: not a single anatomical entity & morphology – a laparoscopic study during TEP hernioplasty

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ABSTRACT

Objective: Posterior rectus canal assumed immense importance with newer laparoscopic technique of total extra-peritoneal pre-peritoneal (TEPP/TEP) hernioplasty for inguinal hernia. However, scientific study of live surgical anatomy of posterior rectus canal is almost totally lacking in the English literature, and hence the present study was conducted.

Material and Methods: 3-midline-port technique through posterior rectus sheath approach; Initial telescopic dissection under direct CO_2 insufflation followed by instrument dissection.

Results: 68 TEPP hernioplasties were successful in 60 patients with mean age of 50.1 ± 17.2 years (range 18-80) and mean BMI of 22.6 ± 2.0 kg/m^2 (range 19.5-31.2). Rectusial fascia was a definite anatomical entity, dividing traditional posterior rectus canal into two channels, namely, true retromuscular space and true posterior rectus canal (T-PRC). Rectusial fascia was variable, i.e., thick diaphanous (n= 47), thick membranous (n= 13), thin membranous (n= 3) and thin flimsy (n= 5). Posterior rectus sheath (PRS) was also variable, incomplete (n= 54) and complete (n= 14). Incomplete PRS showed seven variations in both extent and/or morphology. Complete PRS show five morphological variations. Transversalis fascia demonstrated three morphological variations, namely, single diaphanous (n= 41), single membranous (= 10) and thin flimsy (n= 3). TEPP hernioplasty was readily feasible through avascular true posterior rectus canal.

Conclusion: Posterior rectus canal is divided by 'rectusial fascia' into two channels, namely, true retromuscular space and true posterior rectus canal, latter being proper avascular plane of dissection for TEPP hernioplasty. Rectusial fascia, posterior rectus sheath and transversalis fascia showed morphological variations. Timely recognition of variable real-time anatomy is recommended to perform adequate proper surgical dissection for seamless TEPP hernioplasty with ease, rapidity and safety.

Keywords: Laparoscopic hernioplasty, total extraperitoneal preperitoneal hernioplasty, posterior rectus canal, rectusial fascia, posterior rectus sheath, transversalis fascia

INTRODUCTION

In the modern era, posterior rectus canal has assumed an immense importance with the development of the newer laparoscopic technique of total extra-peritoneal pre-peritoneal (TEPP/TEP) hernioplasty through the posterior rectus approach for adult inguinal hernia. However, despite the current popularity of laparoscopic hernioplasty, scientific study of the live surgical anatomy of the posterior rectus canal is almost totally lacking in the English literature although acutely required because of the new preperitoneal perspective, high magnification with clear visualization of even thinnest fascial layers and recognition of newer visions of the structures, and need of the surgical precision in presence of the frequent anatomic variations (1-9). This paper highlights the laparoscopic live surgical anatomy of the posterior rectus canal as seen during the preperitoneal dissection for the laparoscopic TEPP hernioplasty of the primary inguinal hernias in adult patients.

MATERIAL and METHODS

Laparoscopic total extraperitoneal preperitoneal (TEPP) inguinal hernioplasty was performed in adult patients with uncomplicated primary inguinal hernia under the institutional ethical approval and informed consent at Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University. A prospective doctoral research study was designed and prepared in April, 2010 to January, 2011, and surgery of laparoscopic hernioplasty was carried out from February, 2011 to November, 2015.

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Inclusion criteria included patients with age less than 18 years, uncomplicated primary inguinal hernia, absence of co-morbidity or presence of controlled mild co-morbidity (ASA grade I – II only of American Society of Anesthesiologists), and written informed consent. Exclusion criteria were refusal for laparoscopic repair, patient's age more than 18 years, presence of uncontrolled mild co-morbidity (ASA I and II), presence of severe co-morbidity (ASA grade III-IV), recurrent inguinal hernia after open or laparoscopic surgery, complicated inguinal hernia, presence of femoral or other groin hernia, and history of previous lower abdominal surgery. Calculation of the body mass index (BMI) was done by Deurenberg's formula (10).

Laparoscopic TEPP inguinal hernioplasty was performed through posterior rectus sheath approach with three ports in the midline. Balloon dissector made of a surgical glove was used for the initial dissection within the posterior rectus canal in the first three patients of the study, and the direct telescopic dissection was carried under CO_2 insufflation at a pressure of 12 mmHg in the remaining patients of the study. Details of the surgical technique were consistently the same as reported earlier by the author (4,8,9,11-17).

Statistical Analysis

Most of the statistical computations for the author's doctoral thesis for the award of degree of PhD (Surgery) were performed with the help of SPSS software v. 21 (IBM SPSS Statistics 21.0, USA)) after coding the patients' data and recording in the Microsoft excel spread sheet. Help for some simple statistical analysis was also taken from the On-line Calculators (www.graphad.com/quickcalcs/; www.danielsoper.com/statcalc/). All data analysis was expressed in terms of mean ± s.d. (standard deviation) unless specified otherwise, and a p-value of < 0.05 was considered as significant.

RESULTS

Sixty-three adult males and 3 adult females with uncomplicated primary inguinal hernia were recruited for the study. The three female patients who could not undergo TEPP hernioplasty due to one or more exclusion criteria were excluded from the study. Three male patients who had early forced conversion (Laparoscopic transabdominal repair, 1; Open preperitoneal repair, 1; and Open anterior repair, 1) were also excluded from the study. The cause for the conversion included early peritoneal injury by the 1st optical port, early vascular injury (deep inferior epigastric vessels) by the roughened Maryland dissector, and CO_2 retention with haemodynamic instability just after start of the procedure due to faulty selection of patient. Therefore, the data analysis includes 68 successful TEPP hernioplasties (Unilateral TEPP, 52; Bilateral TEPP, 8) performed in only 60 male patients. Mean age was 50.1 ± 17.2 years (range 18-80), and mean BMI was 22.6 ± 2.0 kg/m^2 (range 19.3-31.2).

Under excellent perspective, lighting and magnification of preperitoneal laparoscopy through posterior rectus sheath approach with direct telescopic dissection under CO2 insufflation, the posterior epimysium of the rectus abdominis muscle was found as a variably condensed and easily recognizable fascial layer which was termed the 'Rectusial Fascia' by the author (Fig. 2) (4). Rectusial fascia was found well-defined thickened in 60 out of 68 cases (Thick Diaphanous, 47; Thick Membranous, 13) and thin flimsy in 8 cases (Thin Membranous, 3; Thin Flimsy, 5) (Table 1) (Figure 1-4). This 'rectusial fascia was found to divide the traditional posterior rectus canal between the rectus abdominis muscle and the posterior rectus sheath into two potential spaces/channels, namely, (1) a true retromuscular space (RMS) anterior to the rectusial fascia, and (2) a true posterior rectus canal (TPRC) posterior to the rectusial fascia (Figure 5-7). Thus the retromuscular space (RMS) was bounded anteriorly by the rectus abdominis muscle and posteriorly by the rectusial fascia; and the true posterior rectus canal (TPRC) was bounded anteriorly by the rectusial fascia and posteriorly by a complete posterior rectus sheath upto the pubic bone only (n= 14) (Figure 1,3-7,11-14). or by an incomplete posterior rectus sheath in upper part and transversalis fascia in lower part (n= 54) (Figure 2,8-10).

The plane of retrofascial dissection posterior to the rectusial fascia in the 'true posterior rectus canal' (TPRC) was found avascular proper surgical plane for further dissection during the TEPP hernioplasty, and inadvertent/deliberate pre-fascial dissection anterior to the rectusial fascia in the retromuscular space (RMS)

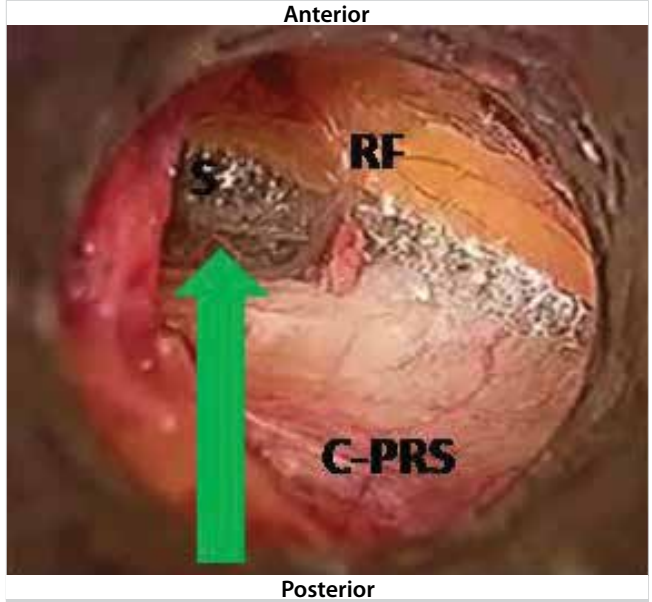

Figure 1. Boundaries of True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty An Adult Patient: Green Arrow, indicates true posterior rectus canal; RF, thick diaphanous rectusial fascia forming anterior boundary of true posterior rectus canal; C-PRS, whole-tendinous complete posterior rectus sheath (C-PRS) forming posterior boundary of true posterior rectus canal; S, sign of lighthouse; (Reproduced with permission from Ansari's Thesis (13).

Table 1. Morphological types of rectusial fascia forming anterior boundary of true posterior rectus canal

S. No.	Rectusial Fascia	Hernias*		Patients	
		N	%	N	%
1.	Thick Diaphanous	47	69.1	41	68.3
2.	Thick Membranous	13	19.1	12	20.0
3.	Thin Membranous	3	4.4	3	5.0
4.	Thin Flimsy	5	7.4	4	6.7
	Total	68	100	60	100

* Inclusive of bilateral hernias.

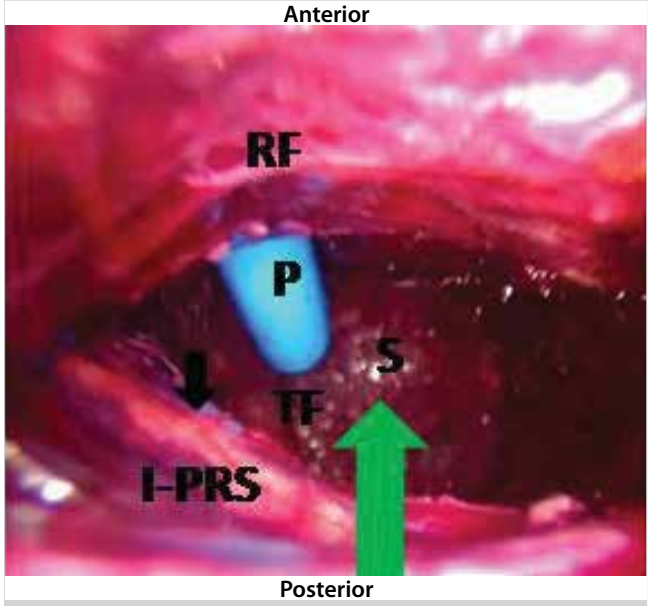

Figure 2. Boundaries of True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty An Adult Patient: Green Arrow, indicates true posterior rectus canal; RF, thick membranous rectusial fascia forming anterior boundary of true posterior rectus canal; C-PRS, long tendinous incomplete posterior rectus sheath (I-PRS) forming posterior boundary of true posterior rectus canal; TF, transversalis fascia; S, sign of light house; P, working port (blue plastic); (Reproduced with permission from Ansari's Thesis (13).

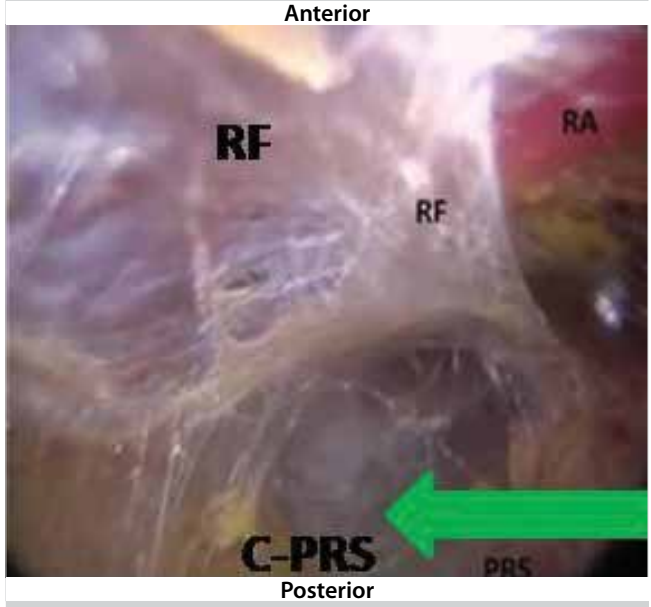

Figure 3. Boundaries of True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty in An Adult Patient: Green Arrow, indicates true posterior rectus canal; RF, thin membranous rectusial fascia forming anterior boundary of true posterior rectus canal; C-PRS, membranous complete posterior rectus sheath (C-PRS) forming posterior boundary of true posterior rectus canal; RA, rectus abdominis muscle covered by rectusial fascia (RF); (Reproduced with permission from Ansari's Thesis (13).

was found bloody with several disadvantages as reported earlier by the author (14).

Posterior boundary of the true posterior rectus canal (TPRC) was also found highly variable in morphology as reported earlier by the author (Figure 1,3-7,11-15) (8,9). Complete posterior rectus sheath (C-PRS) forming the posterior boundary of the T-PRC was found whole-tendinous (CWT, 6), whole-thinned-out (CTO, 3), grossly-attenuated (CGA, 3), musculo-tendinous (CMT, 1), partly-tendinous (CPT, 1) (Table 2). Incomplete posterior rectus sheath (IC-PRS) was also found variable in morphology, namely, normal-length whole tendinous (NWT, 31), normal-length partly tendinous (NPT, 8), short whole-tendinous (SWT, 3), normal-length thinned-out (NTO, 1), normal-length grossly-attenuated (NGA, 1), long partly-tendinous (LPT, 7) and long whole-tendinous (LWT, 3) (Table 2).

When the posterior rectus sheath (PRS) was complete (n= 14) (Figure 2,3,6), it directly formed the posterior wall of the true posterior rectus canal. However, in presence of an incomplete PRS (n= 54) (Figure 2,8-10), the lower posterior wall of the true posterior rectus canal was formed by the transversalis fascia, and the morphology of the transversalis fascia was also found variable, namely, single diaphanous, i.e., single membranous with significant fibro-fatty tissues on its outer side (SD, 41); single membranous with little/no fatty tissue on its outer side (SM, 10), and thin flimsy (FL, 3) (Table 3).

