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Contact
Turkish Journal of Surgery
Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
06810 Çayyolu-Çankaya, Ankara, Turkey
Phone: +90 (312) 241 99 90 **Fax:** +90 (312) 241 99 91
E-mail: editor@turkjsurg.com

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Publishers
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Contact
Bilimsel Tıp Yayınevi
Address : Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Turkey
Phone : +90 (312) 426 47 47 • +90 (312) 466 23 11
Fax : +90 (312) 426 93 93
E-mail : bilimsel@bilimseltipyayinevi.com
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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).

The Turkish Journal of Surgery is currently abstracted/indexed by PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EMBASE, Scopus, EBSCO, CINAHL, and ProQuest.

Processing and publication are free of charge. No fees are requested from the authors at any point throughout the evaluation and publication process. All expenses of the journal are covered by the Turkish Surgical Society.

Manuscripts must be submitted via the online submission system, which is available at www.turkjsurg.com. Journal guidelines, technical information, and the required forms are available on the journal's web page.

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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Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
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Fax: +90 (312) 426 93 93
E-mail: bilimsel@bilimseltipyayinevi.com
Web: www.bilimseltipyayinevi.com

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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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An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement verifying that written informed consent of the patients and volunteers was obtained following a detailed explanation of the procedures should be included. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee, and the ethics committee approval number should also be stated in the Material and Methods section of the manuscript. It is the authors' responsibility to carefully protect patients' anonymity. For photographs that may reveal the identity of the patient, releases signed by the patient or his/herlegal representative should be enclosed.

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.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to cases that cannot be resolved internally. The Editor-in-Chief is the final authority in the decision-making process for all appeals and complaints.

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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:

- Copyright Transfer Form,

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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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Address: Koru Mah. Koru Sitesi, Ihlamur Cad. No: 26
06810 Çayyolu, Ankara, Turkey

Phone: +90 (312) 241 99 90

Fax: +90 (312) 241 99 91

E-mail: editor@turkjsurg.com

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Address: Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Turkey

Phone: +90 (312) 426 47 47 • +90 (312) 466 23 11

Fax: +90 (312) 426 93 93

E-mail: bilimsel@bilimseltipyayinevi.com

Web: www.bilimseltipyayinevi.com

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PREFACE

Actions Taken by the Turkish Surgical Society on COVID-19

Dear Readers and Authors of the Turkish Journal of Surgery,
Dear Members of the Turkish Surgical Society,

As you all know, the world is facing COVID-19 pandemia since December 2019, and the number of people infected, in the ICU or deceased are increasing. Currently, every country is affected, and WHO has issued a public health emergency of international concern. There is evidence suggesting that transmission mode is human to human. Major route of transmission of COVID-19 is droplet and close contact. The spectrum of clinical presentations of COVID-19 has been reported to be ranging from asymptomatic infection to severe respiratory failure. Common clinical laboratory findings include leucopenia and lymphopenia. Lymphopenia is a cardinal feature of COVID-19. Lactate dehydrogenase and creatinine kinase are all elevated. Half of the patients had abnormal liver function, with elevated alanine aminotransferase or aspartate aminotransferase. Although radiologic manifestations of COVID-19 infected patients are diverse, the most common manifestations are patchy ground-glass opacities and patchy consolidation, which were mainly distributed in the middle and outer zone of the lung.

Although a good contact history, systemic symptoms, and radiographic changes of pneumonia make the diagnosis likely, laboratory diagnosis is more reliable. Real time-polymerase chain reaction (RT-PCR) is routinely used to detect causative viruses from respiratory secretions. The results suggest that the sensitivity of chest CT in suspected patients is 97% based on positive RT-PCR result and 75% based on negative RT-PCR results. These findings indicate that chest CT is a sensitive modality to detect COVID-19 infection. Healthy people should be aware of the severity of COVID-19 and take measures to protect themselves, such as staying at home, limiting social contacts, and wearing protective masks in public.

As the time goes on, health-service professionals, doctors, nurses and hospital staff will be under risk of contamination as they will face more and more infected patients. Although all scheduled elective operations have been cancelled or postponed, surgeons and nurses are still under high risk as they will operate on COVID-19 positive patients or patients with high suspicion of infection because of emergency conditions.

Turkish Surgical Society has taken action and prepared an article for the surgical community, which is being published in the present issue of the journal both in Turkish and in English (1,2). Precautions and suggestions by the Society will also be updated regularly and released on the web page of the Society. The announcements will be mailed to all members and health authorities.

In the present issue of the Turkish Journal of Surgery, you can also find fifteen original articles, two case-reports and two letters to the editor. Although all are very important studies, I would like to call attention to two important articles on man-power in surgical practice written by Yasti et al. (3) and an evaluation of the surgical theses during the last 20 years in Turkey by Ferhatoglu et al. (4). These two articles provide noteworthy information not only on the level and the quality of surgical service in Turkey but also give assumptions on the level of surgical education.

I am in strong belief and hope that we will win this battle with as little loss as possible for which I expect from you to follow the suggestions and rules released by the government authorities and our society.

Meanwhile, please do take care of yourself and enjoy the articles,

Yours Sincerely,

M Mahir OZMEN MD MS FACS FRCS FASMBS

Professor of Surgery
Editorial Coordinator, TJS
Executive Committee Member, TSS

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FROM THE EDITOR'S DESK

Dear Authors of Turkish Journal of Surgery,

We are glad to present you the first issue of 2020, which includes various interesting studies. We hope that these outstanding articles will bring you new evidences and trigger your scientific inspirations.

The last year was very busy in the kitchen of our journal, in regards of the "fine tuning" of the editorial work and improvement of publication processes. We have made numerous changes that are -for the moment- not visible for the authors but lead to considerable structural improvement of Turkish Journal of Surgery. I expect that our authors will notice soon these progresses throughout the upcoming issues. In this respect I would like to thank all who have shared their opinions with us. We are always open to your suggestions and critics.

The surgical education and the general surgery as "profession" were always hot topics of discussion and they are still worldwide being discussed. Right after the graduation from the medical school, the professional journey of a surgeon is full of commitments, obligations, efforts and sometimes disappointments. Surgery is not only a medical specialization but also a life style with many academical, professional and social aspects. In this issue you may read two very interesting articles about the surgical education and surgery profession. According to legislative rules in Turkey, one should present a thesis at the end of the residency. Ferhatoğlu and his co-authors analyze the surgical theses in a 20-year period (1). They present interesting data about the qualities of the theses as well as the publication rates in peer-reviewed journals. Furthermore Yastı and his co-authors enlighten the current status of work power of general surgery in Turkey (2). I do believe that these two studies have not only local but also international "take home" messages.

Lastly I would like to remind you all, the biggest surgical meeting in Turkey, the 22nd Turkish National Surgery Congress, that will take place in the upcoming months. It is the most important scientific event for the Turkish surgical family with around 4000 participants. A session about medical publishing takes part in the scientific program of the congress with prominent lecturers. We do hope for fruitful discussions and concrete suggestions regarding the existing problems of medical publishing and the Turkish Journal of Surgery. We look forward to see you all in 22nd Turkish National Surgery Congress in order to benefit from your precious contributions.

We wish you a pleasant and profitable reading.

Kindest regards,

Kaya SARIBEYOĞLU
Professor of Surgery
Turkish Journal of Surgery
Editor

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2. *Yastı AÇ, Uçar AD, Kendirci M. General surgery specialism in Turkey: Work power currently, continuity at quality and quantity. Turk J Surg 2020;36(1):82-95.*

REVIEW
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General Surgery Operating Room Practice in Patients with COVID-19

Ahmet Serdar Karaca **(İD)**, M. Mahir Özmen **(İD)**, Ahmet Deniz Uçar **(İD)**, Ahmet Çınar Yastı **(İD)**, Seher Demirer **(İD)**

On Behalf of the Initiative of the Board on Directors of the Turkish Surgical Society

ABSTRACT

The virus COVID-19, which emerged in China in December 2019, was announced by the World Health Organization as a pandemic in January 2020. It is known that infection is not severe and may even progress without symptoms in patients who have come into contact with COVID-19. Although various organizations have been informed about how to take measures to protect the patient and the surgeon in case of diseases requiring urgent or elective surgery in people infected with COVID-19 or in cases with high suspicion, there is still no definite judgment between patients, physicians and health authorities. In this study, which was prepared with the initiative of the Turkish Surgical Association, we tried to shed light on what should be done and how surgeons should act in patients whose operation is mandatory in light of the available data.

Keywords: COVID-19, coronavirus, surgery, personal protective equipment

Introduction

In January 2020, the COVID-19 pandemic, an unidentified factor-based outbreak, was announced by the World Health Organization for pneumonia cases, which first began increasingly in Wuhan, China in late December 2019. As COVID-19 spread worldwide and in our country, the hospitals designated for the treatment of this disease have also become hazardous areas for transmission. Surgical applications are the cornerstones of every health system contributing to public health in both elective and emergency situations. As healthcare professionals play a role in the treatment of this disease, the risk of disease exposure and illness also increases, which also raises the risk of decreasing health man-power in combating the COVID-19 outbreak (1).

Definition and Review

While non-serious symptoms or symptoms that can go unnoticed can emerge in nearly half of the patients infected with COVID-19, the other half can show primary symptoms such as fatigue, dry cough, myalgia and dyspnea (2,3). Comorbidities such as diabetes mellitus, hypertension and cardiovascular diseases are present in approximately half of the patients. The most common laboratory findings are leukopenia and lymphopenia. Lactate dehydrogenase and creatinine kinase elevation may also be seen. Half of the patients may have abnormal liver function tests like alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation. Although normal serum procalcitonin levels are seen in the majority of patients, C-reactive protein (CRP) levels have been found above the normal range. D-Dimer has been determined high in one third of the patients (4,5).

Operating rooms are high-risk areas for contact contamination through air way or possible splash. Although the operating room systems in hospitals in our country are generally well-designed to deal with this type of high-risk situations, high contamination risk, disease prevalence, limited resources andadditional workload provided by the staff under pressure significantly increase the risk of transmission and the workload on all surgical teams, especially the lead surgeon.

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Corresponding Author
Ahmet Serdar Karaca
E-mail: karacaahmetserdar@gmail.com

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In possible or definitive COVID-19 cases, publications have started to emerge in which safe surgical algorithm or recommendations are compiled. In order to maintain basic surgical care by protecting the surgical staff and the limited but valuable resources, urgent actions must be taken and previously known points must be re-visited and re-underlined.

Due to expecting more number of COVID-19 patients requiring care in the next few weeks, surgical care of the patients must be limited to those whose needs are life-threatening and to those who have active symptoms of advancing malignancy or emergency evaluation. In addition to interventions that will be made on COVID-19 positive patients, surgical interventions should be limited to only this group of patients.

All unnecessary hospital or office staff should be allowed to work from home. All face to face training sessions should be cancelled. Minimum number of people should enter and leave patient rooms for all types of work and procedures, and the widespread use of hand washing, antiseptic procedures and personal protective equipment (PPE) should be ensured and usage rules be strictly followed. When necessary, surgical consultation should only be done by the surgeon who will decide on/perform the final consultation/surgery. All non-urgent procedures should be cancelled or postponed during personal clinic/office visits unless it is necessary to evaluate active symptoms or manage wound care. All patient visits should be made as remotely as possible and only closely when absolutely necessary. Where possible, telemedicine infrastructure or at least personal video calls should be preferred. It should be refrained from going to unnecessary meetings and public places likes restaurants and shops, and grocery shopping should be minimized. The consequences of extreme caution and meticulous precaution and preparation are always better than the consequences of insufficient measure or preparation.

Including prevention and control measures for the medical staff, operating rooms and surgical tools, and more importantly the protection of the wards, healthcare personnel and other patients in the treatment of patients requiring emergency surgery or those having received cancer diagnosis with perioperative treatment, it is a necessity to define and acknowledge in detail the operational, perioperative and postoperative managements of patients diagnosed or suspected with new corona penumonia. This, in turn, will provide other healthcare professionals, especially surgeons, with both disease protection and legal advantages.

The current situation in our country is shown in Figure 1 and is announced daily by the Ministry of Health.

These data, including details such as total number of tests, number of positive cases, number of cases in intensive care, and number of mortality, can be accessed from the relevant website (6).

At this stage, the priority should be to postpone all elective and endoscopic procedures to a more convenient date taking into account the pandemic the world is currently dealing with at the present time. Since this process will be able to minimize the possible risk and provide efficient use of the resources, it is a beneficial application that can be followed by all institutions that havfe prepared guidelines and recommendations on this matter in terms of upcoming plans (3-5).

Precautions and Rules

This period includes three periods as before surgery, during surgery and after surgery. The approach discussed here applies to patients with COVID-19 positivity or highly suspicious COVID-19.

Preoperative period, whether emergency or outpatient, should be carried out according to the patient welcome protocols of the hospital (state, private, university, etc.) you are working at.

In the preliminary evaluation, before getting in contact with the patient, patient's history and any other previous examinations should be reviewed. Afterwards, it is necessary to make preparations for the examination according to the patient's condition. This preparation includes PPE for the entire inspection team.

PPE is extremely important. The examination is completed without any contact with the patient, using overalls, bones, masks,

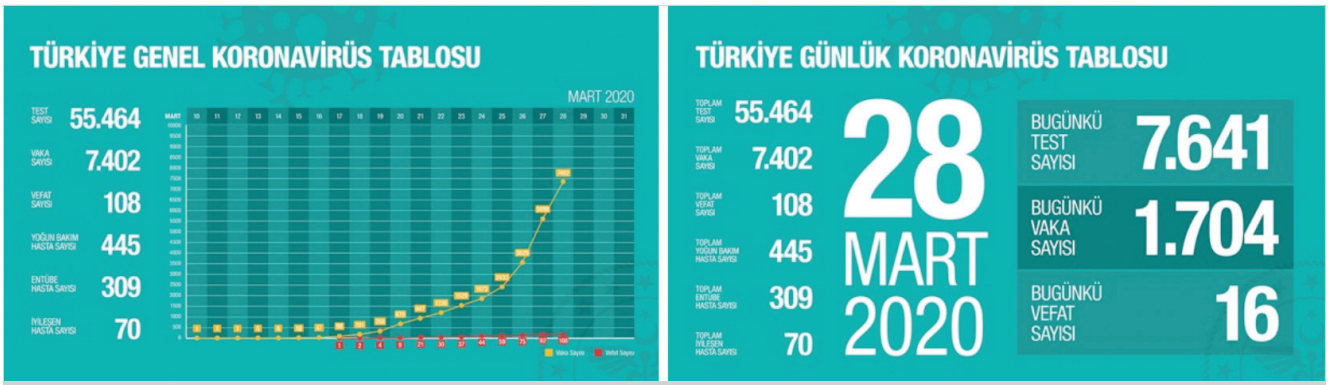

Figure 1. COVID-19 data updated daily by the Ministry of Health of the Republic of Turkey (6).

Table 1. Intercollegiate general surgery guidance on COVID-19

Emergency Surgery - Test for COVID-19 - Treating everyone as positive - See Thoracic Computed Tomography (CT) in the last 24 hours - If Abdominal CT will be performed, add Thorax CT.	**Elective Surgery** - Do risk assessment for COVID-19 - Surgery risk is high - Take the confirmation form. - Use risk reduction strategies (ostomy, etc.)	**PPE** - PPE for all laparotomies (except COVID-19 negatives, but watch out for false negatives) - Add eye protector - Improve the practice of wearing clothes
Operating room - Minimum number of staff possible, - PPE To all staff including visit - Positive Pressure Ventilation Use smoke extraction Intubation/extubation in the operating room	**Laparoscopy** - It should not be used in general - Filter etc. apply difficult - Appendicitis: open/conservative (medical) - Colecystitis: conservative (medical)/cholecystostomy	**Endoscopy** - Only emergencies- - If the upper GIS endoscopy is to be performed completely PPE is a must!

goggles or a face shield, gloves, and after the end of the examination, hands must be disinfected and removed in the same order at each stage using the hand disinfectant.

Other standard procuders like taking necessary consent and bureaucratic procedures should be completed in the same way.

In the preoperative period, after completing the examination of patients in this way, there is no need to wait for definitive diagnosis to be obtained in patients whose diagnosis is not certain but COVID-19 is suspected. These patients should also be treated like patients diagnosed with COVID-19 (Table 1).

Operating Room Conditions

The operating room (OR) should be a room equipped with negative pressure and located in an isolated corner of the operating theatre with a separate access. This hall should be reserved for all confirmed (or suspected) COVID-19 cases. It should consist only of interconnected rooms where the entrance section and anesthesia induction chambers have negative pressure.

Hospital management and safety is responsible for keeping the route from the service / patient bed or intensive care unit (ICU) to the OR, including elevators, clean, open and convenient for use. Service from / transfer to the OR from the patient bed should be carried out be service nurses wearing a N95 mask, goggles or face shield, splash resistant aprons and feet with full personal protective equipment including full cover overshoes (PPE).

The OR and preparation and cleaning rooms must all have positive pressures. It is very important to ensure correct air flow in the operating room to minimize the risk of infection. During the outbreak, the same operating room and the same anesthesia machine should only be used for COVID-19 cases. An additional heat and moisture exchanger filter should be placed at the expiration output of the circuit and should be replaced after each operation. The anesthetic drug cart should be kept in the induction chamber. Before starting each operation, the anesthetist should place all necessary medicines and equipment during the procedure in a tray to prevent the drug trolley from being used during a case.

However, if additional medications are needed, hand hygiene and glove replacement should be made before entering the induction chamber and using the medication cart. A car containing an airway system should also be placed in the induction chamber. Disposable airway equipment should be used whenever possible. The airway should be fixed using the method with the highest chance of success for the first time to avoid repeated instrumentation of the airway, including using a video-laryngoscope. Non-disposable equipment should be thoroughly cleaned and sterilized after use (1) (Table 2).

A special transport ventilator should be used for patients coming from the intensive care unit. In order to prevent aerosolization, gas flow should be closed, and ventilators should be clamped with endotracheal tube forceps. Intensive care personnel should use full PPE with electrically-driven air respirator for transfer. In the induction chamber, a power-induced respirator with an air filter/purification feature must be worn during induction by all personnel within two meters of the patient. For operative airway procedures such as tracheostomy, all staff should keep this open. Regional anesthesia is preferred for other procedures, but if general anesthesia is required, case management is similar to standard procedures. During the procedure, an operating room technician should be placed outside the OR if additional medications or equipment are required. These materials should be placed next to a cart that will be left in the entrance room for the team in the operating room. In contrast, the same process should be used to send samples, such as arterial blood gas samples or frozen studies. This operating room

Table 2. Summary

Viral transmission risks:
• It is especially caused by blood, digestive tract and respiratory tract.
• Procedures with aerosol effect: Intubation/extubation, mask-breathing patient, bronchoscopy, laparoscopic procedures, use of electrocautery
Preparation for surgery:
• High frequency communication with the service, operating room, anesthesia and intensive care team.
• In patients who are likely to go to the postoperative intensive care unit, it may be considered to use the intensive care ventilator in the operating room.
• Night cases operations should be reduced as much as possible.
• Coordination with the OR team on the location and quantity of personal protective equipment
During surgery:
• Only the required (minimum number of) staff in the OR.
• There must be a surgical technician outside the OR
• Telephone, pager, watch, jewelery etc., etc. should be left out of the OR
Personal protective equipment:
• Since surgical procedures are also procedures that create an aerosol effect, N95 masks, surgical glasses, or other PPEs must be used.

technician should definitely wear PPE when entering the OR. In order to prevent contamination of the patients, all operating room personnel should wear their PPE first and wear standard surgical surgery clothes in that way.

PPE

- intubation

- regional anesthesia

- cannulation, catheterization

- surgical intervention is a must in all interventional procedures.

Equipment

1. Liquid proof apron,
2. PPE containing mask; Surgical mask or N95 or FFP group,
3. Face protective transparent barrier,
4. Gloves (Double layer) or biobarrier gloves,
5. Non-perforated shoes or rubber boots, which can be sterilized best, should be used.

If baring occurs on the hands and feet , it is necessary to fix them with adhesive tapes against the risk of contamination.

Operation

Although the evidence value is low, the surgical team's contact with the fluid and tissues of the patient increases with conventional methods; however, there is common concern that the gas used in laparoscopic surgeries may also cause viral contamination. Yu et al., in their study, have reported that SARS-CoV-2 is transmitted by droplet and contact way, and fecal-oral route and aerosol transmission cannot be ignored, and thus laparoscopic surgery can be performed in patients with COVID-19, but laparoscopic gases must be managed well (7). It is recommended to use CO_2 filters for laparoscopic applications. Chen and his colleagues, on the other hand, have indicated that surgical operations should be reduced to prevent cross-infection and recommended multidisciplinary treatments for malignant tumors and the selection of non-surgical anti-tumor therapies with higher priority, and using neoadjuvant therapies for cancer of advanced gastrointestinal system that meet the indications of NCCN guidelines (8). In addition, in patients with obstructed gastric or esophagogastric junction tumors, gastric tube or stent placement to ameliorate symptoms, transnasal enteral feeding tube intubation/percutaneous endoscopic gastrostomy to provide enteral nutrition should per performed, and the need for emergency surgery can be reduced in obstructed colorectal cancers by having stenting procedure bridge elective surgery and decrease the need for emergency surgery, an deven better the outcomes of subsequent surgeries. Standard practices are recommended for the waste of these patients since there is no data about it yet. The same is true for pathological plays.

Staff leaving the operating room should throw their used gowns and gloves in the entrance room and renew hand hygiene before leaving the entrance room. All PPE should be removed outside the entrance room.

Patients who do not require postoperative intensive care unit care should be awakened in the operating room. When the patient is ready to go to the ward, the path to the isolation ward or intensive care unit should be cleaned again. There must be at least one to two hours between cases to allow OR staff to return the patient to the service/bed and to decontaminate all surfaces, screens, keyboards, cables, monitors and anesthesia machine. All unused products in the medication tray and airway cart should be assumed to be contaminated and should be discarded. All staff should take a shower before continuing

their duties. As an additional measure, after approved COVID-19 cases, a hydrogen peroxide evaporator should be used to decontaminate the operating room.

Conclusion

Currently, the COVID-19 pandemic, which affects the whole world, causes a slowdown or even a halt in almost all business lines and professions while the job is loaded mostly on the health system and the risks of health professionals increase in parallel.

The Turkish Surgical Association has listed the situation assessment and measures to be taken with this article, and will announce the arrangements for future developments with its members and the public through its website, e-mail and social media.

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DERLEME-ÖZET
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COVID-19'lu Hastalarda Genel Cerrahi Ameliyathane Uygulamaları

Ahmet Serdar Karaca, M. Mahir Özmen, Ahmet Deniz Uçar, Ahmet Çınar Yastı, Seher Demirer

Türk Cerrahi Derneği Yönetim Kurulu İnisiyatifi Adına

ÖZET

Aralık 2019'da Çin'de ortaya çıkan COVID-19 olarak adlandırılan virüs hastalığı Dünya Sağlık Örgütü tarafından Ocak 2020'de pandemi olarak duyurulmuştur. COVID-19 ile temas etmiş hastaların tümünde enfeksiyonun şiddetli olmadığı ve hatta semptomsuz seyredebileceği de bilinmektedir. Bu kişilerde ya da yüksek şüpheli olgularda acil veya elektif cerrahi yapılmasını gerektiren hastalıklar olması durumunda hastayı ve cerrahı koruyacak önlemlerin nasıl alınması gerektiği konusunda çeşitli organizasyonlarca sürekli bildirimler yapılmasına karşın bugüne kadar gerek hastalar, gerek hekimler gerekse de sağlık otoriteleri nezdinde kesin bir fikir birliğine varılamamıştır. Türk Cerrahi Derneği inisiyatifi ile hazırlanmış olan bu çalışmada eldeki veriler ışığında operasyonu zorunlu olan hastalarda cerrahın nasıl davranması gerektiğine ve perioperatif neler yapılması gerektiğine ışık tutmaya çalıştık.

Anahtar Kelimeler: COVID-19, koronavirüs, cerrahi, kişisel koruyucu ekipman

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COVID-19'lu Hastalarda Genel Cerrahi Ameliyathane Uygulamaları

Ahmet Serdar Karaca (İD), M. Mahir Özmen (İD), Ahmet Deniz Uçar (İD), Ahmet Çınar Yastı (İD), Seher Demirer (İD)

Türk Cerrahi Derneği Yönetim Kurulu İnisiyatifi Adına

ÖZET

Aralık 2019'da Çin'de ortaya çıkan COVID-19 olarak adlandırılan virüs hastalığı Dünya Sağlık Örgütü tarafından Ocak 2020'de pandemi olarak duyurulmuştur. COVID-19 ile temas etmiş hastaların tümünde enfeksiyonun şiddetli olmadığı ve hatta semptomsuz seyredebileceği de bilinmektedir. Bu kişilerde ya da yüksek şüpheli olgularda acil veya elektif cerrahi yapılmasını gerektiren hastalıklar olması durumunda hastayı ve cerrahı koruyacak önlemlerin nasıl alınması gerektiği konusunda çeşitli organizasyonlarca sürekli bildirimler yapılmasına karşın bugüne kadar gerek hastalar, gerek hekimler gerekse de sağlık otoriteleri nezdinde kesin bir fikir birliğine varılamamıştır. Türk Cerrahi Derneği inisiyatifi ile hazırlanmış olan bu çalışmada eldeki veriler ışığında operasyonu zorunlu olan hastalarda cerrahın nasıl davranması gerektiğine ve perioperatif neler yapılması gerektiğine ışık tutmaya çalıştık.

Anhatar Kelimeler: COVID-19, koronavirüs, cerrahi, kişisel koruyucu ekipman

Giriş

İlk olarak Aralık 2019 sonlarında Çin'in Wuhan şehrinde artan oranda görülmeye başlayan pnömoni olgularında izole edilen ve adlandırılamayan etkene dayalı salgın COVID-19 pandemisi olarak Dünya Sağlık Örgütü tarafından Ocak 2020'de duyurulmuştur. Dünyada ve ülkemizde COVID-19 yayıldıkça, bu hastalığın tedavisi için kullanılan hastaneler aynı zamanda bulaş açısından da riskli bölgeler haline gelmiştir. Cerrahi uygulamalar hem elektif hem de acil durumlarda toplum sağlığına katkıda bulunulan her sağlık sisteminin temel taşlarındandır. Sağlık çalışanları, bu hastalığın tedavisinde rol aldıkça hastalığa maruz kalma ve hastalanma riskleri artmakta, aynı zamanda bu durum, COVID-19 salgını ile mücadelede azalan sağlık insan gücü riskini de gündeme taşımaktadır (1).

Sorunun Tanımı ve Genel Değerlendirme

COVID-19 bulaşan kişilerin yaklaşık yarısında ciddi olmayan veya gözden kaçabilecek semptomlar oluşurken, diğer yarısında başlıca semptomlar ateş, yorgunluk, kuru öksürük, miyalji (kas ağrısı) ve dispnedir (2,3). Hastaların yaklaşık yarısında hipertansiyon, diyabet ve kardiyovasküler hastalık gibi yandaş hastalıklar bulunmaktadır (3). En sık laboratuvar bulgusu lökopeni ve lenfopenidir. Laktat dehidrogenaz ve kreatinin kinaz yüksekliği de görülebilir. Hastaların yarısında alanin aminotransferaz (ALT) ya da aspartat aminotransferaz (AST) yüksekliği gibi anormal karaciğer fonksiyon testleri bulunabilir. Hastaların çoğunda normal serum prokalsitonin seviyeleri görülmesine karşılık C-reaktif protein (CRP) düzeyleri normal aralığın üzerinde saptanmıştır. Hastaların üçte birinde D-Dimer yüksektir (4,5).

Ameliyathaneler, hava yolu ya da olası sıçrama, temas bulaşı ile yüksek riskli alanlardır. Her ne kadar ülkemizdeki hastanelerde ameliyathane sistemleri bu tip yüksek riskli durumlarla başa çıkmak için genellikle iyi tasarlanmış olsalar da yüksek bulaş riski, hastalık prevalansı, sınırlı kaynaklar ve baskı altındaki personel tarafından sunulan ek iş yükü, bu pandemi sırasında bulaşma risklerini ve cerrahi uygulamaları gerçekleştiren başta hekim olmak üzere tüm ekip üzerindeki yükü ve riski büyük ölçüde arttırmaktadır.

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Sorumlu Yazar
Ahmet Serdar Karaca
E-mail: karacaahmetserdar@gmail.com

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Olası ya da kesin COVID-19 hastalıklı olgularda güvenli cerrahi algoritma ya da önerilerinin derlendiği yayınlar ortaya çıkmaya başlamıştır. Cerrahi personeli ve mevcut pandemi ile mücadele için değerli ve sınırlı kaynakları koruyarak temel cerrahi bakımı devam ettirebilmek için hemen harekete geçilmesi ve aslında iyi bilinen bazı noktalara da tekrar dikkat çekilmesi gerekmektedir.

Önümüzdeki birkaç hafta içinde sayısının çok daha artması beklenen ve bakım gerektiren COVID-19 hastalarında cerrahi tedavi gereksinimi ortaya çıktığında bu tedaviler hayati tehlike arz eden ve hızlı ilerleyen maligniteler veya acil cerrahi girişim gerektiren süreçlerle sınırlandırılmalıdır, elektif cerrahi ihtiyaçları uygun şartlarda ötelenmelidir.

Gerekli olmayan tüm hastane veya ofis personelinin evde olmasına ve/veya evden çalışmasına izin verilmelidir. Tüm yüz yüze eğitim oturumları iptal edilmelidir. Her tür iş ve işlem için hasta odalarına en az sayıda kişi girip çıkmalıdır ve el yıkama, antiseptik işlemler ile kişisel koruyucu ekipmanlar (KKE)'ın yaygın kullanımı sağlanmalı ve kullanım kurallarına kesinlikle uyulmalıdır. Gerektiğinde, cerrahi konsültasyon sadece konsültan/ameliyata son karar verecek/gerçekleştirecek cerrah tarafından yapılmalıdır. Aktif semptomları değerlendirmek veya yara bakımını yönetmek gerekmedikçe, kişisel klinik/ofis ziyaretlerinde acil olmayan tüm işlemler iptal edilmeli veya ertelenmelidir. Tüm hasta vizitleri mümkün olduğunca uzaktan ve kesinlikle gerekli olduğunda yakından yapılmalıdır. Olanaklar dahilindeyse teletıp altyapısı ya da en azından kişisel görüntülü görüşme yolları tercih edilmelidir. Gereksiz toplantılara, restoranlar ve mağazalar gibi halka açık yerlere gidilmemeli, yiyecek ve alışveriş gezileri en aza indirilmelidir. Aşırı dikkatli ve titiz tedbir ve hazırlığın sonuçları, yetersiz tedbir ya da hazırlığın sonuçlarından, her zaman için daha iyidir.

Acil ameliyat gerektiren ya da kanser tanısı alan hastaların tedavisinde sağlık çalışanlarının ve diğer hastaların korunması, hasta odalarının korunması, perioperatif tedaviler ile daha da önemlisi, tıbbi personel, ameliyathaneler ve cerrahi aletler için önlemler alınması son derece önemlidir.

Yeni korona pnömoni şüphesi veya tanısı alan hastaların operasyonel yönetimi ile perioperatif ve postoperatif yönetiminin ayrıntılı olarak bilinmesi ve tanımlanması gerekmektedir. Bu da cerrahlar başta olmak üzere tüm sağlık çalışanlarına hem hastalıktan korunma, hem hastalıktan koruma hem de hukuki avantajlar sağlayacaktır.

Ülkemizdeki güncel durum Şekil 1'de gösterilmiş olup Sağlık Bakanlığı'nca her gün güncellenmektedir. Toplam test sayısı, pozitif olgu sayısı, yoğun bakımdaki hasta sayısı ve mortalite sayısı gibi detayları içeren bu verilere güncel olarak ilgili web sitesinden ulaşılabilir (6).

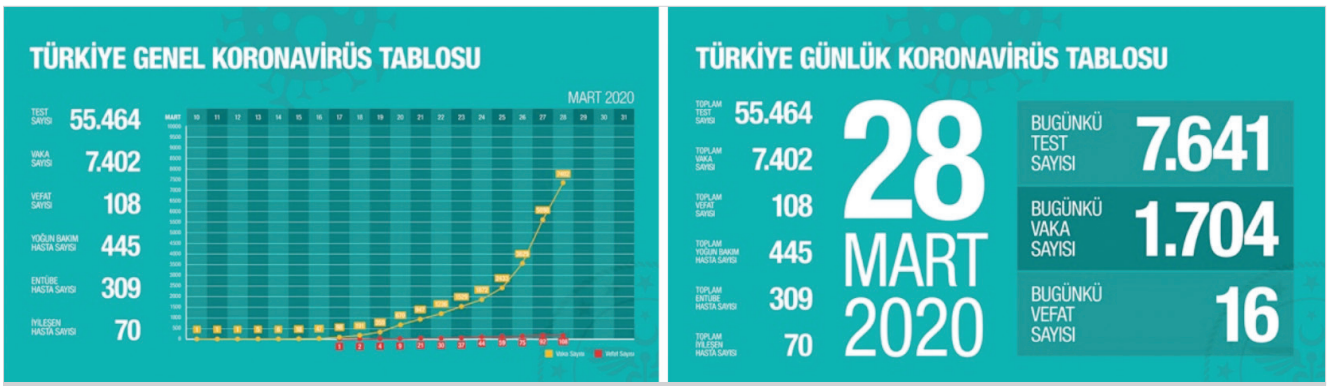
Bu aşamada öncelik, dünyada pandemi olduğu gerçeğini dikkate alarak tüm elektif ve endoskopik işlemlerin daha uygun bir zamana ertelenmesi gereğidir. Bu yaklaşım, olası riski en aza indirmekle beraber kaynakların da etkin kullanımını sağlayacağından önümüzdeki planlamalar açısından bu konuda öneri ve rehber hazırlamış tüm kuruluşlarca yapılması önerilen bir uygulamadır (3-5).

Önlemler-Kurallar

Bu dönem cerrahi açıdan ameliyat öncesi, ameliyat ve ameliyat sonrası olarak üç dönemi kapsamaktadır. Burada ele alınan yaklaşım COVID-19 pozitif ya da COVID-19 yüksek şüpheli hastalar için geçerlidir.

Ameliyat öncesi dönem, ister acil ister poliklinik hastası olsun, çalışmakta olduğunuz hastanedeki (devlet, özel, üniversite vb.) hasta karşılama protokollerine göre yapılmalıdır.

Ön değerlendirmede hasta ile temas etmeden önce, hastanın önceki öyküsü ve varsa daha önce yapılmış tetkikleri incelenmelidir. Sonrasında hastanın durumuna göre muayene hazırlığı yapılması gerekmektedir. Bu hazırlık, muayene ekibinin tamamının KKE'sini gerektirmektedir. KKE son derece önemlidir. Hasta ile temas etmeyecek şekilde, tulum, bone, maske, gözlük ya da yüz koruyucu siper, eldiven kullanılarak muayene ve diğer işlemler tamamlanır. Bundan sonra her aşamada el dezenfektanı kullanılarak eller dezenfekte edilip aynı sırayla çıkarılarak oda terk edilmelidir.



Şekil 1. T.C. Sağlık Bakanlığı tarafından her gün güncellenen Türkiye ülke geneli COVID-19 verileri (6).

Tablo 1. COVID-19 Genel Cerrahi Özet Rehberi		
Acil Cerrahi -COVID-19 için test yap -Herkesi pozitif gibi tedavi et -Son 24 saatteki toraks bilgisayarlı tomografisini (BT) gör -Abdomen BT yapılacaksa toraks BT ekle	**Planlı Cerrahi** -COVID-19 için risk değerlendirmesi yap -Cerrahi risk yüksek -Onam al -Riski azaltma stratejileri kullan (ostomi vb.)	**KKE** -Tüm laparotomiler için KKE (COVID-19 negatifler hariç ama yanlış negatiflere dikkat) -Göz koruyucu önlemleri ekle -Giyme çıkarma pratiğini geliştir
Ameliyathane -Mümkün olan en az sayıda personel, -Ziyaret dahil bütün personele KKE -Pozitif basınçlı ventilasyon yapma -Duman emici (Smoke extraction) kullan -Entübasyon/ekstübasyon ameliyathanede	**Laparoskopi** -Genel olarak KULLANMA -Filtre vb. uygulamak zor -Apandisit: açık/konservatif (medikal) -Kolesistit: konservatif (medikal)/ kolesistostomi	**Endoskopi** -Sadece aciller -Endoskopi derneklerinin rehberini izle -Üst gastrointestinal sistem endoskopi yapılacaksa tamamen KKE şart!