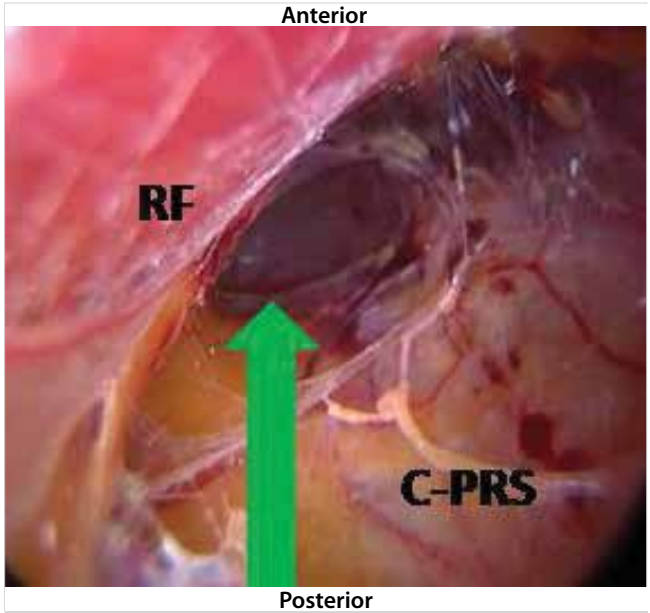

Figure 4. Boundaries of True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty in An Adult Patient: Green Arrow, indicates true posterior rectus canal; RF, thin flimsy rectusial fascia forming anterior boundary of true posterior rectus canal; C-PRS, membranous complete posterior rectus sheath (C-PRS) forming posterior boundary of true posterior rectus canal; (Reproduced with permission from Ansari's Thesis (13).

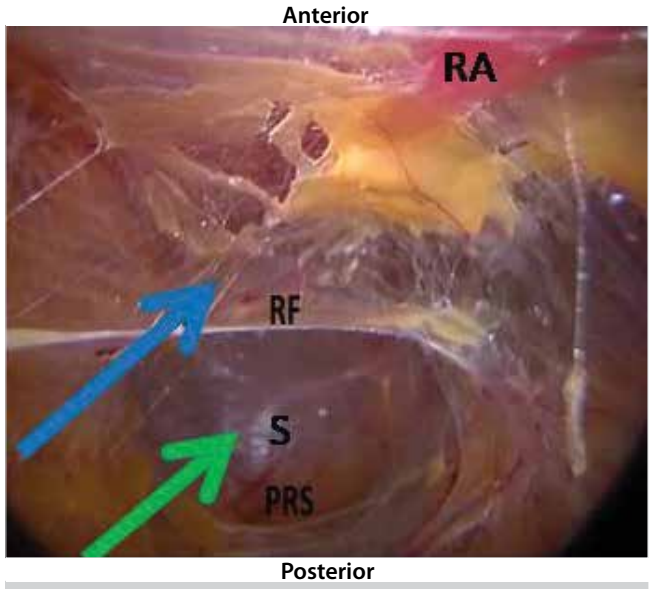

Figure 6. Double-Channelled Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty in An Adult Patient: Green Arrow, indicates true posterior rectus canal between thin membranous rectusial fascia (RF) and membranous complete posterior rectus sheath (C-PRS); Blue Arrow, indicates true retromuscular space between rectus abdominis muscle (RA) and thin membranous rectusial fascia (RF); S, sign of lighthouse; (Reproduced with permission from Ansari's Thesis (13).

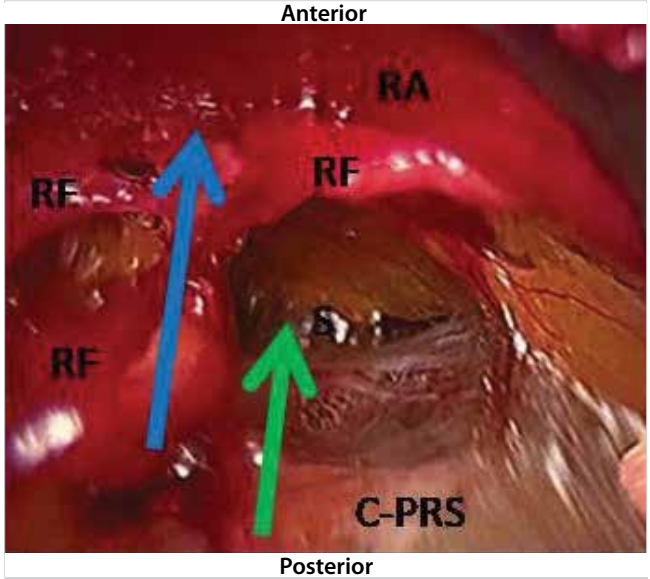

Figure 5. Double-Channelled Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty in An Adult Patient: Green Arrow, indicates true posterior rectus canal between thick diaphanous rectusial fascia (RF) and grossly-attenuated complete posterior rectus sheath (C-PRS); Blue Arrow, indicates true retromuscular space between rectus abdominis muscle (RA) and thick diaphanous rectusial fascia (RF); S, sign of lighthouse; (Reproduced with permission from Ansari's Thesis (13).

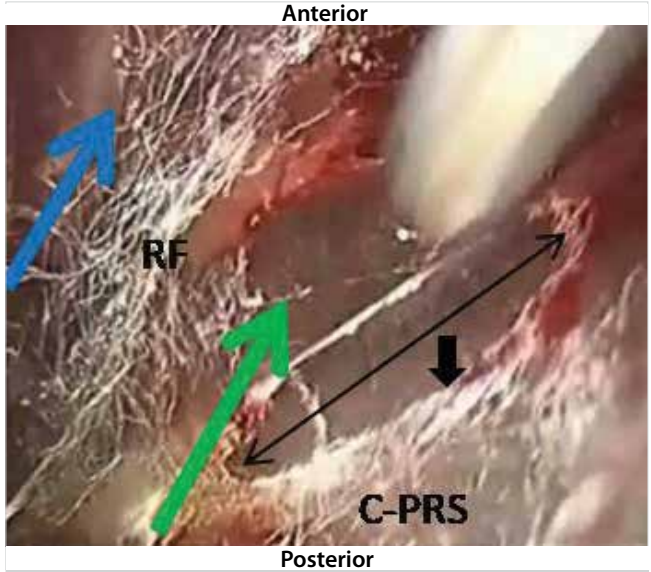

Figure 7. Double-Channelled Posterior Rectus Canal Observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty in An Adult Patient: Green Arrow, indicates true posterior rectus canal between thin flimsy rectusial fascia (RF) and membranous complete posterior rectus sheath (C-PRS); Blue Arrow, indicates true retromuscular space between rectus abdominis muscle (RA) and thin flimsy rectusial fascia (RF); S, sign of lighthouse; Double-Headed Black Arrow, indicates opening made in complete posterior rectus sheath (PRS); Single-Head Black Arrow, indicates artificial arcuate line created in complete posterior rectus sheath (C-PRS); (Reproduced with permission from Ansari's Thesis (13).

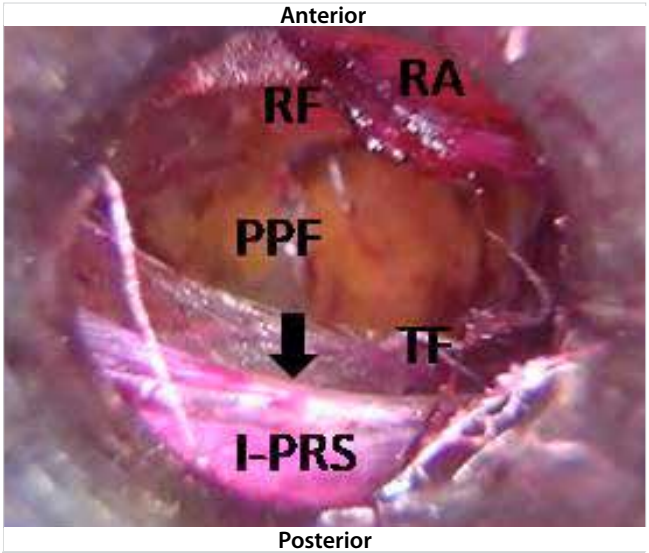

Figure 8. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: I-PRS, tendinous incomplete posterior rectus sheath with well-defined arcuate line (Black arrow); RF, well-formed membranous rectusial fascia covering partly-visible rectus abdominis muscle (RA); TF, transversalis fascia; PPF, preperitoneal fascia; (Reproduced with permission from Ansari's Thesis (13).

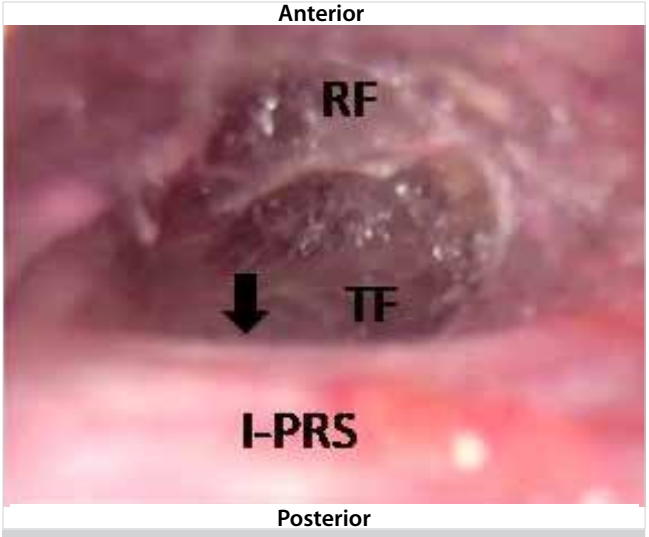

Figure 9. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: I-PRS, tendinous incomplete posterior rectus sheath with well-defined arcuate line (Black arrow); RF, well-formed membranous rectusial fascia covering rectus abdominis muscle (not visible); TF, transversalis fascia; (Reproduced with permission from Ansari's Thesis (13).

Deep inferior epigastric vessels (DIEV) were found running always in the retromuscular space supplying both the rectus muscle and its variably condensed posterior epimysium (rectusial fascia). In patients with incomplete posterior rectus sheath

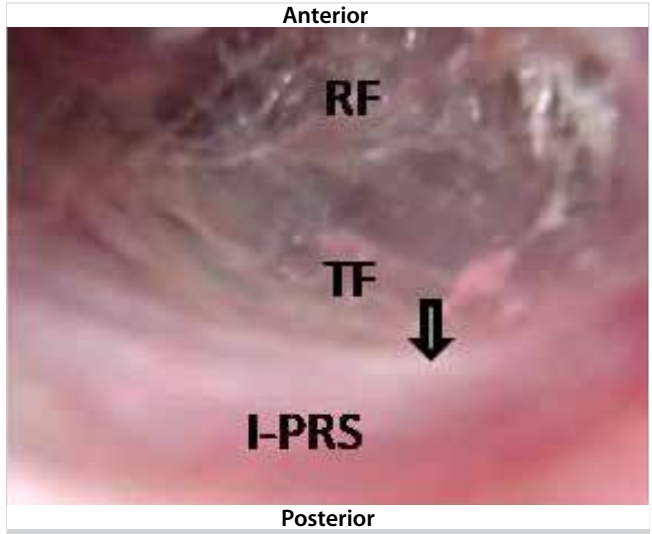

Figure 10. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: I-PRS, partly tendinous (upper part tendinous and lower part attenuated) incomplete posterior rectus sheath with indistinct arcuate line (Truncated black arrow); RF, well-formed membranous rectusial fascia covering rectus abdominis muscle (not visible); TF, transversalis fascia; (Reproduced with permission from Ansari's Thesis (13).

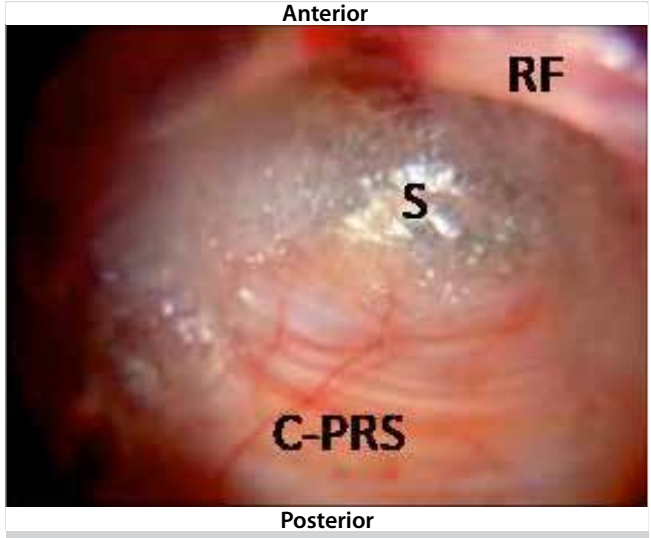

Figure 11. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: C-PRS, whole-tendinous complete posterior rectus sheath with absent arcuate line; RF, thick membranous rectusial fascia covering rectus abdominis muscle (not visible); S, sign of lighthouse; (Reproduced with permission from Ansari's Thesis (13).

(PRS), the DIEV, was initially running within the transversalis fascia and then entered the retromuscular space by piercing the rectusial fascia above the arcuate line. In patients with the complete PRS (8,9,15), the DIEV was found to course within the retromuscular space from just above the symphysis pubis.

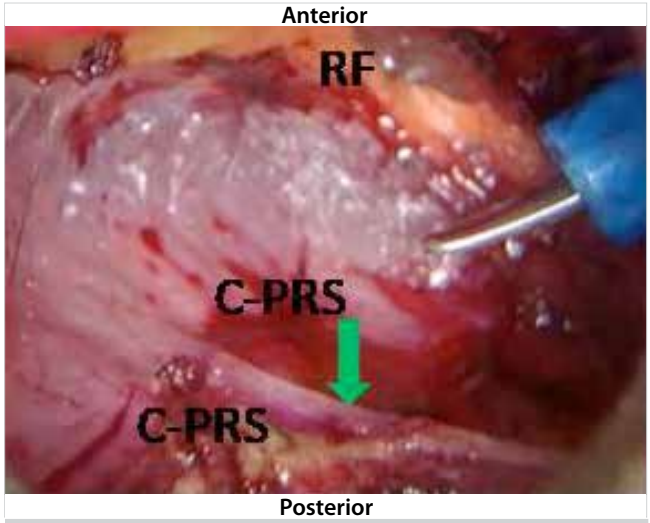

Figure 12. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: C-PRS, membranous complete posterior rectus sheath with a secondary arcuate line (green arrow); RF, thick diaphanous rectusial fascia covering rectus abdominis muscle (not visible); (Reproduced with permission from Ansari's Thesis (13).

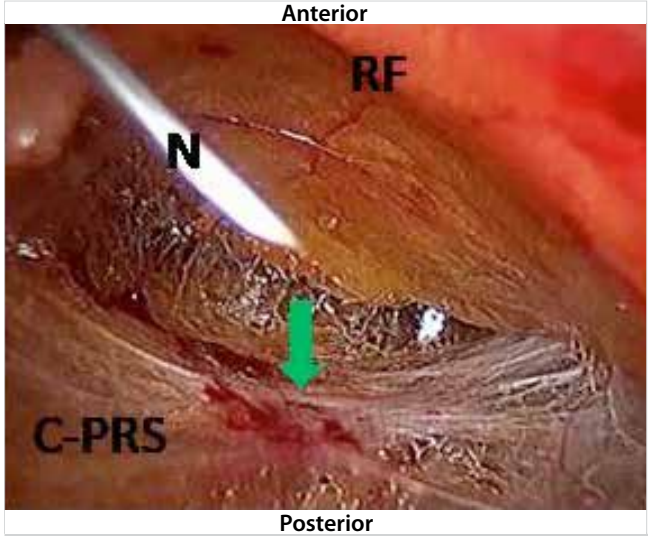

Figure 13. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: C-PRS, grossly-attenuated complete posterior rectus sheath with Henle's Band (green arrow) which is regarded as a secondary arcuate line; RF, thick diaphanous rectusial fascia covering rectus abdominis muscle (not visible); N, hypodermic needle inserted percutaneously for confirmation of axis and depth before placement of working port; (Reproduced with permission from Ansari's Thesis (13).