Diğer standart işlemler, yani onam alınması ve gerekli bürokratik işlemler aynı şekilde tamamlanmalıdır.

Ameliyat öncesi dönemde hastaların muayenesi bu şekilde tamamlandıktan sonra COVID-19 tanısı şüpheli olan hastalarda kesin tanı alınıncaya kadar beklemeye gerek yoktur. COVID-19 tanılı hastalar gibi muamele edilerek ameliyata alınmaları gerekmektedir (Tablo 1).

Ameliyathane Koşulları

Ameliyat salonu ameliyathanenin mümkün olduğunca uzak, izole bir köşesinde bulunan ve ayrı bir erişime sahip, negatif basınç donanımlı bir salon olmalıdır. Bu salon onaylanmış (veya şüphelenilen) tüm COVID-19 olguları için ayrılmalıdır. Sadece giriş bölümü ve anestezi indüksiyon odalarının negatif basınca sahip olduğu birbirine bağlı odalardan oluşmalıdır.

Hastane yönetimi ve güvenliği, asansörler de dahil olmak üzere servisten/hasta yatağından veya yoğun bakım ünitesi (YBÜ)'nden ameliyat salonuna giden yolu temiz, açık ve kullanıma uygun tutmaktan sorumludur. Servisten/hasta yatağından ameliyat salonuna transfer, bir N95 maskesi, gözlük veya yüz siperi, sıçramaya dayanıklı önlük ve ayağı tam kapayan galoş dahil olmak üzere tam KKE ile servis hemşireleri tarafından yapılmalıdır.

Ameliyathanedeki hava akışını doğru sağlamak enfeksiyon riskini en aza indirmek için çok önemlidir. Salgın süresince aynı ameliyat salonu ve aynı anestezi makinesi sadece COVID-19 olguları için kullanılmalıdır. Devrenin ekspirasyon çıkışına ek bir ısı ve nem değiştirici filtre yerleştirilmelidir. Her ameliyattan sonra hem bu filtre hem de soda-lime değiştirilmelidir. Anestezik ilaç arabası indüksiyon odasında tutulmalıdır. Her operasyona başlamadan önce, anestezist, işlem sırasında gerekli olan tüm ilaçları ve ekipmanları, ilaç arabasının ameliyat esnasında kullanılmasını önlemek için, bir tepsiye yerleştirmelidir. Bununla birlikte, ek ilaçlara ihtiyaç varsa, indüksiyon odasına girmeden ve ilaç arabasını kullanmadan önce mutlaka el hijyeni ve eldiven değişimi yapılmalıdır. İndüksiyon odasına bir hava yolu sistemi ihtiva eden araba da yerleştirilmelidir. Mümkün olduğunca tek kullanımlık hava yolu ekipmanı kullanılmalıdır. Hava yolu, video-laringoskop kullanılması da dahil olmak üzere, hava yolunun tekrar tekrar enstrümantasyonundan kaçınmak için, bir defada ve tek uygulama ile başarı şansı en yüksek olan yöntem kullanılarak sabitlenmelidir. Tek kullanımlık olmayan ekipmanlar kullanımdan sonra iyice temizlenip steril edilmelidir (1) (Tablo 2).

Yoğun bakım ünitesinden gelen hastalar için özel bir nakil ventilatörü kullanılmalıdır. Aerosolizasyonu önlemek için gaz akışı kapatılıp ventilatörlerin değiştirilmesi sırasında endotrakeal tüp forseps ile klemplenmelidir. Yoğun bakım personeli, transfer için, elektrikli hava temizleme respiratörü ile tam KKE kullanmalıdır. İndüksiyon odasında, hastanın iki metre dahilindeki tüm personel anestezi indüksiyonu ve uyandırma sırasında bir hava filtre etme/saflaştırma özelliği olan güç kaynaklı respiratuvar giymelidir. Diğer prosedürler için bölgesel anestezi tercih edilir, ancak genel anestezi gerekiyorsa, olgu yönetimi standart işlemlerle benzerdir. Prosedür sırasında, ek ilaçlar veya ekipman gerekiyorsa bir ameliyathane teknikeri ameliyat salonu dışına yerleştirilmelidir. Bu malzemeler ameliyat salonundaki ekibin alması için giriş odasında bırakılacak bir arabanın yanına yerleştirilmelidir. Aynı işlem tersine, arteriyel kan gazı örnekleri veya frozen çalışmaları gibi örnekleri göndermek için de kullanılır. Bu ameliyathane teknikeri ameliyat salonuna girerken mutlaka KKE giymelidir Hastalardan kontaminasyonu önlemek açısından tüm ameliyathane personeli önce KKE'lerini giymeli ve üzerine standart ameliyat cerrahi elbiselerini o şekilde giymelidirler.

Kişisel koruyucu ekipman;

- entübasyon,
- rejyonal anestezi,
- kanülizasyon, kateterizasyon,
- cerrahi müdahale,

kısacası tüm girişimsel işlemler de zorunluluktur.

Tablo 2. Özet

Viral bulaş riskleri:
• Özellikle kan, sindirim kanalı ve solunum yolu kaynaklı.
• Aerosol etkisi gösteren işlemler: Entübasyon/ekstübasyon, maske ile soluyan hasta, bronkoskopi, laparoskopik işlemler, elektrokoter kullanımı

Ameliyata hazırlık:
• Servis, ameliyathane, anestezi, yoğun bakım ekibi ile yakın iletişim
• Postoperatif yoğun bakıma gitme ihtimali yüksek hastalarda, ameliyathanede, yoğun bakım ventiltörünün kullanılması düşünülebilir
• Gece ameliyatları mümkün mertebe azaltılmalı
• Kişisel koruyucu ekipmanların yeri ve miktarı konusunda ameliyat salonu ekibi ile koordinasyon

Ameliyat süresince:
• Sadece gerekli (en az sayıda) personel ameliyat salonunda bulunmalı
• Ameliyat salonu dışında ameliyat teknikeri bulunmalı
• Telefon, çağrı cihazı, saat, takılar vb. ameliyat salonu dışında bırakılmalı

Kişisel koruyucu ekipmanlar:
• Cerrahi işlemler, aynı zamanda aerosol (havada serbest partikül salıcı) etkisi oluşturan işlemler olduğundan N95 maske, ameliyat gözlüğü ya da diğer KKE'ler mutlaka kullanılmalıdır

Ekipman olarak;

1. Sıvı geçirmeyen bir önlük,
2. KKE içeren maske N95 veya FFP grubu üzerine cerrahi maske,
3. Yüz koruyucu şeffaf bariyer,
4. Eldiven (çift kat) ya da biyobariyerli eldiven,
5. Tüm ayağın örtülebildiği deliksiz ayakkabı ya da en iyisi steril edilebilen lastik çizmeler kullanılmalıdır.

El ve ayaklarda açılma olursa bulaş-kontaminasyon riskine karşı yapışkan bantlarla sabitleme gerekmektedir.

Ameliyat

Kanıt değeri düşük olmakla beraber; konvansiyonel yöntemlerle cerrahi ekibin hastanın sıvı ve dokularına teması artıyordur, ancak laparoskopik ameliyatlarda kullanılan gazın da aeresol (havada partiküllerin yayılması) etkisiyle viral kontaminasyona yol açabileceği şeklinde yaygın bir endişe mevcuttur. Yu ve arkadaşları yaptıkları çalışmada SARS-CoV-2'nin damlacık yolu ve temas yolu ile bulaştığını, fekal-oral yol ve aerosol bulaşın da yok sayılamayacağını bu nedenle de COVID-19 ile enfekte kolon kanserli hastalarda laparoskopik cerrahi ameliyatlarının yapılabileceğini ancak laparoskopik gazların iyi yönetilmesi gerektiğini bildirilmişlerdir (7).

Laparoskopik uygulamalar için CO_2 filtrelerinin kullanılması tavsiye edilmektedir. Chen ve arkadaşları ise çapraz enfeksiyonu önlemek için cerrahi operasyonların azaltılması gerektiğini, malign tümörler için multidisipliner tedavilerin önerilmesi ve cerrahi olmayan anti-tümör tedavilerin daha yüksek öncelikle seçilmesi gerektiğini, neoadjuvan tedavilerin, NCCN kılavuzunun endikasyonlarını karşılayan ileri evrelerdeki gastrointestinal sistem kanseri için şiddetle tavsiye edildiğini bildirmişlerdir (8). Bunlara ek olarak obstrüksiyonlu mide veya özofagogastrik bileşke tümörlü hastalarda, semptomları hafifletmek için gastrik tüp veya stent yerleştirilmesi, enteral beslenme teminini sağlamak için transnazal enteral besleme tüpü entübasyonu/perkütan endoskopik gastrostomi uygulanabilineceğini, obstrüksiyon yapmış kolorektal kanserlerde stentleme işleminin elektif cerrahiye köprüleme yapıp acil cerrahi gereksinimini azaltması ve sonraki cerrahi sonuçları da daha iyi hale getirdiğine değinmiştir.

Bu hastaların atıkları için standart uygulamalar önerilmektedir. Çünkü açıkçası bununla ilgili bir veri henüz yoktur. Patolojik piyesler için de keza aynı durum söz konusudur.

Ameliyathaneden çıkan personel, kullanılmış önlüklerini ve eldivenlerini giriş odasında atmalı ve giriş odasından ayrılmadan önce el hijyenini yenilemelidir. Tüm KKE'ler giriş odasının dışında kaldırılmalıdır. Postoperatif YBÜ ihtiyacı olmayan hastalar ameliyathanede uyandırılmalıdır. Hasta servise gitmeye hazır olduğunda, izolasyon odasına veya YBÜ'ye giden yol tekrar temizlenmelidir.

Ameliyat salonu personelinin hastayı servise/yatağına geri göndermesine, tüm yüzeylerin, ekranların, klavyenin, kabloların, monitörlerin ve anestezi makinesinin dekontaminasyonunun sağlanmasına izin vermek için vakalar arasında en az bir-iki saat olmalıdır. İlaç tepsisi ve hava yolu arabasındaki kullanılmayan tüm ürünlerin kontamine olduğu varsayılmalı ve atılmalıdır. Tüm personel, görevlerine devam etmeden önce duş almalıdır.

Ek bir önlem olarak, onaylanmış COVID-19 olgularından sonra, ameliyat odasını dekontamine etmek için bir hidrojen peroksit buharlaştırıcı kullanılmalıdır.

Sonuç

Şu anda tüm dünyayı etkileyen COVID-19 pandemisi neredeyse tüm iş kolları ve meslek gruplarında bir yavaşlama hatta durmaya yol açarken en çok sağlık sistemine iş yüklenmekte ve sağlık çalışanlarının riskleri de buna paralel artmaktadır. Türk Cerrahi Derneği bu makale ile durum değerlendirmesi ve alınacak önlemleri sıralamış olup, bundan sonraki gelişmelere yönelik duyurular ve düzenlemeleri web sitesi, e-posta ve sosyal medya üzerinden tüm üyeleriyle ve kamuoyu ile paylaşacaktır.

Teşekkür

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REVIEW-ABSTRACT
Turk J Surg 2020; 36 (1): VI-X

General Surgery Operating Room Practice in Patients with COVID-19

Ahmet Serdar Karaca, M. Mahir Özmen, Ahmet Deniz Uçar, Ahmet Çınar Yastı, Seher Demirer

On Behalf of the Initiative of the Board on Directors of the Turkish Surgical Society

ABSTRACT

The virus COVID-19, which emerged in China in December 2019, was announced by the World Health Organization as a pandemic in January 2020. It is known that infection is not severe and may even progress without symptoms in patients who have come into contact with COVID-19. Although various organizations have been informed about how to take measures to protect the patient and the surgeon in case of diseases requiring urgent or elective surgery in people infected with COVID-19 or in cases with high suspicion, there is still no definite judgment between patients, physicians and health authorities. In this study, which was prepared with the initiative of the Turkish Surgical Association, we tried to shed light on what should be done and how surgeons should act in patients whose operation is mandatory in light of the available data.

Anahtar Kelimeler: COVID-19, coronavirus, surgery, personal protective equipment

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ORIGINAL ARTICLE
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Stage predictivity of neutrophil/lymphocyte and platelet/lymphocyte ratios in pancreatic neuroendocrine tumors

Kürşat Dikmen[1](ID), Mustafa Kerem[1](ID)

[1] Department of General Surgery, Gazi University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: This study aimed to analyze the correlations between European Neuroendocrine Tumor Society (ENEST), Tumor Node Metastasis (TNM) staging systems and pre-operative neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratios (PLR) in patients with pancreatic neuroendocrine tumor (PNET).

Material and Methods: Forty-four patients with diagnosed PNET were analyzed retrospectively. Accordingly, the patients' blood and clinicopathological parameters were analyzed. The correlations between laboratory parameters and tumor stages were evaluated using Eta correlation analysis. The control group was composed of volunteering healthy participants who had similarities with our study group as regards age and gender.

Results: According to ENETS classification, 34% of the patients were stage I, 25% were stage II, 20.4% were stage III and 20.4% were stage IV. NLR and PLR mean values were 2.4 and 127, respectively. NLR values of the patients in the study group were higher than those of the control group (p= 0.001). NLR and PLR values of stage I, II, III and IV patients tended to increase in parallel to the higher stages according to ENETS system (p= 0.0001 and p= 0.0001, respectively). Similarly, NLR and PLR values increased in parallel to the higher stages according to TNM system (p= 0.0001 and p= 0.0001, respectively). In addition, NLR values were found to be higher in patients with lymph node metastasis than in those without (p= 0.001).

Conclusion: Increased levels of inflammatory mediators such as NLR and PLR are associated with advanced stages of patients with PNET.

Keywords: Pancreas, neuroendocrine tumor, inflammation, stage

INTRODUCTION

Pancreatic neuroendocrine tumors (PNET) are rarely encountered but clinically significant tumors. They are seen approximately at the rate of one out of a hundred thousand all over the world and they constitute 1-2% of malignancy stemming from the pancreas (1-4). Since the majority of PNETs are non-functional tumors, they are usually diagnosed incidentally. Even if they are diagnosed incidentally or at a smaller size, they can display aggressive progression (5). PNETs are heterogeneous neoplasms with biological behaviors at a wide spectrum (6,7). Significant prognostic factors such as mitotic ratio, nuclear grade, vascular invasion, and existence of metastasis, necrosis and Ki-67 expression can only be detected pathologically (2,4). There are no tumor markers used routinely in predicting the prognosis of PNETs especially in the pre-operative period and in determining treatment strategy. Therefore, markers are needed for predicting malign behaviors and prognosis. The gold standard in determining the treatment for PNETs is the stage of the disease. Staging systems adopted by World Health Organization (WHO), American Joint Cancer Commission (AJCC) and European Neuroendocrine Tumor Society (ENETS) are used in staging the disease. While AJCC classification system was created on the basis of TNM system used for pancreatic adenocarcinoma, the ENETS system was created on the basis of studies involving PNET patients with large series. There are differences between the two systems of classification in terms of determining treatment and their effects on prognosis (8,9). The differences are more remarkable especially in stage 1 and stage 3 diseases. Therefore, new markers are needed for guidance in arranging the treatment and for use in estimating prognosis.

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Corresponding Author
Kürşat Dikmen
E-mail: kursatdikmen@yahoo.com

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It is clearly known that cancer is closely related to local and systemic inflammatory response (10). Tumor-related inflammatory response mechanism contains several inflammatory mediators and cells. Besides playing roles in tumor progression and pathogenesis, inflammatory process can also cause changes in response to anti-tumoral treatment. Thus, inflammatory response causes changes in hematological parameters such as neutrophil, lymphocyte, monocyte and platelet. Changes, the increase in the amount of neutrophil and decrease in the number of lymphocytes for instance, are indicators of systemic inflammation. Therefore, neutrophil/lymphocyte ratio (NLR)- which is derived by dividing the number of neutrophils into the number of lymphocytes- and platelet/lymphocyte ratios (PLR)- which is derived by dividing the number of platelet into the number of lymphocytes- have attracted attention recently and become simple and useful prognostic markers in many types of cancer (11). In recent years, increased NLR and PLR values prior to treatment and deteriorated prognosis in colorectal, breast, gastric, liver and pancreatic cancers have been found to be associated with shortening of survival time and with deterioration in responding to treatment (12-15). It has been demonstrated by those studies that indicators of systemic inflammatory response play critical roles in cancer growth (10). Nevertheless, there is small number of studies that evaluated the prognostic role of NLR and PLR in PNETs.

With the hypothesis that NLR and PLR -the indicators of systemic inflammatory response- can vary with the stage of PNETs, this clinical study aimed to analyze the correlations between ENETS and TNM staging systems and pre-operative NLR and PLR levels.

MATERIAL and METHODS

Patients

Clinicopathologic data coming from 44 patients who had been histopathologically diagnosed to have PNET in our hospital in the period between March 2010 and April 2017 were analyzed retrospectively. Ethics committee approval was received for this study from the Ethics Committee of Gazi University (No. 2018/108). Informed consent form was obtained from all patients. The number of neutrophils, lymphocytes and platelets was determined from peripheral blood samples taken in the pre-operative period based on demographic data such as age and gender, and tumors were divided into categories as low, intermediate and high grade according to WHO 2010 (16). The patients were staged according to TNM staging systems adopted by ENETS and AJCC (7^{th} edition). The period between the date of operation and the date of death or of last monitoring was regarded as survival time. Patients with infection, hematologic diseases, renal dysfunctions and earlier cancer history were excluded from the study. The control group was composed of 44 healthy individuals who were consistent with the study group in age and gender and who had consulted our hospital for check-up.

NLR and PLR Calculation

Circulating blood count (CBC), which was routinely checked prior to operations for each patient, was recorded on the database of the study. CBC of the individuals in the control group during check-up was also recorded. NLR was calculated using the proportion of absolute neutrophil count in circulating blood to absolute lymphocyte count. In the same way, it was calculated by dividing PLR absolute platelet count into absolute lymphocyte count.

Statistical Analysis

All statistical analyses were done on IBM SPSS 20.0 (IBM Corp., Armonk, New-York, USA) version, and $p< 0.05$ values were considered statistically significant. Continuous data were analyzed using mean, median, standard deviation and 95% confidence interval. Kolmogrov-Smirnov test was used in finding whether or not the data fit normal distribution. Independent t test was used in comparing the variables consistent with normal distribution, whereas Mann-Whitney U test was used in comparing the variables inconsistent with normal distribution. Eta correlation analysis (Ordinal by interval) was used for the relationship between NLR/PLR and both tumor stages.

RESULTS

Patient Characteristics

Demographic data concerning the patients are shown in Table 1. Median age of the patients was 54 (range: 24-73). Twenty-one of the patients were females while 23 of them were males. Median tumor diameter was 2.7 cm (range: 0.3-10). Patient distribution according to TNM and ENETS stages are presented in Table 1. Comparison of the patients with PNET according to ENETS and TNM classification systems are shown in Table 2. Pathologic evaluation revealed that 18 patients (40.9%) had lymph node metastasis.

Evaluation of Inflammatory Markers (NLR and PLR) in PNET Patients and Control Group

As illustrated in Table 1, neutrophil and platelet counts were higher and lymphocyte counts were lower in PNET patients when compared with controls. Median NLR was 2.4 (range; 1.2-5.2) in PNET patients and in healthy controls, median NLR value was 1.8 (range; 0.9-3.7). Likewise, median PLR level was 122 (range: 71-245) in healthy controls and 127 (range: 59-500) in patients with PNET.

Relationship of NLR and PLR Levels with ENETS Classification in PNET Patients

The correlation between NLR and PLR levels with ENETS stage is shown in Table 3. It was suggested that there was a significant association between tumor stages with NLR, PLR and platelet levels ($p< 0.05$). While stage I had the lowest values, stage IV had the highest values. NLR, PLR and platelet levels had a tendency to increase following the tumor stages and were observed with a

Table 1. Demographic, laboratory, and clinicopathologic features of patients with PNET and healthy control group

	PNET patients	Control	p
Age, year	53 (24-70)	51 (30-88)	0.869
Male/Female	23/21	23/21	0.812
Neutrophil (10^9/L)	4.3 (2.3-9.3)	3.8 (1.7-6.2)	**0.042**
Lymphocyte (10^9/L)	1.5 (0.9-3.3)	2.0 (1.0-2.7)	**0.038**
Platelet (10^9/L)	258 (112-609)	247 (134-442)	0.534
NLR	2.4 (1.2-5.2)	1.8 (0.9-3.7)	**0.001**
PLR	127 (59-500)	122 (71-245)	0.188
Tumor size, cm	2.9 ± 2.6 2.7 (0.3-10)		
Lymph node metastasis Positive Negative	 18 (40.9) 26 (59.0)		
WHO grade, n (%) G1 G2 G3	 26 (59.0) 3 (6.8) 15 (34.0)		
ENETS stage, n (%) Stage 1 Stage 2 Stage 3 Stage 4	 15 (34.0) 11 (25.0) 9 (20.4) 9 (20.4)		
AJCC TNM stage, n (%) Stage 1 Stage 2 Stage 3 Stage 4	 23 (52.2) 9 (20.4) 3 (6.8) 9 (20.4)		

PNET: Pancreatic neuroendocrine tumor, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, WHO: World Health Organization, ENETS: European Neuroendocrine Tumor Society, AJCC TNM: American Joint Cancer Commission.

Table 2. Comparison of patients with PNET according to ENETS and TNM classification systems

	ENETS stage 1	ENETS stage 2	ENETS stage 3	ENETS stage 4
TNM stage 1	15	8	0	0
TNM stage 2	0	3	6	0
TNM stage 3	0	0	3	0
TNM stage 4	0	0	0	9

PNET: Pancreatic neuroendocrine tumor, ENETS: European Neuroendocrine Tumor Society, TNM: Tumor Node Metastasis.

significantly demonstrable higher level as of stage IV. Neutrophil and lymphocyte levels did not significantly correlate with tumor stages, but a tendency to increase for the neutrophil count and a tendency to decrease for the lymphocyte were observed.

In contrast with the controls, rise in NLR started at stage I, and there was tendency to rise in parallel to the increase in stages. While the differences between Stage I patients' NLR and control group's NLR were not statistically significant, the differences between Stage II, III and IV patients' NLR and control group's NLR were statistically significant. Besides, the differences between stage III and IV patients' NLR and stage II patients' NLR were also statistically significant (Table 3).

Yet, rise curve for PLR did not start at stage I. In addition to that, PLR at stage I decreased in comparison to the control group while it increased at stage II and reached the maximum value at stage IV. High values in Stage II patients' PLR were found to

Table 3. The relation between lymphocyte, neutrophil, platelet, NLR and PLR according to ENETS staging system

	Stage I	Stage II	Stage III	Stage IV	Control	p
Lymphocyte	2.0 ± 0.7	1.6 ± 0.5	1.4 ± 0.3	1.3 ± 1.1[a,b]	2.0 ± 0.4	0.066
Neutrophil	4.2 ± 1.6	4.3 ± 0.8	5.1 ± 1.9	5.5 ± 1.7[a]	3.8 ± 1.1	0.242
Platelet	197 ± 65	276 ± 44[a,b]	387 ± 110[a,b,c]	411 ± 92[a,b,c]	247 ± 63	**0.0001**
NLR	2.1 ± 0.5	2.8 ± 0.7[a]	3.4 ± 1.2[a,b]	4.2 ± 1.1[a,b,c]	1.8 ± 0.9	**0.0001**
PLR	107 ± 23	179 ± 51[a,b]	284 ± 129[a,b]	324 ± 105[a,b,c]	122 ± 71	**0.0001**

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ENETS: European Neuroendocrine Tumor Society.
Kruskal-Wallis test; when compared with control group [a] p< 0.05, Compared with Stage I [b] p< 0.05, Compared with Stage II [c] p< 0.05. Bold values are statistically significant.

Table 4. The relation between lymphocyte, neutrophil, platelet, NLR and PLR according to TNM staging system

	Stage I	Stage II	Stage III	Stage IV	Control	p
Lymphocyte	1.9 ± 0.6	1.6 ± 0.5	1.2 ± 0.1	1.3 ± 1.1[b]	2.0 ± 0.4	0.065
Neutrophil	4.3 ± 1.4	4.5 ± 1.7	5.8 ± 1.4	5.5 ± 1.7	3.8 ± 1.1	0.163
Platelet	221 ± 66	332 ± 71[a,b]	468 ± 131[a,b]	411 ± 92[a,b,c]	247 ± 63	**0.0001**
NLR	2.4 ± 0.7	2.7 ± 0.8[a]	4.6 ± 0.8[a,b,c]	4.2 ± 1.1[a,b,c]	1.8 ± 0.9	**0.0001**
PLR	127 ± 53	194 ± 115[a,b]	366 ± 71[a,b]	324 ± 105[a,b,c]	122 ± 71	**0.0001**

NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, TNM: Tumor Node Metastasis.
Kruskal-Wallis test; when compared with control group [a] p< 0.05, Compared with Stage I [b] p< 0.05, Compared with Stage II [c] p< 0.05. Bold values are statistically significant.

be statistically significant in comparison with the control group and stage I group. Similarly, stage IV group- in which maximum PLR values were found- the highness in values was found statistically significant upon comparing it with the values for the control group and the Stage I and Stage II groups (Table 3).

Upon comparing the control group with stage II, III and IV groups in terms of the number of platelets; the differences between stages in the number of lymphocytes and neutrophils were not found significant (Table 3).

There was a strong positive correlation between NLR/PLR and ENETS staging system (r= 0.58 and p= 0.0001, r= 0.76 and p= 0.0001, respectively), which means that NLR levels increase as the ENET stages progress.

Relationship of NLR and PLR Levels with TNM Stages in PNET Patients

The relationship between NLR, PLR and other parameters with TNM stage are presented in Table 4. It was suggested that there was a significant relationship between tumor stages (I to IV) with NLR, PLR and platelet levels (p< 0.05). While stage I had the lowest values, stage IV had the highest values. NLR, PLR and platelet levels had a tendency to increase following the tumor stages and were observed with a significantly detectable higher level as of stage IV. Neutrophil and lymphocyte levels did not significantly correlate with tumor stages, but a tendency to increase for the neutrophil count and a tendency to decrease for the lymphocyte was observed.

In contrast with the control group, rise in NLR started at stage I and tended to increase. While the differences between stage I patients' NLR and control group's NLR were statistically insignificant, the differences between Stage II, III and IV patients' NLR and control group's NLR were significant. Besides, while the differences between stage IV patients' NLR and stage I and II patients' NLR were statistically significant, the differences between stage III patients' NLR were statistically insignificant (Table 4).

In a similar way, rise curve for PLR started at stage I and it reached the maximum value at stage IV. Highness in stage II, II and IV patients' PLR was found to be statistically significant when compared to control group's values. Upon comparing stage II and stage III patients' PLR values, stage III patients' PLR was found to be higher than those of stage II but the high values were not found statistically significant (Table 4). There was a strong positive correlation between NLR/PLR and TNM staging system (r= 0.59 and p= 0.0001, r= 0.74 and p= 0.0001, respectively), which means that NLR levels increase as the TNM stages progress.

Upon comparing the control group with all stage groups in terms of the number of platelets, it was found that the difference between stage IV group and the control group was significant and that the changes in the other groups were also significant. Apart from that, the differences between stages in terms of lymphocyte and neutrophil counts were not statistically significant either (Table 4).

DISCUSSION

Neuroendocrine tumors are a type of cancer associated with inflammation (17). This study, which was conducted with inflammatory markers such as NLR and PLR displaying the inflammatory and immunity situation comprehensively in cancer patients, demonstrated that PNET was a reliable indicator in predicting survival of patients having different types of tumors such as pancreatic adenocarcinoma, colorectal cancer, hepatocellular cancer carcinoma, gastric neuroendocrine tumors and breast cancer (11,13-15,18). It was thought based on these studies that inflammatory markers such as NLR and PLR could be useful in prognosis of PNET patients and of their response to treatment, and this current study analyzed the correlations between NLR, PLR and tumors and TNM and ENETS staging systems separately in patients diagnosed to have PNET. The reason for this is that single staging method is not used in the world today for PNET patients. While ENETS system is frequently used in Europe, AJCC system is often used in the USA (6). For this reason, there is controversy in determining the prognosis for PNET patients and in the selection of treatment protocols. Lou et al. have demonstrated that stage 3 disease rates were rare in AJCC system, that the prognosis of stage 1 and stage 2 patients was similar in ENETS system and that stage 3A patients' prognosis was worse than the prognosis of stage 3B patients (16). Therefore, it is argued that staging systems should be modified.

It was observed in this study that NLR and PLR levels were significantly lower in healthy controls than PNET patients. Moreover, it was seen that NLR and PLR had a tendency to increase at each stage of the disease. Based on these results, it could be claimed that neutrophil and platelet dependent inflammation processes may play active roles at different stages of PNET.

Tong et al. have shown that NLR and PLR levels were higher in metastatic but resectable tumors with PNET patients (advanced stage) (19). These findings are consistent with our study. Increasing levels or both markers are reflective of the active interaction between in vivo tumor loads and host immune system. In addition to demonstrating the importance of NLR and PLR in PNET diagnosis, this study also showed the changes of both markers depending on tumor stages. This study put forth that both NLR and PLR had risen at earlier stages of the tumor. Thus, it is suggested that neutrophil and platelet provided early reaction in PNET's development, which causes the increase in NLR and PLR levels. In addition to the fact that both markers can provide important information in the pre-operative period in early diagnosis of PNET patients, the fact that this situation is not specific to PNET patients is a disadvantage considering that these markers can rise in any inflammation of metabolism.

Salman T et al. have reported that high levels of NLR and PLR are associated with high grade and advanced stage (20). In their prospective study conducted with 97 patients diagnosed to have PNET, Giatanidis et al. have demonstrated that NLR is an independent predictive determiner of survival in PNET patients (21). Besides, preoperative NLR is a potentially independent predictor for disease progression and lower lymphocyte-to-monocyte ratios is an independent predictor or tumor recurrence with PNETs.

In many studies, it has been demonstrated that inflammatory markers such as neutrophils and platelets are played a critically role in tumor development and metastasis (22-24). Higher NLR and PLR is possible with the elevation in neutrophil and thrombocyte counts and with the decrease in lymphocyte counts, which in turn gives mediated anti-tumor immune response with increased neutrophil and increased platelet dependent inflammatory reactions. We believe that NLR and PLR can reflect inflammation cascade results playing roles in the development of cancer in PNET patients. Neutrophils, which are among immunity cells, are rapidly activated and when they encounter inflammatory signals, they migrate to the inflamed region. Continual stimulus to neutrophils depending on chronic inflammation causes severe oxidative stress leading to promutagenic DNA damage (24). The tumor formed causes the release of bio-substances such as interleucin-6 and tissue factor encouraging thrombocyte production and more circulation of activated thrombocytes in circulation (25-27). On the other hand, activated thrombocyte sets granule components such as vascular endothelial growth factor, platelet derived growth factor and transformatory growth factor-β free, and thus, they contribute to tumor growth (22). Inflammatory cells, which also include leukocytes and lymphocytes, play important roles in controlling the proliferation, survival and migration of tumor cells through apoptosis and angiogenesis (28-30).

Zhang et al. have demonstrated that the abundance of tumor-related neutrophils in circulation in patients with advanced cancer inhibited the activation of peripheral leucocytes and contributed to tumor metastasis (31). Other studies showed that tumor-related neutrophils supported tumor proliferation, that they set free pro-angiogenic mediators (VEGF), facilitated metastasis and that they caused more aggressive tumors (32). It has been described in an experimental breast cancer model that the main component and control of metastatic formation in lung tissue was arranged by neutrophil (33). Besides, if neutrophils are activated adequately in endothelial cells, they can support the sticking of tumor cells to a lymphatic endothelial cell (34,35). Both markers in this study changed differently at earlier stages of PNET and they had similarities displaying significant changes at stages II and III. The underlying mechanism is indefinite at present. Nonetheless, NLR and PLR levels had the highest increase at stage III and showed the important role inflammatory response played in the progress of PNET. We observed that myeloid cells created the inflammatory micro

framework necessary for EMT, intravasation and metastasis and they facilitated tumor developments' transition into the other stages. In a study conducted with mouse models, it has been reported that neutrophil-mediated immune response played critical roles in spontaneous breast cancer metastasis (36). The difference between both indices in terms of tumor stage responses should reflect the different pathophysiological roles inflammation in tumor growth. It has been reported that NLR was a superior prognostic and predictive marker in PNETs when compared to PLR (37). In addition to the above-mentioned findings, this current study shows that PLR and NLR are directly related to tumor invasion (T stage) in PNET and prevalence of lymph node metastasis. These observations can be associated with the role thrombocytes, in thrombocyte-cancer interaction cycle, play in favor of releasing thrombocyte granule content and of cancer growth (22). In a similar way, it has been found that malign over cancer cells and thrombocytes which were activated in the process of tumor development had increased tumor cell invasion depending on dose (38). In a recent study, it has been suggested that thrombocytes stimulated colon cancer development. It has been found that thrombocyte derived trombospondin 1 and klusterin increased the gene expression of MMP-9 by means of P38MAPK route (39).

Although the biology underlying the above mentioned changes in NLR and PLR is indefinite, it is widely accepted that tumor development is associated with inflammation and immunity. Inflammatory mediators and cytokines such as epidermal growth factor, transformatory growth factor-beta (TGF-beta), tumor necrosis factor-alpha (TNF-alpha), fibroblast growth factors (FGFs) and interleukins (IL-4, IL-8, IL-10 and IL-13) stimulate angiogenesis as a part of tumor or natural host immune response, cause matrix degradation and cancer progression, and thus, facilitate immunosuppression (29,40). Transcription factors such as NF-kappa B and STAT2 are activated by means of pathophysiological paths, and this causes inflammatory mediators and leukocytes to be suppressed around the tumor (41). Microenvironment, which is together with this inflammatory process, increases tumor development and accelerates the process of metastasis.

This study demonstrated that NLR and PLR values can be included in AJCC (r= 0.59 and p= 0.0001, r= 0.74 and p= 0.0001, respectively) and ENETS staging (r= 0.58 and p= 0.0001, r= 0.76 and p= 0.0001, respectively) systems and that there are strong correlations with the stages of the disease in PNET patients, which means that NLR levels increase as the TNM and ENETS tumor stages progress. This study analyzed the perspectives of correlations between the changes in preoperative NLR and PLR levels and tumor stages. This can also help in the selection of treatment for PNET patients or in evaluating responses to the treatment. Besides, we also believe that the study can inform us whether or not using medicine, which is a derivation of antithrombotic factor, would be useful as PLR levels rise and the stages progress in PNET patients. Another clinic importance of this study is that it can help explain some cancer behaviors, detect PNET patients earlier and find potential markers in order to be able to determine the response to treatment.

On the other hand, this study had certain limitations. Firstly, the study was designed as a retrospective study. Secondly, since NLR and PLR, which were the signs of systemic inflammation, were influenced by several factors such as chronic and acute inflammatory diseases, they reduced the sensitivity of our results. Therefore, these conditions should be verified by studies with prospective and high patient numbers.

CONCLUSION

In conclusion, this study demonstrated that increased level of inflammatory mediators such as NLR and PLR were associated with advanced stages of tumor in PNET patients. Neutrophils and thrombocytes may play important roles in cancer prognosis at different stages. Both parameters showed that there could be simple, potential markers usable in pre-operative period in determining the tumor stages in PNET patients. Prospective studies with the inclusion of bigger number of patients are urgently needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Gazi University (No. 2018/108).

Informed Consent: Informed consent form was obtained from all patients.

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ORİJİNAL ÇALIŞMA-ÖZET
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Pankreatik nöroendokrin tümörlerde nötrofil/lenfosit ve platelet/lenfosit oranlarına göre evre tahmini

Kürşat Dikmen[1], Mustafa Kerem[1]

[1] Gazi Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, pankreas nöroendokrin tümör (PNET) tanılı hastalarda "European Neuroendocrine Tumor Society (ENEST)" ve "Tumor Node Metastasis (TNM)" evreleme sistemlerinin preoperatif nötrofil/lenfosit oranı (NLO) ve platelet/lenfosit oranı (PLO) ile ilişkisini analiz etmektir.

Gereç ve Yöntem: Mart 2010-Nisan 2017 tarihleri arasında histopatolojik alarak tanısı PNET olan 44 hastaya ait veriler retrospektif olarak incelendi. Hastaların preoperatif kan ve klinikopatolojik parametreleri değerlendirildi. Laboratuvar parametreleri ile tümör evreleri arasındaki ilişki Eta korelasyon analizi kullanılarak tespit edildi. Yaş ve cinsiyet bakımından çalışma grubumuzla benzer özellikte olan sağlıklı gönüllüler çalışmamızın kontrol grubu olarak belirlendi.