DISCUSSION

Way back in 1942, Baumann stated that "One might think that the science of anatomy has completed the detailed description of the human body … However, some structures are still problems..." (18). Baumann's statement was ratified as lately as 1997 by Diarra even after the advent of CT, MRI and laparoscopy (19). Despite general accord, the traditional textbook description of

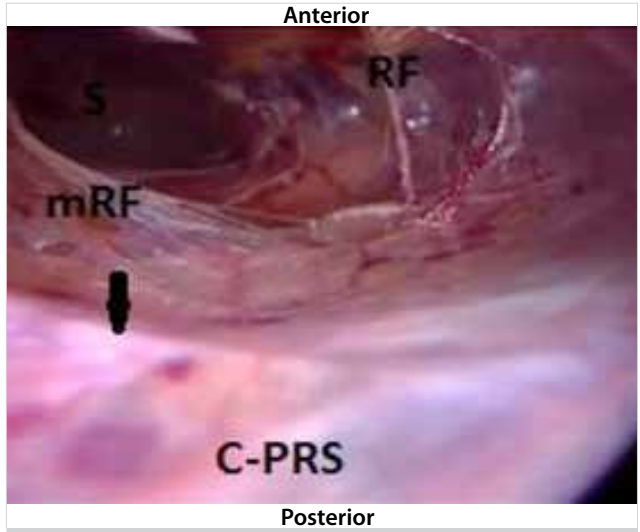

Figure 14. True Posterior Rectus Canal observed during Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) in An Adult Patient: C-PRS, membranous complete posterior rectus sheath with a secondary arcuate line (black arrow); RF, membranous rectusial fascia covering rectus abdominis muscle (not visible); mRF, part of rectusial fascia taken down with the posterior rectus sheath and initially misidentified as transversalis fascia as reported earlier by the author (12); (Reproduced with permission from Ansari's Thesis (13).

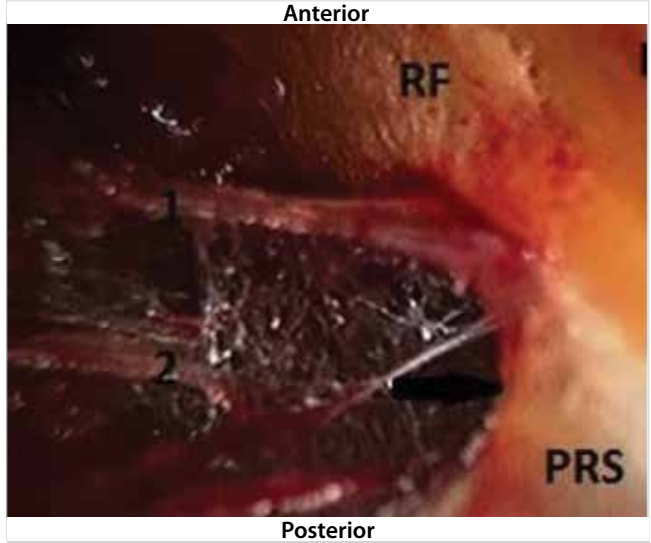

Figure 15. Double-Layered Complete Posterior Rectus Sheath in an Adult Patient Undergoing Laparoscopic Total Extraperitoneal Preperitoneal (TEPP) Hernioplasty: RF, thick diaphanous rectusial fascia covering rectus abdominis muscle (not visible); PRS, complete posterior rectus sheath with creation of artificial arcuate line in progress; 1 and 2, two layers of posterior rectus sheath, the deeper layer being initially misidentified for a moment as transversalis fascia as reported earlier by the author (11); (Reproduced with permission from Ansari's Thesis (13).

Table 2. Morphological types of posterior rectus sheath forming posterior boundary of true posterior rectus canal

S. No.	PRS Type	PRS Subtype	Hernias		Patients	
			N	%	N	%
1.	Complete PRS	CWT	6	16.2	6	18.2
2.		CTO	3	8.1	3	9.1
3.		CGA	3	8.1	3	9.1
4.		CMT	1	2.7	1	3.0
5.		CPT	1	2.7	OS	-
6.	Incomplete PRS	NWT	31	45.6	27	45.00
7.		NPT	8	21.6	7	21.2
8.		SWT	3	8.1	3	9.1
9.		NTO	1	2.7	1	3.0
10.		NGA	1	2.7	OS	-
11.		LPT	7	18.9	7	21.2
12.		LWT	3	8.1	2	6.1
		Total	**68**	**100**	**60**	**100**

PRS: Posterior rectus sheath, CWT: Complete whole-tendinous, CTO: Complete thinned-out, CGA: Complete grossly attenuated, CMT: Complete musculo-tendinous, CPT: Complete partly-tendinous, NWT: Normal-length whole-tendinous, NPT: Normal-length partly tendinous, SWT: Short whole-tendinous, NTO: Normal-length thinned-out, NGA: Normal-length grossly attenuated, LWT: Long whole-tendinous, LPT: Long partly-tendinous.

Table 3. Morphological types of transversalis fascia forming lower posterior boundary of true posterior rectus canal in patients with incomplete PRS (n= 54)

S. No.	Transversalis Fascia	Hernias*		Patients	
		N	%	N	%
1.	SD	41	75.9	38	77.6
2.	SM	10	18.5	8	16.3
3.	FL	3	5.7	3	6.1
	Total	**54**	**100**	**49**	**100**

PRS: Posterior rectus sheath, SD: Single diaphanous (single membranous with significant fibro-fatty tissues on its outer side); SM: Single membranous with little/no fatty tissue on its outer side; FL, thin flimsy.

the rectus sheath formation is not a common arrangement in the opinion of several investigators since long (20-22). Even in 1940, McVay and Anson really commented that "Descriptions of the rectus sheath contained in our textbooks of anatomy are singularly alike; they are stereotyped and oversimplified" (21).

Traditionally, the rectus abdominis muscle is said to be enclosed within a fibrous rectus sheath, with an anterior rectus sheath (ARS) being tendinous and complete extending upto the pubic bone but with a posterior rectus sheath (PRS) being tendinous and incomplete ending below the umbilicus with a well-defined sharp Arcuate Line at ¼th to ½ of the umbilico-pubic distance and not extending upto the pubic bone. Posterior rectus canal, currently the most preferred approach for the laparoscopic total extraperitoneal preperitoneal (TEPP) hernioplasty for the inguinal hernia, is traditionally taught to be bounded anteriorly by the fleshy rectus abdominis muscle and bounded posteriorly by the incomplete aponeurotic posterior rectus sheath in upper part and the transversalis fascia in the lower part. Under excellent lighting and magnification of modern laparoscopy, not only new structures/tissue planes and phenomena have been discovered (2,4,8,9,11-17,23-25), but also the frequent anatomic variations often reported in the previous cadaveric studies were confirmed (7,26-31), which are visualized too clearly to refute even against the prior fixed mindset based on the traditional anatomy classroom teaching (2), although they rarely received the attention of the authors of the traditional textbooks of surgery &/or anatomy commonly read by the medical students. Current bilaminar/trilaminar concept of the posterior rectus sheath in cadaveric studies (27,30,32) is supported by the laparoscopic live anatomical findings of double-/multi-layered posterior rectus sheath (Figure 15) (9,23).

In the modern era, the posterior rectus canal has assumed an immense importance with the development of the newer laparoscopic technique of total extra-peritoneal pre-peritoneal

(TEPP/ TEP) hernioplasty through the posterior rectus approach for the adult inguinal hernia because of the four important reasons, viz., Firstly, "Inguinal anatomy as viewed through the laparoscope is unfamiliar to most surgeons" (1); Secondly, " new surgical techniques provide new vision of structures known for centuries" (3), for example, the 'rectusial fascia', a definite laparoscopic anatomical entity of great surgical importance during TEPP hernioplasty (4,14); Thirdly, very little research is reported in the recent literature regarding the laparoscopic inguinal hernia anatomy many of which lacks anatomical precision (5), and the available material belongs to mainly gross anatomy of cadaveric nature which is often misleading due to embalming-induced hardening, distortion, and fusion of the fascial layers (6,33); Fourthly, wide anatomic variations in the posterior rectus sheath known to occur since the time (1804 AD) of Sir Astley Cooper (34) were re-emphasized by several investigators in recent years but which received little/no attention of not only the anatomists but also the practicing surgeons (7).

As the posterior rectus sheath is often grossly attenuated (9) and fascia-like (Rectus Sheath Fascia of Arregui) (2,35), an adequate and proper preperitoneal dissection for preperitoneal mesh repair (open as well as laparoscopic) depends on an accurate understanding of these fasciae (2). Moreover, timely recognition of the variability of the preperitoneal fascial structures is really important for the success of a seamless laparoscopic hernia repair with better outcomes (2,36).

To conclude, the present laparoscopic study confirmed the age-old opinion of McVay and Anson (21) that the traditional textbook description of the posterior rectus canal formation is oversimplified and stereotyped, and the real-time surgical anatomy is often distinctly different from patient to patient. Traditional posterior rectus canal is not really a single anatomical entity but divided by a newly-discovered 'rectusial fascia' into two distinct potential spaces/channels of great surgical importance during the laparoscopic TEPP hernioplasty, namely, a true retromuscular space and a true posterior rectus canal, the latter being the proper avascular surgical plane of dissection for the TEPP hernioplasty. Present study also confirmed the frequent morphological variations in both the rectusial fascia and the posterior rectus sheath which form the anterior and posterior boundaries of the true posterior rectus canal respectively.

Study Limitations

The present study had four limitations. Firstly, sample size of 68 hernioplasties in the present study was rather small in the light of such a common problem of inguinal hernia, and reasons for this included patient reluctance for newer surgical technique, peer reluctance for laparoscopic TEPP hernioplasty due to the demanding nature of the procedure and increased operating time, and higher cost; and therefore a larger cohort sample appears necessary to validate many of our observations. Secondly, the study included male patients only because of two reasons, i.e., uncommon incidence of inguinal hernia in females and exclusion of the three initially-recruited female patients due to exclusion criteria of the study. Thirdly, the author could not enlist the services of a dedicated anatomist inside the operation theatre for validation and easy recognition of tissues/structures and their morphological variations. Fourthly, the study was conducted with 3-chip endo-camera, and the availability of a high definition endovision might have improved our observations.

CONCLUSION

Traditional posterior rectus canal is not really a single anatomical entity but divided by a newly-discovered 'rectusial fascia' into two distinct potential spaces/channels of great surgical importance during laparoscopic TEPP hernioplasty, namely, (1) a true retromuscular space (RMS) anterior to the rectusial fascia, and (2) a true posterior rectus canal (TPRC) posterior to the rectusial fascia, the latter being the proper avascular surgical plane of dissection for the TEPP hernioplasty. Present study also confirmed frequent morphological variations in both the rectusial fascia and the posterior rectus sheath which form the anterior and posterior boundaries of the true posterior rectus canal respectively, requiring astute attention of the laparoscopic TEPP surgeons for timely recognition of the variable real-time anatomy in order to perform an adequate and proper surgical dissection through the avascular true posterior rectus canal for the seamless TEPP hernioplasty with ease, rapidity and safety.

Ethics Committee Approval: Obtained from the Institutional Ethics Committee of the Faculty of Medicine, Aligarh Muslim University, India (#770/21.08.2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2019; 35 (4): 299-308

Posterior rektus kanalı: tek bir anatomik yapı ve morfoloji değildir-TEP hernioplasti sırasında laparoskopik inceleme

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ÖZET

Giriş ve Amaç: Posterior rektus kanalı, inguinal herni için total ekstraperitoneal preperitoneal (TEPP/TEP) hernioplastinin yeni laparoskopik teknikleri ile büyük bir önem kazanmıştır. Ancak, İngilizce literatürde posterior rektus kanalının canlı cerrahi anatomisinin bilimsel çalışması neredeyse hiç bulunmamaktadır ve bu çalışma bu sebeple gerçekleştirilmiştir.

Gereç ve Yöntem: Üç orta hat port tekniği yoluyla posterior rektus kılıfı yaklaşımı. Başta doğrudan CO_2 insuflasyonu altında teleskopik diseksiyon ve ardından aletli diseksiyon.

Bulgular: Ortalama yaşı 50.1 ± 17.2 yıl (aralık 18-80) ve ortalama VKI 22.6 ± 2.0 kg/m^2 (aralık 19.5-31.2) olan 60 hastada başarılı 68 TEPP hernioplastisi yapıldı. Rektus fasyası, geleneksel posterior rektus kanalı gerçek retromusküler alan ve gerçek posterior rektus kanalı (T-PRC) olarak adlandırılan iki kanala ayıran belirgin bir anatomik varlıktı. Rektus fasyası değişkendi; kalın yarı saydam (n= 47), kalın membranöz (n= 13), ince membranöz (n= 3) ve ince zayıf (n= 5). Posterior rektus kılıfı (PRS) da değişkendi: inkomplet (n= 54) ve kopmlet (n= 14). Inkomplet PRS hem derece hem de morfolojik bakımından yedi varyasyon gösterdi. Komplet PRS beş morfolojik varyasyona sahipti. Transversalis fasya tek yarı saydam (n= 41), tek membranöz (n= 10) ve ince zayıf (n= 3) olarak adlandırılan üç morfolojik varyasyon gösterdi. TEPP hernioplastisi, avasküler gerçek bir rektus kanal aracılığıyla kolaylıkla uygulanabildi.

Sonuç: Posterior rektus kanalı, rektus fasyası tarafından gerçek retromusküler alan ve gerçek posterior rektus kanalı olarak ikiye ayrılır ve sonuncusu TEPP hernioplastisi için uygun avasküler düzlemdir. Rektus fasya, posteriyör rektus kılıfı ve transversalis fasya morfolojik varyasyonlar gösterdi. Değişken gerçek zamanlı anatominin zamanında fark edilmesi kolayca, hızlıca ve güvenli bir şekilde TEPP hernioplasti için düzgün cerrahi diseksiyonun yapılabilmesi için önerilmektedir.

Anahtar Kelimeler: Laparoskopik hernioplasti, total ekstraperitoneal preperitoneal hernioplasti, posterior rektus kanalı, rektus fasya, posterior rektus kılıfı, transversalis fasya

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ORIGINAL ARTICLE
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Abdominal palpation and percussion maneuvers do not affect bowel sounds

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ABSTRACT

Objective: Medical textbooks suggest that the frequency of bowel sounds may be altered by performing auscultation after palpation or percussion. We hypothesize that the frequency of bowel sounds is not affected by the order of abdominal examination.

Material and Methods: Both healthy volunteers (n= 80) and patients (n= 100) were enrolled in this crossover randomized study. Two different examination orders, one as inspection, palpation, percussion, auscultation (IPPA) and the other order as inspection, auscultation, palpation, percussion (IAPP) were used by two observers, one of which was blinded to the order of the physical examination and only performed auscultation. Bowel motilities of 40 participants were analyzed with duplex Doppler USG by a radiologist. The effects of changing the order of abdominal examination and palpation-percussion maneuvers on the frequency of bowel sounds were evaluated.