Bulgular: ENETS sınıflamasına göre hastalar %34 (n= 15) evre 1, %25 (n= 11) evre 2, %20,4 (n= 9) evre 3 ve %20,4 (n= 9) evre 4 idi. TNM evrelemesine göre hastalar %52,2 (n= 23) evre 1, %20,4 (n= 9) evre 2, %6,8 (n= 3) evre 3 ve %20,4 (n= 9) evre 4 idi. Çalışma grubunda NLO ve PLO değerleri ortancaları sırasıyla 2,4 (range: 1,2-5,2) ve 127 (range: 59-500) idi. Çalışma grubundaki hastaların NLO değerleri kontrol grubuna göre yüksekti (p= 0,001). ENETS sistemine göre Evre 1, 2, 3 ve 4 hastaların NLO ve PLO değerleri evre ilerledikçe yükselme eğilimindeydi (sırasıyla p= 0,0001 ve p= 0,0001). Benzer şekilde TNM sistemine göre de NLO ve PLO değerleri evre ilerledikçe artmaktaydı (sırasıyla p= 0,0001 ve p= 0,0001). Ayrıca lenf nodu metastazı olan hastalarda NLO değerleri olmayanlara göre daha yüksek bulunmuştur (p= 0,001).

Sonuç: NLO ve PLO gibi enflamatuvar belirteçlerin yüksek olması PNET'li hastalarda ilerlemiş hastalık ile birliktelik göstermektedir.

Anahtar Kelimeler: Pankreas, nöroendokrin tümör, enflamasyon, evre

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An analysis of general surgery theses set up between years 1998-2018 in Turkey: Evidence levels and publication rates of 1996 theses

Murat Ferhat Ferhatoğlu[1](ID), Taner Kıvılcım[1](ID), Abdulcabbar Kartal[1](ID), Ali İlker Filiz[1](ID), Abut Kebudi[1](ID)

[1] Department of General Surgery, Okan University School of Medicine, Istanbul, Turkey

ABSTRACT

Objective: Setting up and advocating a thesis is mandatory at the end of the residency training program to become a specialist in general surgery according to the regulations on medical specialization in Turkey. Writing a thesis helps the resident to learn to ask structured questions, assembling the most accurate study design, managing the study process, collecting the results and building a conclusion with medical implications. In this descriptive study, we aimed to investigate the publication rates of the theses written in the field of general surgery and to assess the properties of the published theses.

Material and Methods: We performed an online search on September 1, 2018, about the theses of general surgery residents on the website of National Thesis data center of Academic Educational Board in Turkey including theses of medical residents in university-affiliated hospitals and analyzed theses accomplished between 1998-2018. The publication status of the theses was assessed by the entry of author name, the title of the theses and keywords of the theses by using the search engines of PubMed, Google Scholar and Turkish Academic Network and Information Center Turkish Database (ULAKBIM). Data were presented in a descriptive form as absolute numbers and percentages.

Results: Between 1998-2018, 1996 theses were completed. 393 (20.5%) of these were published in a journal, and 288 (14.4%) were published in a journal indexed in SCI/SCIE. According to research methodologies, 79.2% of the experimental studies were published in SCI/SCIE indexed journals.

Conclusion: Publication rates of the theses in the field of general surgery are low as they are in other specialties of medicine. This descriptive study might give an idea about the low scientific publication rates of general surgery theses. Further studies are needed to understand the underlying factors, which are responsible for this scant scientific performance.

Keywords: Thesis, publication, residency, general surgery, surgical education

INTRODUCTION

The first of many scientific steps for a medical resident is to accomplish a thesis in the field of his/her. Creating a thesis enlightens the medical residents about how to ask structured questions, assembling the most accurate study design, manage the study process, collecting the results and building a conclusion with medical implications (1,2). Moreover, publishing a thesis as an article in scientific journals makes it more valuable (3). Also, the publication of a thesis may give an idea about the scientific quality of the institution (4). Setting up a thesis is mandatory to become a specialist in general surgery according to the regulations on medical specialization in Turkey. However, the publication of the thesis in a scientific journal is not obligatory. Publishing thesis in a scientific journal increases the merit and accessibility of the thesis (5). However, rate of the theses published in a scientific journal is not high in our country (1,6). In this descriptive study, we aimed to investigate the publication rates of the theses written in the field of general surgery and to assess the properties of the published theses.

MATERIAL and METHODS

In this retrospective observational study, we performed an online search on September 1, 2018, regarding the theses of general surgery residents on the website of National Thesis data center of Academic Educational Board in Turkey, which includes the theses of medical residents in university-affiliated hospitals, and analyzed the theses conducted between 1998-2018. We selected "General surgery" in the "Department" tab and collected information about the publishing years, author

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Corresponding Author
Murat Ferhat Ferhatoğlu
E-mail: ferhatferhatoglu@gmail.com

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names, thesis names, nature of the theses. The publication status of the theses was assessed by the entry of author name, the title of the theses and keywords of the theses by using the search engines of PubMed, Google Scholar and Turkish Academic Network and Information Center Turkish Database (ULAKBIM).

We divided subjects of the published theses into 14 main topics; endocrine diseases, upper gastrointestinal system diseases (not including bariatric surgery or obesity), bariatric surgery/obesity, intestines and colorectal diseases, breast diseases, hepatopancreaticobiliary diseases, endoscopy, hernia diseases, transplantation, peritoneum/ omentum diseases, surgical diseases of skin, trauma, sepsis-shock and miscellaneous (nursing, patient behaviors, basic science, other topics). Research methodologies of the published thesis were assessed under two groups; clinical and experimental. We analyzed the distribution of the published theses according to journal scope as SCI/SCIE indexed journals, ULAKBIM indexed journals, national and international journals (not indexed in SCI/SCIE, and ULAKBIM). We also determined published theses according to Levels of Evidence and Grades of Recommendation System (Table 1) (7).

Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quadrant, third quadrant, frequency, percentage, minimum, maximum) were used evaluating the study data. Pearson chi-square test, Fisher's exact test and Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was accepted as $p< 0.05$.

RESULTS

Between 1998-2018, 1996 theses were completed. 393 (20.5%) of those theses were published in a journal. And, 288 (14.4%) of those theses were published in a journal indexed in SCI/SCIE. Research methodologies and journal information are shown in Table 2. Publication years of the theses are shown in Figures 1, 2.

According to research methodologies, 79.2% of the experimental studies were published in SCI/SCIE indexed journals (Table 3).

According to the subject of the published theses, the percentage of publication in SCI/SCIE indexed journals was statistically significant ($p< 0.001$). As a result of post-hoc analysis, SCI/SCIE indexed journal publication percentages of the theses on peritoneum/omentum diseases and skin diseases/wound healing were higher ($p= 0.003$ and $p= 0.022$; respectively). In addition, SCI/SCIE indexed journal publication percentages of the theses about upper gastrointestinal system diseases and breast diseases were found to be lower ($p= 0.014$, $p< 0.001$) (Table 4). Sub analysis of the thesis subjects according to research methodology, number of experimental studies in intestines/Colon/Rectum/Anus, hepatopancreaticobiliary system, miscellenous, peritoneum/omentum, endocrine diseases group were 31 (41.3%), 25 (37.3%), 20 (60.6%), 30 (100%), 13 (46.4%), 12 (100%), respectively.

According to Levels of Evidence and Grades of Recommendation System evaluation, 76.8% of the published theses were in Level II (Figure 3).

Table 1. Levels of Evidence and Grades of Recommendation System

Level I	Studies consisted of high-quality randomized controlled trials
Level II	Studies consisted of lesser-quality randomized controlled trials and prospective comparative studies
Level III	Studies were made up of case-control and retrospective comparative studies
Level IV	Case series with no controls

Table 2. Research methodologies and indexation info of the published thesis

		n (%)
Research methodologies	Experimental study Clinical study	194 (49.3) 199 (50.6)
SCI/SCIE indexed journal	Yes	288 (73.2)
ULAKBIM indexed journal	Yes	23 (5.9)
Other journals	Yes	82 (20.8)
International journal	Yes	339 (86.3)
National journal	Yes	54 (13.7)
Publishing time (years)	Mean ± SD Min-max (median)	3.83 ± 2.98 0-17 (3)

SCI/SCIE: Scientific Citation Index/Scientific Citation Index Expended, ULAKBIM: Turkish Academic Network and Information Center Turkish Database.

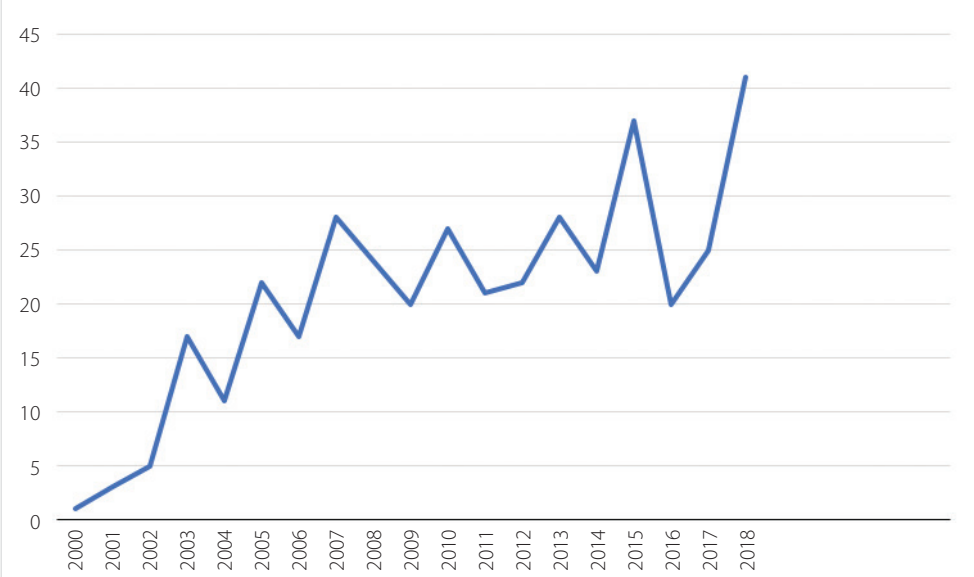

Figure 1. Publication numbers of the theses.

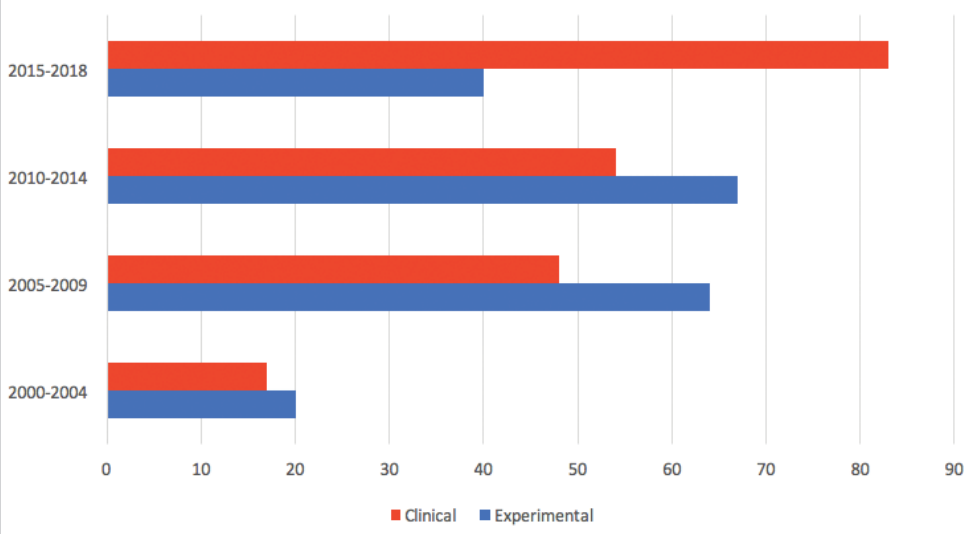

Figure 2. Research methodologies according to 5 year-periods.

Table 3. Publication rates of theses according to research methodologies in international and SCI/SCIE indexed journals

		Research methodologies		p
		Experimental	Clinical	
SCI/SCIE indexed	No	45 (20.8%)	71 (33%)	0.007
	Yes	149 (79.2%)	144 (67%)	
International	No	29 (11.8%)	33 (15.3%)	0.309
	Yes	165 (88.2%)	182 (84.7%)	

Pearson chi-squared test.
SCI/SCIE: Scientific Citation Index/Scientific Citation Index Expended.

Table 4. Subject of the published theses

	Total	SCI/SCIE	p	p (row vs. rest)
Intestines/Colon/Rectum/Anus	100	75 (75%)	< 0.001[a]	0.248[c]
Hepatopancreaticobiliary system	84	67 (83.1%)		0.389[c]
Miscellaneous	41	33 (80.4%)		0.136[c]
Peritoneum/omentum	32	30 (93.7%)		0.003[c]
Endocrine diseases	28	16 (57.1%)		0.111[c]
Skin diseases/wound healing	12	12 (100%)		0.022[b]
Diseases of upper gastrointestinal system	18	8 (44.4%)		0.014[c]
Breast disease	27	10 (37%)		< 0.001[c]
Hernia disease	13	8 (61.5%)		0.539[b]
Bariatric surgery/obesity	8	7 (87.5%)		0.446[b]
Transplantation	14	9 (64.2%)		0.566[b]
Endoscopy	4	4 (100%)		0.324[b]
Trauma	8	5 (62.5%)		0.699[b]
Shock/sepsis	4	4 (100%)		0.324[b]

[a] Fisher-Freeman-Halton exact test.
[b] Fisher's exact test.
[c] Pearson chi-square test.
SCI/SCIE: Scientific Citation Index/Scientific Citation Index Expended.

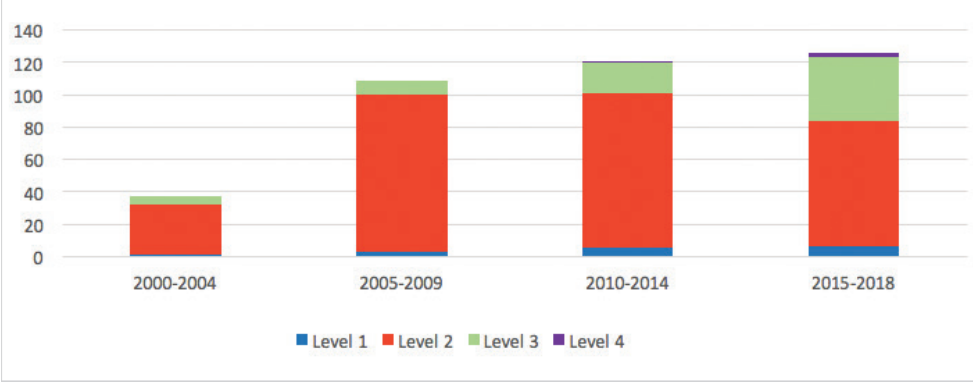

Figure 3. Evaluation of the theses according to Levels of Evidence and Grades of Recommendation System evaluation.

DISCUSSION

According to regulations of residency in medical doctorate and dentistry in Turkey, medical doctors (residents) are obligated to prepare and advocate a medical thesis in their field at the end of their training program (8). Idea setup, questioning, creating the study protocol, collecting the datum, assembling the results, arising the conclusions and concluding a clinical implication are steps of generating a scientific thesis. Accessibility of the scientific thesis is mostly inadequate, unfeasible or dependent on the accessibility of academic libraries. Publishing these valuable scientific papers in internationally indexed scientific journals is the best way to improve accessibility (2,9).

In this study, we noticed that the publication rates of the theses in the field of general surgery in international and SCI/SCIE indexed journals were 16.9% and 14.4%, respectively. In the study of Ogrenci et al., publication rate of the theses in SCI/SCIE indexed journals is 18.2% (9). Another study from Turkey has revealed that the publication rate of the theses on public health in SCI/SCIE indexed journals is 11.9% (1). The study of Ozgen et al. revealed that Turkish medical theses written between years 1980 and 2005 revealed that only 6.2% of the theses were published in MEDLINE indexed journals (6). A recent study of Mayir et al. have also reported that the publication rate of the theses on general surgery in SCI/SCIE indexed journals is 22% (10). Relevant publications on general surgery in the literature

have notified this ratio between 17% and 52% (11-13). Factors considered as obstacles in the release of the theses include the lack of sufficient information in the residency programs on the writing of scientific papers, incapability of writing in foreign languages and the lack of motivating regulations for preparing a scientific publication (14). However, we are of the opinion that the most instrumental reasons of low publication rates may be the inability to allocate sufficient time for developing academic skills due to the excessive workload and the residents' view of the theses as only a ritual or necessity for the completion of the residency program. Lack of motivation in surgery residents could be another cause for low publication rates of the theses since they need to publish their theses in SCI/SCI-E-indexed journals only for the purpose of academic career and clinical promotions in a limited time period of their profession (1,2). In a study presented by Hollmann et al., reasons for not publishing theses have included work load, bias for negative results, insufficient tutor support, insufficient motivation/ personal interest, and family burdens (2). It is also possible that some other theses might have reached publication status after timepoint of retrieval of the dataset in this study. Namdari et al. have shown an inverse correlation between decreasing work-hours and increasing scientific publication rates in medical residents (15). Time spent doing research is the primary determinant of scientific productivity (16). A mentoring program designed for improving scientific skills also has a positive influence on publication rates of the residents (17).

It was seen in this study that an increase was observed in the number of published theses over time, which is compatible with the literature (6). We believe that this increase might be associated with the rise in the number of institutions having residency programs in Turkey.

Although the number of clinical studies was higher, we found that experimental studies were more published in SCI/SCIE indexed journals (p= 0.007). This result correlates with the results of Ogrenci et al. (9).

According to research methodologies, half of the theses were experimental studies. However, as indicated in Figure 2, there is an increasing tendency to clinical studies and quality of the theses demonstrates an upgrading pattern, which is shown in Figure 3. The presented research also reveals that experimental studies have significantly higher publishing rates. The reason of this difference is that clinical studies need more effort, take longer time to be finalized, longer length of follow-up facilitates the loss of patients, and experimental studies have more potential to provide original information which provides a higher potential for scientific publication (10). Although prospective randomized studies are the most valuable studies, these factors create a tendency on residents to compose experimental theses. But in recent years, there has been an increase in the number of clinical studies, which is thought to be due to developments in hospital computing systems and computer technologies that has increased and eased the possibility of data access.

In the study presented here, theses subjecting the diseases of peritoneum/omentum and skin/wound healing had higher publication rates (p= 0.003 and p= 0.022; respectively), and the most dominantly published theses in SCI/SCIE indexed journals were conducted on the intestines/colon/rectum/anus (n= 75). All theses on peritoneum/omentum and skin/wound healing were experimental studies with a higher potential of publishing in SCI/SCIE journals.

Limitations of this study include the website of National Thesis data center of Higher Educational Council of the Republic of Turkey that only collects theses written at university hospital clinics, database center has excluded theses conducted at training hospitals affiliated by Ministry of Health up to 2015, and National Thesis data center records were not complete and the exclusion of the theses which did not allow open access reading. In addition, the indexation status of the journals is variable (i.e., SCI and SCIE are dynamic in and out situations).

CONCLUSION

Surprisingly, an excessive proportion of medical doctoral theses are never published, as recorded by the two international online databases for scientific literature. The main reason for this problem is that the majority of the theses consist of low-level studies and experimental studies. The quality of medical theses needs to be improved, and adequate measures should be taken to advance the scientific merit. We believe that this problem can be solved by encouraging residents to publish in high-quality journals and residents who do not publish their theses, be deemed incomplete in the residency program.

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Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Türkiye'de 1998-2018 yılları arasında yapılan genel cerrahi tezlerinin analizi: 1996 tezin kanıt düzeyleri ve yayın oranlarının değerlendirilmesi

Murat Ferhat Ferhatoğlu[1], Taner Kıvılcım[1], Abdulcabbar Kartal[1], Ali İlker Filiz[1], Abut Kebudi[1]

[1] Okan Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Türkiye'de tıp uzmanlığı ile ilgili yönetmeliklere göre genel cerrahi uzmanı olmak için eğitim programının sonunda bir tez hazırlamak ve savunmak zorunludur. Bir tezin kurgulanması eğitimi devam eden uzman adayının; sorular sormayı, en doğru çalışma tasarımını birleştirmeyi, çalışma sürecini yönetmeyi, sonuçları toplamayı ve bilimsel çıkarımlar oluşturmayı öğrenmesine yardımcı olur. Bu tanımlayıcı çalışmada, genel cerrahi alanında yazılmış tezlerin yayın oranlarını araştırmak ve yayınlanmış tezlerin özelliklerini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Yüksek Öğretim Kurumu Tez Merkezinin internet sitesinde genel cerrahi uzmanlarının tezleri ile ilgili araştırma gerçekleştirildi ve 1998-2018 yılları arasında tamamlanan tezler analiz edildi. Tezlerin yayınlanma durumuna, PubMed, Google Akademik ve Ulusal Akademik Ağ ve Bilgi Merkezi (ULAKBİM) veri tabanlarının arama motorları kullanılarak yazar adı, tezlerin başlığı ve tezlerin anahtar kelimeleri aranarak bakıldı. Veriler, mutlak sayılar ve yüzdeler olarak sunuldu.

Bulgular: Çalışmada, 1998-2018 yılları arasında tamamlanan 1996 tez değerlendirilmiştir. Bu tezlerin 393 (%20,5)'ü bilimsel bir dergide, bunların da 288 (%14,4)'i SCI/SCIE endeksli bir dergide yayınlanmıştır. Araştırma yöntemlerine göre, deneysel çalışmaların %79,2'si SCI/SCIE endeksli dergilerde yayınlanmıştır.

Sonuç: Genel cerrahi alanındaki tezlerin yayın oranları, diğer tıp uzmanlıklarında olduğu gibi düşüktür. Bu tanımlayıcı çalışma, genel cerrahi tezlerinin bilimsel dergilerdeki düşük yayın oranları hakkında bir fikir verebilir. Bu yetersiz bilimsel performanstan sorumlu olan altta yatan faktörleri anlamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Tez, yayın, asistan, genel cerrahi, cerrahi eğitim

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ORIGINAL ARTICLE
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Intralesional epidermal growth factor application is a potential therapeutic strategy to improve diabetic foot ulcer healing and prevent amputation

Ömer Arda Çetinkaya[1] (ID), Süleyman Utku Çelik[2] (ID), Miraç Barış Erzincan[1] (ID), Barış Hazır[1] (ID), Hakan Uncu[1] (ID)

[1] Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey
[2] Clinic of General Surgery, Gulhane Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: This study aimed to investigate the efficacy of intralesional epidermal growth factor (EGF) in preventing the extremity from a major amputation and its effects on wound healing in chronic diabetic foot ulcers (DFUs).

Material and Methods: Thirty-three patients with DFUs were treated with intralesional EGF application between January 2013 and January 2017. The first endpoint was to determine the prevention rate of major amputation within 12 months following treatment. The second endpoints were the recovery of ulcer surface area with ≥ 50% granulation following two months and the healing of ulcer surface area with ≥ 75% granulation following six months after the first application of EGF.

Results: After three patients were excluded because of major side effects in the remaining 30 patients (48 DFUs), granulation rate of ≥ 50% was achieved in 24 (37 DFUs) patients, and not achieved in 6 (11 DFUs) patients eight weeks following the EGF application. A granulation rate of ≥ 75% was achieved in 21 (31 DFUs) patients after six months. At 12 months following the treatment, one major and seven minor amputations were performed, a total of 10 DFUs in five patients were not healed, and the DFUs in 17 patients completely recovered.

Conclusion: Intralesional EGF application has positive results in addition to good foot care in DFUs, and promising results can be obtained by protecting the extremity from amputation by using it in patients whose vascular intervention methods are not appropriate and have DFUs that do not heal with conventional wound care treatments.

Keywords: Amputation, diabetic foot ulcer, epidermal growth factor

INTRODUCTION

The prevalence of type 2 diabetes in the world is higher than expected and continues to rise in all regions. The main reasons for this rise are aging in the world population, economic developments, the proliferation of sedentary lifestyles, and the increase in obesity due to unhealthy food consumption (1). In 2017, there were 425 million diabetic patients in the world, and it is estimated that this number will reach 629 million with a 48% increase in 2045. In addition, there were 58 million diabetic patients which accounts for 8.8% of the population aged 20-79 in the European region whereas, it is estimated that this number will reach 67 million with a 16% increase. Moreover, total healthcare expenditure on diabetes was estimated to be 727 billion dollars (20-79 years) worldwide in 2017 (2).

Diabetic foot is a serious chronic complication consisting of lesions in deep tissues related to peripheral neuropathy and peripheral vascular disease. Its incidence has increased due to the increasing prevalence of diabetes and the prolonged life expectancy in diabetic patients. Diabetic foot ulcer (DFU) is a disease difficult to diagnose and treat and does not improve even with the newest treatment methods used in modern medicine. In diabetic patients, the risk of developing ulcers in lower extremities is 15% during the course of diabetes (3). Besides, amputation rate increases 10-20 times in diabetic patients compared to non-diabetics and the risk of mortality in the first 5 years in patients that underwent lower extremity amputation is nearly 40% (4,5).

In patients with DFU, health expenditures are 5 times higher than diabetic patients without foot ulcers. In 2007, one-third of the expenditures related to diabetes were

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Corresponding Author
Ömer Arda Çetinkaya
E-mail: omerardacetinkaya@yahoo.com

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made to DFUs. In addition, expenditures for the treatment of high-grade foot ulcers are 8 times higher than those with lower grades (6). The incidence of DFU in diabetic patients is 2% in high-income countries, and DFU is the most common cause of non-traumatic amputation and 1% of diabetic patients undergo low extremity amputations. These rates are higher in middle- and low-income countries. Considering this data, it is understood that the number of patients with DFU will increase in the upcoming period and we will continue to fight with this disease. However, DFU often does not respond to conventional and new treatment methods. Unsuccessful results lead to the amputation of the extremity with DFU (3,7).

Main points in the management of DFU are metabolic control, treatment of comorbidities, revascularization, antimicrobial treatment of infections and off-loading the pressure on the wound. In local wound treatment, aggressive debridement, wound dressings with moist healing and bacterial control; and if necessary, advanced treatments such as growth factors and skin produced by tissue engineering can be used (8-13). However, in some cases, the effects of these treatment modalities on clinical practice do not meet the expectations of clinical trials (14).

The healing process of DFU is prevented by local factors affecting all phases of recovery, such as abnormal neutrophil function in the late repair phase, defective fibroblast activity, poor angiogenesis, and lack of cell migration (15,16). Recombinant human epidermal growth factor (rhEGF) is a polypeptide consisting of 53-amino acids, which was isolated from submaxillary glands of rats by Stanley Cohen and Rita Levi-Montalcini in 1962 using DNA technology, which earned them the Nobel Physiology and Medicine Award in 1986 (17). This molecule acts by stimulating extracellular matrix formation, cellular proliferation, and angiogenesis and causes proliferation of fibroblasts, keratinocytes, and vascular endothelial cells (18-20). Its effect mechanism is based on the interaction of specific epidermal growth factor receptor (EGFr) with tyrosine kinase activity (21). Most of these receptors have been reported in human tissue. The rational justification for using rhEGF to treat DFU is mainly based on the reversal of the existing recovery disorder in patients with diabetes, especially the lack of growth factors in the wound area. rhEGF stimulates healing and angiogenesis and protects cells from oxidative and ischemia-reperfusion injury (20-22).

Some clinical studies have been conducted to evaluate the efficacy of topical administration of rhEGF in different indications such as radiogenic ulcers, venous ulcers, and burns (23-25). To obtain adequate activity, growth factor must be present in deeper layers of the wound. This may be limited in topical formulations because the diffusion of the active substance is affected by necrotic tissue, sepsis, inflammation, and wound proteases (25). However, intralesional injection of the growth factor may bring the active substance to the desired site. Therefore, we aimed to investigate the effectiveness of EGF application in the direction of protecting the extremity from the major amputation in this study.

MATERIAL and METHODS

Patients

Thirty-three patients who underwent intralesional EGF application for DFUs admitted to Ankara University School of Medicine, Department of General Surgery, Wound Care Unit between January 2013 and January 2017 were included into this study. Data from a prospectively collected database of patients having DFU, who failed to heal even after three months of conventional wound therapy, were retrospectively analyzed. The study included patients over 18 years of age with advanced DFUs, which failed to heal even after conventional wound treatment methods with a high risk of amputation. There was no distinction between the topographic location of the wound in the lower extremity.

Patients with necrotic tissue and/or advanced/non-treatable osteomyelitis in DFU, patients who were eligible for revascularization in DFU treatment according to clinical and radiological evaluations, patients with a history of malignancy, radiotherapy, sepsis, or known allergies to rhEGF, and patients who did not wish to participate in the study were excluded. Patients with renal or liver failure and patients who used immunosuppressive treatment or corticosteroids were also not included in the study. All patients were informed about the aim and methods of the research both verbally and in written form; written consent was also obtained from the patients before the completion of study measurement. The study protocol was approved by a local ethics committee (03-153-18) and was conducted following the Declaration of Helsinki.

Treatment Protocols

All patients were hospitalized during their treatment. Patients received severe glycemic control, and were treated for their comorbidities, and in patients who were eligible for revascularization, rhEGF (Heberprot-P®, Has Biotech, Turkey) was started afterward. In the local treatment of ulcers, adequate debridement was performed, and necrotic tissues were removed. Toe amputation, and if necessary, metatarsophalangeal amputation was performed when the toes were necrosed and then rhEGF was applied. Antimicrobial treatment of the infections was provided by appropriate local and systemic antibiotics according to tissue culture results and antimicrobial dressings were used when necessary. Before rhEGF administration, all ulcers were cleared of infection, which was proven by tissue cultures. Pressure reduction (off-loading) on the wound was ensured by bed rest, the use of a walker and, if necessary, performing an off-loading plaster.

While applying rhEGF to DFU, injectors with 75 µg of rhEGF diluted in 5 mL saline were prepared. rhEGF was injected into the

wound and to its peripheral tissue starting from deep layers in DFU that had been cleaned of dead tissues (with appropriate antibiotics if infected) before. Applications continued 3 days per week consecutively until full wound healing was achieved, or 8 weeks of treatment was done (a maximum of 24 doses). Treatment was stopped when successful healing tissue was obtained or the wound was completely closed or the wound area was less than 1 cm^2 with granulation. The safety of rhEGF was checked by symptoms and physical examination at each visit. Local and systemic side effects of rhEGF were classified as mild, moderate, severe, and very serious.

Follow-up

Diabetic scar ulcers of the patients were measured every two weeks before, during and after rhEGF treatment. Wound length, width, and depth were recorded using a measuring scale. For digital image analysis, standard photographs were taken by placing the scale on the border of the wound. The ulcer areas were measured in square centimeter (cm^2) by measuring the longest width and length of the ulcer after debridement. Recurrence and other long-term side effects were also checked during the follow-ups in the first year after the end of rhEGF treatment.

Outcome

The first endpoint of the study was to show that the extremity was rescued from major amputation within 12 months following the end of the treatment. The second endpoints of the study were the recovery of ulcer surface area with ≥ 50% granulation tissue two months after the first application of rhEGF and the healing of ulcer surface area with ≥ 75% granulation tissue six months after the first application.

Statistical Analysis

Data were expressed as mean ± standard deviation and range for continuous variables and frequency for categorical variables. All statistical data were analyzed with the use of Statistical Package for the Social Sciences version 16.0 for Windows (SPSS, Chicago, IL).

RESULTS

Thirty-five lower extremities were treated in 33 patients (24 male and 9 female) with a mean age of 61.7 years. Of the patients, 42.4% (n= 14) had a history of smoking with an average of 31.3 pack-years. Concomitant comorbidities were hypertension (81.8%), peripheral arterial disease (81.8%), atherosclerotic heart disease (57.5%), hyperlipidemia (30.3%), chronic kidney disease (21.2%), and chronic liver failure (9.1%). Only 12.1% (n= 4) of the patients did not have comorbidities. Mean duration of diabetes mellitus was 20.5 ± 10.5 years and the average HbA1c was 8.4 ± 3.6. Vast majority of the patients (81.8%) were using insulin therapy and the mean duration of insulin use was 12.1 ± 7.9 years. Ankle-brachial index (ABI) could not be evaluated in 6 lower extremities; mean ABI of the 29 extremities was 0.81 ± 0.18. Table 1 shows the baseline demographic and clinical characteristics of the patients.

A total of 52 DFUs in 35 lower extremities of 33 patients were treated. Mean size of the ulcers was 26.8 ± 6.1 cm^2. Foot ulcer was divided into three severity-level categories according to Wagner ulcer classification system (26): grade 3 (33 ulcers, 63.5%), grade 2 (2 ulcers, 3.8%), and grade 1 (17 ulcers, 32.7%). 32.6% (n= 17) of the DFUs were on the amputation stump, 21.1% (n= 11) were on the foot dorsum, 19.2% (n= 10) were on the heel, 17.3% (n= 9) were in the plantar region, and 9.8% (n= 5) were in other regions. In addition to conventional wound care methods, negative pressure wound therapy (NPWT) was performed in 54.5% (n= 18) of the patients, antibacterial passive wound care coverings were

Table 1. Demographics and the clinical characteristics of the patients

Characteristics	
Number of patients	33
Number of low extremities	35
Number of DFUs	52
Gender (female/male)	9 / 24
Age (years)	61.7 ± 12.1
Smoking history	
Positive history	11 (42.4%)
Mean package-year	31.3 ± 18.6
Comorbidities	
Hypertension	27 (81.8%)
PAD	27 (81.8%)
ASHD	19 (57.5%)
Hyperlipidemia	10 (30.3%)
CKD	7 (21.2%)
CLD	3 (9.1%)
Duration of diabetes (years)	20.5 ± 10.5
HbA1c (%)	8.4 ± 3.6
Wagner ulcer classification	
Grade 1	2 (3.8%)
Grade 2	17 (32.7%)
Grade 3	33 (63.5%)
Location of ulcers	
Amputation stump	17 (32.7%)
Foot dorsum	11 (21.2%)
Heel	10 (19.2%)
Plantar region	9 (17.3%)
Others (toe, medial malleolus etc.)	5 (9.6%)

DFU: Diabetic foot ulcer, PAD: Peripheral arterial disease, ASHD: Atherosclerotic heart disease, CKD: Chronic kidney disease, CLD: Chronic liver disease.

used in 21.2% (n= 7) and grafting with cellutone method was performed in 9.1% (n= 3).

The most common minor side effects were local burning and pain. Patients with minor side effects were treated with antihistamines, analgesics, and antiemetics if necessary. Despite minor reactions, rhEGF administration was continued. Anaphylactic reaction developed in one patient after the first administration of rhEGF and in another patient after the second administration of rhEGF. In one patient, syncope developed in the 5th session of rhEGF administration. These three patients were excluded from the study because of major drug side effects. In the remaining 30 (48 DFUs) patients, an average granulation rate of 72.2% was obtained after 8 weeks of treatment (Figure 1).

After eight weeks, which was the second endpoint of our study, granulation rate of 50% and above was achieved in 24 (37 DFUs) patients (Figure 2), and not achieved in 6 (11 DFUs) patients. In 21 (31 DFUs) of the 24 (37 DFUs) patients who had a granulation rate of 50% or more after eight weeks, a granulation rate of 75% or more was achieved after six months. Twenty-three of the 31 DFUs were fully healed and epithelialized, in 8 of them, wound size significantly decreased and granulation rate was above 95%. At 1-year follow-up of these 21 patients, 17 had no recurrence of ulcers, 4 of the patients had recurrent ulcers and three had toe amputation and one of them underwent a below-knee amputation. In the remaining 3 (6 DFUs) patients, granulation could not be ensured at 75% or more at six months despite 50% or more granulation at the 8th week. Although no improvement

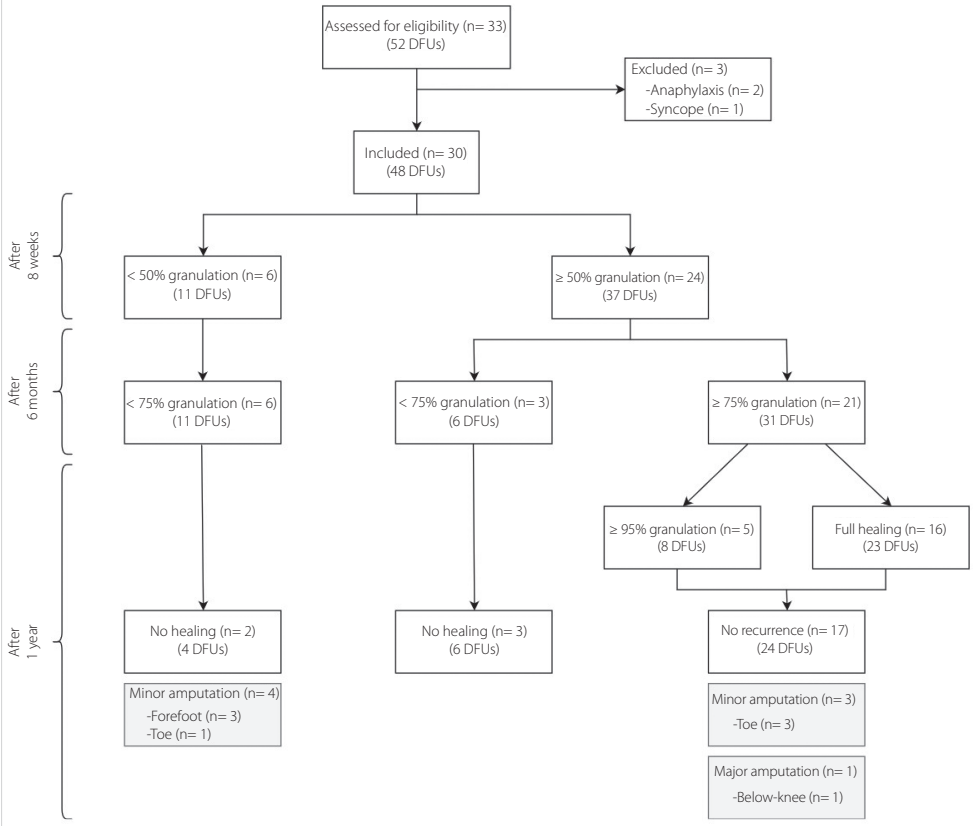

Figure 1. CONSORT flow diagram.