Results: Gender distribution was similar between the healthy patients and controls, and mean age of the entire study population was 47 (18-60) years. Differences between the mean bowel sound frequencies for abdominal examinations in order IPPA-IAPP versus IAPP-IPPA were evaluated for both healthy subjects and the patients. There were no differences between the first and second listening, nor were there differences between examinations performed in either order. Duplex Doppler Ultrasonographic (USG) assessments were performed on 20 healthy subjects and 20 patients before and after palpation and percussion; there were no statistically significant differences between the two listenings (p= 0.694).

Conclusion: According to both abdominal examinations and Doppler USG, the order of auscultation, whether performed before or after palpation or percussion, did not change the frequency of bowel sounds in this subject population.

Keywords: Abdominal examination, bowel sounds, physical examination order

INTRODUCTION

History and physical examination are essential in treating patients across all medical fields. They are the most important and valuable stages in the practice of medicine. Further, they are often the first interaction between patient and doctor; if clinicians properly perform these steps, they can provide all of the information required for further diagnostics and appropriate therapies. Specifically, abdominal examination provides information regarding abdominal organs and structures (1-6).

It is recognized that auscultation provides information crucial to determining diseases of the respiratory and cardiovascular systems as well as the gastrointestinal tract. It was suggested early in the twentieth century that abdominal auscultation might indicate disorders of the gastrointestinal system (7). However, since then, little research has been done to define and specify the relationship between bowel sounds and their diagnostic value. In addition, there is uncertainty about the order in which auscultation should be performed during an ordinary abdominal examination. Classical textbooks claim that the accepted order of steps for an ordinary physical examination (i.e., inspection, palpation, percussion, and auscultation) should be changed for abdominal examinations because palpation or percussion before auscultation may affect the frequency of bowel sounds. In this study, we aimed to determine whether

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or not the order of the physical examination steps causes changes in the frequency of bowel sounds.

MATERIAL and METHODS

This study included healthy volunteers and patients admitted to the Ankara University Faculty of Medicine, Department of General Surgery. One hundred healthy volunteers and 120 eligible patients were included into this study between February 2014 and June 2014. Inclusion criteria for the healthy volunteers were as follows: not having any gastrointestinal system (GIS) disease, defecating a maximum of twice a day, not using any medication that affects the GIS, not having undergone any operation, and being between the ages of 18 and 60 years old. The same criteria were also applied to the patients admitted to the hospital for surgery because of cholelithiasis (n= 30), euthyroid multinodular goiter (n= 23), breast mass (n= 32) and inguinal hernia (n= 25). Duplex Doppler Ultrasonographic (USG) (Siemens G60, Siemens, Erlangen, Germany) assessments were performed on 20 healthy volunteers and 20 patients.

This study was approved by the Ankara University Faculty of Medicine "Clinical Research Ethics Committee" [Date: 27th January 2014, Number: 02-60-14]. All subjects provided informed consent prior to the start of the study.

Study Design

This was a crossover randomized trial. Subjects (healthy volunteers = 80; patients = 100) were randomized via a random number generator program to receive the first abdominal examination in order inspection, palpation, percussion, auscultation (IPPA); healthy volunteers = 40, patients = 50 or order inspection, auscultation, palpation, percussion (IAPP); healthy volunteers = 40, patients = 50. This was followed by a "wash-out" period of one-hour and a crossover second examination in the other order. Physical examination was performed at least two and a half hours postprandially, and auscultation was performed for two minutes on each subject. For both the healthy controls and patients, an observer who was blinded to the physical examination order noted the bowel sound frequency.

Further, the effects of the order of physical examination were evaluated by abdominal ultrasonography (USG) and duplex Doppler USG in healthy volunteers (n= 20) and patients (n= 20).

Abdominal Examination

Subjects were examined in the supine position. Two third-year medical students who were trained in abdominal examination (both had previous experience on more than 50 healthy volunteers and patients) performed the examinations. One of the medical students ("the observer") performed the step-by-step physical examination in order IPPA or IAPP, but the other medical student ("the blind observer") joined only for the auscultation stage. The bowel sounds for each subject were listened to with Littman stethoscopes (3M, Littmann, USA) in one quadrant for two minutes by both the research student performing the whole exam and the blinded student.

Doppler USG

Duplex Doppler USG allowed for the visualization of bowel motility and at the same time allowed us to obtain the Doppler signals created by the motility of the bowel wall. Doppler signals were counted for one minute by a radiology specialist from Ankara University Faculty of Medicine Department of Radiology. The radiologist was blinded to the research protocol. The order of USG examination was as follows: first duplex Doppler USG – palpation – percussion – second duplex Doppler USG.

Sample Size

The sample size was calculated based on the non-inferiority between order IPPA/IAPP and order IAPP/IPPA in terms of the mean bowel sound frequency. When the true difference between the means was assumed to be zero, the margin of non-inferiority was selected as -0.5, and the significance level (a) of the test was 0.05. Group sample sizes of 51 and 51 achieved 81% power to detect non-inferiority using a one-sided, two-sample t-test.

Statistical Analysis

The agreement between observers ("the observer" vs. "the blind observer") was calculated as the intraclass correlation coefficient (ICC) with a 95% confidence interval (CI). The effect of the order of the abdominal physical examination on bowel sound frequency was evaluated by a repeated measures analysis of variance (ANOVA) and a paired t test. Descriptive statistics were presented as Mean ± standard deviation (SD). Values of $p< 0.05$ were considered statistically significant.

RESULTS

Abdominal examination analyses were performed on 80 healthy subjects and 100 patients. Genders were equally distributed among both healthy subjects and patients. Mean age and body mass index of the entire study population were 47 (18-60) years and 27 (21-42) BMI.

The agreement of auscultation between observers ("the observer" vs. "the blind observer") was determined to be good (ICC of 0.710 [95% CI: 0.612-0.784] for the first listening (a) and 0.773 [95% CI: 0.696-0.831] for the second listening (b).

The differences in mean bowel frequencies between the groups that were examined in order IPPA/IAPP versus order IAPP/IPPA were evaluated for both the healthy volunteers and the patients. Mean bowel sound frequencies were a little higher in subjects examined with the IAPP/IPAA, order, at both first and second listening, but the differences did not reach statistical significance (Table 1).

Duplex Doppler USG assessments were performed on 20 healthy subjects (10 females) and 20 patients (11 females). When Doppler USG assessments were evaluated for both groups, de-

Table 1. Comparison of the groups in terms of listening findings

Group	Listening	Order	Mean ± SD$^{\beta}$	Factor*	p
Patients (n= 100)	First listening (a)	**IPPA**/IAPP	13.84 ± 2.63	Listening	0.973
		IAPP/IPPA	14.12 ± 2.95	Order	0.468
	Second listening (b)	IPPA/**IAPP**	13.84 ± 2.22	Listening* Order	0.973
		IAPP/**IPPA**	14.14 ± 2.03		
Healthy volunteers (n= 80)	First listening (a)	**IPPA**/IAPP	14.85 ± 3.26	Listening	0.748
		IAPP/IPPA	15.73 ± 3.78	Order	0.068
	Second listening (b)	IPPA/**IAPP**	14.38 ± 3.48	Listening* Order	0.431
		IAPP/**IPPA**	15.93 ± 3.45		
Overall (n= 180)	First listening (a)	**IPPA**/IAPP	14.29 ± 2.95	Listening	0.824
		IAPP/IPPA	14.83 ± 3.42	Order	0.065
	Second listening (b)	IPPA/**IAPP**	14.08 ± 2.85	Listening* Order	0.535
		IAPP/IPPA	14.93 ± 2.88		

SD: Standard deviation.
* Factor corresponds to the variability sources in repeated measures ANOVA. The "listening", "order" and "listening*order" refer to time effect, group effect, time*group interaction effect, respectively.
$^{\beta}$ mean bowel sounds with in 2 min.

Table 2. The results of Doppler USG assessments by group

Group	First listening$^{\alpha}$	Second listening$^{\alpha}$	p
Patients (n= 20)	6.85 ± 4.07 [6 (1-17)]	6.85 ± 4.72 [6.5 (0-20)]	1.000
Healthy volunteers (n= 20)	8.15 ± 3.56 [8 (3-18)]	8.15 ± 5.11 [8 (1-22)]	1.000

α: Mean bowel sound assessed by Doppler USG within one minute.

scriptive statistics {mean ± SD [median (minimum-maximum)]} of the first and second listening were 7.50 ± 3.83 [7 (1-18)] and 7.50 ± 4.90 [7 (0-22)], respectively (p= 0.694). Group-based results are presented in Table 2.

DISCUSSION

Despite developing technologies, physical examination still plays the most important role in the diagnosis and treatment of the diseases today. It is accepted that all laboratory, imaging, and biological tests only make sense when performed in conjunction with physical examination. In other words, laboratory and imaging techniques are only of value in cases where there is accordance between the tests and clinical physical examination.

Historically, physical examinations were performed in the order of inspection, palpation, percussion, and auscultation. However, the order for abdominal physical examination has recently been changed to inspection, auscultation, palpation, and percussion since it has been suggested that performing auscultation prior to palpation and percussion maneuvers may prevent possible effects on bowel sounds. Most of the medical faculties all over the world currently use and teach this order as a standard of care.

Reviewing the literature, we realized that there were scarce and inconsistent publications on the value of auscultation. Moreover, none investigated the relationship between the order of the physical examination and bowel motility. Our current randomized crossover study revealed that palpation and percussion maneuvers had no negative impact on the results obtained during auscultation in healthy subjects and patients without GIS disease. In addition, the results of the Duplex-Doppler ultrasonography, an acceptable method for evaluating intestinal motility (8), also supported our findings. Thus, our results indicate that it is not the order of physical examination that is crucial step for confirming the diagnosis but precise history and physical examination.

Although the auscultation of bowel sounds is considered an essential component of an adequate physical examination, its clinical value remains largely unstudied and subjective. It is now more than 100 years since Cannon described the rhythmic bowel sounds and their possible relationship with intestinal disorders (7), however there is little published information regarding the value of auscultation, and contradictory findings exist in the literature (9). Gu et al. (10) have concluded that the auscultation of bowel sounds is useful, especially in detecting ileus with a high positive predictive value. Similarly, Sugrue et al. (11) have found that the sound duration, interval and amplitude all significantly increased in bowel obstruction when compared to control subjects. In contrast, Ching & Tan have assessed the spectral analysis of bowel

sounds in intestinal obstruction using an electronic stethoscope. They found that bowel sound characteristics were not different among patients with acute, subacute or no intestinal obstruction using the commonly compared parameters including sound duration, sound-to-sound interval, and dominant and peak frequencies (12). In another study, the authors concluded that auscultation of bowel sounds is not a useful clinical practice when differentiating patients with normal versus pat hologic bowel sounds (13). This has been echoed in other studies as well (14-16).

Furthermore, peristaltic movements, and associated bowel sounds, can vary with the course of disease. For example, in diarrhea, peristaltic movements increase occasionally, but return to normal after defecation. In cases of bowel obstruction, bowel motility increases while trying to overcome the obstacle, but after a while, there is a reduction or a stoppage of bowel motility due to tired intestinal muscles and atony. Whereas further research needs to be done to clarify the clinical value of bowel sounds, it nevertheless remains an integral part of the physical exam as taught in medical schools.

The major disadvantage of this prospective randomized study is the lack of underlying GIS disease in the patients included in this study. We could not assess the importance of changing the order of physical examination in patients with intestinal obstruction since crossover randomization in such patients would be inappropriate.

CONCLUSION

The results of this study indicate that the order of physical examination does not make a significant difference in terms of bowel motility. Therefore, the order of physical examination is not important. This information will be helpful to both the tutors of medicine and the clinicians who perform abdominal examinations.

Ethics Committee Approval: This study was approved by the Ankara University Faculty of Medicine "Clinical Research Ethics Committee" [Date: 27th January 2014, Number: 02-60-14]. All subjects provided informed consent prior to the start of the study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Abdominal palpasyon ve perküsyon manevraları bağırsak seslerini etkilemez

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ÖZET

Giriş ve Amaç: Tıbbi ders kitapları, fizik muayenede oskültasyonun palpasyon veya perküsyondan sonra yapıldığında bağırsak seslerinin sıklığının değişebileceğini öne sürmektedir. Bu çalışmanın amacı, abdominal muayene sırasının bağırsak seslerinin sıklığını etkileyip etkilemediğini belirlemektir.

Gereç ve Yöntem: Bu randomize çalışmaya hem sağlıklı gönüllüler (n= 80) hem de hastalar (n= 100) dahil edildi. Biri inspeksiyon, palpasyon, perküsyon, oskültasyon (IPPA), diğeri inspeksiyon, oskültasyon, palpasyon, perküsyon (IAPP) olmak üzere iki farklı muayene sıralaması, biri fizik muayene sırasına göre kör olan ve sadece oskültasyon yapan iki gözlemci tarafından kullanıldı. Kırk katılımcının bağırsak hareketleri, bir radyolog tarafından dupleks Doppler ultrasonografi ile analiz edildi. Abdominal muayene sırasındaki değişiklik ve palpasyon perküsyon manevralarının bağırsak seslerinin sıklığı üzerindeki etkileri değerlendirildi.

Bulgular: Her iki grupta cinsiyet dağılımı benzerdi ve tüm çalışma popülasyonunun yaş ortalaması 47 (18-60) idi. Ortalama bağırsak ses frekansları farklı karın muayene sıraları olan sağlıklı ve hasta bireylerde değerlendirildi. İlk ve ikinci dinleme arasında hiçbir fark yoktu. Dupleks Doppler USG değerlendirmeleri 20 sağlıklı bireyde ve 20 hasta üzerinde palpasyon ve perküsyon öncesi ve sonrası yapıldı; iki grup arasında istatistiksel olarak anlamlı fark yoktu (p= 0.694).

Sonuç: Değerlendirilen gruplarda abdominal muayeneye ve Doppler USG'ye göre, oskültasyonun palpasyon ve perküsyondan önce veya sonra yapılmasının bağırsak seslerinin sıklığını değiştirmediği görüldü.

Anahtar Kelimeler: Karın muayenesi, bağırsak sesleri, Fiziksel muayene sırası

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ORIGINAL ARTICLE
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Investigating the effect of gold nanoparticles on hydatid cyst protoscolices under low-power green laser irradiation

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ABSTRACT

Objective: Various scolicidal agents are applied for the destruction of protoscolices in cysts media. Undesirable complications of the scolicidal agents limit the techniques to treat the cyst disease. Therefore, new non-toxic scolicidal agents are needed. Upon laser light irradiation, the photothermal gold nanoparticles (AuNPs) convert the absorbed laser light into heat through photothermal effect which kills the surrounding protoscolices by rising the temperature of the cysts media. In this study, we introduced biocompatible AuNPs as a non-toxic scolicidal agent to cure liver hydatid cysts.

Material and Methods: The protoscoleces were collected from the livers of naturally infected sheeps. In each experimental group, 1.5 mL suspensions of hydatid liquid containing protoscolices were added to test tubes. The test tubes were divided into five groups. Control, AuNPs only, Green laser only, High-dose AuNPs + laser and Low-dose AuNPs + laser groups. Two concentrations (0.4 and 0.8 mL) of AuNPs and three laser powers (30, 50, 150 mW) were applied for 30, 60 and 120 minutes to the groups. Then the ciysts liquid assessed under a light microscope and determined the viability of protoscoleces.

Results: Protoscolices in high-dose AuNPs group were destructed up to 89.30% deaths under 150 mW laser power for 120 minutes. However, negligible cell deaths were observed in cases where only AuNPs added or only laser irradiated groups. Increasing the dose of AuNPs or laser power or duration of aplication increased the protoscolosidal death rate.

Conclusion: In the study, we have successfully demonstrated that the AuNPs are an effective therapeutic and scolicidal agent to cure hydatid cyst disease under laser irradiation.

Keywords: Gold, nanoparticle, laser, hydatid cyst

INTRODUCTION

Cystic echinococcosis is a zoonosis disease characterized by the formation of cysts in the internal organs of most humans caused by the larvae of a tape worm called *Echinococcus granulosus* (EG) (1). In humans, this infection involves cyst evolution in the lungs, liver and other organs (2,3). In some cases, hydatid cysts are fatal. This disease occurs in many countries worldwide and poses major challenges to human health and economy (4).

There is no ideal non-invasive treatment to cure hydatid cyst disease. Current treatment methods for this disease in the liver are surgery, percutaneous aspiration, and drug treatment (mebendazole and albendazole) (5,6). Among these, Puncture-Aspiration-Injection-Reaspiration (PAIR) method, as a percutaneous aspiration treatment, has recently gained much attention as a superior method to treat the hydatid cyst disease, especially gharbi type 1,2 cysts (7). Various scolicidal agents including albendazole, 95% alcohol, hypertonic saline, hydrogen peroxide, silver nitrate, cetrimide and ethyl alcoholare used in PAIR method for the sterilization of the cyst contents (7). However, scolicidal agents lead to many complications and the most important adverse effects of these agents are sclerosis and chemical cholangitis (8-10). The undesirable complications of the scolicidal agents limit the PAIR technique to be a non-invasive method to treat the cyst disease (11). Therefore, new non-invasive scolicidal agents are desperately needed to cure hydatid cysts.

In this study, we introduced biocompatible photothermal gold nanoparticles (AuNPs) as a non-invasive scolicidal agent to treat liver hydatid cysts via PAIR meth-

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od (12). Upon laser light irradiation, the AuNPs absorb the light and convert into heat through photothermal effect which destructs the surrounding hydatid cystsby rising the temperature of the cysts media. We evaluated the scolicidal effect of AuNPs under different laser powers against protoscolices of hydatid cysts in this study.

MATERIAL and METHODS

Ethics approval for this study was granted by the ethical committee. The protoscoleces of *E. granulosus* were collected from the livers of naturally infected sheep and goats. In each experimental group, 1.5 mL suspensions of hydatid liquid containing protoscolices were added to 42 test tubes in total. All the experimental test tubes were randomly assigned to five groups. Each study was repeated five times.

Synthesis of Gold Nanoparticles (AuNPs)

The gold nanoparticles were produced by Turkevitch method (13). In typical synthesis, 1 mL of 12.7 mM aqueous chloroauric acid ($HAuCl_4$) solution was added to 49 mL of deionized water. The mixture was heated till boiling while stirring. After 5 minutes, 0.94 mL of 38.8 M trisodium citrate solution was added to the boiling mixture. Within 2-3 minutes, the color of the mixture turned to red. The mixture was stirred for 15 minutes and cooled to room temperature. The samples were centrifuged and washed several times with distilled water to generate AuNPs.

Collection of Protoscolices

The hydatid fluid was aspirated by a syringe and aseptically transferred in to a flask. This was centrifuged at 2500 rpm for 7 minutes by using centrifuge (Nuve NF 1200R multi-purpose centrifuge, Istanbul, Turkey) . The supernatant was discarded and the protoscoleces precipitates were washed two times with PBS (pH 7.2) solution. The number of protoscolices per ml was adjusted as 2×10^3 protoscolices in 0.9% NaCl solution with at least 90% viability rate. The viability of the protoscolices was confirmed by their flame cell motility and impermeability to 0.1% eosin solution under a light microscope. The cysts which did not have any protoscolices or sufficient number of live protoscolices were not included in the study.

Experiment Groups

Two concentrations (0.4 and 0.8 mL) of AuNPs and three laser powers (30, 50, 150 mW) were applied for 30, 60 and 120 minutes. 1.5 mL of each hydatid liquid was placed in test tubes and these hydatid liquids were gently mixed. The test tubes were divided into five groups. CNI 532 nm green laser (Changchun New Industries Optoelectronics Technology Co., Ltd. Jilin, China) was used as the laser source.

Groups: There were 42 test tubes in total. Each test was repeated five times. 42 test tubes were used for each repeat

Group C: (control group) There were 12 tubes in this group. This group is the test tubes containing hydatid liquid. No laser was applied and no AuNPs was added.

Group A: (AuNPs group only) There were 3 tubes in this group. AuNPs were added to test tubes containing hydatid liquid. No laser was applied. (AuNPs-30 min, AuNPs-60 min, AuNPs-120 min).

Group G: (Green laser group only) There were 9 tubes in this group. Test tubes containing hydatid liquid were only exposed to laser. AuNPs were not added to the test tubes. These test tubes were exposed to 30 mW (30 mW-30 min, 30 mW-60 min, 30 mW-120 min), 50 mW (50 mW-30 min, 50 mW-60 min, 50 mW-120 min) and 150 mW (150 mW-30 min, 150 mW-60 min, 150 mW-120 min) green lasers.

Group H: (High-dose AuNPs group) There were 9 tubes in this group. A high dose of AuNPs (0.8 mL) was added to the test tubes containing hydatid liquid. Then, these tubes were exposed to 30 mW (30 mW-30 min, 30 mW-60 min, 30 mW-120 min), 50 mW (50 mW-30 min, 50 mW-60 min, 50 mW-120 min) and 150 mW (150 mW-30 min, 150 mW-60 min, 150 mW-120 min) green lasers.

Group L: (Low-dose AuNPs group) There were 9 tubes in this group. A low dose of AuNPs (0.4 mL) was added to hydatid liquid containing test tubes. Then, these tubes were exposed to 30 mW (30 mW-30 min, 30 mW-60 min, 30 mW-120 min), 50 mW (50 mW-30 min, 50 mW-60 min, 50 mW-120 min) and 150 mW (150 mW-30 min, 150 mW-60 min, 150 mW-120 min) green lasers.

Processes of Exposed of Groups

Group A: 0.8 mL of AuNPs were added to all the test tubes containing 1.5 mL cyst fluid. Laser was not applied. These tubes were kept for 30, 60 and 120 minutes. At the end of the period, 1.5 mL of 1% Eosin Y was added to each test tubes and then the test tubes were kept in the incubator (37°C) for five minutes. After dyeing process completion, equal amounts of cells were taken from each test tube and then assessed under a light microscope.

Group G: AuNPs were not added to any of the test tubes containing 1.5 mL cyst fluid. A power of 30 mW, 50 mW or 150 mW green laser was applied for 30, 60, 120 minutes. At the end of the period, the test tubes were taken and 1.5 mL of 1% Eosin Y was added to each of the test tubes. After keeping these test tubes in the incubator (37°C) for five minutes, equal amounts of cells were taken from each test tube. These cell samples were assessed under a light microscope.

Group L: A low dose (0.4 mL) of AuNPs was added to all the test tubes having 1.5 mL of cyst fluid. A power of 30 mW, 50 mW or 150 mW green laser was applied for 30, 60, 120 minutes. At the end of the period, 1.5 mL of 1% Eosin Y was added to each test tubes and these test tubes were kept in the incubator (37°C) for five minutes. The dyeing process was completed. Equal amounts

of cells were taken from each test tube and these cell samples were assessed under a light microscope.

Group H: A high dose (0.8 mL) of AuNPs was added to all the test tubes containing 1.5 mL of cyst fluid. Laser power of 30 mW, 50 mW or 150 mW was applied for 30, 60 and 120 minutes. At the end of the period, the test tubes were taken and 1.5 mL of 1% Eosin Y was added to each test tubes. Then these were kept in the incubator (37°C) for five minutes for dyeing process. Equal amounts of cells were taken from each test tube and the samples were assessed under a light microscope.

Viability Test

Eosin exclusion test was used to determine the viability of protoscoleces (14). After exposure to the eosin 0.1% (1 g of eosin powder in 1000 mL distilled water), the alive and dead protoscoleces were analyzed. Alive protoscoleces remain colorless and show characteristic muscular movements and flame cell activity, while dead protoscoleces absorb eosin and have a red color.

Statistical Analysis

Mortality rate of protoscolices (%) = the number of dead protoscolices/total number of protoscolices x 100% (15).

All the experiments were performed in quintuplicate. Data collection was performed using Microsoft Excel 2007 (Microsoft, Remond, WA, USA), and statistical analysis was undertaken using Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, IL, USA) with the analysis of variance (ANOVA). Moreover, Tukey's Honest Significant Difference (HSD) test was used for categorical variables. Continuous variables were reported as the mean ± standard deviation. A value of $p< 0.01$ indicated significant differences between groups.

RESULTS

Results of Ex-Vivo Microbiological Examinations

Protoscolex death was only observed in the groups with AuNPs containing protoscolices in hydatid cyst liquid under laser irradiation (group L and group H) (Table 1). In these groups, the amount of cell deaths depends on the duration of laser irradiation and the laser power. Whenever the duration of the laser irradiation or laser power increases, the amount of cell deaths rises. For instance, protoscolices in group H were destructed up to 89.30 % deaths under 150 mW laser power for 120 minutes. However, negligible cell deaths were observed in cases where only AuNPs added or only laser irradiated samples which are group G and group A.

In conclusion, a significant increase for the number of protoscolices deaths in hydatid cyst liquid is observed whenever longer laser irradiation, higher laser power or higher amount of AuNPs is applied.

Statistical Analysis Results

Groups were compared according to their AuNPs doses and laser irradiation (low-dose AuNPs with laser, high-dose AuNPs with laser, only laser, and only AuNPs). The highest mean was associated with the high-dose AuNPs group (Group H), then the low-dose AuNP group (Group L) followed by only laser (Group G) and then only AuNP group (Group A) ($p< 0.01$).

In addition, the groups were also compared according to their processing times (30 min, 60 min, 120 min). The highest mean was associated with the 120 min process groups, followed by the 60 min process groups, and then the 30 min process groups ($p< 0.01$).

According to the power of the laser applied (30 mW, 50 mW, 150 mW), the groups were compared. The highest mean was associated with the 150 mW group, followed by the 50 mW group, and then 30 mW group.

When the AuNP dose, process time and laser power were taken into account, the highest average protoscolices deaths in hydatid cyst liquid was associated with the group H having high-dose AuNPs which exposed to 150 mW laser power for 120 minutes irradiation ($p< 0.01$) as shown in Figure 1. In contrast, the lowest average protoscolices deaths was associated with the group G or group A which are having AuNPs without any laser exposure or only laser irradiation without any AuNPs addition, respectively ($p< 0.01$) (Figure 2).

Table 1. The death rates of protoscolices in group L and group H

Death rates of protoscolices in Group L and Group H				
		30 min	**60 min**	**120 min**
30 mW	Group L	34.60%	41.60%	54.50%
	Group H	55.80%	58.00%	67.10%
50 mW	Group L	43.60%	52.20%	61.30%
	Group H	58.60%	64.80%	70.30%
150 mW	Group L	65.80%	71.70%	82.60%
	Group H	72.20%	78.60%	89.30%

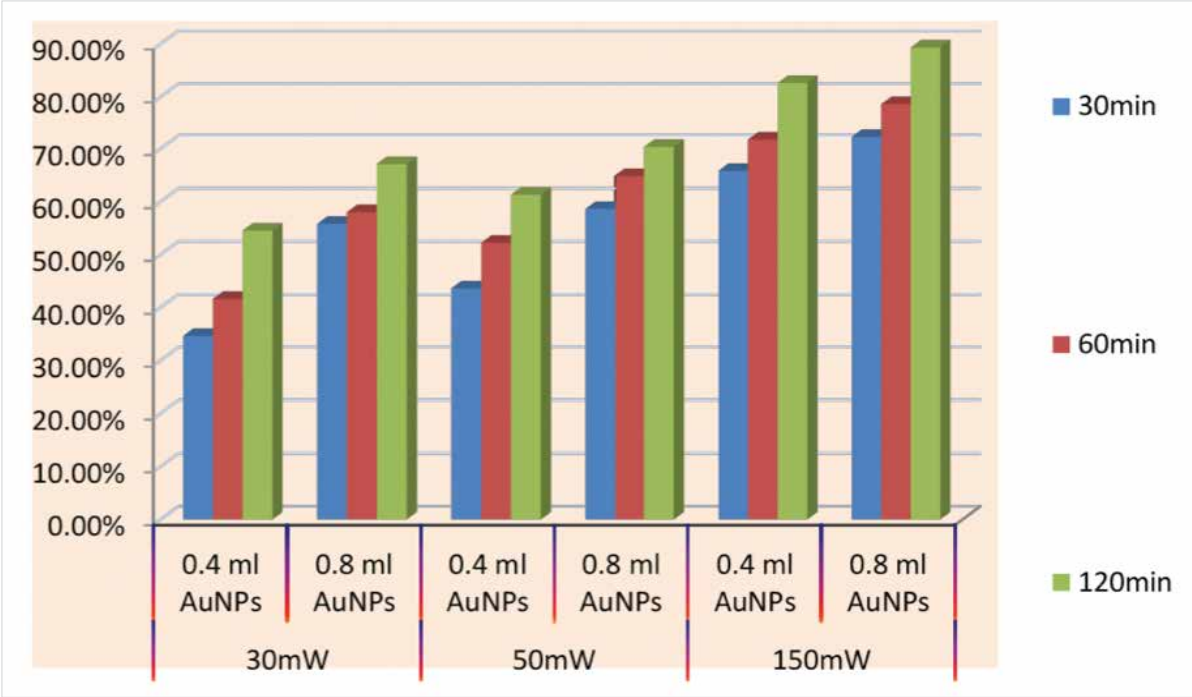

Figure 1. The death rates of protoscolices treated with laser (30 mW, 50 mW, 150 mW) and AuNPs (0.4 mL, 0.8 mL) in anisochrony (30 min, 60 min, 120 min).

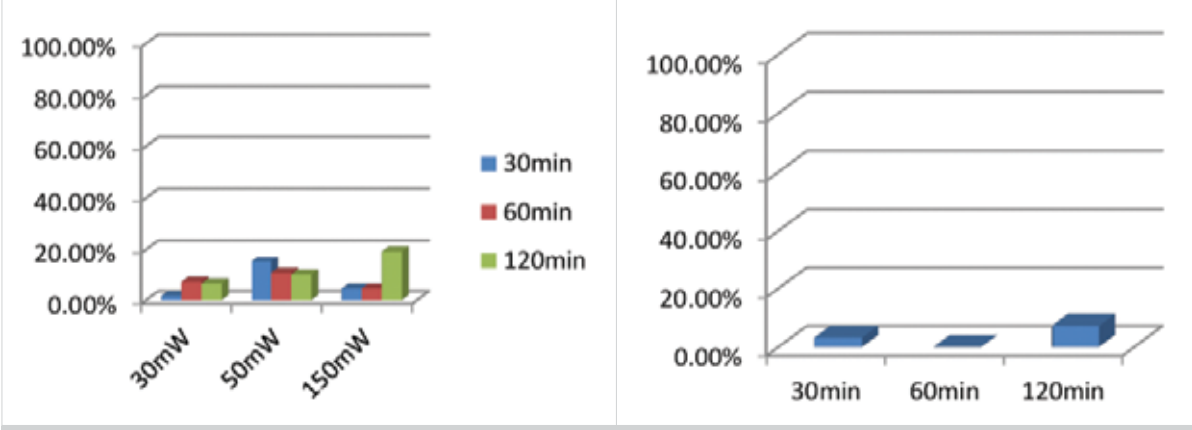

Figure 2. (Left) the death rates of protoscolices treated with laser solely (30 mW, 50 mW, 150 mW) for different durations (30 min, 60 min, 120 min); (right) the death rates of protoscolices treated with AuNPs only (0.4 mL, 0.8 mL) for different durations (30 min, 60 min, 120 min).