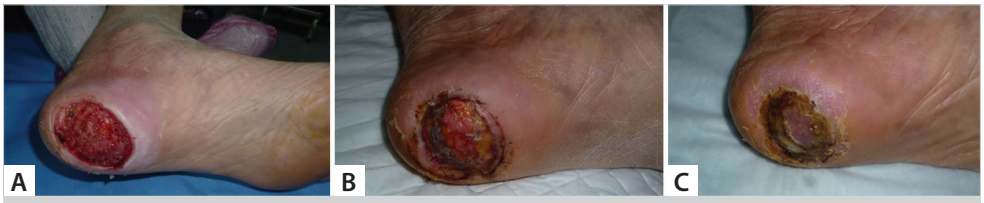

Figure 2. Chronological evoluation of a diabetic foot ulcer classified as Wagner grade 2 of a 55-years-old female. **A.** Initial appearance of the ulcer; **B.** A granulation rate of ≥ 50% (eight weeks after intralesional epidermal growth factor application), **C.** ≥ 95% granulation rate six months after the initial treatment.

was observed in the ulcers at the 1-year follow-up of these patients, they did not progress to amputation.

In 6 (11 DFUs) patients who did not have granulation of 50% or more after eight weeks, the rate of granulation was less than 75% at the end of 6th month. Despite rhEGF treatment in four of these patients, no improvement could be achieved and three had an amputation of the forefoot and one had an amputation of the toe. There was no improvement in the remaining two patients.

The second endpoint of our study was achieved in a total of 21 patients with a granulation rate of 75% and above after six months. The first endpoint of our study was the recovery of the extremity from major amputation within 12 months following the treatment and it was achieved in all patients except for one. In one patient, DFU recovered after rhEGF administration and even though the wound was completely closed after 14 weeks, it recurred in the same localization nine weeks after recovery. Despite all treatments, there was no improvement in the wound and the patient had to undergo a below-knee amputation. Except for this patient, minor amputation was performed in the lower extremity of seven patients in the first year. In three of them, even though the wound size decreased and more than 95% granulation tissue was formed and then complete recovery was achieved, the ulcers had progressed by recurrence and resulted in a toe amputation. In the remaining four patients, no improvement could be achieved and three had anterior foot amputation and one had toe amputation.

DISCUSSION

Several studies have suggested that growth factors and rhEGF contribute positively to wound healing. rhEGF stimulates epidermal repair in animal excisional and thermal injury models and may also stimulate dermal repair (27). In a study using wound model on pigs, Nanney et al. have found that there was an increase in the thickness of granulation tissue depending on the rhEGF dose and reported the relationship between rhEGF and epithelization (28). Cooper et al. have shown that some growth factors were significantly reduced in chronic wound fluid compared to acute wounds (29). In their meta-analysis, Zhang et al. have found that the addition of growth factors to standard wound care in partial-thickness burns was effective and safe (30). In a Cochrane systematic review by Marti-Carvajal et al., it has been shown that growth factors would increase the chance of complete healing of foot ulcers in patients with diabetes (31). Gomez-Villa et al. have also indicated that patients with DFU who received intralesional rhEGF was achieved more complete wound healing compared to standard wound care patients and rhEGF promoted epithelization of the wound bed and significantly reduced the area of treated ulcer (32).

As a result of our study, we observed that 29 of 30 patients with DFU who had undergone rhEGF treatment were rescued from major amputation. The ulcers completely healed in 21 patients and most of them (80.9%) did not recur. However, four of the 21 cases recurred within one year after treatment and three of them progressed minor amputations and in one patient the ulcer recurred after nine weeks and progressed to a below-knee amputation. As no adequate granulation was achieved, DFUs did not heal in nine patients in the one-year follow-up period. It was seen that the ulcers of five patients did not progress to any amputation, and in four patients ulcers progressed further to minor amputation. The most important result of our study, in DFUs where the known treatment methods had failed before, intralesional rhEGF application was an effective and reliable treatment that protected the extremity from major amputation. In contrast to other studies, 81.8% of the patients had peripheral arterial disease, 57.5% atherosclerotic heart disease, and 21.2% chronic kidney disease. Besides, 63.5% of the ulcers were grade 3 and 32.6% were located on the amputation stump. Although the rate of major amputation was low in our study, we thought that the high minor amputation and non-healing ulcer ratio were due to these reasons.

All patients in the study were hospitalized, their metabolic control was improved, and comorbidities were treated. Before rhEGF treatment was applied, tissue culture was taken from all patients' DFUs and then surgical debridement was performed and necrotic tissues and fibrins on the wound were removed. Wounds were washed with saline and when necessary, antibacterial passive wound dressings and NPWT were applied. According to the results of tissue cultures, appropriate local and systemic antibiotics were used and rhEGF treatment was started only when there was no reproduction in the tissue culture. Pressure reduction (off-loading) on the wound was ensured by bed rest, use of walkers and off-loading plaster when necessary. Despite all these treatments and rhEGF treatment, seven patients had to undergo minor amputation and one patient had to undergo major amputation.

In the study by Kahraman et al. evaluating long-term results of 34 patients with DFU undergoing intralesional rhEGF, patients received an average of 18 doses of rhEGF (33). In the five-year follow-up, four patients died due to diabetic complications. Of the remaining 29 patients, 27 had no recurrence of ulcers, while 1 had first toe amputation due to ischemic necrosis. In another study with 17 patients, complete wound closure was achieved in 16 of the patients, and only one patient had a recurrence of ulcers at 1-year follow-up (34). In a randomized controlled trial of hEGF-containing cream in 61 patients with DFU, Tsang et al. have randomly divided patients into three groups to investigate the effect of hEGF on healing (35). The first group was placebo, the second group was treated with low-dose hEGF containing cream, and the third group was treated with high-dose hEGF containing cream. As a result of the study, it was seen that com-

plete recovery rate was higher and recovery time was shorter in the third group compared to other groups. There was no significant difference in healing time between the placebo group and low-dose hEGF group. Therefore, the authors linked dose sensitivity to the need for continuous hEGF in wound healing and the dose-dependent effect of rhEGF on granulation tissue formation. They also thought that the threshold value required to show the therapeutic effect of hEGF could be influenced by the presence of growth factor inhibitors or proteases in the microenvironment of the wound, or that higher levels of rhEGF would increase other cytokine levels needed to heal the wound. In a phase 3 study published by Park et al., it has been suggested that 0.005% rhEGF administered in topical spray form had a faster recovery process and a higher complete recovery rate than the placebo group, regardless of HbA1c level (36). Yang et al. have reported that topically administered rhEGF had a statistically significant higher complete cure rate than the control group in their meta-analysis with data from four randomized controlled trials involving 294 patients (37). Acosta et al. have applied 25 micrograms of rhEGF to 29 patients with Wagner grade 3 to 4 DFUs or amputation stump ulcers three times per week (9). As a result of the study, the desired granulation level was reached in 86% of the patients in the eighth application, and 17 patients were rescued from amputation and only one of these patients had a recurrence. In a study by Romero Prada et al. comparing rhEGF administration and conventional treatment; in the rhEGF-treated group, the number of amputations was lower, survival was longer, and rhEGF was cost-effective (38). In a study by Fernandez-Montequin et al. performed in patients with Wagner grade 3-4 diabetic ulcer patients with 25 mg rhEGF, 75 mg rhEGF, and a control group; complete granulation response and wound closure rate were the lowest in the control group and highest in the 75 mg rhEGF group and the time to reach complete granulation was the longest in the control group and the shortest in the 75 mg rhEGF group (39). As a result of the study, rhEGF was shown to increase the dose-dependent effect of ulcer healing. Aktas et al. have conducted a study investigating the efficacy of intralesional rhEGF in saving the extremity from amputation in DFUs with ischemic components (40). Although the patients included in this study had previously a revascularization, NPWT, and standard wound care treatments, there was not enough healing in DFUs. In these patients who were suggested to undergo amputation as a last option, intralesional rhEGF treatment was applied and 9 of 11 patients were rescued from amputation. However, topical rhEGF formulas have significant advantages over intralesional formulas in terms of ease of use and accessibility. In our study, to avoid growth factor inhibitors and proteases and to bring the active agent into the desired region, and therefore to gain maximum effects of the growth factor, intralesional injection of rhEGF was administered.

Peripheral artery disease (PAD) is one of the well-known risk factors for the progression of DFUs to amputation (9,40). In our study, PAD was present in nearly 80% of the patients in whom we could complete rhEGF treatment and these patients did not have any chance of revascularization. In our study, we think that the high rate of non-healing ulcers and minor amputations was because of the high prevalence of PAD as a concomitant disease. Another finding of our study was that patients with a granulation rate of < 50% after eight weeks and those with < 75% granulation after six months failed to achieve complete healing at the end of one-year follow-up. This showed us that the healing in the early period was an important parameter to predict the complete healing of a DFU in patients treated with rhEGF.

There are several limitations to our study. First, the small size of our sample and the lack of our control group limited the reliability of the study. Secondly, DFUs of different localization originate from different etiologies, so recovery rates and durations will be different. In our study, our patients' DFUs were in different localizations and we could not establish a standard in this regard. Thirdly, our retrospective study will be supported by prospective studies and more reliable results will be achieved. Finally, this is a single-center study and multicenter studies should be supported.

CONCLUSION

Intralesional growth factor application had positive results in addition to good foot care in DFUs ranging from grade 1 to 3 according to Wagner classification. Promising results can be obtained by protecting the extremity from major amputation by using intralesional growth factor in DFUs which are not suitable for vascular intervention methods and not healing with conventional wound care treatments. Further study is required to define the optimal dose of rhEGF, the frequency of optimal administration, and potential rhEGF interaction with other growth factors such as PDGF in enhancing the healing of the wound. In the future, it is also important to examine the cost effects in terms of wound healing and amputation prevention.

Ethics Committee Approval: The study protocol was approved by a local ethics committee (03-153-18) and was conducted following the Declaration of Helsinki.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.A.Ç., H.U.; Design - Ö.A.Ç., S.U.Ç., H.U.; Supervision - Ö.A.Ç., S.U.Ç.; Resource - Ö.A.Ç., H.U.; Materials - Ö.A.Ç., S.U.Ç., M.B.E., B.H., H.U.; Data Collection and/or Processing - S.U.Ç., M.B.E., B.H.; Analysis and Interpretation - Ö.A.Ç., S.U.Ç.; Literature Review - M.B.E., B.H.; Writing Manuscript - Ö.A.Ç, S.U.C., M.B.E., B.H.; Critical Reviews - Ö.A.Ç, S.U.Ç.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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İntralezyonal epidermal büyüme faktörü uygulaması diyabetik ayak ülseri iyileşmesine ve ampütasyonu önlemeye katkı sağlayan potansiyel bir tedavidir

Ömer Arda Çetinkaya[1], Süleyman Utku Çelik[2], Miraç Barış Erzincan[1], Barış Hazır[1], Hakan Uncu[1]

[1] Ankara Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Ankara, Türkiye
[2] Gülhane Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Çalışmanın amacı, kronik diyabetik ayak ülseri (DAÜ) olan hastalarda intralezyonal epidermal büyüme faktörü (EBF) uygulamasının yara iyileşmesi üzerine etkisini ve ekstremiteyi majör ampütasyondan koruma etkinliğini araştırmaktır.

Gereç ve Yöntem: DAÜ olan 33 hasta Ocak 2013-Ocak 2017 tarihleri arasında intralezyonal EBF uygulaması ile tedavi edildi. Öncelikli amacımız, tedaviyi takip eden 12 ay içinde majör ampütasyonu önleme oranını belirlemekti. İkincil amaçlarımız ise EBF'nin ilk uygulamasından altı ay sonra ≥ %50 granülasyon ile ülser yüzey alanının iyileşmesini ve altı ay sonra en az %75 granülasyon ile gerçekleşen iyileşme oranını belirlemekti.

Bulgular: Üç hasta majör ilaç yan etkileri nedeniyle çalışma dışı bırakıldıktan sonra, toplam 30 (48 DAÜ) hastanın, 24 (37 DAÜ)'ünde EBF tedavisinin başlangıcından sekiz hafta sonra ≥ %50 granülasyon elde edilirken, 6 (11 DAÜ) hastada istenilen düzeyde granülasyon sağlanamamıştır. Tedavinin altıncı ayında ise toplam 21 (31 DAÜ) hastada %75 ve üzeri granülasyon oranı elde edilmiştir. Son olarak tedaviyi takip eden 12. ayda bir majör ve yedi minör ampütasyon yapılırken beş hastada toplam 10 DAÜ'de iyileşme gösterilememiş, 17 hastada ise DAÜ tamamen düzelmiştir.

Sonuç: İntralezyonal EBF uygulamasının, iyi ayak bakımına ek olarak, DAÜ olan hastalarda olumlu sonuçları görülmektedir. Ayrıca, vasküler girişimlerin uygun olmadığı ve konvansiyonel yara bakımı yöntemleriyle iyileşmeyen DAÜ'lerde ekstremitenin ampütasyondan korunması ile ilgili umut verici sonuçlara sahiptir.

Anahtar Kelimeler: Ampütasyon, diyabetik ayak ülseri, epidermal büyüme faktörü

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Should there be a specific length of the colon-rectum segment to be resected for an adequate number of lymph nodes in cases of colorectal cancers? A retrospective multi-center study

Orhan Üreyen[1](ID), Cemal Ulusoy[2](ID), Atahan Acar[3](ID), Fazıl Sağlam[2](ID), İlker Kızıloğlu[1](ID), Ali Alemdar[2](ID), Kemal Murat Atahan[3](ID), Emrah Dadalı[1](ID), Serkan Karaisli[3](ID), Mehmet Can Aydın[2](ID), Enver İlhan[1](ID), Hakan Güven[2](ID)

[1] Clinic of General Surgery, Health Sciences University, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey
[2] Clinic of General Surgery, Health Sciences University, Istanbul Okmeydani Training and Research Hospital, Istanbul, Turkey
[3] Clinic of General Surgery, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

ABSTRACT

Objective: This study aimed to evaluate the question as to whether there should be a certain length of the colon-rectum segment to be resected for correct lymph node staging in cases with colorectal cancer.

Material and Methods: The files and electronic datas of the patients had been undergone surgery for colorectal cancer between January 2011 and June 2016 were evaluated. The patients were divided into two groups; Group I= ≥ 12 lymph nodes, and Group II= lymph nodes less than 12 (< 12) lymph nodes.

Results: Mean age of the 327 participants in this study was 64.30 ± 12.20. Mean length of resected colon-rectum segment was 25.61 (± 14.07) cm; mean number of dissected lymph nodes was 20.63 ± 12.30. Median length of the resected colon was 24 cm (range: 145-6) in Group I and 20 cm (range: 52-9) in Group II; a significant difference was found between the groups (p= 0.002). Factors associated with adequate lymph node dissection included type of the operation (p= 0.001), tumor location (p= 0.005), tumor T stage (p= 0.001), condition of metastasis in the lymph node (p= 0.008) and stage of the disease (p= 0.031). Overall survival was 62.4 ± 1.31 months, and Group I and Group II survival was 61.4 ± 1.39 months and 66.7 ± 3.25 months, respectively (p= 0.449).

Conclusion: Results of the study showed that ≥ 12 lymph nodes would likely be dissected when the length of the resected colon-rectum segment is > 21 cm. We conclude that the removed colonic size can be significant when performed with oncological surgical standardization.

Keywords: Colorectal cancer, colectomy, lymph nodes

INTRODUCTION

Presence of lymph node metastasis represents the main basic prognostic factor in cases with non-metastatic colorectal cancers (1,2). Correct staging of lymph node status is important in the identification of patients cancer stage with colorectal cancer (CRC) who need adjuvant therapy to treat the microscopically prevalent disease (3).

In stage II cases, theoretically, more extensive removal of the isolated tumor cells or lymph nodes containing micro-metastases leads to increased survival by inhibiting locoregional or systemic metastasis at the site. Recently, the presence of tumor deposits in regional lymph nodes has also been reported as a poor prognostic factor in node-negative cases (4). All surgeons agree on the prevention of tumor cell spillage while removal of primary tumor bed with lymphatic drainage and resection of the surrounding organ invasion (5).

Prognosis of colorectal cancers are mainly determined by the tumor-node-metastasis (TNM) classification. The 7th American Joint Committee on Cancer (AJCC)-resistant system, which is currently widely accepted, is based on the lymph node (N) and tumor colon-rectum wall status (T) (6). Lymph node status plays a key role

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Corresponding Author
Orhan Üreyen
E-mail: drureyen@yahoo.com

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in determining the TNM classification and stage of disease and the creation of postoperative adjuvant chemotherapy protocol. Chemotherapy represents the standard treatment modality in CRC patients with lymph node involvement (7). In the event of an inadequate number of dissected lymph nodes, it is suggested that surgical surgery and pathological classification were inadequate (1). Although the number of dissected lymph nodes for proper staging might be controversial, the generally and clinically accepted fact is that ≥ 12 lymph nodes should be dissected. However, this number is not always attained (8,9).

The number of dissected lymph nodes depends on factors such as age, tumor location, type of surgical operation, experience of the surgeon and pathologist, histopathologic property, and the length of resected colon segment (10,11). However, no rules have been established and no standardization made to achieve optimal lymph node dissection and adequate number of lymph nodes (3). The relationship between resected colon segment and lymph nodes has been investigated in recently conducted studies, and the discussion has focused on the necessity of a specific colon-rectum length for adequate lymph node excision (1,3,7).

In our study, we aimed to evaluate the question as to whether there should be a certain length of the colon-rectum segment to be resected for correct lymph node staging in cases with CRC, and if so for how long. We also aimed at investigating whether there was any relationship between the number of lymph nodes dissected, lymph node positivity, and lymph node status.

MATERIAL and METHODS

The files and electronic datas of patients with colorectal cancer who had undergone surgery either by emergency or through elective conventional methods between January 2011 and June 2016 at the General Surgery Clinics of three different Training and Research Hospitals were retrospectively evaluatedPatients were divided into two groups as those with adequately dissected number of lymph nodes (Group I= ≥ 12 lymph nodes) and those with inadequately dissected number of lymph nodes (Group II= number of lymph nodes less than 12). The groups were evaluated in terms of factors such as age, sex, tumor location, length of resected colon-rectum segment, number of dissected lymph nodes, number of metastatic lymph nodes, and histologic grade. In addition, patients' overall survival from the time of diagnosis was calculated. Overall survival was compared according to the length of the resected colon found for at least 12 lymph nodes. Lymph node dissection was performed in the resection materials of pericolic fat tissue by experienced pathologists. The sections were dyed with Hematoxylin Eosin, immunohistochemical dyeing was performed in which required cases after light microscopic examination. Lymph node metastasis size larger than 0.2 mm or isolated tumor cells were considered positive for lymph node. The cases were evaluated for adjuvant chemotherapy according to postoperative status and disease stages. Stage 3 and stage 2 cases were treated with adjuvant chemotherapy according to poor prognostic factors (obstruction, perforation, perineural invasion, lymphovascular invasion, etc.). Stage 1 cases were followed up without treatment. Patients who underwent palliative surgery (patients with colostomy), patients with peritonitis carcinomatosis, those who underwent metastatic, preoperative neoadjuvant therapy, total or subtotal colectomy, those whose data could not be accessed and patients with synchronous tumors in different segments were excluded from the study. Patient consent was not taken because of the retrospective design of the study. Approval was obtained from the Clinical Research Ethics Committee (Application date: 08/02/2017; Application No: 20, Dated: 15/02/2017 with Decision No: 1).

Statistical Analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were used for the statistical analysis. Shapiro-Wilk test and variance homogeneity Levene test were used for evaluating the suitability of data for normal distribution. Independent-samples t-test was used in conjunction with Bootstrap results, while the Mann-Whitney U test was used with Monte Carlo results to compare quantitative data between two independent groups. Pearson chi-square and Fisher's Exact tests were tested with the Monte Carlo Simulation technique for comparison of categorical variables. Relative sensitivity and specificity between the classification and actual classification of the cutoff values calculated according to the group variables were examined and expressed by the Receiver Operating Curve (ROC) analysis. Variables were expressed in 95% confidence interval (CI), and a p value of < 0.05 was considered statistically significant.

RESULTS

Mean age of the 327 participants in the study was 64.30 ± 12.20. Mean length of the resected colon-rectum segment was 25.61 (± 14.07) cm; mean number of dissected lymph nodes was 20.63 ± 12.30, mean number of metastatic lymph nodes was 2.11 (0-31), and mean tumor size was 4.62 ± 2.05 cm.

Median length of the resected colon was 24 cm (range= 145-6) in Group I and 20 cm (range= 52-9) in Group II (p= 0.002). Mean length of the resected colon-rectum in Group I and Group II, in patients who underwent anterior resection was 22.45 ± 7.62 cm and 18.00 ± 7.41 cm (p= 0.1480), respectively; in cases with Low Anterior resection it was 22.25 (42-6) and 16 (52-9) cm in Group I and Group II, respectively (p= 0.010); in those who underwent right hemicolectomy it was 25 cm (125-12) and 21 cm (39-10) in Group I and Group II, respectively (p= 0.452); whereas in patients with sigmoid + left hemicolectomy it was reported to be 25.25 cm (145-10) and 20 (46-9) cm in Group I and Group II, respectively (p= 0.029). Detailed analyses of the cases are presented in Table 1. Data collected from each hospital is shown in Table 2.

Table 1. Comparison of the groups according to surgical type

	Groups		
	Group I	Group II	
Type of surgery	[1]Mean ± SD/[2]Median (Max-Min)	[1]Mean ± SD/[2]Median (Max-Min)	p
Anterior resection			
Total length of resected colon-rectum segment[1]	22.45 ± 7.62	18.00 ± 7.41	0.148
Number of metastatic lymph nodes[2]	0 (14-0)	0 (1-0)	0.365
Tumor size[1]	4.39 ± 1.66	4.35 ± 2.11	0.954
Tumor-proximal border distance[2]	10 (30-3)	9 (16-4)	0.275
Tumor-distal border distance[2]	5 (24.5-1)	4 (10-1.5)	0.450
Low anterior resection			
Total length of resected colon-rectum segment[2]	22.25 (42-6)	16 (52-9)	**0.010**
Number of metastatic lymph nodes[2]	1 (20-0)	0 (4-0)	0.134
Tumor size[1]	4.25 ± 1.56	3.31 ± 1.59	**0.047**
Tumor-proximal border distance[2]	12 (36-2)	10.75 (44-1)	0.626
Tumor-distal border distance[2]	4 (21-1)	2 (5-1)	**0.001**
Abdomino perineal resection			
Total length of resected colon-rectum segment[2]	27 (32-17.5)	33 (36.5-22.5)	0.125
Number of metastatic lymph nodes[2]	3 (31-0)	0 (4-0)	0.211
Tumor size[1]	5.11 ± 1.58	3.60 ± 2.16	0.158
Tumor-proximalborderdistance[2]	16 (24-3)	20 (28-11)	0.317
Tumor-distal border distance[1]	3.64 ± 1.88	7.3 ± 2.22	**0.007**
Right hemicolectomy			
Total length of resected colon-rectum segment[2]	25 (125-12)	21 (39-10)	0.452
Number of metastatic lymph nodes[2]	0.5 (31-0)	0 (6-0)	0.168
Tumor size[1]	5 (13-1.5)	4.75 (10-1.5)	0.866
Tumor-proximal borderdistance[2]	7.5 (36-0)	5 (14-1)	0.319
Tumor-distal border distance[2]	12 (74-2)	12 (24-2)	0.741
Sigmoid + left hemicolectomy			
Total length of resected colon-rectum segment[2]	25.25 (145-10)	20 (46-9)	**0.029**
Number of metastatic lymph nodes[2]	1 (12-0)	0 (4-0)	0.150
Tumor size[1]	4 (10-1.5)	3.75 (9-2)	**0.046**
Tumor-proximal border distance[2]	10 (109-1.5)	9 (24-1.8)	0.181
Tumor-distal border distance[2]	7 (26-1.7)	6.25 (30-1)	0.303
Total			
Total length of resected colon-rectum segment[2]	24 (145-6)	20 (52-9)	**0.002**
Number of metastatic lymph nodes[2]	1 (31-0)	0 (6-0)	**0.012**
Tumor size[1]	4.5 (13-0)	3.5 (10-1)	**0.001**
Tumor-proximal border distance[2]	10 (109-0)	9 (44-1)	0.669
Tumor-distal border distance[2]	7 (74-1)	4.75 (30-1)	**0.001**

Independent T Test (Bootstrap)-Mann-Whitney U Test (Monte Carlo).
SD: Standard deviation, Max: Maximum, Min: Minimum.

Less than 12 lymph nodes were found to have been removed in 60 (18.3%) cases. Factors associated with adequate/inadequate lymph node dissection are shown in Table 3.

It was demonstrated that mean length of the resected colon-rectum and the number of lymph nodes dissected did not affect the presence of metastatic lymph nodes (p= 0.853 and p= 0.088, respectively). Factors associated with the status of lymph node metastasis and lymph node grade are presented in Table 4. Evaluation of the factors associated with the number of dissected lymph nodes demonstrated that it was associated with the number of metastatic lymph nodes (p= 0.003), the mean length

Table 2. Mean colon lengths according to the surgical method of each hospital

	A Hospital		B Hospital		C Hospital	
Surgery type	Group I Mean ± SD/Median (Max-Min)	Group II Mean ± SD/Median (Max-Min)	Group I Mean ± SD/Median (Max-Min)	Group II Mean ± SD/Median (Max-Min)	Group I Mean ± SD/Median (Max-Min)	Group II Mean ± SD/Median (Max-Min)
Anterior resection	20.33 ± 6.32	18.00 ± 5.28	22.5 (± 13)	22.6 (± 9.82)	21 (± 6.8)	20.5 (± 5.6)
Low anterior resection	24.8 ± 10	19.6 (± 6.8)	23.5 (± 10.5)	18 (12-33)	15 (6-42)	23 (± 9.7)
Abdomino perineal resection	25.5 ± 7.1	-	25.3 (± 8.7)	30.4 (± 7.2)	-	-
Right hemicolectomy	24.8 (15-128)	29 (19-39)	29.8 (± 11.2)	27 (18-36)	26 (± 11.2)	23 (12-33)
Sigmoid + left hemicolectomy	28.4 ± 8.8	18.9 (± 6.7)	31.8 (± 11.3)	24 (± 13.2)	29.8 (± 7.4)	24 (13-46)
Total length of colon-rectum segment	25 (8-114)	24.5 (8-145)	25 (8-64.5)	22.5 (12-36)	23 (± 7.7)	21.9 (± 7.7)

of resected colon (p≤ 0.001), tumor size (p≤ 0.001), and distal surgical border (p≤ 0.001). Factors associated with the number of dissected lymph nodes and the number of metastatic lymph nodes are shown in Table 5.

According to the surgical operation, the colon-rectum segment should be resected for a length of > 21 cm during low anterior resection (p= 0.027) and a length of > 20 cm during sigmoid + left hemicolectomy (p= 0.027) (Table 6). The possibility of dissecting ≥ 12 lymph nodes was found to be significant when > 21 cm of the colon-rectum segment was resected in respect of the cut-off value (p= 0.005) (Figure 1). The rate of patients receiving adjuvant therapy was 62% (Group I and Group II, respectively 63%, and 57%). Overall survival was 62.4 ± 1.31 months, and Group I and Group II survival were 61.4 ± 1.39 months and 66.7 ± 3.25 months, respectively (p= 0.449). In the absence of lymph node metastasis, survival was 71.4 ± 1.75 months and survival was 54.3 ± 1.99 months in the presence of metastatic lymph node (p= 0.001). Survival analysis was 63 ± 1.65 months in patients with a colon length greater than 21 cm and 61.6 ± 2.07 months in those with a smaller colon length (p= 0.801).

DISCUSSION

The rate of inadequately dissected lymph nodes has been on a decrease these past years; it is around 25% and continues to pose a health problem (3). The relationship of resected colon-rectum segment with lymph nodes has been investigated in various studies. Stracci et al. have reported inadequate lymph node dissection below 20 cm (7). In this study, ≥ 12 lymph nodes were observed to have been dissected in 50% of the cases when the 10-19 cm colon segment was resected, and in 38% of cases when less than 16 cm were resected. On the other hand, resection of less than 10 cm saw showed us the dissection of an adequate number of lymph nodes in only 19.5% of the cases. In that study, the rate of dissecting ≥ 12 lymph nodes has been observed to increase as the years progressed; in 2002 the rate was 43%, whereas in 2008 it was found to have increased to 68% (7). In our study, this rate was reported to be good at 81.7%. In some rare literature studies, this rate has been found to have approached 96%. No difference was found in the number of dissected lymph nodes between the currently widely is used laparoscopic surgery and conventional surgery in patients with CRC (5,7).

In another study, Gravante et al. have shown that tumors might vary depending on their location, and as a result, a general view might be overlooked; however, it is their suggestion that it would be appropriate to resect 36 cm of the segment during surgical procedure in the rectum and 42 cm of the segment during the Hartmann procedure (3). The length of the colon segment here mentioned seems to be longer when compared to results from literature studies and results of our study. Moreover, in this study, < 12 lymph nodes are dissected in 30.3% of the cases.

Neufeld et al. have demonstrated that < 12 lymph nodes were dissected from sigmoid colon resections less than 15.1 cm, whereas > 12 lymph nodes were dissected from segments more than 20.3 cm (12). The authors have argued that surgeons have an important role in determining lymph node spread. In the study conducted by Valsecchi et al., it has been demonstrated that < 12 lymph nodes were dissected when the resected

Table 3. Comparison of the groups according to demographic data

	Groups		
	Group I	Group II	
	n (%)	n (%)	p
Gender			
Female	106 (39.7)	19 (31.7)	0.247
Male	161 (60.3)	41 (68.3)	
Type of surgery			
Anterior resection	58 (21.7)	7 (11.7)	**0.001**
Low anterior resection	42 (15.7)	16 (26.7)	
Abdominoperineal resection	9 (3.4)	5 (8.3)	
Right hemicolectomy	96 (36)	10 (16.7)	
Sigmoid colon + Left hemicolectomy	62 (23.2)	22 (36.7)	
Tumor location			**0.005**
Left colon	33 (12.4)	13 (21.7)	
Rectum	52 (19.5)	21 (35)	
Right colon	86 (32.2)	9 (15)	
Sigmoid colon	84 (31.5)	16 (26.7)	
Transverse colon	12 (4.5)	1 (1.7)	
T Stage			**0.001**
T0	1 (0.4)	0 (0)	
T1	9 (3.4)	5 (8.3)	
T2	18 (6.7)	12 (20)	
T3	140 (52.4)	28 (46.7)	
T4	98 (36.7)	13 (21.7)	
Tis	1 (0.4)	2 (3.3)	
N Stage			**0.024**
N0	119 (44.6)	35 (58.3)	
N1	85 (31.8)	20 (33.3)	
N2	63 (23.6)	5 (8.3)	
Lymph node metastasis			0.107
No	125 (46.8)	35 (58.3)	
Yes	142 (53.2)	25 (41.7)	
Histological grade			
Well	57 (22)	10 (16.9)	0.138
Moderately	149 (57.5)	42 (71.2)	
Poor	53 (20.5)	7 (11.9)	
TNM stage			
Stage 0	2 (0.7)	2 (3.3)	**0.031**
Stage 1	21 (7.9)	10 (16.7)	
Stage 2	98 (36.7)	24 (40)	
Stage 3	146 (54.7)	24 (40)	
Elective/Emergency surgery			
Emergency surgery	28 (10.5)	14 (23.3)	**0.007**
Elective surgery	239 (89.5)	46 (76.7)	
Lymphovascular Invasion			
No	159 (59.6)	42 (70)	0.133
Yes	108 (40.4)	18 (30)	
Perineural invasion			
No	189 (70.8)	47 (78.3)	0.239
Yes	78 (29.2)	13 (21.2)	

Pearson Chi-Square Test (Monte Carlo), Fisher Exact Test (Exact).

Table 4. Factors associated with the lymph node stage and status of lymph node metastasis

	N Stage			p	Lymph node metastasis		p
	N0	N1	N2		No	Yes	
	Median (Max-Min)	Median (Max-Min)	Median (Max-Min)		Median (Max-Min)	Median (Max-Min)	
Age	66 (96-38)	64 (93-21)	65 (86-35)	0.661	66 (96-38)	64 (93-21)	0.267
Total length of resected colon-rectum segment	23 (114-6)	23 (75-9)	23 (145-8)	0.948	23 (114-6)	23 (145-8)	0.853
Dissected number of lymph nodes	16 (75-0)	17 (73-3)	20 (81-9)	**0.004**	16 (75-0)	18 (81-3)	0.088
Tumor size	4 (13-0)	4.5 (10-1.5)	4 (13-1.5)	0.534	4 (13-0)	4.5 (13-1.5)	0.192
Gender, n (%)							
Female	58 (37.7)	35 (33.3)	32 (41.1)	0.189	61 (38.1)	64 (38.3)	0.971
Male	96 (62.3)	70 (66.7)	36 (52.9)		99 (61.9)	103 (61.7)	
Type of surgery, n (%)							
Anterior resection	33 (21.4)	22 (21)	10 (14.7)	0.711	34 (21.3)	31 (18.6)	0.831
Low anterior resection	26 (16.9)	17 (16.2)	15 (22.1)		26 (16.3)	32 (19.2)	
Abdominoperineal resection	6 (3.9)	3 (2.9)	5 (7.4)		6 (3.8)	8 (4.8)	
Right hemicolectomy	53 (34.4)	32 (30.5)	21 (30.9)		55 (34.4)	51 (30.5)	
Sigmoid colon + Left hemicolectomy	36 (23.4)	31 (29.5)	17 (25)		39 (24.4)	45 (26.9)	
Tumor location, n (%)							
Left colon	20 (13)	17 (16.2)	9 (13.2)	0.718	22 (13.8)	24 (14.4)	0.859
Rectum	33 (21.4)	20 (19)	20 (29.4)		33 (20.6)	40 (24)	
Right colon	45 (29.2)	29 (27.6)	21 (30.9)		47 (29.4)	48 (28.7)	
Sigmoid colon	48 (31.2)	35 (33.3)	17 (25)		50 (31.3)	50 (29.9)	
Transverse colon	8 (5.2)	4 (3.8)	1 (1.5)		8 (5)	5 (3)	
Histological Grade, n (%)							
Well	33 (21.7)	22 (22)	12 (18.2)	0.390	35 (22.2)	32 (20)	0.249
Moderately	97 (63.8)	56 (56)	38 (57.6)		99 (62.7)	92 (57.5)	
Poor	22 (14.5)	22 (22)	16 (24.2)		24 (15.2)	36 (22.5)	
Elective/Emergency surgery, n (%)							
Emergency surgery	29 (18.8)	9 (8.6)	4 (5.9)	**0.008**	29 (18.1)	13 (7.8)	**0.005**
Elective surgery	125 (81.2)	96 (91.4)	64 (94.1)		131 (81.9)	154 (92.2)	
Lymphovascular Invasion, n (%)							
No	108 (70.1)	56 (53.3)	37 (54.4)	**0.010**	37 (54.4)	88 (52.7)	**0.001**
Yes	46 (29.9)	49 (46.7)	31 (45.6)		31 (45.6)	79 (47.3)	
Perineural invasion, n (%)							
No	115 (74.7)	75 (71.4)	46 (67.6)	0.548	120 (75)	116 (69.5)	0.264
Yes	39 (25.3)	30 (28.6)	22 (32.4)		40 (25)	51 (30.5)	

Pearson Chi-Square Test (Monte Carlo), Fisher Exact Test (Exact), Kruskal Wallis Test (Monte Carlo), Post Hoc Test: Dunn's Test. Max: Maximum, Min: Minimum.

colon segment was less than 19.6 cm, whereas ≥ 12 lymph nodes were dissected with over 29.9 cm of resected colon segment (9). It has been indicated that the mean number of lymph nodes was significantly higher in the ascending colon and cecum when evaluation was made according to tumor location; and during right hemicolectomy and subtotal colectomy when evaluation was made according to mode of surgery.

Unlike in these studies, the case series by Lav et al. involving 205 cases have demonstrated that lymph nodes were dissected more with right colon tumors than with left colon tumors (1). Especially for right colon resection, the authors did not suggest any length. However, there were certain handicaps in this study such as the small sample size, and a wide range of resection types all divided into three categories including cases with right hemicolectomy, left colon + sigmoid resection and subtotal resection. In another study, it was suggested that the pedicle or mesocolon and not the resected colonic segment was more important (13).

Comparison of our study with the studies mentioned above demonstrates that an adequate number of lymph nodes was

Table 5. Factors associated with the number of metastatic lymph nodes and the number of dissected lymph nodes

Metastatic lymph nodes	**r**	**p**
Total length of resected colon-rectum segment	0.033	0.558
Dissected number of lymph nodes	0.166	**0.003**
Tumor size	0.063	0.258
Tumor-proximal border distance	-0.055	0.322
Tumor-distal border distance	0.036	0.520
Dissected lymph nodes	**r**	**p**
Total length of resected colon-rectum segment	0.305	**< 0.001**
Number of metastatic lymph nodes	0.166	**0.003**
Tumor size	0.258	**< 0.001**
Tumor-proximal border distance	0.017	0.758
Tumor-distal border distance	0.265	**< 0.001**

Partial Correlaction Test/Control Variables: Age & Gender. r: Correlation coefficient.

Table 6. Relationship between surgical types and removal of at least 12 lymph nodes

		Dissected number of lymph nodes (≥ 12/< 12)				
		Cut-off	**Sensitivity**	**Specificity**	**AUC ± SH**	**p**
Total	**Total length of resected colon-rectum**	> 21	0.60	0.63	0.610 ± 0.039	**0.005**
Type of surgery						
Anterior resection		> 21	0.53	0.86	0.68 ± 0.11	0.126
Low anterior resection		> 21	0.52	0.75	0.65 ± 0.07	**0.027**
Abdominoperineal resection		> 37	0.29	1.00	0.51 ± 0.11	0.957
Right hemicolectomy		> 21	0.71	0.60	0.58 ± 0.11	0.429
Sigmoid + Left hemicolectomy		> 20	0.67	0.59	0.66 ± 0.07	**0.027**

ROC: Receiver Operating Curve, Analysis: Honley&Mc Nell-Youden index J, AUC: Area under the ROC curve, SE: Standard error.

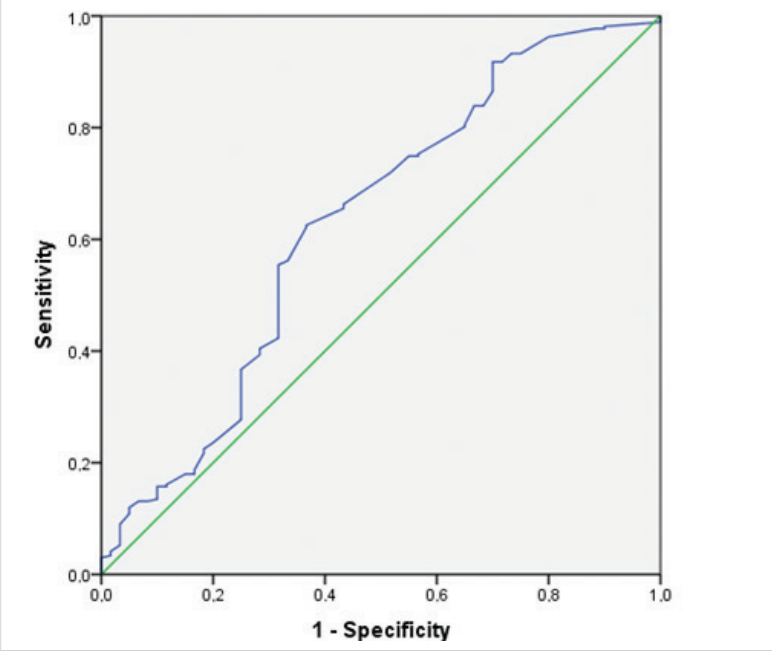

Figure 1. The predictive values' total length of the resected colon-rectum were evaluated by ROC curve analysis.

considered to have been dissected when a colon-rectum length of more than 21 cm was resected regardless of the mode of the surgical operation or tumor location. On the other hand, classification according to surgical operation showed that the length of resected colon-rectum was significant with low anterior resection and sigmoid+ left hemicolectomy. The use of limited segmental colonic resections is traditionally not recommended because of the potential for local recurrence or metastatic disease and may increase the risk of skipping lymph nodes containing metastatic deposits (14). In addition, in stage-II patients, the dissection of more lymph nodes in theory, including isolated tumor cells or micro-metastases, leads to increased survival by preventing both locoregional and systemic recurrence (15). Norwood et al., in their case series involving 2449 cases, have found that an adequate number of lymph nodes varied according to preoperative chemotherapy, age, length of resected colon segment, and the type of surgical operation; and observed that there was less survival in the group with inadequately dissected lymph nodes (16). On the other hand, Tsai et al. have demonstrated that survival was higher in N0 patients with ≥ 18 dissected lymph nodes (8). In high-volume hospitals, colorectal surgery specialists tend to perform more extensive lymphadenectomy operations through the resection of more colonic segments (1).

It has also been suggested that metastatic lymph nodes may be found approximately 8 to 10 cm of the colonic segment around the tumor, and hence the removal of the distal and proximal surgical margin with a 5 cm safety margin is recommended (17). In our study, median length of the proximal margin was found to be 10 cm, while mean distal margin length was 6.5 cm. However, comparison of the groups with adequate and inadequate lymph node dissection demonstrated that the proximal surgical margin was 10 cm in the group with adequate lymph node dissection and 9 cm in the group with inadequate lymph node dissection both groups, whereas the median length of distal surgical margin was 7 cm in the group with adequate lymph node dissection and 4.75 cm in the group with inadequate lymph node dissection; the difference between the groups was found to be significant. This result shows that there was a relationship between the increased safety of the surgical margin and the number of dissected lymph nodes.

Consistent with the literature datas, our study demonstrated that the mean number of dissected lymph nodes did not affect the node positive or node negative rate (15). However, when compared with the dissection of ≥ 12 lymph nodes, dissection of an adequate number of lymph nodes was found to be significant in the presence of metastatic lymph nodes. In addition, evaluation of lymph node status demonstrates that the mean number of total dissected lymph nodes was 16 in N0, 17 in N1 and 20 in N2. A significant inter-relationship was found, which shows that the correct classification/staging could be performed as the number of dissected lymph nodes increased. Correct staging would also allow us to comment on the prognosis of the disease and guide us in the creation of a chemotherapy scheme.

Lymph node dissection has been in practice for the past 100 years; however, the current commonly accepted technique involves removal of the pedicle from the main vascular pedicle preceding the main lymphatic duct of each colonic segment (14). In our study, no relation was found between lymph node dissection and sex, histologic grade, lymphovascular, or perineural invasion; however, similar to literature studies a relation was found in respect of tumor location, presence of elective-emergency surgical intervention, disease stage and type of surgery (1,3,18). The total length of resected colon-rectum in our study was also not shown to change with emergency or elective surgery. However, the number of lymph nodes dissected during elective surgery was found to be significantly high, similar to other literature studies, which suggests that meso-excision may be extensive during elective surgery (5,16).

Overall survival is known to be affected by many factors such as tumor type, tumor differentiation, tumor localization, tumor size, disease stage, lymph node involvement (19). In our study, if the length of the removed column is over 21 cm or the number of removed lymph nodes is 12 or greater did not provide survival advantage. In addition, we found that the presence of metastatic lymph nodes worsened overall survival like the literature.

Limitations

Our study is a retrospective study. Furthermore, due to the very centered nature of the study, no uniformity was created during the examination of the specimens. In addition, although surgery was performed according to surgical principles, no standardization was established for the width of the mesocolon and attachment level of the main vascular structure. In addition, it should be kept in mind that patients with advanced rectal cancer were not included in the study due to neoadjuvant treatment. While these results are interpreted; it should be kept in mind that the measurements are made after 10% formol fixation, which may lead to a reduction of about 30-40% of the final length according to the measurements during surgery (20).

In conclusion, the results of this study show that in colorectal cancer operations, at least 12 lymph nodes could be removed when the colon resection was over 21 cm long. However, we found that the length of the removed colon did not show survival advantage independent from the disease stage. We conclude that the removed colonic size can be significant when performed with mesodissection with as oncologic standard surgery.

Ethics Committee Approval: Approval was obtained from the Clinical Research Ethics Committee (Application date: 08/02/2017; Application No: 20, Dated: 15/02/2017 with Decision No: 1).

Informed Consent: Patient consent was obtained.

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ORİJİNAL ÇALIŞMA-ÖZET
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Kolorektal kanserlerde yeterli lenf nodu sayısı için çıkarılacak kolon-rektum segmentinin belirli bir uzunluğu olmalı mı? Retrospektif çok merkezli bir çalışma

Orhan Üreyen[1], Cemal Ulusoy[2], Atahan Acar[3], Fazıl Sağlam[2], İlker Kızıloğlu[1], Ali Alemdar[2], Kemal Murat Atahan[3], Emrah Dadalı[1], Serkan Karaisli[3], Mehmet Can Aydın[2], Enver İlhan[1], Hakan Güven[2]

[1] Sağlık Bilimleri Üniversitesi, İzmir Bozyaka Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye
[2] Sağlık Bilimleri Üniversitesi, İstanbul Okmeydanı Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye
[3] İzmir Katip Çelebi Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışma, kolorektal kanserli olgularda doğru lenf nodu evrelemesi için rezeke edilecek kolon-rektum segmentinin belirli bir uzunluğunun olup olmadığı sorusunu değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Kolorektal kanserli hastaların Ocak 2011-Haziran 2016 tarihleri arasında ameliyat geçiren dosyaları ve elektronik verileri değerlendirildi. Hastalar iki gruba ayrıldı; Grup I= ≥ 12 lenf nodu ve Grup II= 12'den az lenf nodu sayısı.

Bulgular: Çalışmaya yaş ortalaması 64,30 ± 12,20 olan 327 olgu dahil edilmiştir. Rezeke edilen kolon-rektum segmentinin ortalama toplam uzunluğu 25,61 (± 14,07) cm; diseke edilen ortalama lenf nodu sayısı 20,63 ± 12,30 idi. Çıkarılan ortalama kolon-rektum uzunluğu Grup I'de 24 cm (145-6) ve Grup II'de 20 cm (52-9) olup gruplar arasında anlamlı fark bulunmuştur (p= 0,002). Yeterli lenf nodu diseksiyonu ile ilişkili faktörler; operasyonun türü (p= 0,001), tümör yeri (p= 0,005), tümör T evresi (p= 0,001), lenf nodunda metastaz durumu (p= 0,008) ve hastalığın evresi (p= 0,031) olarak bulunmuştur. Ortalama sağkalım 62,4 ± 1,31 ay idi. Grup I ve Grup II'de sırasıyla, 61,4 ± 1,39 ay ve 66,7 ± 3,25 idi (p= 0,449).

Sonuç: Bu çalışma, çıkarılan kolon-rektum uzunluğu > 21 cm olduğunda ≥ 12 lenf nodu çıkarılabileceğini gösterdi. Çıkarılan bu kolon-rektum uzunluğunun onkolojik cerrahi standardizasyonuyla beraber yapıldığında anlamlı olacağını düşünüyoruz.

Anahtar Kelimeler: Kolorektal kanser, kolektomi, lenf nodu

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ORIGINAL ARTICLE
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Is peritoneal dialysis prior to kidney transplantation a risk factor for ureteral stenosis after adult to adult live kidney transplantation

Koray Kutlutürk[1](ID), Tevfik Tolga Şahin[1](ID), Serhan Çimen[2](ID), Yasin Dalda[1](ID), Fatih Gönültaş[1](ID), Sait Murat Doğan[1](ID), Sibel Altunışık Toplu[3](ID), Bülent Ünal[4](ID), Turgut Pişkin[1](ID)

[1] Department of General Surgery, Inonu University School of Medicine, Malatya, Turkey
[2] Clinic of Urology, Malatya Education and Research Hospital, Malatya, Turkey
[3] Department of Infectious Diseases and Clinical Microbiology, Inonu University School of Medicine, Malatya, Turkey
[4] Department of General Surgery, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey

ABSTRACT

Objective: Major urinary complications such as urinary leaks, stenosis or urinary tract infections after kidney transplantation can lead to graft or patient loss. The effect of peritoneal dialysis on post-kidney transplantation complications have been discussed but its effect on ureteral stenosis is unknown. In this study, it was aimed to analyze factors effecting major ureteral complications after living donor kidney transplantation and impact of peritoneal dialysis and double J-stents (JJ stents).

Material and Methods: This study included 116 adult to adult living donor kidney transplant patients. Factors effecting major urologic complications after living donor kidney transplantation were analyzed. The donors were primary relatives of the recipients.

Results: Major urologic complications after living donor kidney transplantation was 8/116 (6.9%). Urinary leak was present in 2 (1.7%) patients. Ureteral stenosis was encountered in 6 (5.2%) patients. Double J stents were used in 84 (72.4%) of the cases. The effect of JJ ureteral stent was not statistically significant for urinary leak, ureteral stenosis (p= 0.074, p= 0.470, respectively). A total of 29 (25%) patients had peritoneal dialysis before kidney transplantation. Preoperative peritoneal dialyses and bacteriuria after kidney transplantation were independent risk factors for ureteral stenosis in multivariate analysis (p= 0.013, and p= 0.010 respectively).

Conclusion: In the guidance of the results of the present study, peritoneal dialysis prior to kidney transplantation and bacteriuria are independent risk factors for ureteral stenosis after living donor kidney transplantation. JJ stents have no effect on urologic complications after living donor kidney transplantation.

Keywords: Renal transplantation, urologic complications, peritoneal dialysis, ureteral stenosis

INTRODUCTION

Kidney transplantation is the definitive treatment option for patients with end-stage renal disease. Major urinary complications such as urinary leaks, ureteral stenosis or urinary tract infections after kidney transplantation can lead to graft or patient loss and in different transplantation centers, its incidence varies from 2.5-14% (1-5). Ureterovesical anastomosis is the most frequent source of morbidity following kidney transplantation. Many ureterovesical anastomotic techniques are described: Intravesical Politano-Leadbetter (PL), the extravesical Campos Freire technique, better known as Lich-Gregoir (LG) and the Taguchi or U-stitch (U) technique. Current approaches show that LG ureterovesical anastomotic technique results in fewer post-operative urological complications (6). The main objective of the centers dealing with solid organ transplantation is to reduce surgical site complications in order to improve the success of transplantation (7). The impact of peritoneal dialysis before kidney transplantation on urinary complications after kidney transplantation is still a matter of debate, and there are many controversies regarding which strategy to use the double J (JJ) stents (8-17).

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Corresponding Author
Koray Kutlutürk
E-mail: kkutluturk@gmail.com

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The aim of this study was to analyze the factors effecting major urinary complications, especially ureteral stenosis, after living donor kidney transplantation. Furthermore, we analyzed the impact of preoperative peritoneal dialysis and JJ stents on ureteral stenosis following living donor kidney transplantation.

MATERIAL and METHODS

Selection and Exclusion Criteria for the Patients

Between November 2010 and April 2017, 149 adult to adult living donor kidney transplantations were performed in our center. After excluding 23 patients lost during follow up, 4 early deaths not related to urologic complications, 1 patient with double ureter anastomosis, and 4 grafts harvested laparoscopically from the donor; 116 patients were included for the evaluation in the study. The data of these patients were collected retrospectively from the electronic patient database. In our institution, living donors are first till fourth degree relatives of the recipients.

Study Parameters and Definition of Urinary Complications

All of the ureter anastomosis was performed with extravesical Lich-Gregoir thecnique (6). Age, sex induction immunosuppression protocols, graft type (left versus right), implantation area, total ischemia time, re-exploration on/any invasive procedure after transplantation within one month, use of JJ stents while performing ureteral anastomosis, dialysis status (peritoneal, hemodialysis or preemptive) and dialysis time before transplantation, intraoperative complications, suction drain use, postoperative urinary culture results, presence of urinary leak and stenosis were retrospectively collected and evaluated. Bacteriuria was defined as presence of $\geq 10^5$ colony forming unit of bacteria in the postoperative urinary culture taken in any time point. Patients who had increasing serum creatinine level, hydronephrosis in transplanted kidney in imaging and also those who required radiologic or surgical intervention were considered to have ureteral stenosis. In stented patients, the stents were removed 4-6 weeks after the operation. In all patients, urinary Foley catheter was removed 5 days after the operation.

Postoperative Management Protocol

Tacrolimus, mycophenolic acid and corticosteroids were used as maintenance immunosuppression after transplantation if there was no contraindication or adverse effect. Perioperative single dose 1 gr cefazolin sodium was given intravenously for antimicrobial prophylaxis. Trimethoprim-sulfometaxazole was used for six months for pneumocystis carinii prophylaxis. Ureteral stenosis and urinary leaks were treated percutaneously as an initial management approach. In case of a failure, reoperation and ureteroneocystostomy was performed.

Statistical Analysis

Continuous variables were expressed as median and range. Discrete variables were expressed as the number of patients affected together with the percentage. The relationship between the dependent and independent variable was performed using parametric tests including chi-square test. Any p value less than or equal to 0.05 was considered as statistically significant. Univariate and multivariate logistic regression analyses were performed in order to determine the risk factors for urologic complications. The variables that showed a p values less than 0.2 in univariate analysis were included in the multivariate analysis. All statistical evaluations were performed on Statistical Program for Social Sciences software v 20 (SPSS v20, IBM, USA).

As this was a retrospective study, we did not apply for ethical committee approval. It was conducted according to the principles set forth by the Helsinki Declaration.

RESULTS

Median age of the patients 34.5 (20-40) and female/male ratio was 39/77 (0.5). Totally, 34 right kidney and 82 left kidney grafts were used.

The implantation site was explored in the early postoperative period in 12 patients. The causes of reoperation were hematoma in three patients, hemorrhage from renal artery anastomosis in one patient, retroperitoneal hemorrhage in one patient, and urinary leakage in one patient, renal vein anastomotic stenosis in one patient in whom fibrous bands were found to be responsible for the stenosis. Four patients were operated for oliguria or anuria, and no surgical pathology had been found. One patient with anuria was explored, and Doppler USG revealed reduced arterial flow of graft and renal artery anastomosis was re-performed. In another patient, cystoscopy was performed on postoperative 3rd day and evacuation of the hematoma was performed. Percutaneous drainage catheter was placed in two patients due to postoperative lymphocele (n= 1) on postoperative 14th day and implantation site hematoma (n= 1) on postoperative 25th day. There was no statistically significant difference in the development of urologic complication amongst the patients with or without reoperation/interventional radiologic procedures (p= 0.187).

Major urologic complications after living donor kidney transplantation in our study group was 8/116 (6.9%). Preoperative peritoneal dialysis was present in 29 (25%) patients. JJ stents were used in 84 (72.4%) cases. Demographic characteristics of the patients were similar in stented and non-stented patients. In one patient, the JJ stent perforated the renal pelvis of the renal graft at operation and primary repair was performed intraoperatively. In the postoperative follow up period, no complication was encountered due to this condition. Median Double j stent removal time was 33 (7-105) days following the operation which was performed by cystoscopy under sedation.

Urinary leak was observed in only 2 (1.7%) patients during the study period. Both of them were in non-stented patients. One of them was diagnosed six days after operation. Reoperation was

Table 1. Univariate and multivariate analyses of the factors effecting ureteral stenosis

	Ureteral stenosis		p	
	Yes	No	Univariate	Multivariate
Age [year, median (Range)]	27 [20-41]	35 [20-60]	0.109	
Sex (n, percent) Male Female	 6 (7.8%) -	 71 (92.2%) 39 (100%)	0.096	
Dialysis status (n, percent) Peritoneal dialysis Hemodialysis or preemptive	 4 (13.8%) 2 (2.3%)	 25 (86.2%) 85 (97.7%)	**0.034**	**0.013**
Dialysis time (month)	24 (2-60)	10 (1-156)	0.980	
Total ischemia time (min)	85 (66-115)	97 (63-204)	0.202	
Induction IS (n, percent) ATG Basiliximab	 5 (5.1%) 1 (5.6%)	 93 (94.9%) 17 (94.4%)	1,000	
Graft (n, percent) Left Right	 5 (6.1%) 1 (2.9%)	 77 (93.9%) 33 (97.1%)	0.669	
Graft artery number (n, percent) 1 > 1	 6 (6.1%) -	 93 (93.9%) 17 (100%)	0.590	
Double J Stent (n, percent) Yes No	 5 (6.0%) 1 (3.1%)	 79 (94.0%) 31 (96.9%)	1.000	
Suction drain (n, percent) Yes No	 3 (6.5%) 3 (4.3%)	 43 (93.5%) 67 (95.7%)	0.680	
Reoperation or any invazive procedure (n, percent) Yes No	 1 (6.7%) 5 (5.0%)	 14 (93.3%) 96 (95.0%)	0.573	
Bacteriuria after transplantation (n, percent) Yes No	 4 (12.9%) 2 (2.4%)	 27 (87.1%) 83 (97.6%)	**0.043**	**0.010**
Total (n, percent)	**6 (5.2%)**	**110 (94.8%)**		

IS: Immunosuppression, ATG: Anti-thymocyte globulin.

done and re-anastomosis performed with the placement of a JJ stent. The other patient was diagnosed on postoperative 16th day and was treated with percutaneous nephrostomy catheter, and a JJ stent was placed later on. The effect of JJ ureteral stent was not statistically significant for urinary leak after living donor kidney transplantation (p= 0.074).

Factors effecting ureteral stenosis is summarized in Table 1. Ureteral stenosis was encountered in 6 (5.2%) patients; 5/84 (6.0%) in stented and 1/32 (3.1%) in non-stented patients. JJ stent use did not have a significant effect on ureteral stenosis (p= 1.000). The number of ureteral stenosis in peritoneal dialysis patients was 4 (13.8%) and in non-peritoneal dialysis patients was 2 (2.8%) and it was statistically significant (p= 0.034). Median time between ureteral stenosis and transplantation was 5.7 ± 1.4 months. All of the patients who developed ureteral stenosis after transplantation were males; however, sex was not a risk factor in statistical analyses (p= 0.096). Peritoneal dialysis before transplantation and bacteriuria in the urine culture after transplantation were independent risk factors for the development of ureteral stenosis in our study (p= 0.013, OR= 21.574, 95% CI= 1.924-241.911 and, p= 0.010, OR= 23.876, 95% CI= 2.131-267.474, respectively). As for the treatment of stenosis, three of the six patients with ureteral stenosis were treated with percutaneous nephrostomy and placement of JJ stent. The remaining three patients required ureteroneocystostomy.

DISCUSSION

Urinary leaks and ureteral stenosis are the two most common urological complications after renal transplantation and its incidence is reported between 2.5-14% (1-5). It's a preventable cause of graft loss and necessary precautions should be taken by the

physician. In our study, the incidence of major urologic complications was 6.9% and it was compatible with the literature.

The impact of ureteral stenting on postoperative urinary leak, ureteral stenosis and bacteriuria after kidney transplantation is still a matter of debate. Various studies discuss the impact of JJ ureteral stent on postoperative major urologic complications and bacteriuria after kidney transplantation (8-17). Some of the studies support the use of JJ stents in order to prevent major urologic complications (10,11). On the other hand, other studies contradict routine use and suggest using JJ stents in selected cases to prevent urologic complications (8,15,17). Our findings showed that there was no correlation between use of JJ stent and major urologic complications such as urinary leak or ureteral stenosis. A prospective randomized controlled trial by Tavakoli et al. has shown that JJ stenting reduced the early major complications following renal transplantation such as leakage and stenosis but they have found a higher incidence of urinary tract infections in the stented patients (12). Fayek et al. have found that JJ stenting had a significant impact on prevention of major urinary complications following renal transplantation using cadaveric organs, however they stated that JJ stenting did not have a significant effect on the complication rates following living donor kidney transplantation (14).

Incidence of urinary leak after kidney transplantation ranges 0% to 8.9% (18). We observed only two (1.7%) urinary leaks after transplantation in our study. These two patients were in non-stented group but it was not statistically significant. This may be due to the small number of patients in whom urinary leakage was observed.

Pretransplant peritoneal dialysis and its effects on postoperative complications are discussed in many studies (19-22). These studies state that urologic complications are reported to be similar in peritoneal dialysis group and others. In our study, we found similar results as these studies when we analyzed the effects of pretransplant peritoneal dialysis on posttransplant major urologic complications. However, these studies did not specifically investigate the effects of peritoneal dialysis on ureteral stenosis. When we analyzed factors affecting ureteral stenosis after living donor kidney transplantation, we found that peritoneal dialysis before transplantation and bacteriuria after transplantation were independent risk factors. We speculate that inflammation or immunologic mechanisms due to peritoneal dialysis can affect posttransplant ureteral stenosis. The composition of peritoneal dialysis solutions and patients' attitude during dialysis affects the development of peritonitis following the procedure. Ayar et al. have stated that icodextrin-based regimens during peritoneal dialysis before kidney transplantation more frequently caused encapsulating peritonitis (23).

In the present study, we didn't find any association between graft artery number and ureteral stenosis after kidney transplantation as reported before in some other studies (24,25). Effect of graft artery number on urologic complications after kidney transplantation is still controversial. Karam et al. and various other researchers have reported that multiple graft arteries is a one of risk factor for ureteral stenosis after renal transplantation (26-28).

Although various studies report male sex as a risk factor for post-transplant urinary stenosis, in the present study, we did not find male sex as a risk factor even if all the patients with stenosis were males (1,29). This may be related with the patient volume of the study and with increasing number of patients a clear difference amongst the gender in terms of ureteral stenosis will be defined.

There is no significant impact of JJ stent on the development of ureteral stenosis or urinary leaks. In the guidance of the results of the present study, it is our suggestion that patients with post-transplant positive urinary cultures and/or a history of pre-transplant peritoneal dialysis have an increased risk of ureteral stenosis and therefore, attending physicians should take the necessary precautions. JJ stenting should be performed in selected high-risk patients or not be performed by centers which are early in the learning curve for living donor kidney transplantation. Prospective randomized trials are required in order to evaluate the effect of different peritoneal dialysis solutions on post-transplant urinary complications. Furthermore, the role of JJ stenting on post-transplant ureteral stenosis in a subgroup of patients with peritoneal dialysis should be evaluated.

Ethics Committee Approval: As this was a retrospective study, we did not apply for ethical committee approval. It was conducted according to the principles set forth by the Helsinki Declaration.

Informed Consent: This was a retrospective study.

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ORİJİNAL ÇALIŞMA-ÖZET
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Böbrek nakli öncesi periton diyalizi erişkin canlı vericili böbrek nakli sonrası üreteral stenoz için risk faktörü müdür?

Koray Kutlutürk[1], Tevfik Tolga Şahin[1], Serhan Çimen[2], Yasin Dalda[1], Fatih Gönültaş[1], Sait Murat Doğan[1], Sibel Altunışık Toplu[3], Bülent Ünal[4], Turgut Pişkin[1]

[1] İnönü Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Malatya, Türkiye
[2] Malatya Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, Malatya, Türkiye
[3] İnönü Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Malatya, Türkiye
[4] Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Eskişehir, Türkiye

ÖZET

Giriş ve Amaç: Böbrek nakli sonrası oluşan üriner kaçak, üreteral darlık veya idrar yolu infeksiyonları gibi majör ürolojik komplikasyonlar greft veya hasta kaybına neden olabilir. Periton diyalizinin böbrek nakli sonrası komplikasyonlar üzerine etkisi tartışılmıştır ancak üreteral darlık üzerindeki etkisi bilinmemektedir. Bu çalışmada, canlı vericili böbrek nakli sonrası majör ürolojik komplikasyonlara etki eden faktörleri ve periton diyalizi ve double J-stentlerin (JJ stentler) etkisini analiz etmek amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma canlı vericili böbrek nakli yapılan 116 hastayı içermektedir. Çalışmada, canlı vericili böbrek nakli sonrası majör ürolojik komplikasyonları etkileyen faktörler analiz edildi. Donörler, alıcıların birincil akrabaları idi.

Bulgular: Canlı vericili böbrek nakli sonrası majör ürolojik komplikasyonlar 8/116 (%6,9) idi. İki (%1,7) hastada üriner kaçak, 6 (%5,2) hastada üreteral darlık saptanmış, 84 (%72,4) olguda JJ stent kullanılmıştır. Üriner kaçak, üreteral darlık açısından JJ stent kullanımının istatistiksel olarak anlamlı bir etkisi saptanmamıştır (p= 0,074, p= 0,470). Toplam 29 (%25) hastada böbrek nakli öncesi periton diyalizi öyküsü vardı. Preoperatif periton diyalizi ve böbrek nakli sonrası bakteriüri, multivaryant analizde üreteral darlık için bağımsız risk faktörleri olarak saptanmıştır (p= 0,013 ve p= 0,010).

Sonuç: Bu çalışmanın sonuçlarında canlı vericili böbrek nakli öncesi hastalarda periton diyalizi öyküsünün ve nakil sonrası bakteriürinin olması, nakil sonrası üreteral darlık için bağımsız risk faktörleri olarak saptanmıştır. Canlı vericili böbrek nakli sonrası ürolojik komplikasyonlar üzerine JJ stentlerin etkisi saptanmamıştır.

Anahtar Kelimeler: Böbrek nakli, ürolojik komplikasyonlar, periton diyalizi, üreteral darlık

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ORIGINAL ARTICLE
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The efficacy of clinical pathway in gastric cancer surgery

Ali Güner[1,2] (ID)

[1] Department of General Surgery, Karadeniz Technical University School of Medicine, Trabzon, Turkey
[2] Department of Biostatistics and Medical Informatics, Karadeniz Technical University Institute of Medical Science, Trabzon, Turkey

ABSTRACT

Objective: Clinical pathways are useful tools for surgical quality improvement and better peri-operative clinical outcomes for patients undergoing major surgery. This study aimed to evaluate the influence of clinical pathway on early postoperative outcomes for gastric cancer patients.

Material and Methods: The study was designed as a retrospective cohort observational study. Patients who had undergone curative gastrectomy for gastric cancer were evaluated by using the gastric cancer database, which was prospectively maintained. The patients were divided into two groups based on the date when the clinical pathway was first used: The control group (May 2015-May 2016) and the clinical pathway group (June 2016-December 2017). Early postoperative outcomes including the length of hospital stay, start of the day of diet, and 30-day complications including reoperation, and operative mortality were compared after propensity score matching.

Results: A total of 101 patients were analyzed, and the data of 70 patients (35 patients in each group) were compared after matching. Clinical pathway group demonstrated shorter hospital stay, earlier nasogastric tube removal, and start of earlier liquid/soft diet. Overall complication rate was lower in the clinical pathway group, while there was no statistically significant difference in major complication rates. No statistically significant difference was observed between the groups in terms of reoperation and operative mortality.

Conclusion: Clinical pathway may shorten the postoperative length of hospital stay and reduce the overall complication rate without increasing major morbidity in patients undergoing elective gastric cancer surgery.

Keywords: Gastrectomy, gastric cancer, clinical pathway, perioperative care, recovery of function, quality improvement

INTRODUCTION

Hospitals, which are complex organizations consisting of many interconnected actions, are designed for patient-centered and effective healthcare (1,2). Having been managed with traditional concepts for many years, total quality management is now a new paradigm in healthcare organizations (3,4). Various strategies, such as enhanced recovery, outcome management, and integrated care pathways can be used as part of total quality management (5). Clinical pathways (CP), which are standardized comprehensive management systems, are useful tools for surgical quality improvement, designed to improve peri-operative outcomes such as hospital stay, morbidity, and cost (6,7). Effectiveness of CP for cardiothoracic, liver, and bariatric surgery has been shown in recent studies (7-10).

One of the major causes of cancer-related deaths, the only treatment option of gastric cancer in a majority of patients is surgical resection (11,12). However, gastrectomy for gastric cancer remains a high-risk procedure with significant morbidity and mortality (13,14). Clinical pathway has also been used for gastric cancer surgery, and studies have demonstrated improvement in peri-operative outcomes (15-18). Enhanced Recovery After Surgery (ERAS) protocol is an evidence-based model of standardized clinical pathway system, which has been considered safe and effective in a recent meta-analysis in gastrectomy for gastric cancer patients (19). Besides, consensus guidelines for enhanced recovery after gastrectomy has been published by the ERAS® society (20). However, majority of the evidence regarding enhanced recovery pathways has originated from studies conducted in far eastern countries. Convincing evidence from western patient population is limited, and thus, the feasibility of clinical pathways in all gastric cancer patients, particularly in developing countries, remains controversial.

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Corresponding Author
Ali Güner
E-mail: draliguner@yahoo.com

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Clinical pathway system, as part of a quality improvement program for gastric cancer patients, was implemented in June 2016 in a tertiary center from Turkey. In the present study, the influence of clinical pathway on early postoperative outcomes for gastric cancer patients was evaluated.

MATERIAL and METHODS

Patients and Data Collection

The study was designed as a retrospective cohort observational study. The database prospectively maintained for patients who had undergone surgical treatment for gastric cancer was reviewed. CP for gastric cancer surgery was implemented in June 2016 and modified in December 2017 with the use of a checklist system. Therefore, patients operated on in this period were selected as test group (CP group). Before the implementation of CP, patients were managed without any specific protocol, and these patients were selected as the historic control group (control group). Patients operated on before May 2015 were excluded to decrease the risk of experience bias. Signed informed consent was obtained from all patients prior to surgery. Ethics permission for the study was obtained from the ethics committee (2019/177).

All consecutive patients who had undergone gastrectomy for gastric malignancy between May 2015 and December 2017 were evaluated. Exclusion criteria were: (1) patients who did not have gastric resection, (2) patients who only had palliative procedure including bypass or palliative resection (3) patients having distant metastasis, (4) patients requiring thoracotomy, (5) emergency surgery, and (6) patients who had malignancy other than adenocarcinoma.

All data were retrieved from the electronic database developed in 2013 for patients who underwent upper gastrointestinal cancer surgery. The following data regarding patient demographics and clinical characteristics were extracted: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, history of previous abdominal surgery, smoking habits, hemoglobin level, albumin level, tumor size, histologic differentiation, type of gastrectomy, type of lymphadenectomy, source of tumor, presence of neoadjuvant treatment, pathological stage, total number of removed lymph nodes. Surgical principles were in accordance with the Korean and Japanese gastric cancer treatment guidelines (21,22). D2 lymphadenectomy for advanced gastric cancer and D1+ lymphadenectomy for early gastric cancer were standard approaches, while D1 gastrectomy was used seldom in high-risk patients (23). Tumors were staged according to the 8th edition of the American Joint Committee on Cancer Staging System (24,25).

Outcome measures were the length of hospital stay, the day of nasogastric tube removal, the day of starting sips of water (SOW), the day of starting soft diet, the day of drain removal, 30-day complication rate, 30-day reoperation rate, and operative mortality. Adverse events occurring within 30 days after surgery or within the hospitalization period were considered postoperative complications. Complications were classified according to the Clavien-Dindo classification system (26). Complications classified as grade 3 or higher were defined as major complications. Mortality that occurred within 30 days after surgery or during initial hospitalization was defined as operative mortality.

Clinical Pathway for Gastric Cancer Surgery

CP for gastric cancer surgery has initially been developed according to the current evidence on CP and published ERAS protocol for gastric cancer surgery and modified based on the institutional facilities and personal experiences (20). CP is summarized in Table 1. In brief, we divided peri-operative process into three main periods. The first period (preoperative preparation period) starts at the time when the patient's initial diagnosis of gastric cancer is established and is is primarily focused on the conformity of indication of surgical treatment, optimizing chronic diseases, nutritional counseling, and patient/family member's education.