DISCUSSION

Hydatid cyst disease is an important and common public health problem worldwide. In the endemic areas of countries and regions such as Peru, Argentina, East Africa, Middle Asia and China, the disease affects 50 out of 100,000 people each year while its prevalence is between 5% and 10% (1,2).

The present optional therapies for hydatid cyst disease are problematic in many ways. Surgical methods are all invasive and come with the risk of recurrence and the rupture and spillage of the contents (14). Where chemotherapy is concerned, albendazole and mebendazole are the preferred drugs. However, their concentrations in the hydatid cyst are not sufficient to cure the disease because the cyst's wall is too thick (16). Clinical studies have shown that the medication used for treatment could not always kill the protoscoleces (17). Percutaneous aspiration, injection and reaspiration (PAIR) is a percutaneous technique which is a significant and versatile alternative for the conventional methods, especially in the treatment of early-stage cysts (18).

There is a desperate need for a scolicidal agent to be used in PAIR method to effectively cure hydatid cyst protoscoleces.

According to the literature, a large number of scolicidal agents are used in PAIR, such as; Albendazole, 95% alcohol, hypertonic saline, hydrogen peroxide, silver nitrate, cetrimide and ethyl alcohol. However, many of these agents have adverse effects, therefore, limit their usage in the treatment of hydatid cyst disease (19). Formalin was the first scolicidal agent used, however, it is not used today due to its toxic effect (20). Radiologists prefer using another scolicidal agent, ethyl alcohol, which is inflammable and volatile (21). This characteristic of ethyl alcohol has led to the restriction of its use in surgery. Also, ethyl alcoholcan damage the bile duct's epithelium, leading to sclerosing cholangitis (22). That is why, it is not used to treat hydatid cysts which have bile duct communication. In addition, due to low scolicidal efficiency and the resultant complications, the usage of hydrogen peroxide as a scolicidal agentin the treatment of hydatid disease is very limited (23). A disinfectant chemical, povidone-iodine (PVP-I), is also used as a scolicidal agent. The complications of PVP-I are PVP (polyvinlpyrrolidone) storage disease, renal shutdown and sclerosing serositis (23). Nowadays, most effective scolicidal agent frequently used is hypertonic saline. Hypertonic saline is nearly 100% effective on protoscolices (24); however, it could lead to hypernatremia, neurological side effects and intracranial bleeding (25). Furthermore, the use of hypertonic saline should be avoided in treatments ofcysts which open to the bile duct due to very high possibility to have chronic sclerosing cholangitis disease (20). Another effective scolicidal agent is cetrimide-chlorhexidine (Savlon) and it hasa scolicidal effect even a minimal usage of 0.1%. However, like hypertonic saline, cetrimide-chlorhexidine should also not be used to treat cysts associated with the bile duct (26). Although effective cure rate of scolicidal agents are present for the treatment of hydatid cyst protoscoleces, these agents possess very harmful adverse effects including chronic sclerosing cholangitis (12,14). Even if the surgeons are not willing to use these toxic agents, the usage of these agents is unfortunately a common practice in clinic due to deficiency of ideal non-toxic scolicidal agent (27). Therefore, there is an extreme need for a non-invasive agent which has a significant scolicidal effect to cure the hydatid cyst protoscoleces without any harmful effects and complications.

Anderson and Loveless have reported a successful destruction of protoscoleces, namely, *E. granulosus* protoscolices, by varying temperature in cyst media (28). In their study, different degrees of temperature were applied to protoscolices in cyst fluid from the lungs and livers of infected sheep. The durations of the protoscolices deaths were 16 days at 20°C, 8 days at 30°C, 4 days at 40°C, and 2 hours at 50°C. According to this study, high temperatures above 40°C effectively kill the protoscolices which is also reported in various studies in literature (29,30). As a result, a scolicidal agent which releases heat to the surroundings meaning increase the temperature of the protoscolices media above 40°C could be used as a new scolicidal agent to cure the protoscolices in cyst fluid.

In this study, non-toxic AuNPs was introduced and successfully applied as a new scolicidal agent to cure the hydatid cysts protoscolices in the liver. Under laser irradiation, the AuNPs is a heat generator which increase the temperature of the surroundings, protoscolices in this case, and eventually kill the protoscolices. Under different laser powers and irradiation durations, we evaluated the scolicidal effect of AuNPs against protoscolices of hydatid cysts on ex-vivo model.

Gold nanoparticles are considered as harmless, stable and biocompatible materials which are frequently used in medical research (15). Various reports in literature have shown that AuNPs do not possess anycytotoxic and genotoxic effects, and any known systematic or local side effects (31,32). Besides the inertness and non-toxic character, AuNPs have a unique property which is called "photothermal effect". Spherical AuNPs can transform the absorbed green laser light energy into heat energy through photothermal effect (33,34). The heat will dissipate into the surrounding media and this localized heating by using AuNPs can cause thermal cellular destruction (35,36). We benefit this destruction process in the treatment of protoscolices in liver hydatid cysts and kill this protoscolices via the temperature increase after localized heating by AuNPs. That is to say, this study facilitated the application of laser to AuNPs in order to rise the temperature of the cyst fluid which eventually cause the deaths of all the protoscolices.

In the present study, besides a control group (Group C), we used 4 different groups such as; only AuNPs added samples (Group A), only laser irradiation applied samples (Group G), low-dose AuNPs added and laser irradiated groups (Group L), high-dose AuNPs added and laser irradiated groups (Group H). We applied three different laser powers of 30 mW, 50 mW, and 150 mW for different durations (30 min, 60 min, 120 min). Due to the usage of low-power and harmless laser powers, we irradiated the cyst liquid containing protoscolices for longer periods in order to result a successful mortality. The experimental results show that scolicidal activity of AuNPswas increased by raising the laser power with higher concentrations of AuNP dose and extending the duration of irradiation process. These result a rise in temperature of the hydatid cysts media which kills protoscolicesin significant incidences of mortality. However, when only irradiation of laser or only inclusion of AuNPs to hydatid cysts liquid, there was only negligible deaths of protoscolices which is within the range of acceptable deviation.

CONCLUSION

We have successfully demonstrated the usage of AuNPs as a therapeutic and scolicidal agent to cure hydatid cyst disease under laser irradiation. The main advantages of AuNPs compared

with the other scolicidal agents are non-invasive and biocompatible scolicidal agent. Our results show that higher laser powers and AuNPs amounts with longer irradiation durations result effective destruction of protoscolices in liver hydatid cysts due to a sharp increase in temperature. AuNPs possess a scolicidal effect and could use in PAIR applications. Hence, this approach could produce a better treatment for various hydatid cyst diseases, even in the treatment of cysts associated with the bile duct.

Ethics Committee Approval: Ethics approval for this study was granted by the ethical committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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ORİJİNAL ÇALIŞMA-ÖZET
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Düşük güçte lazer uygulanmış altın nanoparçacıklarının hidatik kist protoskoleksleri üzerine etkisinin araştırılması

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ÖZET

Giriş ve Amaç: Hidatik kistin içindeki protoskoleksleri öldürmek için çeşitli skolosidal ajanlar kullanılmıştır. Skolosidal ajanların istenmeyen komplikasyonları, hidatik kistin tedavi yöntemini sınırlandırmaktadır. Bu nedenle vücuda zararlı olmayan yeni skolosidal ajanlara ihtiyaç duyulmaktadır. Fototermal altın nanopartikülleri (AuNPs) kist sıvısı içindeki protoskolekslerin etrafını sararak lazer ışını altında, ışınların enerjisini absorbe edip ısı enerjisine dönüştürmek suretiyle protoskoleksleri öldürmektedir. Çalışmada, biyo-uyumlu fototermal altın nanopartiküllerini (AuNPs) karaciğer hidatik kistlerini tedavi etmek için toksik olmayan bir skolosidal ajan olarak uyguladık.

Gereç ve Yöntem: Protoskoleksler infekte koyun karaciğerlerinden elde edildi. Her bir çalışma grubu için içinde 1,5 mL kist sıvısı içeren tüpler oluşturuldu. Tüpler 5 gruba ayrıldı. Kontrol grubu, sadece AuNPs eklenen grup, sadece lazer uygulanan grup, yüksek doz AuNPs eklenip lazer uygulanan grup, düşük doz AuNPs eklenip lazer uygulanan gruplar idi. İki farklı konsantrasyonda (0,4 ve 0,8 mL) AuNPs ve üç farklı güçte lazer (30, 50, 150 mW), 30, 60, 120 dakika sürelerle gruplara uygulandı. Daha sonra kist sıvıları ışık mikroskobu altında incelendi ve protoskolekslerin canlılıkları değerlendirildi.

Bulgular: Yüksek doz AuNPs eklenen ve 150 mW lazerin 120 dakika uygulandığı grupta %89.30 protoskoleks ölümü sağlandı. Fakat sadece AuNPs eklenen ve sadece lazer uygulanan gruplarda anlamlı ölüm oranları ile karşılaşılmadı. AuNPs dozunun, lazer gücünün veya sürenin arttırılması ile protoskoleks ölümünün de arttığı tespit edildi.

Sonuç: Çalışmada, AuNPs'nin lazer ışını altında, hidatik kist tedavisinde etkili bir skolosidal ajan olabildiği başarılı bir şekilde gösterildi.

Anahtar Kelimeler: Altın, nanoparçacık, lazer, hidatik kist

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CASE SERIES
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Adult morgagni hernia: a single center experience of 5 cases and review of literature

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ABSTRACT

Morgagni hernia is a rare congenital anomaly arising through the fusion defect between the septum transversum and sternum. Diagnosis is usually confusing as the presentation may be asymptomatic as well as with respiratory symptoms, abdominal and/or retrosternal pain, abdominal fullness or gastrointestinal obstruction. In this paper, we discussed the clinical presentation and management of this rare situation with five consecutive cases. Between 2009 and 2015, five cases underwent surgery for Morgagni hernia (3 laparoscopic and 2 open repair); one patient had recurrent hernia after 7 months from laparoscopic surgery. This case is the first recurrence in the literature after laparoscopic repair in an adult group. In Morgagni hernias, the only treatment is surgery, which can be performed by transthoracic, transabdominal, laparoscopic or thoracoscopic approaches. The issues of using mesh and reducing the hernia sac are still controversial.

Keywords: Laparoscopic repair, morgagni hernia, diafragmatic hernia

INTRODUCTION

Morgagni hernia was first described by an Italian anatomist and pathologist Giovanni Morgagni in 1769 (1,2). This para-retrosternal defect between the septum transversum and sternum is called foramen larrey or foramen Morgagni (1). Incidence is 1/2000-5000 and Morgagni hernia constitutes 3-4% of all congenital diaphragmatic hernias (3). Abdominal organs herniate to the thorax through a retrosternal diaphragmatic defect from the right side in 90% of the cases. Pericardium has been considered to be responsible for the decreased incidence of left-sided Morgagni hernia. Bilateral cases have been reported uncommonly (4). Increased intraabdominal pressure have been associated with Morgagni hernia, especially in the adult age group.

Chest x-ray and thorax computed tomography (CT) are helpful in diagnosis. Omentum, transvers colon and less often stomach and small bowel are herniating organs to thorax. Treatment is surgery which can be performed with transthoracic, transabdominal, laparoscopic or thoracoscopic approaches.

Our aim in this study was to discuss the clinical presentation and management of these rare cases in adults.

CASE REPORTS

All patients gave their informed consent about the publishing of their operation data and documents for scientific purposes.

Case 1

A 74-year-old female patient presented with abdominal pain, nausea, vomiting, and anorexia. Her chest x-ray showed a right paracardiac opacity (Figure 1A). Morgagni's hernia was suspected and confirmed by thoracoabdominal CT (Figure 1B). The patient was operated on through an upper midline incision and found to have bilateral Morgagni hernia. There were hernia sacs on both sides (Figure 1C). The left one contained the stomach and large bowel and the right one contained the omentum. The contents were reduced and the sacs were not excised. Repair of both defects was carried out using expanded polytetrafluoroethylene (E-PTFE) mesh (Figure 1D).

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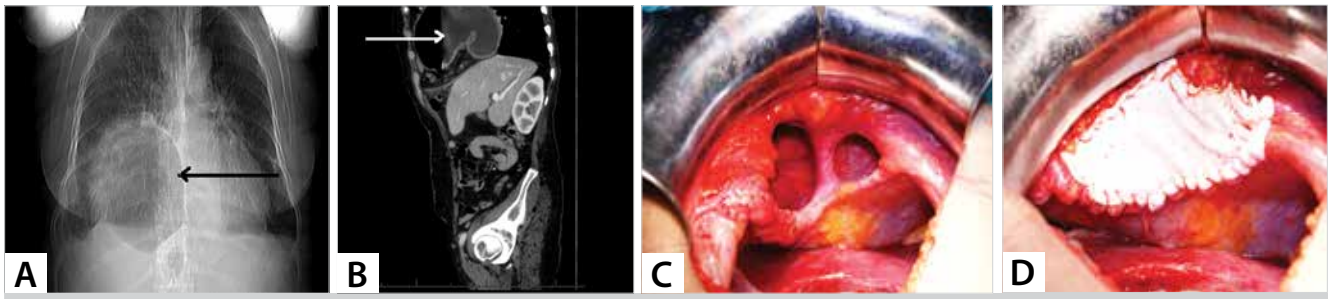

Figure 1. A. Right paracardiac opacity in chest x-ray. **B.** Herniated stomach in left Morgagni hernia sac. **C.** Bilateral Morgagni defects. **D.** Repair with ePTFE mesh.

Post-operatively, the patient did well and was discharged on postoperative day 4. On postoperative day 32, the patient presented with seroma in the repaired defect. The fluid was aspirated under ultrasound guidance. No further complications including recurrent seroma occurred during 63 months of follow up.

Case 2

A 62-year-old woman was referred from another institute with the diagnosis of Morgagni hernia. Her complaints were dyspnea, nausea, vomiting and episodic right flank pain. Thoracoabdominal CT revealed Morgagni hernia, cholelithiasis and umbilical hernia. The patient was considered for laparoscopic repair. Gastric and omental herniation to the thorax via a 4-cm diaphragmatic unilateral defect was seen in laparoscopic exploration (Figure 2A). The stomach and omentum were reduced into the abdominal cavity, and the diaphragmatic defect was repaired with polypropylene stitches (Figures 2B, 2C and 2D). Hernia sac was not resected, and a silicon drain was placed in the sac. The operation was completed after laparoscopic cholecystectomy and umbilical hernia repair. The patient was discharged on postoperative day 5. She has been followed for 58 months without any complications.