The second period (operative period) starts with the patient's admission for surgery, typically one day before the scheduled operation date, and ends when the patient comes back to the wardroom after surgery. Confirming the completeness of the preparation and the surgical procedure are the main elements of the second period. During operation, intra-abdominal drain and nasogastric tube are routinely used regardless of the gastrectomy type. Because the majority of the patients had advanced gastric cancer or tumors requiring total gastrectomy, laparoscopic approach was seldom used in the study period only for early gastric cancers requiring distal gastrectomy (23).

The third period (postoperative care) primarily focused on postoperative care and ended when the patient was discharged from the hospital. Discharge criteria were; adequate mobilization, adequate pain management with oral analgesics, patient's willingness to be discharged, no fever, the ability to eat a soft diet, no vomiting/nausea, and no major complication. One week after discharge, all patients were invited to the outpatient clinic for early follow-up. Written clinical pathway was distributed to the surgical team members responsible for patient care, and they were educated on the items of the path.

Before the implementation of CP, there was no specific written protocol on items such as nutritional counseling, postoperative diet instructions, catheter removal, drain removal, discharge criteria, and etc. Patients having gastrectomy were managed traditionally by the members of the surgical team. All surgical procedures during the study period were carried out by the same upper gastrointestinal surgeon.

Table 1. Clinical pathway for gastric cancer surgery

Preoperative preparation period	**Diagnosis of gastric cancer and first admission to the hospital**							
	Preoperative tumor staging Preoperative endoscopy for tumor localization ± Endosonography Multidisciplinary board meeting Smoking cessation Nutritional counseling / Enteral nutrition for severe malnourished patients Enteral immunonutrition with glutamine-containing supplements Breathing physiotherapy with incentive spirometry Comorbidity/Medication management Complete informed consent Correct anemia Education for patient /family members							
Operative period	**Admission for surgery**							
	Day -1	Reassess the patient and laboratory values Check for surgical equipment No bowel preparation No restriction on eating until midnight Single dose LMWH						
	Day 0	WHO Surgical safety checklist Compression stockings Antibiotic prophylaxis with 2 g intravenous cefazolin						
	In the operating room							
	WHO Surgical safety checklist Epidural catheter Patient positioning Forced-air warming Operative steps including wound management				Repeat antibiotic if needed (> 4 hours) Counting procedures Specimen preparation and documentation Record operation details Database entry			
	After surgery							
Postoperative care	Action	POD0	POD1	POD2	POD3	POD4	POD5	≥ POD6
	Monitor vitals	+	+	+	+	+	+	+
	Monitor laboratory values†	+	+	+	+	+	+	+
	Pain management	+	+	+	+	+	+	+
	Immunization if required	+						
	Fresh frozen plasma	+						
	Mobilization		+	+	+	+	+	+
	Incentive spirometry		+	+	+	+	+	+
	LMWH		+	+	+	+	+	+
	Metoclopramide		+	+	+	+	+	+
	Epidural catheter removal				+			
	Nasogastric tube removal		+					
	Urinary catheter removal		+					
	Blue dye test				+			
	Initiate sips of water				+			
	Immunonutrition					+	+	+
	Initiate liquid/soft diet‡				+	+		
	Drain amylase-triglyceride check						+	
	Consider drain removal						+	+
	Check discharge criteria						+	+
	Orders on discharge						+	+
	Database check							+

†: including hemoglobin, amylase and glucose levels.
‡: The only difference between distal and total gastrectomy is the day of liquid diet initiation (POD3 vs POD4).
Abbr: LMWH: Low Molecular Weight Heparin, WHO: World Health Organization, POD: Postoperative day.

Statistics Analysis

Continuous variables were presented as mean ± standard deviation for parametric distribution and as median (1st-3rd quartile) for nonparametric distribution. Chi-square test or Fisher's exact test (when 20% of expected frequencies in any cell was ≤ 5), Student's t-test and Mann-Whitney test were used for comparing the groups based on the type and characteristics of the data. All p values were two-sided, and statistical significance was defined as p< 0.05. R software (R Foundation for Statistical Computing, Vienna, Austria) with required packages was used for statistical analyses. To reduce selection bias, the "MatchIt" package with nearest-neighbor 1-1 matching was used to conduct a propensity-score matching analysis. Age, sex, albumin level, pathological stage, ASA score, and type of gastrectomy were used as covariates.

RESULTS

A total of 147 patients underwent surgery due to gastric cancer during the study period. After the application of exclusion criteria, 101 patients were included into the analysis. Among them, thirty-five patients were managed with the traditional approach (control group), and sixty-six patients were managed with the clinical pathway approach (all-CP group). Propensity score matching generated a sample of 70 patients (35 patients in the control group and 35 patients in the matched-CP group).

Comparison of Baseline Characteristics Between the Groups

The comparison of baseline patient demographics is presented in Table 2. In the non-matched analysis, there were no statistically significant differences between the control group and the all-CP group concerning sex, BMI, ASA score, history of previous abdominal surgery, smoking status, and hemoglobin levels. However, the all-CP group tended to be older (not statistically significant) and had higher albumin levels (p= 0.049). In the matched analysis, there were no statistically significant differences between the control group and the matched-CP group concerning baseline patient demographics.

The comparison of oncologic and surgical factors is presented in Table 3. In the non-matched analysis, there were no statistically significant differences between the control group and the all-CP group concerning tumor size, histological differentiation, type of gastrectomy, source of tumor, neoadjuvant chemotherapy, pathological stage, and the total number of removed lymph nodes. There was a statistically significant difference in the type of lymphadenectomy. More D2 lymphadenectomy was performed in the all-CP group compared to the control group (p= 0.047). In the matched analysis, there was no statistically significant difference between the control group and the matched-CP group concerning the type of lymphadenectomy as well as other factors.

Table 2. Comparison of baseline patient demographics

	Control group	Clinical pathway group			
		All-CP group		Matched-CP group	
Variables	**n= 35**	**n= 66**	**p†**	**n= 35**	**p‡**
Age (years)	59.57 ± 11.61	63.92 ± 12.04	0.083	60.71 ± 13.04	0.700
Sex					
Female	14 (40%)	18 (27.3%)	0.190	11 (31.4%)	0.454
Male	21 (60%)	48 (72.7%)		24 (68.6%)	
Body mass index (kg/m^2)	23.44 (21.45-27.62)	24.70 (22.51-29.31)	0.188	24.70 (22.58-29.53)	0.213
ASA score					
ASA I	7 (20.0%)	6 (9.1%)	0.328	5 (14.3%)	0.946
ASA II	18 (51.4%)	43 (65.2%)		19 (54.2%)	
ASA III	9 (25.7%)	16 (24.2%)		10 (28.6%)	
ASA IV	1 (2.9%)	1 (1.5%)		1 (2.9%)	
Previous abdominal surgery	7 (20%)	16 (24.2%)	0.628	9 (25.7%)	0.569
Smoking					
Current	7 (20.0%)	11 (16.7%)	0.769	4 (11.4%)	0.630
Ex-smoker (< 6 weeks)	1 (2.9%)	5 (7.6%)		3 (8.6%)	
Ex-smoker (> 6 weeks)	8 (22.8%)	18 (27.2%)		9 (25.7%)	
Never smoked	19 (54.3%)	32 (48.4%)		19 (54.3%)	
Hemoglobin (g/dL)	11.65 ± 1.89	11.90 ± 2.03	0.543	11.85 ± 2.10	0.667
Albumin (g/dL)	3.60 (3.10-3.90)	3.80 (3.40-4.20)	0.049	3.60 (3.10-4.10)	0.552

Data were presented as mean ± standard deviation, median (1st-3rd quartile) or number of patients (percentage).
†: Control group vs. All-CP group, ‡: Control group vs. matched-CP group.
CP: Clinical pathway, ASA: American Society of Anesthesiologists.

Table 3. Comparison of oncologic and surgical factors

	Control group	Clinical pathway group			
		All-CP group		Matched-CP group	
Variables	**n= 35**	**n= 66**	**p†**	**n= 35**	**p‡**
Tumor size (cm)	6.00 (2.75-8.00)	5.00 (3.50-7.00)	0.892	5.20 (4.25-9.25)	0.406
Histology					
Differentiated	16 (45.7%)	35 (53.0%)	0.484	14 (40%)	0.629
Undifferentiated	19 (54.3%)	31 (47.0%)		21 (60%)	
Type of gastrectomy					
Extended TG	4 (11.4%)	9 (13.6%)	0.373	5 (14.3%)	0.921
TG	10 (28.6%)	11 (16.7%)		9 (25.7%)	
DG	21 (60.0%)	46 (69.7%)		21 (60.0%)	
Type of lymphadenectomy					
D1/D1+	9 (25.7%)	7 (10.6%)	0.047	6 (17.1%)	0.382
D2	26 (74.3%)	59 (89.4%)		29 (82.9%)	
Source					
EGJ	3 (8.6%)	8 (12.1%)	0.743	4 (11.4%)	1
Stomach	32 (91.4%)	58 (87.9%)		31 (88.6%)	
Neoadjuvant CT	3 (8.6%)	8 (12.1%)	0.743	4 (11.4%)	1
Pathologic stage					
Stage I	8 (22.8%)	14 (21.2%)	0.145	7 (20%)	0.809
Stage II	5 (14.3%)	21 (31.8%)		7 (20%)	
Stage III	22 (62.9%)	31 (47.0%)		21 (60%)	
Removed lymph nodes (n)	35.00 (28.50-42.00)	36.00 (28.25-46.75)	0.612	36.00 (26.50-45.00)	0.801

Data were presented as mean ± standard deviation, median (1st-3rd quartile) or number of patients (percentage).
†: Control group vs. All-CP group, ‡: Control group vs. matched-CP group.
CP: Clinical pathway, TG: Total gastrectomy, DG: Distal gastrectomy, EGJ: Esophagogastric junction.

Baseline demographics, oncological factors, and surgical factors were well balanced between the control group and the matched-CP group.

Comparison of Postoperative Outcomes Between the Control Group and the Matched-CP Group

Postoperative clinical outcomes are presented in Table 4. Significantly shorter hospital stay (median 11 days vs. 9 days, p< 0.001), earlier nasogastric tube removal (median 4 days vs. 2 days, p< 0.001), shorter time from surgery to first SOW (median 4 days vs. 4 days, p< 0.001) and soft diet (median 5 days vs. 5 days, p= 0.013) were observed in the matched-CP group compared to the control group. There was no statistically significant difference between the control group and the matched-CP group concerning time to drain removal (median 6 days vs. 6 days, p= 0.851).

The overall complication rate was lower in the matched-CP group, while there was no statistically significant difference in major complication rates. Sixty percent of the patients in the control group and 31.4% of the patients in the matched-CP group experienced complications (p= 0.016). Only one patient (2.9%) in the control group and two patients (5.7%) in the matched-CP group experienced major complications. Besides, although there was no difference in terms of the distribution of complication grades, 20 patients (57.1%) in the control group and nine patients (25.7%) in the matched-CP group experienced grade-I or grade-II complications (p= 0.007).

Neither anastomotic leakage nor bleeding was observed in the study population. Major complications were as follows: A patient from the control group experienced right pleural effusion following extended total gastrectomy, and tube thoracostomy was required. A patient from the matched-CP group was readmitted to the hospital after discharge (on postoperative 21st day) with the complaint of acute mechanical small bowel obstruction. Adhesive band was found during surgery; the problem was solved with adhesiolysis, and the patient was discharged three days after reoperation. One other patient from the matched-CP group (with no surgery-related complication) experienced operative mortality on the 4th postoperative day due to cardiac arrest. No statistically significant difference was observed between the groups in terms of reoperation and operative mortality.

Table 4. Postoperative clinical outcomes			
Variables	**Control group (n= 35)**	**CP group (n= 35)**	**p**
Hospital stay (days)	11.00 (9.00-12.50)	9.00 (7.00-10.00)	< 0.001
Nasogastric tube removal (days)	4.00 (3.00-4.50)	2.00 (2.00-2.00)	< 0.001
Sips of water (days)	4.00 (4.00-5.00)	4.00 (3.00-4.00)	< 0.001
Soft diet (days)	5.00 (5.00-6.00)	5.00 (5.00-5.50)	0.013
Drain removal (days)	6.00 (6.00-7.00)	6.00 (6.00-7.00)	0.851
All complications	21 (60%)	11 (31.4%)	0.016
Major complications	1 (2.9%)	2 (5.7%)	1
Grade I-II complication	20 (57.1%)	9 (25.7%)	0.007
Reoperation	0	1 (2.9%)	1
Operative mortality	0	1 (2.9%)	1
Complication grade			
Grade I	8 (38.1%)	3 (27.3%)	0.558
Grade II	12 (57.1%)	6 (54.5%)	
Grade III	1 (4.8%)	1 (9.1%)	
Grade IV	0	0	
Grade V	0	1 (9.1%)	

Data were presented as median (1st-3rd quartile) or number of patients (percentage).
CP: Clinical pathway.

DISCUSSION

The presented study investigated the influence of implementing a clinical pathway for patients undergoing elective gastric cancer surgery. Although both groups were comparable in terms of clinically relevant baseline characteristics, propensity score matching was used to decrease potential selection bias. Patients in the clinical pathway group demonstrated shorter hospital stay, earlier removal of the nasogastric tube, shorter time to diet while there was no difference in drain removal time. Using a clinical pathway also demonstrated less overall complication rate without increasing major complications.

Although the concept of peri-operative interventions is defined by different names such as ERAS, fast-track, critical pathway, and clinical pathway, the primary purpose is to optimize the patient in the preoperative period, to reduce the metabolic stress resulting from surgical trauma during the operation and to return to normal life as soon as possible (27,28). Early studies for enhanced recovery protocols on gastrectomy for gastric cancer has started in Far Eastern countries where early-stage cancers constituted the majority of patients (16,29). In subsequent studies, the implementation of various protocols by each institute has made the standardization of enhanced recovery problematic. In 2014, the first comprehensive and evidence-based framework recommendations were published (20). A total of 25 items, 8 of which were procedure-specific, included different recommendation grades with different evidence levels. While deciding on the clinical pathway in our practice, we used institutional factors and personal experiences in addition to the available evidence and recommendations. Most of the general items (not-procedure specific) were included in our clinical pathway except for the items related to anesthesia. Among procedure-specific items, preoperative nutrition (strong recommendation), preoperative oral immunonutrition (weak recommendation), and systematic audit (strong recommendation) were included in our clinical pathway. However, we showed a selective approach in the use of some crucial elements of ERAS such as the use of laparoscopic surgery (strong recommendation for early gastric cancer requiring distal gastrectomy, weak recommendation for advanced gastric cancer and total gastrectomy), selective use of nasogastric decompression (strong recommendation), avoiding the use of abdominal drain (strong recommendation) and very early initiation of diet (weak recommendation). Surgical dogmas, as well as personal experiences, are likely to have affected this selective approach, even for highly experienced gastric cancer surgeons (30). However, the implementation of a novel approach has always been slow due to surgical dogmas but has finally been. It is to our belief that all essential items may be included in clinical pathway with increasing evidence and experience.

One of the most important goals of the clinical pathway concept is shortening hospital stay, and shorter hospital stay was demonstrated in the presented study (median 11 days vs. 9

days, p< 0.001). Many factors, such as the defined discharge criteria in the clinical pathway group, earlier removal of the nasogastric tube, earlier initiation of oral food intake, and fewer complications may affect this shortening. Shortened hospital stay has been demonstrated in randomized studies evaluating the feasibility of enhanced recovery programs in gastric cancer patients. In the first randomized controlled trial, median hospital stay was six days in the fast-track protocol group, while the conventional group had 8-days length of hospital stay (p< 0.001) (29). In a subsequent randomized trial, shorter hospital stay has also been demonstrated in an enhanced recovery group (median 10 days vs. 9 days, p= 0.037) (31). Besides, in a recent study from the United States, the ERAS group has demonstrated shorter hospital stay with a mean difference of 2.3 days (mean 7.8 ± 3.6 days vs. 5.5 ± 2.0 days, p= 0.010) (18). The only study that showed that the ERAS program did not affect the length of hospital stay was the study published in Japan in 2012 (32). However, as the authors indicated, this result was probably due to the item "normal laboratory data on POD 7" which was included in the discharge criteria. Although the median 9-day hospital-stay in the presented study, which included mostly stage-III patients, is comparable to previous reports, we believe that this period may be shortened more by modifying the criteria together with the increasing experience.

The biggest drawback of surgeons in the implementation of an enhanced recovery program is the possibility of increased complication rates. However, until now, there has been no increase in complication rates in both ERAS studies and studies that are specific to ERAS items. On the contrary, fewer complications have been obtained in the enhanced recovery group compared to the conventional group (31). In the presented study, Clavien-Dindo classification system was used to define the severity of the complications, and a decrease in the overall complication rate was demonstrated (60% vs. 31.4%, p= 0.016). While there was no significant difference between the two groups in major complications, particularly the difference in grade I/II complication rates (57.1% vs. 25.7%, p= 0.007) likely caused this improvement. The patients were more optimized for surgery with the help of the preoperative items such as nutritional support, breathing physiotherapy, and patient education on the process. In addition to optimal patient, postoperative care items such as early mobilization may explain the decrease in non-major complications.

When creating the presented clinical pathway protocol, not only the enhanced recovery items but also surgical safety issues as part of surgical quality improvement were considered. In the "Optimal Resources for Surgical Quality and Safety" manual published by the American College of Surgeons in 2017, physician-led, team-based care was emphasized, and surgical care divided into five phases (33). Four of these phases were present in the presented clinical pathway; only the items for the post-discharge period were not included. In the future, the creation of systems using various tools, not only enhanced recovery items but also items from all phases of peri-operative care, will help us develop an ideal patient care program. Implementing a peri-operative patient care program is more feasible in developed countries such as the United States and Japan, in developing countries like Turkey, there is still a way to go. However, the presented study showed that better outcomes could be achieved by integrating evidence-based models into practice.

The presented clinical pathway protocol has some points that need to be improved. Most importantly, we used a surgeon-led structure with the support of the members of the surgical team, ward nurses, and surgical residents to develop the protocol. However, ideal clinical pathway should be designed by a multidisciplinary team consisting of anesthesiologists, dieticians, and physiotherapists. Anesthesia-related items, which are the significant shortfall in the presented pathway, can only be resolved with a multidisciplinary approach. Another point that needs to be improved is the more use of the laparoscopic approach. The evidence on the feasibility and oncological safety of laparoscopic surgery in advanced gastric cancer is still being waited and possibly will be integrated into the algorithm in the near future (34,35).

The presented study has an unavoidable selection bias, which is one of the main limitations of retrospective studies. Although patient characteristics such as age, sex, stage, type of gastrectomy were comparable in both groups, lymphadenectomy and albumin levels were different. Therefore, propensity-score matching was used to reduce selection bias, and ultimately, appropriately comparable groups were obtained. Another possible limitation in comparison with the historical cohort is the experience bias, although a single surgeon performed all surgeries. Early-period records were excluded to decrease this bias, and the study was limited to a narrow period. Despite these limitations, the presented study supports the contribution of clinical pathway to enhanced recovery in patients undergoing gastric cancer surgery in a developing country. Multidisciplinary, multicenter studies in which outcome measures such as cost analysis, compliance rates, patient experiences, and quality of life are included have more potential to demonstrate the effectiveness of enhanced recovery programs.

CONCLUSION

Clinical pathway can safely be implemented for patients undergoing elective gastric cancer surgery. Using clinical pathway may shorten the postoperative length of hospital stay and reduce the rate of complications without increasing major morbidity.

Ethics Committee Approval: Ethics permission for the study was obtained from the ethics committee (2019/177).

Informed Consent: Written consent of all the patients was received.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.G.; Design - A.G.; Supervision - A.G.; Resource - A.G.; Data Collection and/or Processing - A.G.; Analysis and/or Interpretation - A.G.; Writing Manuscript - A.G.; Critical Reviews - A.G.

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ORİJİNAL ÇALIŞMA-ÖZET
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Mide kanseri cerrahisinde klinik yolak kullanımının etkinliği

Ali Güner[1,2]

[1] Karadeniz Teknik Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Trabzon, Türkiye
[2] Karadeniz Teknik Üniversitesi Tıp Bilimleri Enstitüsü, Biyoistatistik ve Tıp Bilişimi Anabilim Dalı, Trabzon, Türkiye

ÖZET

Giriş ve Amaç: Klinik yolaklar cerrahi kalitenin iyileştirilmesinde kullanılan yararlı araçlardır ve majör cerrahi geçiren hastalarda ameliyat sonrası daha iyi klinik sonuç elde edilmesinde yardımcı olur. Bu çalışmada, mide kanseri hastalarında klinik yolak kullanımının erken postoperatif sonuçlar üzerine olan etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma retrospektif bir kohort çalışma olarak dizayn edildi. Prospektif olarak kayıt yapılan veritabanından, mide kanseri nedeniyle ameliyat edilen hastaların verileri elde edildi. Hastalar klinik yolağın kullanıma girdiği tarihe göre iki gruba ayrıldı: kontrol grup (Mayıs 2015-Mayıs 2016) ve klinik yolak grubu (Haziran 2016-Aralık 2017). Eşleştirilmiş gruplarda hastaların hastanede kalış süresi, oral gıda başlama zamanı ve 30 gün komplikasyon oranları gibi erken dönem klinik sonuçları karşılaştırıldı.

Bulgular: Toplam 101 hasta analiz edilmiştir ve eşleştirme sonrası 70 hastanın (her grupta 35 hasta) verileri karşılaştırılmıştır. Klinik yolak grubundaki hastaların daha kısa süre hastanede kaldığı, nazogastrik tüpün daha erken çıkarıldığı ve sıvı/yumuşak gıdaya daha erken dönemde başlandığı tespit edilmiştir. Tüm komplikasyon oranı klinik yolak grubunda daha düşük iken, majör komplikasyon açısından gruplar arasında istatistiksel açıdan fark görülmemiştir. Reoperasyon ve mortalite açısından da istatistiksel olarak anlamlı bir fark saptanmamıştır.

Sonuç: Klinik yolak kullanımı mide kanseri nedeniyle elektif ameliyat edilen hastalarda hastanede kalış süresini kısaltabilir ve majör komplikasyonu artırmadan tüm komplikasyon oranlarını azaltabilir.

Anahtar Kelimeler: Gastrektomi, mide kanseri, klinik yolak, perioperatif bakım, fonksiyonların düzelmesi, kalitenin geliştirilmesi

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ORIGINAL ARTICLE
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Comparison of prolene and progrip meshes in inguinal hernia repair in terms of post-operative pain, limitation of movement and quality of life

Ahmet Kaya[1](ID), Semra Tutcu Şahin[2](ID), Yavuz Kaya[2](ID), Teoman Coşkun[2](ID), Aslan Sakarya[2](ID)

[1] Division of Surgical Oncology, Sakarya University School of Medicine, Sakarya, Turkey

[2] Department of General Surgery, Celal Bayar University School of Medicine, Manisa, Turkey

ABSTRACT

Objective: The study aimed to compare the techniques applying prolene mesh and progrip-self fixating mesh in terms of post-operative pain, limitation of movement and quality of life.

Material and Methods: The study was conducted from November 2014 to January 2016 in Department of Surgery, Manisa Celal Bayar University Hospital. The study recruited 50 male patients, aged 18 and over and was carried out as a double blinded procedure. Twenty-five patients were randomly selected to receive hernia repair by progrip self-fixating mesh and 25 patients were treated with hernia repair with suture fixation method by using prolene grafts, and patients' pain follow-up was performed with face-to-face or telephone interviews with VAS (Visual Analogue Scale) and return to daily routine activities were evaluated with SF-36 (Short Form-36) quality of life scale. Recurrent hernias and emergency cases were excluded.

Results: The pain scores were lower and a statistically significant difference was achieved in patients in whom progrip self-fixating mesh was used in the early postoperative period. Both methods gave statistically similar results in terms of pain and quality of life.

Conclusion: In the literature, there are some evidence that the repair applied with progrip self-fixating graft has more positive outcomes compared to the repairs applied with suture fixation. It is concluded that there is a need for longer follow-ups and larger series of cases in order to achieve a definite result.

Keywords: Inguinal hernia, pain, progrip mesh, prolene mesh, quality of life

INTRODUCTION

Inguinal hernia is one of the most common diseases in the society, and many repair techniques have been described throughout history. Advancements in perioperative anesthesia and operative technique have made this an outpatient ambulatory operation with low recurrence rates and morbidity. Given this success, quality of life and the avoidance of chronic pain have become the most important considerations in hernia repair (1). Today, tension-free repairs are accepted as the golden standard, and the problem of pain still remains in the post-operative period. Abdominal wall hernias are the displacement of intra-abdominal organs due to a gap between abdominal wall muscles and fascia layers, mesenteries or around the organs. Inguinal hernia is one of the most common abdominal wall hernias. Hernias seen in the inguinal and femoral regions are often categorized together and are called inguinal hernias. Approximately 75% of abdominal wall hernias occur in the groin. The lifetime risk of inguinal hernia is 27% in men and 3% in women (2). Of inguinal hernia repairs, 90% are performed in men and 10% in women. The incidence of inguinal hernias in males has a bimodal distribution, with peaks before the first year of age and after age 40. Abramson demonstrated the age dependence of inguinal hernias in 1978. Ages 25 to 34 years had a lifetime prevalence rate of 15%, whereas ages 75 years and over had a rate of 47%. Approximately 70% of femoral hernia repairs are performed in women; however, inguinal hernias are five times

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Corresponding Author
Ahmet Kaya
E-mail: ahmet.kaya@cbu.edu.tr

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more common than femoral hernias. The most common subtype of groin hernia in men and women is the indirect inguinal hernia (1). Chronic pain emerges as an important problem after hernia repair carried out with mesh. Although prolene meshes are most frequently used in hernia operations, progrip - self fixating mesh frequency has been increasing in recent years. Pain level and the time required to return to normal daily activities in a complete manner following the hernia surgery appear as the criteria used to measure the quality of life. In this study, it was aimed to compare the techniques applying prolene mesh-Surgipro™ Covidien, A4B0694X, Mansfield/USA) -and progrip-self fixating- Parietene progrip© (Covidien TEM1208GL-TEM1208GR, Berlin/Germany) mesh in terms of post-operative pain, limitation of movement and quality of life.

MATERIAL and METHODS

Fifty male patients who consulted the General Surgery Policlinic of Manisa Celal Bayar University Hospital with complaints of groin swelling and/or groin pain and were diagnosed with inguinal hernia between November 2014 and January 2016 were included in this prospective, randomized clinical study. These patients were applied with inguinal hernia repair with prolene mesh (Surgipro™ Covidien, A4B0694X, Mansfield/USA) or self-fixating mesh (Progrip, Covidien, TEM1208GL-TEM1208GR, Berlin/Germany). This scientific study began with the approval of the Manisa Celal Bayar University Local Ethics Committee (decision numbered 16/07/2014 / 20478486-271). Written consent of all the patients was received. The inguinal region shave of the patients was performed just before the operation. Antibiotic prophylaxis was applied to the patients by using cefazolin sodium 1 g intravenous (IV) (Cefozin, J01DB04, Bilim Ilaç San. ve Tic. AŞ, Beyoglu/ISTANBUL) half an hour before the operation. The study was carried out as a double blinded procedure. Pain inquiries of the patients were performed on the postoperative 1st, 3rd, 7th, 14th and 60th days by using the visual pain scale (VAS). On the postoperative 60th day, Short Form-36 (SF-36) was evaluated in terms of quality of life. The inquiries were maintained as face-to-face during the hospitalization and by means of phones or policlinic controls during the post-discharge period.

Group 1 (n= 25) was applied with repair by using prolene graft.

Group 2 (n= 25) was applied with repair by using a progrip self-fixating graft.

Recurrent hernia, bilateral hernias, emergency cases and female patients were not included into the study. Post-operative analgesia was performed on the first day by using dexketoprofen trometamol bid (IV) and metamizole sodium qid (IV). From the first postoperative day, analgesia was achieved by using dexketoprofen trometamol bid [peroral (PO)]. It was projected to apply narcotic analgesic Tramadol HCL (drops) as an addition if analgesia could not be achieved with current treatments. Pain assessment was performed using visual pain scale (VAS). Statistical evaluation of this study was carried out with SPSS (Statistical Package for Social Sciences) program. The obtained data were entered into the database created in the SPSS 15 program and statistical analysis of the data was performed with the same program as well. Mean, standard deviation, median, minimum and maximum values of continuous variables and their subgroups and frequency numbers and percentages of class variables were presented. Independent group comparisons were made using the Independent Samples Test and the Mann-Whitney U test. Paired Samples t-Test, and Wilcoxon Signed Ranks Test methods were used in paired groups. Analysis of variance (ANOVA) for repeated measurement was used in the comparison within groups, and intra-group comparison was performed using single-factor ANOVA. For all tests, type 1 error margin was selected as alpha: 0.05 and the difference between the groups was considered statistically significant if the value of p was less than 0.05.

RESULTS

The age range of 50 male patients participated in the study was 20-83 (mean 52.42); the age range of 25 participants in the prolene group was 23-83 (mean 54.72); the age range of 25 participants in the progrip group was 20-76 (mean 50.12) and there was no statistically significant difference (p> 0.05) (Table 1). There were right inguinal hernias in 26 (52%) of the patients and left inguinal hernias in 24 (48%) of the patients. Direct inguinal hernia was detected in 12 (24%) patients, indirect inguinal hernia was detected in 29 (58%) patients, and direct + indirect inguinal hernia were detected in the remaining 9 (18%) patients (Table 2). On the 1st postoperative day, mean pain was determined as 2.32 in the prolene group and as 1.52 in the progrip group (p< 0.05).

On the 3rd postoperative day, mean pain score was determined as 1.32 in the prolene group; and as 0.72 in the progrip group

Table 1. Case numbers, age range and SF-36 score range

	Number	Min	Max	Mean	SD	p
Age (prolen group)	25	23	83	54.72	16.90	0.15
Age (progrip group)	25	20	76	50.12	17.52	
SF score (prolen group)	25	86	146	116.24	16.09	0.21
SF score (progrip group)	25	85	144	124.20	17.07	

SD: Standard deviation.

Table 2. Type of hernia

	Number	Percent
Direct	12	24
Indirect	29	58
Direct + Indirect	9	18
Total	50	100

Table 3. Postoperative pain and SF-36 scores according to graft types

Graft type		Postop 1st day pain	Postop 3rd day pain	Postop 7th day pain	Postop 14th day pain	Postop 60th day pain	SF-36 score
Prolene	Mean	2.32	1.32	0.76	0.48	0.16	116.24
	N	25	25	25	25	25	25
	SD	1.31	0.62	0.43	0.50	0.37	16.09
Progrip	Mean	1.52	0.72	0.24	0.16	0.08	124.20
	N	25	25	25	25	25	25
	SD	0.50	0.67	0.43	0.37	0.27	17.07
Total	Mean	1.92	1.02	0.50	0.32	0.12	120.22
	N	50	50	50	50	50	50
	SD	1.06	0.71	0.50	0.47	0.32	16.90
Mann-Whitney U		168.00	174.50	162.50	225.00	287.50	194.50
Wilcoxon W		493.00	499.50	487.50	550.00	612.50	519.50
Z		-3.06	-2.98	-3.36	-2.13	-1.03	-2.29
Asymp. Sig. (2-tailed)		0.002	0.003	0.001	0.03	0.30	0.21

[a] Grouping Variable: graft types.
SD: Standard deviation.

($p< 0.05$). On the 7th postoperative day, mean pain score was determined as 0.76 in the prolene group; and as 0.24 in the progrip group ($p< 0.05$). On the 14th postoperative day, mean pain was determined as 0.48 in the prolene group and as 0.16 in the progrip group ($p< 0.05$). On the 60th postoperative day, mean pain was determined as 0.16 in the prolene group and as 0.08 in the progrip group ($p< 0.05$) (Table 3). SF-36 score was determined 86 as the lowest, and although the progrip group seemed more advantageous in SF-36 scoring, a statistically significant difference was not determined. SF-36 score was determined 86 as the lowest and 146 the highest in the prolene group (mean= 116.24) and 85 as the lowest and 144 as the highest in the progrip group (mean= 124.20) ($p> 0.05$) (Table 3).

DISCUSSION

Inguinal hernia repair is still one of the most common practical applications in the world of daily surgery practice. Although it is seen in 75% of all hernias and 3.6% of the whole society, the best repair method is not certain yet. Hernia repair is expected to be simple and easy to apply. In the early period, patient comfort, a minimum cost of surgery, loss of workforce, length of stay in hospital and return to work and minimizing the recurrences are expected (2). Although the use of mesh in hernia repair reduces recurrence rates below 5%, it also poses a major problem, such as chronic pain. Whether post-operative pain and returning to daily routine activities change according to the material and procedure applied in the surgery has also come to the fore and some studies have been carried out in this regard.

In a series of 60 cases published in 2013, Yilmaz et al. found that patients who were repaired with progrip self-fixating mesh had faster return to work and less postoperative pain compared to the patients repaired with prolene graft (3). The follow-up period of the study was four months and long-term outcomes are unknown. In our study the two-month period is based on and long-term results are also unknown. Observing long-term results may be important in determining the graft type to be used. In a series of 50 cases published in 2009, Kapischke et al. (2009) reported that the pain scores were lower in the progrip group than in the prolene group, but no statistically significant difference was found and longer follow-up was required as a result of the 6-month follow-up (4). In a complete series of 52 cases in 2008,

Chastan et al. reported that none of the 52 patients followed up for 2 years with progrip had chronic pain or recurrence and that this could be the golden standard procedure for hernia repair (5). Since there is no control group in this study, it is not possible to assess whether the results are due to the experience of the surgical team or the method used. In this regard, the results obtained should be re-assessed by making a comparison with the control group.

In a similar study, Ozis et al. found that there was no significant difference between the two groups in terms of chronic pain in a series of 53 cases published in 2015 (6). In a series of 540 cases conducted between 2007 and 2012, Batabyal et al. evaluated the duration of operation during repairs made with two types of grafts and the duration of return to daily activities in the post-operative period. It was determined that the operation time in repairs applied with progrip self-fixating mesh was shorter compared to prolene repair and had more rapid return to daily activities than prolene graft (7). In this study, early period outcomes were based and no comment was made on chronic pain or long-term quality of life, therefore it is difficult to argue that there is a significant advantage in favour of progrip self-fixating with the available outcome.

Progrip or prolene repair was applied to 90 cases included in a prospective study conducted by Wang et al. between 2012 and 2013. It was determined that progrip graft was significantly superior in terms of post-operative pain and returning to work as a result of 6-month follow-up (8).

In our study, we determined that the pain measured by visual analogue scale (VAS) in the early postoperative period was significantly lower at a statistical level but there was no statistical significance in the second month and there was no statistically significant difference in SF-36 score at the end of the 2nd month in daily routine activities in progrip self-fixating mesh group. In the followed-up patients, only one patient developed additional dose of analgesic need on the early periods such as 1st and 3rd post-operative days in the prolene group and contramal drops were applied to this patient, which may have affected the early VAS scores of this patient but did not affect the reliability of the data because it would not change the average of the entire group (8). In the meta-analysis of 1170 cases, Pandana et al. have compared progrip mesh and prolene mesh in terms of post-operative pain and found that there was no statistically significant difference (9). In a study of 1353 cases involving 6 randomized controlled studies published in 2014, Fang et al. determined that the operation time was shorter in the repairs applied with progrip. It was stated that there was no significant difference between postoperative pain and returning to daily activities during 12 months of follow-up (10). It was concluded that better organized studies with longer follow-up periods were required although one-year follow-up time was a good period.

CONCLUSION

Considering the literature related to this subject, there are some evidence that the repair applied with progrip self-fixating graft has more positive outcomes compared to the repairs applied with suture fixation; however, there are also some conflicting results. It is concluded that there is a need for longer follow-ups and larger series of cases in order to achieve a definite result.

Ethics Committee Approval: This scientific study began with the approval of the Manisa Celal Bayar University Local Ethics Committee (decision numbered 16/07/2014 / 20478486-271).

Informed Consent: Written consent of all the patients was received.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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İnguinal herni onarımında prolen ve progrip yamalarının postoperatif ağrı, hareket kısıtlılığı ve yaşam kalitesi açısından karşılaştırılması

Ahmet Kaya[1], Semra Tutcu Şahin[2], Yavuz Kaya[2], Teoman Coşkun[2], Aslan Sakarya[2]

[1] Sakarya Üniversitesi Tıp Fakültesi, Cerrahi Onkoloji Bilim Dalı, Sakarya, Türkiye
[2] Celal Bayar Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Manisa, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmada amaç, ameliyat sonrası ağrı, hareket kısıtlaması ve yaşam kalitesi açısından prolen mesh ve progrip-self fiksasyon mesh uygulama tekniklerini karşılaştırmaktır.

Gereç ve Yöntem: Çalışma Kasım 2014-Ocak 2016 tarihleri arasında Manisa Celal Bayar Üniversitesi Hastanesinde yapıldı. Çalışmaya 18 yaşından büyük 50 erkek hasta alındı ve çalışma çift-kör prosedürle gerçekleştirildi. Yirmi beş hasta progrip yama yöntemiyle, 25 hasta ise prolen greftleri kullanılarak dikiş fiksasyon yöntemiyle tedavi edildi ve hastaların ağrı takibi yüz yüze ya da telefon görüşmeleriyle yapıldı. VAS (Görsel Analog Skala) ve günlük rutin aktivitelere dönüş, SF-36 (Kısa Form-36) yaşam kalitesi ölçeği ile değerlendirildi. Tekrarlayan fıtıklar ve acil durumlar çalışma kapsamına alınmadı. Veriler, SPSS paket programı kullanılarak analiz edildi.

Bulgular: Yapılan değerlendirmeler sonucunda, ameliyat sonrası erken dönemde progrip kendinden fikse mesh kullanan hastalarda ağrı skorlarının daha düşük ve istatistiksel olarak anlamlı olduğu bulunmuştur. Uzun dönemde her iki yöntem de ağrı ve yaşam kalitesi açısından istatistiksel olarak benzer sonuçlar vermiştir.

Sonuç: Bu konuyla ilgili literatür göz önüne alındığında, progrip kendinden fiksasyon grefti ile yapılan onarımın, dikiş fiksasyonu ile yapılan onarımlara kıyasla daha olumlu sonuçlara sahip olduğuna dair bazı kanıtlar vardır, ancak bazı çelişkili sonuçlar da vardır. Kesin bir sonuç elde etmek için daha uzun takiplere ve daha geniş olgu serilerine ihtiyaç olduğu sonucuna varılmıştır.

Anahtar Kelimeler: İnguinal herni, ağrı, progrip yama, prolen yama, yaşam kalitesi

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ORIGINAL ARTICLE
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Evaluation of the efficacy of platelet-rich plasma in preventing postoperative intraabdominal adhesions

Ersin Turan[1](ID), Barış Ayhan[2](ID), Süleyman Kargın[3](ID), Osman Doğru[4](ID), Nevzat Serdar Uğraş[5](ID)

[1] Clinic of General Surgery, Beyhekim State Hospital, Konya, Turkey
[2] Clinic of General Surgery, Private Akademi Hospital, Konya, Turkey
[3] Department of General Surgery, KTO Karatay University School of Medicine, Konya, Turkey
[4] Clinic of General Surgery, Konya Training and Research Hospital, Konya, Turkey
[5] Department of General Surgery, Selcuk University School of Medicine, Konya, Turkey

ABSTRACT

Objective: Postoperative intraabdominal adhesions still maintain their currency as serious causes of morbidity and mortality. This study aimed at evaluating the role of platelet-rich plasma (PRP) in the prevention of intraabdominal adhesions.

Material and Methods: A total of 16 healthy rabbits were used within the scope of the study. The animals were allocated into two groups as Group 1 (control group) and Group 2 (study group). In all subjects, cecal abrasion was formed by laparotomy. In the study group, platelet rich plasma was administered intraabdominally. At the end of the study, the adhesions were evaluated by Nair's Score.

Results: Total adhesion score in Group 1 was 8, while the mean score was 1. On the other hand, total adhesion score in Group 2 was 12, while the mean score was 1.5. There was no statistical difference between both groups by total adhesion score and mean fibrosis score. However, mean scores for inflammatory cell infiltration and angiogenesis were higher in Group 2 and the differences were statistically significant (p= 0.021).

Conclusion: We were not able to report the positive results of PRP; however, we believe that we shed an important light for future studies which might be conducted using the combination of different methods.

Keywords: Platelet-rich plasma, laparotomy, adhesions

INTRODUCTION

Fibrous bands, which develop between the serosal surfaces of one or more tissues or organs in the ventral cavity, cause postoperative intraabdominal adhesions. Problems like mechanical or functional intestinal obstructions, volvuluses, infertility, and abdominal pain can be seen in time because of these adhesions. Therefore, postoperative intraabdominal adhesions still maintain their currency as serious causes of morbidity and mortality. Patients frequently present to hospitals with recurrent intestinal obstruction and abdominal pain, and they usually have to be admitted to the hospital to be treated. Many studies aiming to prevent adhesions could not reach a final conclusion about the subject (1,2). Although adhesions can be partially prevented through the developments in laparoscopic methods, they still account for one of the most significant postoperative problems for both physicians and patients.

The peritoneum has a structure which can be subjected to re-epithelization rapidly and in a short span of time and which can continuously enable secretion and absorption. This kind of histological structure and physiological function plays an important role in the formation or prevention of intraabdominal adhesions. Accordingly, causes of intraabdominal adhesions and practices about these causes differ from one patient to the other but it is not possible to talk about a standard treatment or measures to be taken to prevent them. In our study, we aimed at preventing adhesions by utilizing growth factor platelet-rich plasma (PRP) whose positive impact on wound healing has been proven (Table 1). We investigated the positive impacts of the factors contained by platelets on adhesions. We formed experimental adhesions using rabbit subjects and evaluated the efficiency of PRP.

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Corresponding Author
Süleyman Kargın
E-mail: drs.kargin@hotmail.com

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Table 1. The primary growth factors in PRP content
Platelet derived growth factor: Accelerates cellular replication and angiogenesis
Vascular endothelial growth factor: Accelerates angiogenesis
Transforming growth factor group: At least 3 factors are in this group. They play a key role in fibrosis and muscular cell balance
Fibroblast growth factor: Stimulates myoblast proliferation as well as playing a role in angiogenesis
Epidermal growth factor: Modulates epithelial and mesenchymal cell proliferation
Hepatocyte growth factor: Accelerates angiogenesis
Insulin-like growth factor: Mediates muscular growth and repair, myoblast and fibroblast stimulation

The aim of this study was to contribute to the development of standard treatment strategies by investigating the efficiency of PRP in preventing postoperative intraabdominal adhesions.

MATERIAL and METHODS

Our study was conducted upon the consent of Necmettin Erbakan University Experimental Research and Practice Center's Board of Ethics for Experimental Animals and carried out at the same center (2013-022). A total of 16 healthy rabbits, whose live weights varied between 2.3-3.7 kg, were used within the scope of the study. The rabbits were fed by standard rabbit feed during the adaptation period, 12 hours before the procedures, and during the postoperative period and water was kept ready at all times. The animals were allocated into two groups as Group 1 (control group) and Group 2 (study group). While the study group was given PRP, the control group was not. Each group had eight experimental animals.

PRP Preparation

Initially, 20 mL of blood -in the form of 10 mL/kg- was drawn in order to obtain PRP from the animals in Group 2. 20 mL of blood was also drawn from each animal in Group 1 in order not to affect experiment results and enable similar conditions. The blood drawn from Group 1; however, was not subjected to any process. The venous blood drawn from the animals in Group 2 was placed in 10 mL sterile tubes containing 3.8% citrate phosphate dextrose adenine. In order to fractionate the drawn venous blood into its components, it was initially centrifuged for 10 minutes at 1000 cycle/minute based on studies about obtaining the right platelet concentration for PRP (1-3). The blood was separated into 3 components through this procedure: at the base was the red blood cells, in the middle was PRP, and at the top was platelet-poor plasma. PRP and poor plasma were placed into a different sterile vacuum tube by a sterile injector for a second centrifuge. The second centrifuge was carried out at 1300 cycle/minute for 10 minutes. While PRP remained at the bottom of the tube, platelet-poor plasma stayed on top. Following the drawing of platelet-poor plasma by a sterile injector, PRP remained at the bottom of the vacuum tube. Studies have shown that 4 times more than the amount of normal platelet concentration was able to be obtained through this method (1-3). Within the scope of our study, 2 mL of PRP was obtained from each 20 mL venous blood. PRP was administered to the study group by a sterile injector at a rate of 1/6 by mixing it with 10% calcium gluconate (3,4).

The animals in both groups were anesthetized by intramuscular injections of 35 mg/kg Ketamine HCl (Ketalar; Pfizer, Ortaköy, İstanbul) and 15 mg/kg Xylazine 2% HCl (XylazinBio, Bioveta PLC, Ivanovice na Hane, Czech Republic). The cecum was exposed through laparotomy. Abrasion was performed by a sponge till small bleeds were visible. Following the cecal abrasion, the abdomens of the animals in Group 1 were closed up by continuous 2/0 prolene sutures. The abrasion procedure was done in the same way to the animals in the PRP group and the PRP, which was separately obtained for each animal, was sprayed by a sterile injector on to the abrasion area. The abdomens of the animals in the PRP group were also closed up by continuous 2/0 prolene sutures.

The animals were sacrificed by high doses of anesthesia after 14-day follow-up. We entered the abdomens of the animals by a new U-shape incision, which was 2 cm lateral to the previous incision line. A surgeon blind to the groups graded the adhesions according to Nair's adhesion classification system (Table 2).

Table 2. Nair's adhesion classification system
Grade 0: No adhesions
Grade 1: Single adhesion band between an organ and the peritoneum
Grade2: Two adhesion bands between an organ and the peritoneum
Grade 3: Adhesions between more than one organ and the peritoneum
Grade 4: Organs are adherent to the peritoneum or widespread adhesions

Pathological Investigation

The abraded intestinal segments were removed for pathological investigation. 1 x 1 cm-sized tissues removed from the adhesion areas of the rabbits in both groups were fixed in 10% buffered formalin for two days. Tissue samples taken from these were buried in paraffin following routine tissue processing procedures. 4-micron sections obtained from paraffin blocks were stained in hematoxylin-eosin to evaluate inflammatory cell infiltration and in Masson's trichrome stain to evaluate fibroblastic activation. The tissues in both groups were analyzed for fibroblastic activation, angiogenesis, and inflammatory cell infiltration by using a light microscope.

Statistical Evaluation

The evaluation of all statistical data was conducted by SPSS version 15.0. Fibroblastic activation, angiogenesis, and inflammatory cell infiltration scores achieved through histopathological analysis were compared by chi-squared test, while the existence of adhesions in the groups was compared by Fisher's exact chi-square test. Mann-Whitney U test was utilized in the comparison of nonparametric values. Statistical significance for all tests was taken to be $p< 0.05$.

RESULTS

A surgeon blind to the groups graded the adhesions according to Nair's adhesion classification system by laparotomy following the sacrification of animals (Tables 3). While 5 animals had adhesions in Group 1, 6 animals had adhesions in Group 2.

Total adhesion score in Group 1 was 8, while the mean score was 1. On the other hand, total adhesion score in Group 2 was 12, while the mean score was 1.5 (Table 3). Mean score for the PRP group was higher than that of the non-PRP group but the difference between the groups was not statistically significant ($p= 0.321$).

Fibrosis, inflammatory cell infiltration, and angiogenesis were pathologically investigated in the experimental animals (Figure 1, Table 4). Mean fibrosis score in Group 2 was higher than that of Group 1 but there was no statistical significance ($p= 0.065$; Table 5). Further, mean scores for inflammatory cell infiltration and angiogenesis were higher in Group 2 and the differences were statistically significant ($p= 0.021$; Table 5).

DISCUSSION

It has been reported that mechanical traumas and surgical procedures in abdominal organs and the serosal surfaces of tissues give way to tissue damage and therefore provide the basis for the development of peritoneal adhesions through pulling the cells into these areas by inflammatory exudates (5). In studies conducted for the prevention of the development of intraabdominal adhesions, anti-inflammatory and cytotoxic agents have been used to decrease fibrinous exudation, heparin and oxalates have been used for the inhibition of coagulation, plasminogen stimulants, pepsin, trypcin, streptokinase, and urokinase have been used for the stimulation of fibrinolitic activity and hydroflotation effective agents and drugs like carboxymethyl cellulose, amnion liquid, oil, vaseline, and dextran which enable the mechanical separation of serosal surfaces have also been used (6-12).

The effect of PRP on intraabdominal adhesions is still controversial. The experimental study by Kaya et al. have demonstrated that PRP neither reduces nor exacerbates postoperative adhesions (13). On the other hand, Oz et al. in the experimental study comparing the effect of hyaluronic acid PRP on adhesions has claimed that PRP leads to a significant decrease in adhesion scores (14). We investigated the efficacy of growth factor rich PRP, whose positive impact on wound healing have been proven, on adhesions in our study (Table 1). We also aimed to utilize the positive impacts of PRP, which has been started to be used in

Table 3. Evaluation of the groups' identified adhesions in laparotomy and Nair's score

	Control group		Study group		p
Animal	**Nair's Score**	**Adhesions**	**Nairs's Score**	**Adhesions**	
1st	1	Single adhesion band	3	Multiple adhesion bands	
2nd	2	Two adhesion bands	2	Two adhesion bands	
3rd	0	No adhesions	2	Two adhesion bands	
4th	1	Single adhesion band	0	No adhesions	
5th	0	No adhesions	1	Single adhesion band	
6th	1	Single adhesion band	1	Single adhesion band	
7th	3	Multiple adhesion bands	0	No adhesions	
8th	0	No adhesions	3	Multiple adhesion bands	
Total score/mean score	8/1		12/1.5		0.321

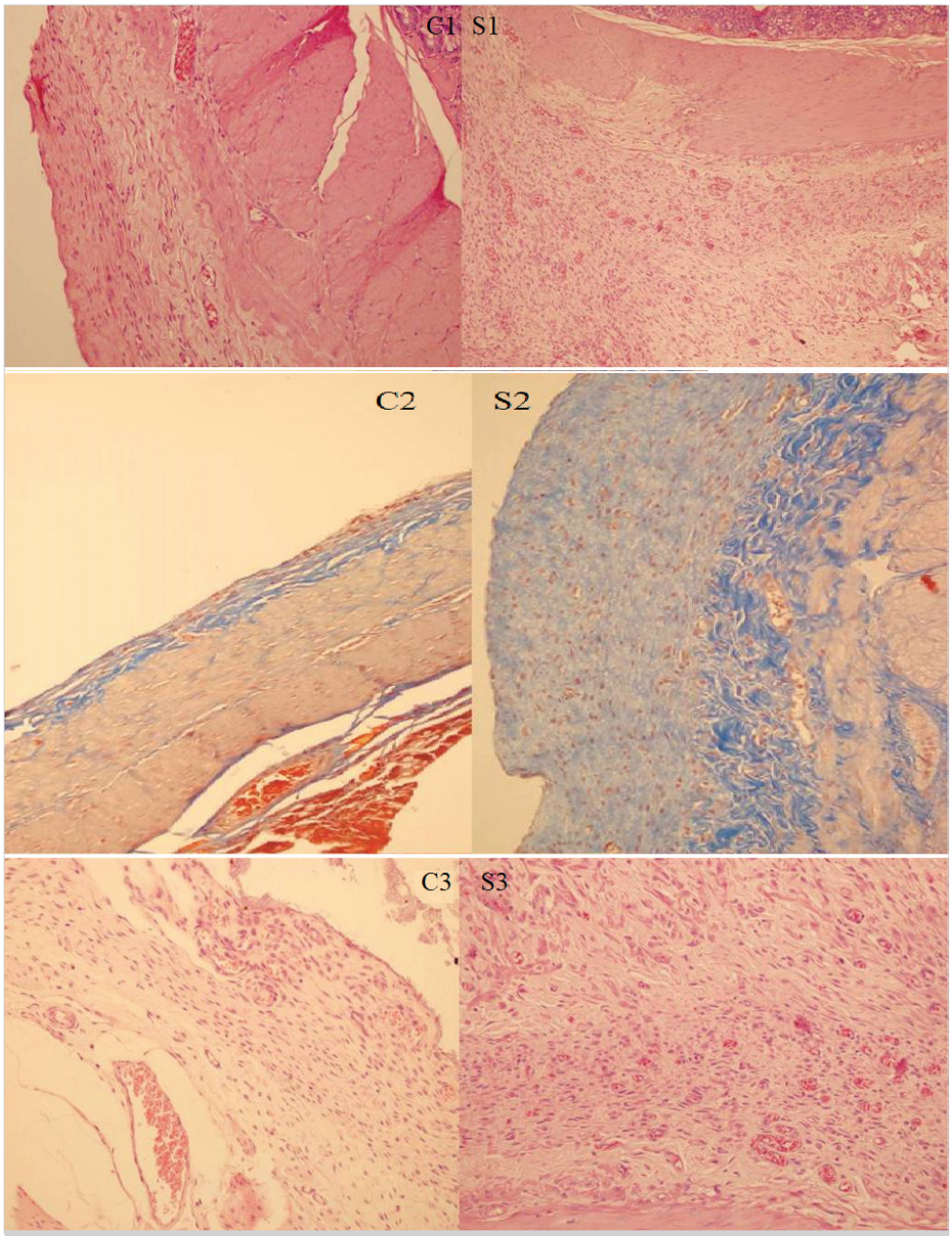

Figure 1. Pathological examination of the samples taken that fibrosis (C1 and S1, Hematoxylin-Eosin, original magnification, 200x), inflammatory cell infiltration (C2 and S2, Masson's Trichrome, original magnification, 200x), and angiogenesis (C3 and S3, Hematoxylin-Eosin, original magnification, 200x) in groups. C: Control group; S: Study group.

such fields as dentistry, orthopedics, plastic surgery, and burn treatment, on wound healing although it causes an increase in fibroblast activity (1,3,4).

Anitua et al. described pure platelet-rich plasma in 1999 for the first time (2). He took out the part over the buffy coat, which remained between the serum at the top and the decayed part at the bottom, by centrifuging the venous blood in citrated tubes. This part is the one containing the most platelets. The first use of platelet concentrations, however, began in 1997 with Whitman DH et al.'s oral and maxillofacial surgical procedures (15). We formed experimental adhesions on rabbit subjects and evaluated the efficacy of PRP. While the mean Nair's Score for the non-PRP group in our study was 1, it was 1.5 for the PRP group. The difference between the groups was not statistically significant (p= 0.321) and it was not possible to state that PRP had a positive impact on the prevention of adhesions. Pathological analyses of

Table 4. Pathological evaluation of the groups

	Group 1			Group 2		
Subject	**Fibrosis**	**Inflammation**	**Angiogenesis**	**Fibrosis**	**Inflammation**	**Angiogenesis**
Subject1	++	-	+	++	+++	++
Subject2	++	+	+	+	+	+++
Subject3	-	-	-	++	+	++
Subject4	+	+	+	-	-	-
Subject5	-	-	-	+	+	+
Subject6	+	+	+	+	+	+
Subject7	++	+	++	-	-	-
Subject8	-	-	-	+++	++	+++

+++: Severe, ++: Moderate, +: Mild, -: None.

Table 5. Comparison of the subjects without adhesion and with adhesion as pathological data

		Fibrosis Total/Mean score	**Inflammation Total/Mean score**	**Angiogenesis Total/Mean score**
Subject without adhesion	Group 1 (8 subjects)	8/1	4/0.5	6/0.75
	Group 2 8 subjects)	10/1.25	9/1.1	12/1.5
Subject with adhesion	Group 1 (5 subjects)	8/1.6	4/0.8	6/1.2
	Group 2 (6 subjects)	10/1.6	9/1.5	12/2
p		0.065	0.165	**0.021**

In calculation of those scores every + in table 4 are equal to 1 point.

the groups revealed that the fibrosis score of the PRP group was higher than that of the non-PRP group but the difference was not statistically significant either (p= 0.065). It was ascertained that inflammatory cell infiltration and angiogenesis were increased by PRP, which was statistically significant (p= 0.021). It might be argued that PRP might have given way to an increase in postoperative intraabdominal adhesions through its impact on the increase in fibroblast activity. The results of our study did not reveal a significant increase in adhesions but it can also be put forward that PRP, which had positive effects on wound healing, increased fibrosis as well although no statistically significant result was obtained. We attempted to utilize the factors contained by platelets in order to rapidly eliminate tissue damage on the serosal surface due to mechanical trauma. Although we aimed at preventing adhesions through the impact of these factors, we were not able to achieve a statistically significant result.

Koc et al. have investigated the effects of methylprednisolone and dimethyl sulphoxide on the prevention of intraabdominal adhesions in rabbits and obtained positive results with anti- inflammatory effect (5). Anti-inflammatory effect; however, can have a negative impact on the normal wound healing process besides adhesions. Thus, one can question the safety of an anastomosis performed in this way. Yeo et al. have utilized hyaluronic acid hydrogels in order to prevent postoperative intraabdominal adhesions and achieved positive results (16). One cannot argue for a standard treatment although many similar studies have concluded that adhesions are experimentally prevented.

CONCLUSION

We were not able to report the positive results of our PRP use in neither macroscopic nor pathological ways but we believe that we shed an important light for future studies which might be conducted using the combination of different methods.

Ethics Committee Approval: Our study was conducted upon the consent of Necmettin Erbakan University Experimental Research and Practice Center's Board of Ethics for Experimental Animals and carried out at the same center (2013-022).

Informed Consent: This research was not need any informed consent for experimental study.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Postoperatif intraabdominal adezyonları önlemede trombositten zengin plazmanın etkinliğinin değerlendirilmesi

Ersin Turan[1], Barış Ayhan[2], Süleyman Kargın[3], Osman Doğru[4], Nevzat Serdar Uğraş[5]

[1] Beyhekim Devlet Hastanesi, Genel Cerrahi Kliniği, Konya, Türkiye
[2] Özel Akademi Hastanesi, Genel Cerrahi Kliniği, Konya, Türkiye
[3] KTO Karatay Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Konya, Türkiye
[4] Konya Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Konya, Türkiye
[5] Selçuk Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Konya, Türkiye

ÖZET

Giriş ve Amaç: Postoperatif intraabdominal adezyonlar, günümüzde hala ciddi morbidite ve mortalite nedenidir. Bu çalışmada, trombositten zengin plazma (PRP)'nın intraabdominal adezyonların önlenmesindeki rolünün değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışma kapsamında toplam 16 sağlıklı tavşan kullanıldı. Hayvanlar, Grup 1 (kontrol grubu) ve Grup 2 (çalışma grubu) olarak iki gruba ayrıldı. Tüm deneklerde laparotomi ile çekal abrazyon oluşturuldu. Çalışma grubunda PRP intraabdominal olarak uygulandı. Çalışmanın sonunda adezyonlar Nair's Skoru ile değerlendirildi.

Bulgular: Grup 1'deki toplam adezyon skoru 8 iken, ortalama skor 1 idi. Öte yandan, Grup 2'deki toplam adezyon skoru 12 iken, ortalama skor 1,5 idi. Her iki grup arasında toplam adezyon skoru ve ortalama fibroz skoru açısından istatistiksel olarak bir fark yoktu. Ancak, enflamatuvar hücre enfiltrasyonu ve anjiyogenez skorları Grup 2'de istatistiksel olarak daha yüksekti (p= 0,021).

Sonuç: PRP'nin postoperatif intraabdominal adezyonları önlemesine dair olumlu sonuçları bulamadık. Ancak, farklı yöntemlerin kombinasyonu kullanılarak yapılabilecek gelecekteki çalışmalar için bu çalışmanın önemli bir ışık tutacağına inanıyoruz.

Anahtar Kelimeler: Trombositten zengin plazma, laparotomi, adezyon

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ORIGINAL ARTICLE
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Comparison of postoperative quality of life of Limberg flap and Karydakis flap in pilonidal sinus operations

Sabahattin Destek[1](ID), Hüseyin Kazım Bektaşoğlu[1](ID), Enver Kunduz[1](ID), Merve Nil Akyüz[2](ID)

[1] Department of General Surgery, Bezmialem Vakif University School of Medicine, Istanbul, Turkey
[2] Department of Internship, Bezmialem Vakif University School of Medicine, Istanbul, Turkey

ABSTRACT

Objective: Pilonidal sinus disease (PSD), most commonly seen in young men, is a chronic disease resulting from the pilosebaceous in the sacrococcygeal region. There is still no standardization in surgical treatment. In this study, the effectiveness, follow up outcomes and quality of life level were compared between Karydakis flap (KF) and Limberg flap (LF) operations.

Material and Methods: Among the patients who had undergone PSD surgery in our clinic between 2015 and 2016, those who could be reached and who received KF (n= 53) and LF (n= 51) operations were included into the study. Clinical data of these patients were retrospectively evaluated. Postoperative satisfaction levels of the patients were determined with Cardiff wound healing survey questions and visual analog scale.

Results: Mean operational time was 54 (44-75) minutes in the LF group and 45 (35-60) minutes in the KF group, and it was statistically significant (p= 0.001). Mean time to return to work was 14.3 (9-28) days in the LF group and 17.6 (10-30) days in the CF group and was statistically significant (p= 0.001). The rates of complications and recurrence were lower in the LF group although the difference was not statistically significant between the groups (p> 0.05). Mean psychosocial assessment score was 70.3 (57.5-88.7) in the KF group and 73.4 (53.5-87.5) in the LF group and the difference was statistically significant (p= 0.001).

Conclusion: LF was a more reliable and preferable method compared to KF because of earlier return-to-work, lower rate of recurrence at long term follow up, and higher psychosocial satisfaction.

Keywords: Pilonidal sinus disease, Karydakis flap, Limberg flap, quality of life

INTRODUCTION

Pilonidal sinus disease (PSD) which was described for the first time by Herbert Mayo in 1833, is seen in 0.7% of the world population (1). Of all PSD cases, 97.8% are observed in the sacrococcygeal region, and 2.2% in extra sacrococcygeal regions such as fingers, umbilicus and neck (1,2). PSD has been mostly defined in young men (1). Both environmental and genetic factors are thought to play a role in the etiology of the disease (3). The major pathogenic cause for PSD is local and repeating minor trauma in hairy areas (1,2). PSD is chronic, but occasionally becomes abscessed with acute exacerbations (3).

Many conservative and surgical methods are used in the treatment of PSD (3). Numerous surgical methods including sinus excision and primary closure, cryosurgery, marsupialization, Limberg flap (LF), Karydakis flap (KF), V-Y flap, and Z-plasty are used for the treatment of PSD (1,4). However, current recurrence rates are high at 5-22% (3,4). Debates about the ideal treatment methods are continuing since recurrence rates are high, and various advantages and disadvantages of treatment methods, and novel techniques are being continuously developed (4). In this study, we aimed to evaluate the outcomes of KF and LF methods used for PSD to assess postoperative quality of life and to determine which method is superior by comparisons.

MATERIAL and METHODS

Study Groups

Patients who had undergone sacrococcygeal PSD in our clinic between 2015 and 2016 were evaluated for relevance of the time period to better determine

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Corresponding Author
Sabahattin Destek
E-mail: sebahattindestek@yahoo.com

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follow-up process and development of recurrences. This study was approved by the local ethics committee of the university with 18/09/2018 dated and 17/722 numbered decision. Patients who were regularly followed-up in the postoperative period for at least two years and who could be reached via phone were included into the study. KF (n= 53) and LF (n= 51) groups were randomly formed with these patients. Clinical files of the patients were retrospectively screened, and demographic features, primary or secondary (recurrence) status, the surgical technique performed, healing duration, complication status and recurrence rates of these patients were evaluated.

A questionnaire was applied postoperatively in order to compare life comfort of all the patients. Cardiff wound healing survey developed by the Wales University Medical Faculty, Wound Healing Research Department was used as the questionnaire (5). Overall quality of life score, postoperative satisfaction score, psychosocial assessment score, and physical assessment score of the patients were determined using visual analog scale (VAS) with the answers given to this questionnaire (6). Patients were asked to choose the level corresponding to their own status on a line divided as 100 mm for each score to be determined with VAS.

Statistical Analysis

Data obtained from the study was statistically analyzed using SPSS (Statistical Package for Social Sciences) for Windows version 23.0 (SPSS Inc. Chicago, IL, USA). Power analysis was used to determine the number of patients. Data were evaluated with a biostatistics specialist at 95% confidence interval and $p< 0.05$ significance level. According to data distribution, normally distributed variables were compared between the two groups using Student's t test, and non-normally distributed variables using Mann-Whitney U test, while categorical variables were compared using Chi-square method. Comparison of the Cardiff wound healing satisfaction survey scores between the two groups was carried out with Mann-Whitney U tests.

RESULTS

In the KF group, age range was found as 17-49 (mean 29.1) years. Of the patients in the KF group, 81.1% (n= 43) were males and 18.9% (n= 10) were females. Of these patients, 75.5% (n= 40) were primary and 24.5% (n= 13) were secondary (recurrence) cases. Duration of symptoms was determined as 2-36 (mean 8) months in patients who usually presented with sensation of sting, swelling and/or discharge in the sacrococcygeal region. Mean operational time was measured as 35-60 (mean 45) minutes, and length of hospital stay as 1-5 (mean 2.5) days. All patients were drained, with a duration between 3-7 (mean 4.2) days. The duration of healing and return-to-work was 10-30 (mean 17.6) days (Figure 1).

In the LF group, age range was found as 15-57 (mean 28.3) years. Of the patients in the LF group, 76.5% (n= 39) were males and 23.5% (n= 12) were females. Of these patients, 82.4% (n= 42) were primary and 17.6% (n= 9) secondary (recurrence) cases. Duration of symptoms was determined as 1-33 (mean 6) months. Operational time was measured as 44-75 (mean 54) minutes, and this was significantly longer compared to the KF group ($p= 0.001$). Length of hospital stay was found as 1-5 (mean 2.3) days. Again, all patients in this group were drained with a duration of 3-8 (mean 4.6) days. Duration of healing and return-to-work was found as 9-28 (mean 14.2) days, which was statistically shorter compared to the KF group ($p= 0.001$) (Figure 2). No statistically significant difference was found between the groups in terms of other parameters ($p> 0.05$) (Table 1).

In the KF group, 4 (7.5%) patients developed seroma in the wound site, 1 (1.9%) hematoma in the wound site, 2 (3.8%) wound site infection, and 2 (3.8%) dehiscence of incision when skin sutures were removed. During follow up, recurrence was found as 7.5% (n= 4) in the KF group with a mean duration to recurrence as 20 (16-22) months.

In the LF group, 3 (5.9%) developed seroma in the wound site, 1 (2%) hematoma in the wound site, 1 (2%) wound site infection

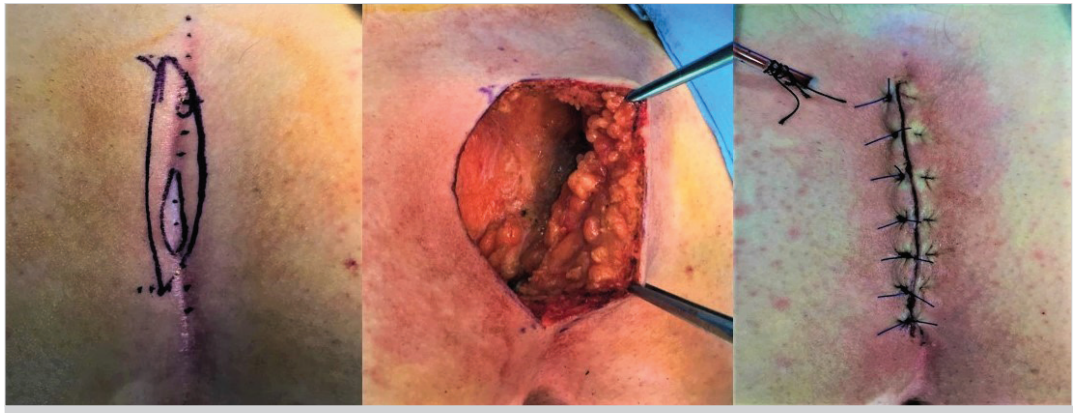

Figure 1. Karydakis flap application in pilonidal sinus disease (preoperative appearance, flap preparation, postoperative appearance).

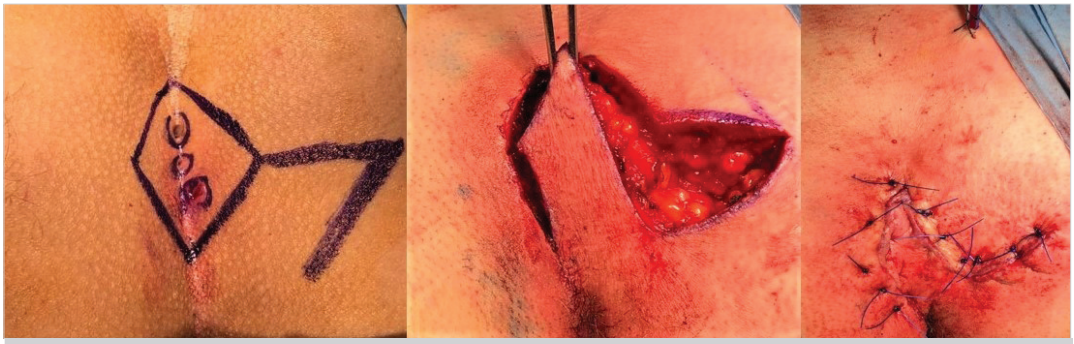

Figure 2. Limberg flap application in pilonidal sinus disease (preoperative appearance, flap preparation, postoperative appearance).

Table 1. Demographic data and clinical results of Karydakis flap and Limberg flap groups

Demographic and clinical features	Karydakis flap group (n= 53)	Limberg flap group (n= 51)	p
Age (years)	17-49 (mean 29.1)	15-57 (mean 28.3)	0.613[a]
Gender (female/male)	10/43	12/39	0.560[b]
Primary/secondary (recurrence) status	40/13	42/9	0.390[b]
Symptom duration (month)	2-36 (mean 8)	1-33 (mean 6)	0.527[c]
Operational time (minutes)	35-60 (mean 45)	44-75 (mean 54)	**0.001[c]**
Duration of hospitalization (days)	1-5 (mean 2.5)	1-5 (mean 2.3)	0.574[c]
Duration of drainage (days)	3-7 (mean.4.2)	3-8 (mean 4.6)	0.50[c]
Duration of return-to-work (days)	10-30 (mean 17.6)	9-28 (mean 14.3)	**0.001[c]**

[a] Student's t test.
[b] Chi-square analysis.
[c] Mann-Whitney U test.

Table 2. Complications and recurrence in Karydakis flap and Limberg flap groups

Complications/recurrence	Karydakis flap group (n= 53)	Limberg flap group (n= 51)	p
Seroma in the wound site	4 (7.5%)	3 (5.9)	0.314[a]
Hematoma in the wound site	1 (1.9%)	1 (2%)	0.546[a]
Wound site infection	2 (3.8%)	1 (2%)	0.491[a]
Suture dehiscence	2 (3.8%)	1 (2%)	0.491[a]
Recurrence	4 (7.5%)	3 (5.9%)	0.314[a]
Time to recurrence (months)	16-22 (mean 20)	15-24 (mean 22)	**0.001[b]**

[a] Chi-square analysis
[b] Mann-Whitney U test.

and 1 (2%) dehiscence of incision when skin sutures were removed. During follow up, recurrence was found as 5.9% (n= 3) in the LF group with a mean duration to recurrence as 22 (15-24) months. Duration to recurrence was statistically shorter in the KF group compared to the LF group (p= 0.001). No statistically significant difference was found between the groups in terms of other parameters (p> 0.05) (Table 2).

In the KF group, overall life satisfaction score was found as 5-9 (mean 6.5), postoperative satisfaction score as 4-9 (mean 6.7), psychosocial assessment score as 54.1-78.9 (mean 68.3), and physical assessment score as 57.5-88.7 (mean 70.3). In the lF group, overall life satisfaction score was found as 5-8 (mean 6.7), postoperative satisfaction score as 4-8 (mean 6.3), psychosocial assessment score as 53.5-87.5 (mean 73.4), and physical assessment score as 42.7-95.8 (mean 67.9). Psychosocial assessment score was significantly higher in the LF group compared to KF group (p= 0.001). No statistically significant difference was found between the groups in terms of other parameters (p> 0.05) (Table 3).

Table 3. Cardiff wound healing scores in Karydakis flap and Limberg flap groups

Cardiff wound healing survey questions	Karydakis flap group (n= 53)	Limberg flap group (n= 51)	p
Overall life satisfaction	5-9 (mean 6.5)	4-9 (mean 6.7)	0.484[a]
Postoperative satisfaction	4-9 (mean 6.7)	4-8 (mean 6.3)	0.258[a]
Psychosocial assessment	54.1-78.9 (mean 68.3)	53.5-87.5 (mean 73.4)	**0.001[a]**
Physical assessment	57.5-88.7 (mean 70.3)	42.7-95.3 (mean 67.9)	0.261[a]

[a] Mann-Whitney U test.