Case 3

A 63-year-old female patient consulted to the emergency department with abdominal pain, nausea and vomiting. The patient had signs of ileus on abdominal x-ray, and there were no signs of free subdiaphragmatic air but diaphragmatic hernia in chest x-ray. Thoracoabdominal CT revealed ileal and colonic dilatation and diaphragmatic hernia. Exploration through an upper midline incision revealed dilated ileal segments in accordance with the ileus and a 9-cm unilateral diaphragmatic hernia defect consisting of the omentum and transverse colon. The colon and omentum were reduced into the abdominal cavity, and the diaphragmatic defect was repaired with no.1 polypropylene stitches. The ptient was discharged uneventfully on postoperative day 5. No complication or recurrence was seen in the 44th month of follow up.

Case 4

A 63-year-old female patient was referred to our clinic with incidentally diagnosed diaphragma hernia in chest x-ray performed for her chest pain. The patient had had gastroesophageal reflux and grade-b esophagitis for 6 years in her medical history. Thoracoabdominal CT was compatible with Morgagni hernia. Laparoscopic exploration revealed thoracic herniation of transverse colon. Bilateral Morgagni defects of 6 cm on the right side and 3 cm on the left side were detected after reducing the colon. Hernia sac was not resected, and the defect was closed with no.1 polypropylene stitches. Laparoscopic nissen fundoplication was performed for gastroesophageal reflux. A silicon drain was placed in the hernia sac, and the operation was completed. The patient was discharged on postoperative day 6 uneventfully. On postoperative day 45, the patient was admitted with dyspnea. Chest x-ray revealed air-fluid level in the hernia sac and 200 cc seroma was drained with ultrasound guidance. Culture of the aspirated fluid was negative. Seroma did not recur but 6 months later, the patient consulted for dyspnea. Recurrent hernia was detected on thoracoabdominal CT. Open repair with E-PTFE mesh was performed. During the 36 months after second surgery, no further problem was seen.

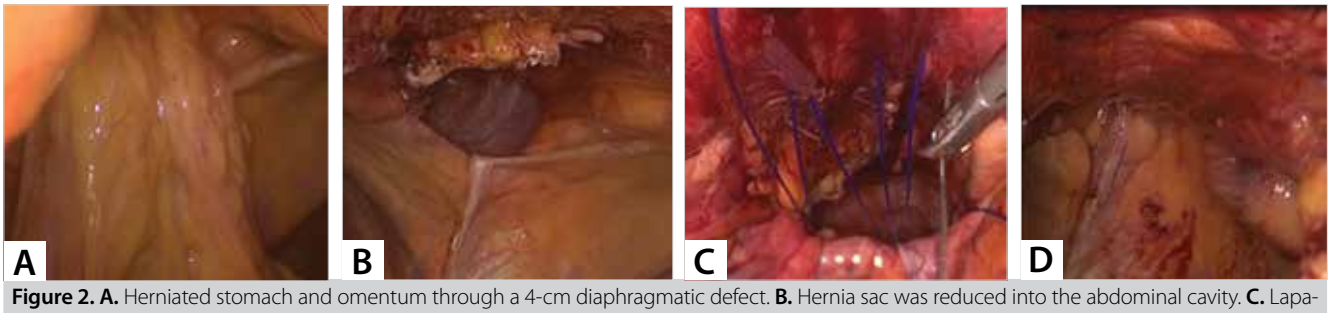

Figure 2. A. Herniated stomach and omentum through a 4-cm diaphragmatic defect. **B.** Hernia sac was reduced into the abdominal cavity. **C.** Laparoscopic primary closure of the defect with polypropylene stitches. **D.** Intraoperative view after primary repair.

Case 5

A 51-year-old male patient presented with abdominal distention and vomiting. The patient had hypertension in his medical history. Chest x-ray showed air-fluid levels over the diaphragm compatible with herniated intestinal segments to the thorax. Laparoscopy revealed a left Morgagni hernia consisting of the transverse colon. The sac was reduced, and the defect was closed primarily with no.1 polypropylene stitches. A silicone drain was placed in the hernia sac. The patient was discharged on postoperative day 5 and followed up uneventfully during 15 months.

DISCUSSION

The classical Bochdalek hernia accounts for nearly 80% of all congenital diaphragm hernias, whereas Morgagni hernia constitutes about 3-4% of both children and adult diaphragm hernias (3). In Morgagni hernia, the defect is usually small and complaints are related to the size and content of the hernia. The content of the herniation most frequently includes the omentum and colon segments; however, stomach, liver and small intestines might also be herniated (5). Morgagni hernias are right sided in 90% of the cases, left sided in 8% and bilateral in 2% (4). In our cases, three of the 5 patients had unilateral and the other 2 patients had bilateral hernias.

Series have eported that 62% of the cases are female, and mean age of diagnosis is 53 (5). Four of the five cases were female, and the mean age at diagnosis was 62.6 (51-74) years in our series.

The symptomatology of Morgagni hernia is completely variable; the cases can be asymptomatic or may present with a clinical picture of acute respiratory distress (6). In diaphragmatic hernia cases, a decrease in the respiratory sounds or presence of colonic sounds on chest examination is a significant finding in diagnosis. All of our patients had symptoms related with hernia varying between retrosternal pain and ileus. Chest x-ray and thorax CT are useful in diagnosis (7). Signs in chest x-ray may mimic mediastinal mass in some cases with the hernia sac consisting of the omentum alone. We preferred to see thoracoabdominal CT to confirm diagnosis after chest x-ray.

Surgery is the curative treatment in Morgagni hernia. Transthoracic, transabdominal and laparoscopic approaches may be performed. Thoracoscopic repair has reported in two patients from the UK (8-9). Laparoscopic approaches are more favored with less complication and hospital stay rates. Open surgery also has some advantages: reduction of the herniated organs is easier. In addition, functional status and circulation of the organs may be evaluated better in open surgery and it also provides to detect a bilateral Morgagni defect easily. Besides thoracic surgery allows easier dissection of mediastinal and pleural adhesions (5,10-11). We performed two transabdominal and 3 laparoscopic surgery.

About 95% of the Morgagni hernias comprise a hernia sac. Resection of the hernia sac is still controversial. Some authors suggest leaving the sac in order to avoid massive pneumomediastinum and injury of the phrenic nerve (12). Rau et al. have remarked that leaving the sac may result in thoracic cystic lesions and recommended the resection of the hernia sac (13). We preferred to leave the sac in all cases so as to avoid pneumothorax and nerve injury.

In the literature, transabdominal approaches have been performed by primary repair in 88% of the cases and mesh repair was preferred in 6%. Primary and mesh repair rates have been reported as 29% and 64%, respectively, in laparoscopic approaches (5).

Thoman et al. have suggested that mesh repair may be favorable in defects larger than 20-30 cm^2 (14). The results of primary and mesh repairs are similar (5). Recurrence after transthoracic Morgagni hernia repair in adults has been reported in one patient. Other surgical methods have not been reported for recurrence in adults (5), and Case Four in our study is the first recurrence in the literature after laparoscopic repair in the adult group. Recurrence in five of 12 children has been reported in a laparoscopic repair series (15). We performed four primary stitching (3 laparoscopic) and one mesh repair (open transabdominal). Recurrence of a laparoscopic primary repair was restored with open mesh repair.

Complications after transabdominal surgery are pleural effusion, surgical site infection, atelectasis, deep venous thrombosis and pulmonary embolism. Pneumonia and sepsis have been reported after transthoracic surgery. Thirty-day mortality has been reported in four patients after transabdominal surgery (5).

In our patients, mean hospital stay was five days. Thirty-day mortality was not seen. Seroma was seen on postoperative days 32 and 45 in two patients after one transabdominal and one laparoscopic surgery and did not recur after drainage. In our clinical experience, one patient had recurrent hernia after 7 months from laparoscopic surgery (case 4) and we performed open redo repair.

CONCLUSION

Morgagni hernia is a rare type of hernia especially in adult patients but may cause intestinal obstruction and may present as an emergency due to the strangulation of the herniating viscera. Once diagnosed, surgery should be recommended even in asymptomatic patients in order to prevent the risk of complications. Different surgical techniques can be used efficiently in Morgagni hernia repair, and the choice of surgical procedure is based on peculiar criteria of the patient.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.A., K.A.; Design - C.A., K.A., S.B.; Supervision - C.A., Ç.A., Z.S.D.; Resource - C.A., K.A., Z.S.D., S.B.; Materials - C.A., K.A., Ç.A.; Data

Collection and/or Processing - C.A., Ç.A., Z.S.D.; Analysis and/or Interpretation - C.A., Ç.A.; Literature Search - C.A., K.A., Ç.A.; Writing Manuscript - C.A., K.A., Ç.A., Z.S.D., S.B.; Critical Reviews - C.A., S.B.

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OLGU SERİSİ-ÖZET
Turk J Surg 2019; 35 (4): 321-324

Erişkin Morgagni hernileri: tek merkezden 5 olguluk deneyim ve literatürün gözden geçirilmesi

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ÖZET

Morgagni hernisi nadir olarak karşılaşılan; bir konjenital anomali olup septum transversum ve sternum arasındaki yetersiz füzyon sonucunda oluşur. Tanısı oldukça güçtür, hastalar asemptomatik olabileceği gibi solunum sistemine ait şikayetler, ağrı, dolgunluk hissi ve gastrointestinal sisteme ait obstruksiyon bulgularıyla başvurabilirler. Bu olgu serisinde Morgagni hernisi nedeniyle 2009-2015 yılları arasında kliniğimizde üçü laparoskopik, ikisi açık yöntemle opere edilen beş olgumuz sunulmuştur. Laparoskopik onarım sonrası bir hastamızda yedinci ayda nüks gelişmiştir, bu olgu literatürdeki erişkin gruptaki ilk laparoskopik onarım sonrası nüks olması nedeniyle önemlidir. Morgagni hernilerinde tek tedavi seçeneği ameliyattır. Cerrahi transtorakal, transabdominal, laparoskopik veya torakoskopik olarak uygulanabilir. Meş kullanımı ve herni kesesinin çıkarılması konularında tartışma sürmektedir.

Anahtar Kelimeler: Morgagni fıtığı, diyafram fıtığı, laparoskopik onarım

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CASE SERIES
Turk J Surg 2019; 35 (4): 325-328

Colon resection for endometriosis

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ABSTRACT

Endometriosis affects the women during reproductive period and can cause functional disorders. Sometimes general surgical intervention is necessary because of disease boundary. Especially the sigmoid colon and rectum are affected due to the close neighboring. In such a case, treatment must be individualized according to the patient and symptoms. If the lesion has penetrated the entire bowel wall, bowel resection may be inevitable. Laparoscopic resection of the sigmoid colon or rectum can be performed safely in this situation. When laparoscopic resection cannot be possible because of technical difficulties, open resection may be performed for treatment. Here we present two cases, one open and one laparoscopic colon resection performed due to endometriosis.

Keywords: Endometriosis, colon resection , hysterectomy

INTRODUCTION

Endometriosis, the presence of endometrial cells outside of the uterine cavity, is a benign condition which affects women during the reproductive period (1). This disease affects approximately 10 % of the general population, and 25%-50% of the infertile women suffer from this condition (2,3). Treatment must be individualized according to the patient's age, fertility status, symptoms and extensity of the disease. Full-thickness excision, shaving or resection are the treatment of choice in case of bowel involvement. This study aimed to present two cases of deeply infiltrative endometriosis treated by hysterectomy, oophorectomy, and anterior resection due to bowel involvement which causes luminal narrowing.

CASE REPORTS

Case 1

A 39-year-old female was admitted to the gynecology clinic because of menstrual pelvic pain and constipation. The patient's medical history included medical treatment and four times open surgery for deeply infiltrative endometriosis. Pelvic magnetic resonance imaging revealed multiloculated cystic mass with a close neighboring to the sigmoid colon (Figure1,2).

As the patient stated that she had completed childbearing and desired voluntary sterility, total abdominal hysterectomy, bilateral salpingo-oophorectomy and anterior resection were performed. Patient's postoperative course was uneventful and was discharged from hospital postoperative on the sixth day. The pathology report was compatible with endometriosis invading the serosa, subserosa and muscular layers of a colon. Colonic mucosa was intact. One year after surgery, the patient has no complaints.

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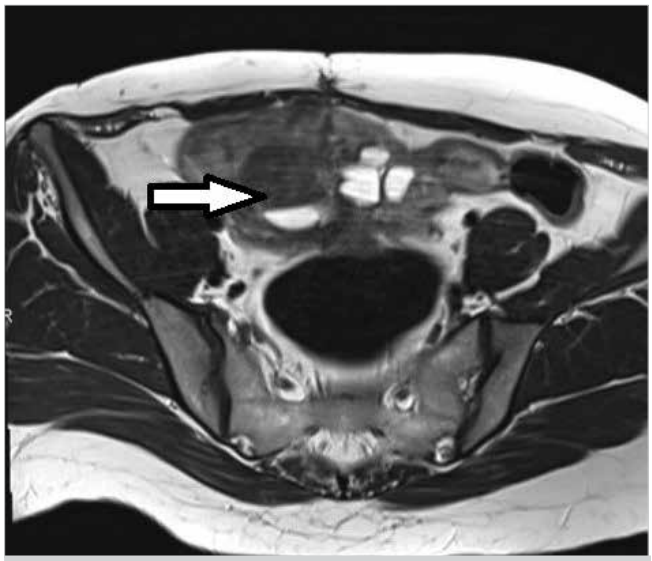

Figure 1. Ax T2: Heterogenous, hyperintense, multiloculated complex cystic mass is present. The fat plane effected between the cyst and the neighboring sigmoid colon and uterus.

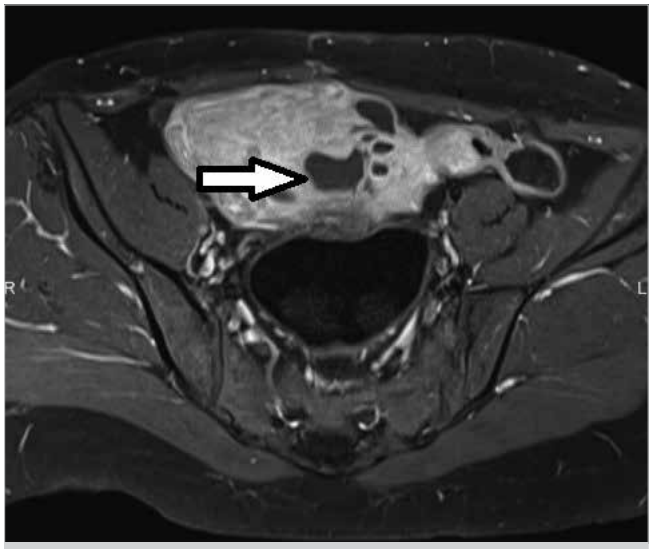

Figure 2. Ax T1: postcontrast FS T1: Image shows the linear enhancement of the walls of the multiloculated cystic mass.

Case 2

A 42-year-old female was admitted to the gynecology clinic because of a recently diagnosed right ovarian cyst. Laparoscopic right oophorectomy and bilateral salpingectomy were performed. Pathology result was endometriotic cyst for all specimens. Six months later, colonoscopy was performed due to constipation and bowel habit changes, and luminal restriction due to extrinsic compression was diagnosed. The colonoscope could not pass this restricted segment (Figure 3).

Magnetic resonance imaging showed loculated endometriosis focus which pushed the uterus anteriorly to a close neighboring with the colon (Figure 4,5).

Figure 3. Appearance of colonic compression due to deeply invasive endometriosis during colonoscopy.

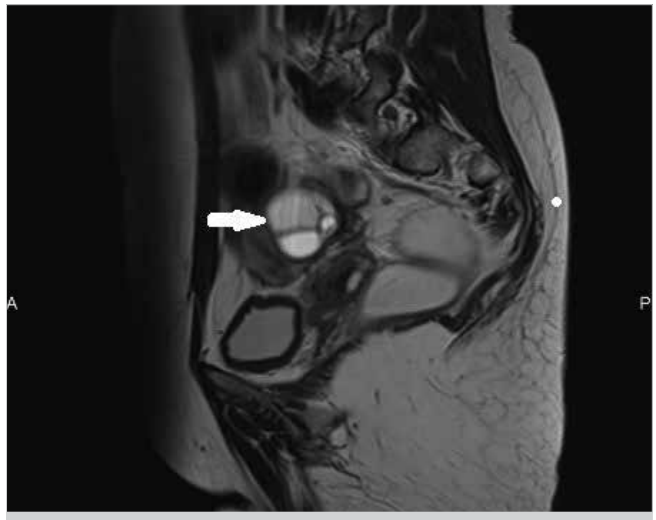

Figure 4. Sag. T2 WI: Cystic mass has T1 hyperintense T2 mild hyperintense, dense content at some locations.

As the patient stated that she had completed childbearing and desired voluntary sterility, laparoscopic hysterectomy, left oophorectomy and anterior resection were performed. Patient's postoperative course was uneventful and was discharged from hospital six days after surgery. Eight months after this operation, the patient was operated on for acute cholecystitis because of a recently diagnosed gall bladder stone, and during laparoscopic exploration, no endometriosis foci were present. The patient has no complaints two years after surgery. Pathology of the patient reported as endometriosis restricting the colon lumen at two different points.

Informed consent obtained from both of the patients.

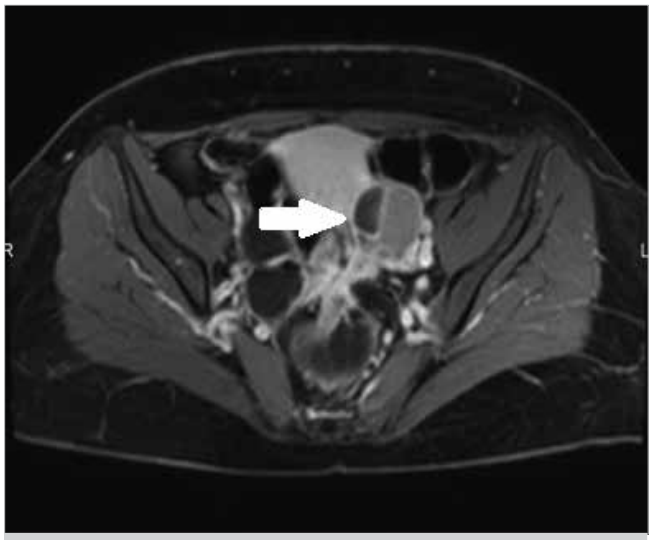

Figure 5. Ax, postcontrast T1 FS image: Linear wall enhancement at the dense loculated component. The mass pushes the uterus anteriorly.

DISCUSSION

Endometriosis has three clinical forms as peritoneal endometriosis, endometriotic ovarian cysts (endometriomas) and a deeply infiltrative form. Among these forms, deeply infiltrative endometriosis (DIE) is the most aggressive and problematic one.

DIE is defined as the infiltration of the peritoneum more than 5mm (4). Pelvis is the most-frequent location and approximately 24% of the patients have sigmoid colon or rectum involvement (5). This disease can cause different symptoms, and treatment must be individualized according to symptoms, clinical condition and fertility status (6). Menstrual irregularities, dysmenorrhea, dyspareunia, chronic pelvic pain, mictalgia, and dyschezia are the main symptoms of deeply infiltrative endometriosis. In conjunction with these symptoms, involvement of the colon or rectum can cause functional disorders. Constipation, tenesmus, rectal bleeding or intestinal obstruction are some of these disorders which can be associated with bowel involvement (1,7,8).

Surgery is a suppressive treatment for endometriosis if ovaries are left producing estrogen. Estrogen is the fuel of endometriotic focus. During the reproductive period, endometriosis tissue continues to grow if no hormonal treatment is applied. Its hormonal suppression using continuous dienogest or cyclic combined drospirenone and ethinyl estradiol is another option for treatment which also supports surgical therapy.

Endometriosis disease has 4 stages which produce obliterated cul de sac at stage 4. Endometriotic tissue at the rectovaginal septum is responsible for dyspareunia during intercourse. The probability of colonic involvement is high during stage 4 disease.

Stage 4 endometriosis may also affect the urinary tract in addition to the bowel involvement supporting a multidisciplinary approach for deep endometriosis surgery which includes gynecologist, general surgeon, and urologist.

Decision to perform surgery for DIE mainly clinical (4). Relieving pain and maintaining fertility with low recurrence rates are the main goals of endometriosis surgery for women during their reproductive period. However, for patients who have already completed childbearing, hysterectomy with or without bilateral salpingo-oophorectomy can be considered as an option for treatment (9). Although there is no guideline for patient selection or optimal treatment for DIE with colonic involvement full thickness excision, shaving or bowel resection are possible treatment modalities to remove the endometrioid foci and improve clinical outcome of the functional disorders (10-12). Clear indication of performing shaving or resection surgery is a matter of debate for centers of excellence studying endometriosis surgery. Although complication rates of bowel resection especially for lower rectal resections are higher, bowel resection can be suitable for lesions greater than 30 mm which cause obstruction or involve more than 1/3 of the intestinal circumference (13). Laparoscopic sigmoid colon or rectal resection is possible and can be combined with gynecologic procedures safely.

CONCLUSION

Treatment of deeply infiltrative endometriosis with colonic or rectal invasion may be problematic. There is no guideline present for patient selection or treatment options in case of colonic or rectal invasion. Colon resection, laparoscopic or open may be performed in conjunction with hysterectomy and bilateral salpingo-oophorectomy for the selected patients who complete childbearing.

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Peer-review: Externally peer-reviewed.

Author Contributions: Concept - All of authors; Design - All of authors; Supervision - T.E., E.R.; Materials - All of authors; Analysis and/or Interpretation - All of authors; Literature Search - T.E., E.R.; Writing Manuscript - T.E.; Critical Reviews - T.E., E.R., Ö.K.

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OLGU SERİSİ-ÖZET
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Endometriozis için kolon rezeksiyonu

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ÖZET

Endometriozis doğurganlık çağındaki kadınları etkiler ve fonksiyonel bozukluklara yol açabilir. Bazen hastalığın sınırları genel cerrahi yönünden müdahale etmeyi gerektirebilir. Özellikle yakın komşuluk nedeniyle sigmoid kolon ve rektum etkilenebilir. Böyle bir durumda tedavi hasta ve semptomlar göre bireyselleştirilmelidir. Lezyon tüm bağırsak duvarını penetre etmiş ise bağırsak rezeksiyonu kaçınılmaz olabilir. Laparoskopik sigmoid kolon ya da rektum rezeksiyonu bu durumda güven ile yapılabilir. Teknik zorluklar nedeniyle laparoskopik rezeksiyonun mümkün olmadığı durumlarda ise tedavi için açık rezeksiyon yapılabilir. Burada, endometriozis nedeniyle biri açık biri laparoskopik olarak yapılan kolon rezeksiyonu olguları sunulmaktadır.

Anahtar Kelimeler: Endometriozis, kolon rezeksiyonu, histerektomi

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CASE REPORT
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Thyroid hemiagenesis: a case report

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ABSTRACT

Thyroid hemiagenesis is a rare entity in the literature. Developmental hemi-thyroid anomalies can result from either an abnormal descent or an agenesis of one lobe of the thyroid gland. This study aimed at presenting a thyroid hemiagenesis case incidentally diagnosed by neck ultrasonography (USG), who had complaints of pain and swelling in the neck. USG examination revealed lack of left thyroid lobe and multiple nodules in the right lobe. Fine Needle Aspiration Biopsy (FNAB) showed follicular neoplasia, and right subtotal thyroidectomy was performed. We report the rarity of the condition and emphasize the role of imaging techniques in preoperative diagnosis and subsequent management.

Keywords: Thyroid, hemiagenesis, surgery

INTRODUCTION

Thyroid hemiagenesis is a rare thyroid pathology characterized by the deficient development of a single thyroid lobe or both a thyroid lobe and the isthmus (1), which was first reported by Handfield-Jones in 1866 (2). Thyroid hemiagenesis is usually identified incidentally with imaging techniques for the investigation of thyroid hormone disorders or evaluation of other complaints. A prevalence study with USG has indicated an incidence of 0.05% (3). We aimed to present a thyroid hemiagenesis case incidentally diagnosed by neck ultrasonography, who presented with complaints of pain and swelling in the neck.

CASE REPORT

The patient was a 32-year-old female, under follow-up for type-II diabetes mellitus (DM) for 7 years, who was presented with chief complaint of neck pain and swelling and underwent neck ultrasonography. Ultrasonography examination revealed lack of left thyroid lobe and multiple nodules in the right lobe, the largest measuring 12.8 x 7.1 mm. Laboratory values were as follows; FT3: 2.84 pg/mL, FT4: 1.15 ng/dL, TSH: 2.8 uU/mL (euthyroidism). Fine Needle Aspiration Biopsy showed follicular neoplasia, and she was referred to our out-patient clinic. Neck examination was within normal limits. Scintigraphy examination revealed lack of left thyroid lobe and hypoactive nodules in right lobe (Figure 1). Surgery was planned. Patient underwent right lobectomy. Left thyroid region was empty and a parathyroid-like yellow tissue was present in that region (Figure 2). Post-operative period was uneventful and the patient was discharged on the second post-operative day. Informed consent was obtained from the patient for both operation and presentation.

DISCUSSION

According to the literature, thyroid hemiagenesis is associated with a female predominance of 3:1, and it more often affects the left lobe, at a ratio of 4:1, as in our patient (3,4). The etiology of thyroid hemiagenesis is not clearly known. Aberrant thyroid migration and genetic component involving mutations in one or several genes that are known to control thyroid morphogenesis/migration have been suggested (5). The isthmus was present in about half of the reported cases although it was absent in our patient (6,7). These patients may have follicular and papillary neoplasms, Graves' disease with thyrotoxicosis, hypothyroidism or hyperthyroidism and as in our case, surgery may be indicated (6-8).

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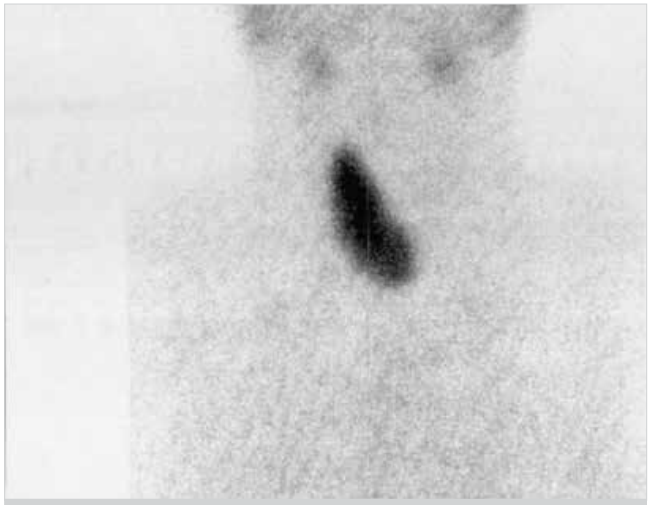

Figure 1. Scintigraphic examination.

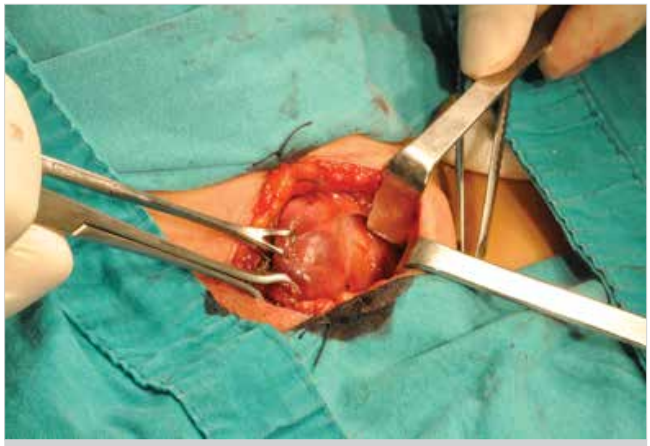

Figure 2. Peri-operative image.

The incidence of thyroid hemiagenesis is uncertain since patients are usually in euthyroid state without any abnormalities. There could be many cases of undiagnosed thyroid hemiagenesis, or as in our case, diagnosed incidentally by an imaging technique (8).

Many studies indicate that USG has the key role in diagnosing thyroid hemiagenesis, and thyroid scintigraphy, laboratory tests and FNAB aid in the detection of accompanying thyroid gland pathologies and imaging ectopic thyroid tissue (3-7). USG is not only useful in lack of a single lobe or single lobe with the isthmus, but also detects hyperplasia in the lobe, or as in our case, additional pathologies such as nodules (8). Scintigraphy shows substance uptake of the remaining thyroid tissue and may detect ectopic thyroid tissues such as a sublingual thyroid, not revealed by ultrasound, which strays the diagnosis from hemiagenesis. Ectopic thyroid tissue was absent in the scintigraphic image of our patient, whereby the diagnosis of thyroid hemiagenesis was confirmed pre-operatively (8,9). The pathologic study of the FNAB sample from the nodule, identified in USG, revealed follicular neoplasia and surgery was indicated; scintigraphy was performed for investigation of ectopic focus.

Thyroid hemiagenesis is usually diagnosed incidentally; pre-operative thyroid gland imaging is useful for diagnosis of the anomaly even if laboratory data are within normal limits. We assume that pre-operative diagnosis of the anomaly prevents unnecessary surgical interventions and decreases possible secondary morbidity.

CONCLUSION

Thyroid hemiagenesis is a rare developmental anomaly of unknown etiology, usually identified incidentally with imaging techniques. Pre-operative diagnosis of thyroid hemiagenesis prevents unnecessary surgical interventions.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Tiroid hemiagenezisi: Bir olgu sunumu

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ÖZET

Tiroid hemiagenezisi literatürde çok seyrek görülür. Hemitiroid anomalilerinin oluşumu, bir tiroid lobunun anormal inişine ya da tamamen yokluğuna bağlı olarak oluşabilir. Bir tiroid hemiagenezi olgusu, boyunda şişlik ve ağrı şikayetleri nedeniyle çekilen ultrasonografi (USG) ile insidental olarak saptanıp polikliniğimize başvurdu. USG'de sol tiroid lobunun olmadığı ve sağ tiroid lobunda multipl nodüllerin olduğu görüldü. İnce iğne aspirasyon biyopsisinde folliküler neoplazi tespit edilmesi üzerine sağ total tiroidektomi uygulandı. Biz seyrek olarak görülen bu hastalığı ve görüntüleme tekniklerinin preoperatif tanı ve tedavideki rolünü vurgulamak istedik.

Anahtar Kelimeler: Tiroid, hemiagenezi, cerrahi

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