DISCUSSION

PSD is a chronic disease seen especially in young men and in the navicular area in the intergluteal region, which involves the natal cleft. In general, the incidence of PSD is reported as 26/100.000 (7). PSD reaches the highest incidence between 15-30 years of life and is seen 3-4 times higher in men than in women (1,7). The disease is more common in the Middle East and Caucasians (1,2). In Turkey, the disease is generally seen by 6.6%. PSD is seen 16 times more common in men, with being most frequently found in 19-20 years of age in Turkey (8).

The etiology of this disease is still not fully understood (8). Nevertheless, the disease is thought to be associated with hormonal changes that lead to hair obstruction and development of hair follicles in the pilosebaceous glands in the sacrococcygeal region (1,2). The known major risk factors include obesity (BMI > 25 kg/m^2), local trauma, prolonged sitting, deep natal clefts in the navicular area, hormonal disturbances such as increased total testosterone and prolactin, poor hygienic behaviours, hairy body type, and positive family history (8-10). In several studies, family history has been reported in 17-71. 7% of the patients (1,8,9). Recent studies have reported that the disease was most commonly seen in the profession requiring prolonged sitting and students (70.1%) (8,9).

Although various studies have been conducted for the classification of disease severity and treatment choice, no an ideal system could still be established (11). Among the current classifications, the most common is the classification by Dr. Tezel (12). Common complaints frequently seen in chronically symptomatic patients are discharge (100%), pain (61%), swelling (43%) and bleeding (5%) (9,10). Clinical picture can be asymptomatic in 4.5% of the patients (8). Acute abscess requiring surgical drainage is developed in 9-28% of the patients (9,10). Chronic cases manifest with discharge by development of complex sinus and fistula tracts (2,9). Duration of the disease is between 1 and 84 months, with a mean duration of 14.7 months (9,10).

In differential diagnosis; sebaceous cysts, lipoma, fibroma, fibrous dysplasia, epidermoid cysts, dermoid cysts, Hidradenitis suppurativa, and Ewing's sarcoma should be taken into account (1,3). Repeating PSD can cause fistulas to the anal canal, lumbar osteomyelitis, epidural abscess, and malignant transformations such as rarely developed squamous cell carcinoma (13-15).

Although numerous conservative and surgical treatment methods have been described for PSD, the rates of surgery related complications and recurrences remain high, and the search for an ideal treatment method is continuing (1,2). The goal of treatment is to provide good wound healing, short duration of hospitalization, less complications, low recurrence rate, and high patient satisfaction (2,16). The principle in PSD surgery is to remove the pilonidal sinus tissue and epithelium-lined fistulas. Wound closure is performed using mid-line and extramid-line techniques including primary closure, Z-plasty, VY advancement, Karydakis transposition, and Limbert rotation flap. Recently, extramid-line closure or flap techniques are more often preferred because of the lower recurrence rates compared to other methods (2,16).

Early period complications of surgical treatment include infection, hematoma, and seroma, dehiscence, while late period complications involve numbness, pain, itching, cosmetic problems and recurrence. Different rates of complications and recurrences have been reported in different series. A conservative approach is suitable for asymptomatic patients (16). Studies have reported recurrence rates after a 5-year follow up as 40.2% in incision and drainage, 13.1% in excision and secondary healing, 16.8% in excision and primary closure, 15.6% in Bascom technique, 1.9% in KF method, and 5.2% in LF methods (2,16). Among the minimally invasive surgeries, recurrence has developed by 6.3% in endoscopic pilonidal sinus treatment and 40.4% in sinus phenolization (16). Scar tissue remaining in the cleft after primary closure is shown as the most important cause of recurrence. On the other hand, incomplete resection, postoperative dead areas, over flap tension and local ischemia, chronic inflammation, trauma, and secondary infections also increase the risk of recurrence (1-3).

Flap methods providing removal of the intergluteal sulcus enable excision of more pilonidal sinus tissue and decrease the tension in the incision site (16,17). Although currently the most commonly performed extra midline closure methods are KF and LF, still an extra midline closure flap technique that would be most practical could not be determined (17,18).

Studies comparing KF and LF methods have reported different results. Looking to various meta-analyses involving randomized controlled studies comparing KF and LF methods, rates of se-

roma have been found significantly higher with KF technique. No significant difference was found in terms of recurrence rates and other variables (19-22).

In our study, operational time was statistically shorter in the KF group, and duration of return-to work was statistically shorter in the LF group. The rates of complications and recurrence were lower in LF group, but the differences were not statistically significant. Duration to recurrence was significantly shorter in the KF group. Psychosocial satisfaction score was significantly higher in the LF group compared to the KF group.

CONCLUSION

In conclusion, both KF and LF methods have their own advantages and disadvantages. However, it was seen in our study that LF is a more reliable and preferable method compared to the KF method because of earlier return-to-work and lower rate of recurrence. Patients undergoing LF are psychosocially more satisfied in terms of life comfort.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). This study was approved by the local ethics committee of Bezmialem University with 18/09/2018 dated and 17/722 numbered decision.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.D., M.N.A; Design - S.D., M.N.A; Supervision - E.K., H.K.B; Resource - S.D., H.K.B.; Materials - S.D., H.K.B.; Data Collection and/or Processing - S.D., E.K., H.K.B., M.N.A.; Analysis and/or Interpretation - S.D., E.K.; Literature Review - S.D., M.N.A.; Writing Manuscript - S.D., H.K.B.; Critical Reviews - S.D., E.K., H.K.B.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (1): 59-64

Pilonidal sinüs ameliyatlarında Limberg flap ve Karydakis flap yöntemlerinin ameliyat sonrası hayat kalitesi açısından karşılaştırılması

Sabahattin Destek[1], Hüseyin Kazım Bektaşoğlu[1], Enver Kunduz[1], Merve Nil Akyüz[2]

[1] Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye
[2] Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Staj Bölümü, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Pilonidal sinüs hastalığı (PSH) sakrokoksigeal bölgede bulunan ve çoğunlukla genç erkeklerde görülen pilosebase kaynaklı kronik bir hastalıktır. Cerrahi tedavisinde hala standardizasyon yoktur. Bu çalışmada, kliniğimizde yapılan Karydakis flep (KF) ve Limberg flep (LF) ameliyatlarının etkinlik, takip sonuçları ve yaşam kalitesi karşılaştırılmıştır.

Gereç ve Yöntem: 2015-2016 yılları arasında kliniğimizde PSH tanısı ile ameliyat edilen hastalar arasından iletişim kurulabilen KF (n= 53) ve LF (n= 51) yapılan hastalar çalışmaya alındı. Bu hastaların klinik verileri retrospektif olarak değerlendirildi. Hastaların ameliyat sonrası memnuniyet düzeyleri, Cardiff yara iyileşme anket soruları ve görsel analog skalası ile belirlendi.

Bulgular: Çalışmamızda ortalama operasyon süresi LF grubunda 54 (44-75) dakika, KF grubunda 45 (35-60) dakika idi ve istatistiksel olarak anlamlıydı (p= 0,001). İşe geri dönme süresi LF grubunda 14,3 (9-28) gün, KF grubunda 17,6 (10-30) gündü ve yine istatistiksel olarak anlamlıydı (p= 0,001). Her iki grup arasındaki istatistiksel olarak anlamlı fark olmasa da, komplikasyon ve nüks oranı LF grubunda düşüktü (p> 0,05). Ortalama psikososyal değerlendirme skoru KF grubunda 70,3 (57,5-88,7), LF grubunda 73,4 (53,5-87,5) idi ve istatistiksel olarak anlamlıydı (p= 0,001).

Sonuç: LF, işe geri dönüş süresi, uzun süreli takiplerde daha düşük nüks oranları ve daha yüksek psikososyal memnuniyet nedeniyle KF yöntemine kıyasla daha güvenilir ve tercih edilen bir yöntemdir.

Anahtar Kelimeler: Pilonidal sinüs hastalığı, Karydakis flep, Limberg flep, hayat kalitesi

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Both a biopsy method and a therapeutic procedure in BI-RADS 4A and 4B lesions: Ultrasound-guided vacuum-assisted breast biopsy

Funda Dinç Elibol[1](ID), Yelda Dere[2](ID), Ahmet Korkut Belli[3](ID), Cenk Elibol[1](ID), Özcan Dere[3](ID), Okay Nazlı[3](ID)

[1] Department of Radiology, Mugla Sitki Kocman University School of Medicine, Mugla, Turkey
[2] Department of Pathology, Mugla Sitki Kocman University School of Medicine, Pathology, Mugla, Turkey
[3] Department of General Surgery, Mugla Sitki Kocman University School of Medicine, Mugla, Turkey

ABSTRACT

Objective: This study aimed to evaluate outcomes, complications, and follow-up results of ultrasound-guided vacuum-assisted breast biopsy (UG-VABB) in BI-RADS 4 A and B lesions.

Material and Methods: Between Agust 2014 to January 2018, fifty BI-RADS 4A and BI-RADS 4B lesions of 41 patients biopsied with 10G vacuum needle by a single radiologist were retrospectively evaluated.

Results: All patients were females and mean age of the 41 patients was 50.12 ± 8.63. Of all lesions, 84% was benign, 6% was ADH, 4% was in-situ cancer, and 6% was diagnosed as malign. Follow-up duration after VABB was 0-51 months and mean was 20.92 months. Complications were as vasovagal-induced seizure in 3 patients (7.3%) and intramammary hematoma in 16 patients (39%). Hematoma was diagnosed in 3 patients (7.3%) at the 6th month follow-up and it was resolved in all patients at the 12th month follow-up. Higher breast density resulted in higher hematoma rates. There was no relationship between lesion BI-RADS subgroups, lesion size or sample number and hematoma development. During the follow-up, residue lesion in 1 (2.4%) patient and scar tissue in 2 (4.9%) patients was detected.

Conclusion: US-guided VABB, with low complication rates and low scar development, is also a therapeutic excision method without remaining residue, which should be primarily preferred in smaller than 2 cm BI-RADS 4A and 4B lesions whose malignancy rates are relatively low. Hematoma, which is the most frequent complication, resorbed entirely in the 12th month in all patients.

Keywords: Ultrasound-guided, vacuum-aspiration biopsy, BI-RADS, complication, treatment

INTRODUCTION

Percutaneous imaging-guided breast biopsies are easy, reliable and cost-effective that has taken the place of excisional biopsies and thus, the form of standard diagnostic procedure (1-4). Percutaneous biopsies could be performed through stereotactic or ultrasound guidance. It is a biopsy method primarily preferred and used very commonly with mammography in stereotactic vacuum-assisted breast biopsy (VABB) for microcalcifications (2). In the literature regarding VABB, greatest majority of the studies are about mammography guided stereotactic microcalcification biopsies or MRI guided biopsies of MRI-only lesions (5,6). Ultrasound (US)-guided VABB, which can even be used in biopsies of calcifications, is a real-time biopsy method preferred in breast biopsies that does not involve ionizing radiation (2,7). Besides, it has been indicated that it is a method which can be preferred confidently in complete excision of benign lesions and can be tolerated by patients easily (8-10). In this manner, our aim in this study was to assess outcomes, complications, and follow-up results of US-guided VABB performed in lesions classified as category 4A and 4B in which malignancy rates are relatively low according to breast imaging-reporting and data system (BI-RADS).

MATERIAL and METHODS

We analyzed 58 breast lesions of 48 consecutive patients who underwent US-guided VABB in our hospital from August 2014 to January 2018. In BI-RADS 3 lesions, US-guided VABB was performed for total excision of the lesion due to the request

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Corresponding Author
Funda Dinç Elibol
E-mail: fundadi@yahoo.com

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of the patients and clinicians. In BI-RADS 4C and 5 lesions which were biopsied with vacuum-aspiration, this biopsy method was preferred to decrease false negativity of the biopsy depending on the lesions small size. Patients classified as BI-RADS 4A and BI-RADS 4B were biopsied with the vacuum-aspiration method if the longest diameter of the lesion was ≤ 20 mm. US-guided VABB was performed in consecutive patients who accepted this procedure and provided appropriate conditions.

BI-RADS 3 lesions were excluded from the study as their benignancy was over 98% and BI-RADS category 4C lesions were also excluded due to their high malignancy rates. Totally, 7 cases and their 8 lesions (BI-RADS 3: 5 lesions in 4 patients, BI-RADS 4C: 2 lesion in 2 patients, BI-RADS 5: 1 lesion in 1 patient) were excluded from the study. Fifty BI-RADS 4A and BI-RADS 4B lesions, belonging totally to 41 patients, were included into the study. Stereotactic vacuum aspiration biopsies administrated for microcalcifications were not included in the study. All patients were assessed by only one radiologist prior to biopsy, and ultrasonography of all patients were executed by the same radiologist. In the patients treated with warfarin or aspirin, a method other than US-guided VABB was preferred for biopsy.

All biopsies were performed with a 10G needle using the BARD Encore Enspire (BDI, Becton Dickinson, New Jersey America) multidirectional VABB device. The device has a suction chamber attached to the needle. The needle has a rotary blade and blade can rotate 60, 120, 180, and 360 degrees. The vacuum draws the tissue into the aperture of the needle and the rotary blade slices the lesion. Each specimen is transported to a port chamber by the effect of vacuum. VABB was performed with the guidance of real-time ultrasound, Toshiba Aplio 500 (Toshiba Medical System Corporation, Tokyo, Japan) with a 7-12 MHz probe.

Following the cleaning and covering of the biopsy site, covering the ultrasound probe with a sterile tunic, and after practicing standard 10 mL local anesthetic (2% prilocaine) to the site of the tractus, an approximately 5 mm incision was made in sterile conditions. Vacuum aspiration needle was placed in the guidance of the US to the center or posterior of the lesion according to the position of the lesion, and rotary cutting of the lesions was performed under US monitoring. Aspiration biopsy in various angles (60 to 360 degrees) continued till the lesion could not be entirely monitored. 5-29 times aspiration was executed for the patients according to the dimension of the lesions. A 10 cc more local anesthetic was injected through the VABB device without pulling the needle to the patients who felt pain during the biopsy. The aspiration feature of the device was benefitted from in providing hemostasis and manual compression after pulling the needle. Completed excision of the mass was described as documentation of the absence of any residual lesion seen by obtaining longitudinal and transverse sonograms to the area of excision. Successful excision was also established by first-year control mammography of the lesions in which index lesion was able to be seen in initial mammograms. Follow up data of the patients were performed by the same radiologist in the first month, 6^{th} month with ultrasonography and 1^{st} year with ultrasonography and mammography. Complications, which developed during the operation, were recorded and biopsy site was evaluated in terms of the residual lesion, hematoma and scar tissue in the follow-up. After the biopsy, the samples were examined by routine histopathological procedures. All biopsies were reviewed and diagnosed by the same pathologist.

This study had been approved by our medical school's Institutional Reviews Board (number 04/III date 05.04.2018). Informed consent was taken from all patients prior to biopsy.

Statistical Analysis

The shapes of distribution of the measured variables were demonstrated using the Shapiro-Wilk method. The test results indicated a normal distribution of data, allowing parametric tests to proceed for further analysis. Mean and standard deviation values of the parameters were executed to describe scale variables. Independent samples t-test was administrated for normally distributed parameters. Inter-group difference for categorical variables was evaluated by the Chi-square test and presented with the percentage along with the number of observations. In order to understand the cause and effect relationship between continuous variable (as an independent factor) and the categorical variable (as a dependent factor), binary logistic regression analysis was employed since the outcome variable consisted two subcategories. Statistical analyses were performed using the SPSS version 25 (SPSS Incorporated, Chicago, Illinois, USA) software. A p value of < 0.05 was considered statistically significant for all test results in the manuscript.

RESULTS

All of the patients who were included into the study were females, and mean age of the 41 patients was found as 50.12 ± 8.63 (range= 36-71 years). While 19 of the patients were premenopausal or perimenopausal, 22 were postmenopausal. The average number of labor of the patients was 1.93 ± 0.68 (0-3), and their average breastfeeding durations were 19.56 ± 14.08 (0-72) months. First degree relatives of 7 cases, to whom biopsy was performed, had a history of breast cancer. Two of the patients had the history of breast cancer themselves and 1 of them had the history of ovarian cancer.

Distribution of breast lesions in breast quadrants and sonographic breast compositions assessed with ultrasound prior biopsy are shown in Figures 1a and 1b. Lesion dimensions were (4-20) x (3.5-10) x (3-14) mm, the longest diameter of all lesions

was ≤ 20 mm. Mean of the longest dimension of all lesions was 9.04 ± 3.5 cm. The volume of lesions was between 0.018-1.05 cm^3 and mean volume of lesions was found as 0.206 cm^3. Histopathologic diagnosis of the lesions was as follows: 16 fibroadenoma, 11 intraductal papilloma, 3 invasive carcinoma, 2 in situ carcinoma, 1 fat necrosis, 1 extensive fibrosis, 15 patients had benign diagnosis like fibrocystic changes, fibroadenomatoid changes, and adenosis. In 3 cases of fibroadenoma and papilloma, one of the high-risk lesions, atypical ductal hyperplasia (ADH), was also reported. In addition to fibroadenoma and papilloma, sclerosing adenosis was reported in 3 cases ans fat necrosis in one. Histopathologic results and BI-RADS category of the lesions are given in Table 1. Of the total 50 lesions, while 1 (2.5%) of the lesions categorized as BI-RADS 4A was malignant, 2 (20%) of the lesions categorized as BI-RADS 4B were malignant and 2 (20%) of them were diagnosed as in-situ cancer (Table 1). Of all the lesions, 84% was benign, 6% was ADH, 4% was in-situ cancer, and 6% was diagnosed as malign.

Complications of the 41 patients during biopsy were as follows: vasovagal-induced seizure/syncope in 3 (7.3%) patients and

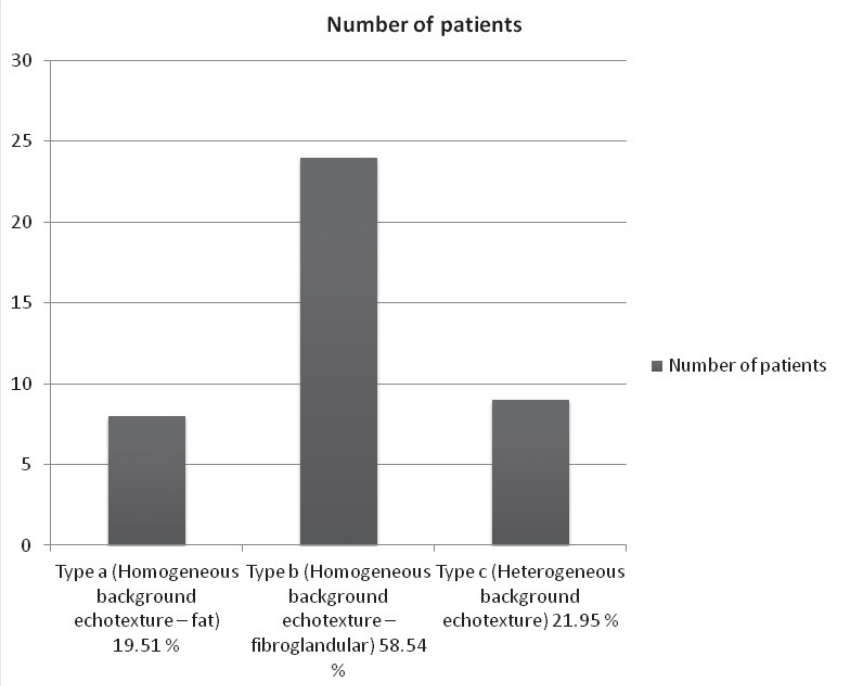

Figure 1. Breast compositions assessed with ultrasound.

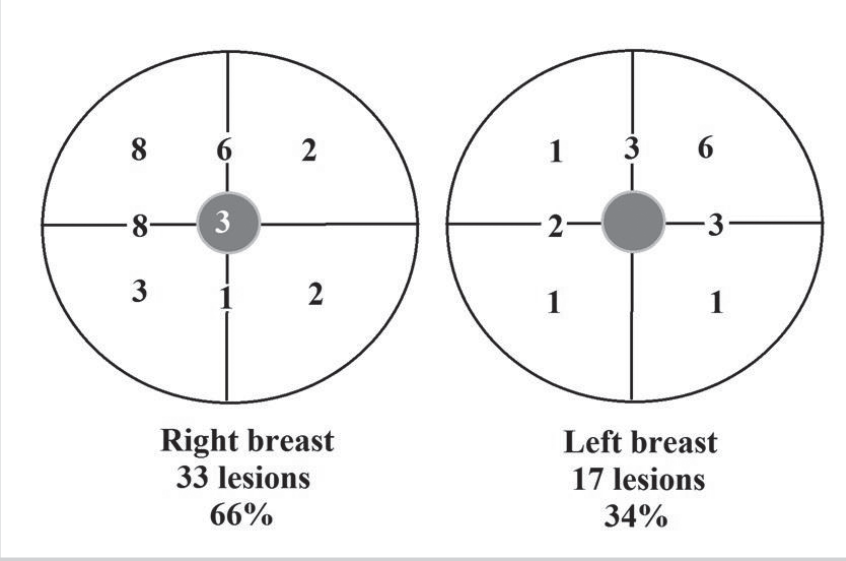

Figure 2. Distribution of lesions with regard to breast quadrants.

Table 1. Histopathologic results due to BI-RADS category of lesions

BI-RADS category	n	Pathological results of US-guided VABB			
		Invasive carcinoma	In situ carcinoma	Atypic ductal hyperplasia	Benign
4A	40	1 (2.5%)	0 (0%)	3 (7.5%)	36 (90%)
4B	10	2 (20%)	2 (20%)	0 (0%)	6 (60%)

US-guided VABB: Ultrasound-guided vacuum-assisted breast biopsy, BI-RADS: Breast imaging-reporting and data system.

Table 2. The relationship between BI-RADS and hematoma development

	Hematoma presence	Hematoma absence	p
BI-RADS 4A	11 (27.5%)	29 (72.5%)	0.172
BI-RADS 4B	5 (50.0%)	5 (50.0%)	

p value obtained with chi-square test.

intramammary hematoma in 16 (39%) patients. In a patient, bleeding as leakage continued for 24 hours from the incision line and limited itself in 24 hours. During US-guided VABB, hematoma was detected in all 3 patients whose lesions were diagnosed as invasive cancer. Of all the 50 lesions, five were diagnosed as invasive or in situ cancer, and curative surgery was performed on these patients. Patients underwent breast-sparing surgery and sentinel lymph node sampling. After US-guided VABB, with the occurrence of hematoma, the lesion site became palpable. Hematoma and tissue changes were used in localizing surgery area and to these lesions, additional wire placement was not executed in our three patients.

The patients who underwent curative surgery were excluded from the follow-up evaluation in terms of the changes at the wound site. Also, two patients (3 lesions) did not attend follow-up ultrasound. A patient attended just 3rd-month ultrasound control and another patient attended 6th month follow-up. The follow-up duration for the rest of the patients was one year or above. Follow-up duration of the patients was between 0-51 months and mean was 20.92 months. Of the 41 lesions (after subtracting malign-premalignant ones and the ones who did not attend follow-up), organized hematoma was diagnosed in 3 (7.3%) at the 6th month follow-up. Hematoma disappeared in all of the 13 patients (the patients for whom hematoma developed and followed-up) in the 12th month.

Breast compositions of the patients who developed hematoma were ACR type in 2 patients (25% of all type a), ACR type b in 10 patients (41% of all type b), and ACR type c in 4 patients (44% of all type c). While the average sample number in the group which developed hematoma during the procedure was 14.63 ± 5.12, it was 12.82 ± 5.96 in the group without hematoma development. According to t-test results, there was no significant difference between the groups on the sample number of vacuum aspiration [t (48)= -1.041, p= 0.303].

Hematoma was detected in 11 of 40 BI-RADS 4A lesions (0.275) and 5 of 10 BI-RADS 4B lesions (0.5). T-test was utilized to understand whether the mean sample number of vacuum aspiration varied by BI-RADS subgroups (4A and 4B). According to t-test results, there was no difference between the BI-RADS subgroups (4A and 4B) on the sample number of vacuum aspiration [t (48)= -0.927, p= 0.359]. Mean number of vacuum aspirations were recorded as 13.03 ± 5.59 for BI-RADS 4A and 14.9 ± 6.28 for BI-RADS 4B. Hematoma was observed in 11 (27.5%) cases within BI-RADS 4A group where hematoma was not seen in 29 (72.5%) cases. On the other hand, BI-RADS 4B group involved 5 (50.0%) cases with hematoma and 5 (50.0%) cases without hematoma. In order to understand group-wise differences between the BI-RADS subgroups and hematoma development, chi-square test was implemented. Test results revealed that there was no significant difference between BI-RADS subgroups and hematoma development [X^2 (1)= 1.861, p= 0.172, Table 2].

A binary logistic regression was performed to ascertain the effects of vacuum aspiration sample numbers and lesions volume on the likelihood of hematoma development. The logistic regression model was not significant for the relationship between vacuum aspiration sample number and hematoma development X^2 (1)= 1.089, p= 0.297. The model explained only 3% (Nagelkerke R^2) of the variance in hematoma development and correctly classified 66.0% of the cases. Increasing vacuum aspiration was associated with an increased likelihood of exhibiting hematoma development at b = 0.056; however, this association was not significant (p= 0.299). In a similar vein, lesion size, which was initially considered as a predictor of hematoma development, was not supported according to the logistic regression model X^2 (1)= 0.086, p= 0.769. The model explained only 0.2% (Nagelkerke R^2) of the variance in hematoma development and correctly classified 68.0% of the cases. Increasing lesion volume was associated with a reduction in the likelihood of exhibiting hematoma development at b= -0.434; however, this association was not statistically significant p= 0.772 (Table 3).

During follow-up, resiude lesion in 1 (2.4%) patient and scar tissue in 2 (4.9%) patients scar were detected. The dimension of

Table 3. Binary logistic regression results for the relationships between lesion/vacuum aspirations and hematoma development

Models	Variables	B	s.e.	Wald	df	p*	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
1	vacuum aspirations	0.056	0.053	1.079	1	0.299	1.057	0.952	1.174
2	lesion	-0.434	1.5	0.084	1	0.772	0.648	0.034	12.247

Dependent variable = hematoma development (0 = absence and 1 = presence)
p value obtained from the variable in the equation.

the lesion was 10 x 7 x 10 mm for the residue lesion , and it was sampled 8 times. Histopathologic diagnosis of 2 cases, in whom scar developed, was fibrocystic changes and sclerosing adenosis, and both lesions were sampled 14 times.

DISCUSSION

This study showed that hematoma, which is the most common early complication in US-guided VABB, disappeared in all of the patients in the 12th month. It was also shown that US-guided VABB should be the primarily preferred biopsy method in BI-RADS 4A and 4B lesions which are smaller than 2 cm due to its low complication rates, low scar formation in follow-up and low residue rates with its curative property. Today, percutaneous imaging-guided breast biopsies have replaced excisional biopsies and become the gold standard biopsy method (2). When core biopsy and vacuum biopsy are compared, lower underestimation, rebiopsy, and false negative rates are among the superiorities of VABB (7,11). VABB is a biopsy method performed easily within the US, and complications like hematoma can be followed with real-time US (7).

According to the American College of Radiology, risk estimates for malignancy in BI-RADS 4A category (low suspicious) is ≥ 2 to < 10, in BI-RADS 4B category (moderate suspicious), is ≥ 10 to < 50 and in BI-RADS 4C category (high suspicious) is ≥ 50 to < 95 (12). Among all lesions on which biopsy was performed, 6% (2.5% of BI-RADS 4A, 20% of BI-RADS 4B) was diagnosed as malign. VABB provides full excision in BI-RADS 4A and 4B lesions which have a relatively low probability of malignancy if lesions are small in size and benign, thus it inhibits complications and expenses of additional surgery. In the case of malign diagnosis, performing curative cavity surgery is compulsory since surgical margin positivity can not be assessed.

VABB could also be used in BI-RADS 3 lesions like fibroadenomas as a therapeutic procedure, in addition to the use for diagnostic purpose in malignant lesions (9,13). In our study, 84% (n= 42) of all lesions was diagnosed as benign, and residue was detected only in one of them during follow-up. In this study population, the therapeutic effect of VABB benefited in nearly all of the cases which were histopathologically benign. In the literature, residue/recurrence was not detected in 84.9% of the lesions in more than one year follow up US-guided VABB (7). The largest diameter of the lesions was 2 cm and the rate of residual lesion was found as 2.4% in our series. ADH accompanied three benign lesions in our study. In the literature, it is shown that underestimation rates of ADH are very low in US-guided VABB (14). In our study, open surgery was not performed in the cases diagnosed as ADH with VABB due to very low rates of underestimation, but they were followed radiologically. In these three patients, mass development or recurrence was not detected at the biopsy site.

In our study, intramammary hematoma developed in 16 (39%) patients during biopsy. A study held with an 11G needle US-guided biopsy performed in 406 patients has shown that the most frequent complication was bleeding and hematoma, and minor complication rates have been reported as 9%. However, when the complications occurred was not specified and late-period complications were not mentioned in the aforementioned study (15). In another study, in which late-period complication follow-up was not fulfilled, the rate of early complications was reported as 1% and hematoma was the most frequent one (7). Higher hematoma rates in our study compared to those of the literature may originate from the goal of excising all lesions or early periods of the follow-up ultrasound. In a study, the rate of hematoma detected by USG has been given as 94% in the 1st week and 55% in the 3rd week following stereotactic VABB (16). Hematomas were resorbed during follow-up and the rates of hematoma decreased in follow-up in our study, too. In addition to that, the rate of hematoma was 7.3% in the 6th month andall hematomas disappeared in the 1st year follow-up in our study. Similar to our study, 9.6% of the hematomaa was identified in a study in which US-guided VABB was performed for benign breast lesions, and then 97.0% of the hematomas was entirely absorbed in the 6th month (17).

In our study, higher breast density resulted in higher hematoma rates, and breast density might be a risk factor in hematoma development. Besides, when patients who had a hematoma were considered, no difference was shown between the breast composition types on the sample number. So, breast composition may have an effect in the development of hematoma independent of the sample number. No significant difference between lesion BI-RADS subgroups (4A and 4B) and hematoma development was shown in our study. To our knowledge, there was no study evaluating the effect of breast composition or lesion BI-RADS subgroup on hematoma development with this procedure. To understand the relationship, further studies are needed.

In our study, hematoma occurred in all three patients, who were diagnosed as invasive cancer, during VABB, which may be related to neovascularization of the tumor. In a study, risk factors of hematoma occurrence after US-guided has been evaluated and the size and number of the nodules, menstrual status, and breast shape have been found as independent risk factors associated with hematoma development (17). As opposed to that study, in our study, we found that the occurrence of hematoma after VABB was not associated with the the size of the lesion or the sampling number of vacuum aspiration. Hematoma development might be related to the abundance of surrounding blood vessels adjunct to the lesions. Vascular structures around the lesion and the tractus visible on the US may be evaluated to understand the relationship between hematoma occurrence and location of the vascular structures. The sampling number of vacuum aspiration may correlate with the experience of the operator. In our study, we didn't find any relation with the number of sampling and hematoma, and to our knowledge, there is no study mentioning or evaluating this parameter.

In our patient group, we took advantage of hematoma occurrence in malignant lesions in determining the site of the lesion without the necessity of additional wire guiding before cavity surgery. Studies are needed to show its applicability in routine practice.

Vasovagal-induced seizure/syncope occurred in three patients (7.3%) during biopsy. In a study, in which US-guided VABB was performed on 67 patients, this rate was found as 1% (18). Our vasovagal seizure/syncope rate was higher than this study. As the mechanism of this complication is about fear in patients, socio-cultural differences might explain the high rate in our study. In our study, scar tissue developed in two lesions (4.9%), sampled for 14 times. In another study similar to ours, in which stereotactic VABB using 11G needle was assessed, scar development was found as 4.3%, and these cases were ensampled averagely for 12 times (19).

In our study, we showed that US-Guided VABB inhibits additional surgery in BI-RADS 4A and 4B breast lesions which are smaller than 2 cm and pathologically proven as benign lesions with low complication rates, and it is both a biopsy and treatment method in these lesions. Due to these superior properties, US-guided VABB should be the initial biopsy method in BI-RADS 4A and 4B lesions whose malignancy rates are as low (2.5%-6% in our series), by considering its easy applicability, providing a sufficient number of sample and therapeutic effects in breast lesions.

The main limitation of our study is the retrospective design and the limited number of cases. The other limitation of this study is all breast ultrasounds and US-guided vacuum-aspiration biopsies were performed by only one radiologist. Therefore, we cannot evaluate the interoperator variabilities of complications and rates. Further studies should consider at least two independent observers (or radiologist) in order to assess the agreement between the raters which may help us evaluate the reliability of the measurements in a more objective manner. Moreover, a follow-up evaluation of 6 patients were less than 6 months. The number of BI-RADS 4A and 4B lesions was not equal, and malignant results were very low in number.

CONCLUSION

US-guided VABB, which can be tolerated easily and have low rates of complication and scar development, is also a therapeutic excision method without residual lesion, which should be primarily preferred in BI-RADS 4A and 4B lesions smaller than 2 cm with low malignancy rates. Hematoma, which is the most frequent complication in US-guided VABB, is also useful in determining the site of lesion in complementary surgery regarding the cases diagnosed as malignant tumor. Hematomas may spontaneously be resorbed entirely in the 12th month.

Ethics Committee Approval: This study had been approved by our medical school's Institutional Reviews Board (number 04/III date 05.04.2018).

Informed Consent: Informed consent was taken from all patients prior to biopsy.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.D.E.; Design - F.D.E., C.E., O.N.; Supervision - F.D.E., A.K.B.; Resource - F.D.E., Y.D., A.K.B., Ö.D.; Materials - Y.D., F.D.E.; Data Collection and/or Processing - C.E., Ö.D., Y.D., O.N.; Analysis and Interpretation - A.K.B., C.E., F.D.E.; Literature Review - F.D.E., C.E.; Writing Manuscript - F.D.E., O.N.; Critical Reviews - F.D.E., Y.D., A.K.B., C.E., Ö.D., O.N.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (1): 65-71

BI-RADS 4A ve 4B lezyonlarda hem bir tanı hem de tedavi yöntemi: Ultrason eşliğinde vakum aspirasyon biyopsisi

Funda Dinç Elibol[1], Yelda Dere[2], Ahmet Korkut Belli[3], Cenk Elibol[1], Özcan Dere[3], Okay Nazlı[3]

[1] Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Muğla, Türkiye
[2] Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Muğla, Türkiye
[3] Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Muğla, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmada, ultrason eşliğinde vakum aspirasyon biyopsisi yapılan BI-RADS 4A ve 4B lezyonlarda sonuçların, komplikasyonların ve takip sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada Ağustos 2014-Ocak 2018 tarihleri arasında hastanemizde tek bir radyolog tarafından 10G vakum aspirasyon biyopsi iğnesi ile biyopsisi yapılan 50 BI-RADS 4A ve 4B lezyona ait veriler retrospektif olarak değerlendirildi.

Bulgular: Tüm hastalar kadındı ve yaş ortalaması 50,12 ± 8,63 yıl idi. Tüm lezyonların %84'ü benign, %6'sı ADH, %4'ü in situ kanser ve %6'sı malign tanı almıştır. Biyopsi sonrası takip süresi 0-51 ay olup ortalaması 20,92 ay olarak bulunmuştur. İşlem sırasında komplikasyonlar; 3 (%7,3) hastada vazovagal senkop, 16 (%39) hastada meme içi hematom şeklindeydi. Hematom altıncı ay kontrolünde 3 (%7,3) hastada saptanırken, 12. ay kontrolünde tüm hematomlar kaybolmuştur. Lezyon BI-RADS alt grupları, boyutu veya örnek sayısı ile hematom gelişimi açısından anlamlı bulunmamıştır. Takipte 1 (%2,4) hastada rezidü lezyon, 2 (%4,9) hastada ise skar dokusu saptanmıştır.

Sonuç: Ultrason eşliğinde vakum aspirasyon biyopsisi düşük komplikasyon ve skar oranları olan ve rezidü bırakmadan tedavi edici eksizyon da sağlayan, 2 cm'den küçük, malignite olasılıkları nispeten düşük BI-RADS 4A ve 4B lezyonlarda ilk terich edilmesi uygun olan biyopsi yöntemidir. Hematom en sık komplikasyonu olup, 12. ayda tüm olgularda tümüyle kaybolmuştur.

Anahtar Kelimeler: Ultrason eşliğinde vakum aspirasyon biyopsisi, BI-RADS, komplikasyon, tedavi

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ORIGINAL ARTICLE
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Intraoperative hemorrhage and increased spleen volume are risk factors for conversion to open surgery in patients undergoing elective robotic and laparoscopic splenectomy

Mehmet Aziret[1](ID), Bülent Koyun[1](ID), Kerem Karaman[1](ID), Cenk Sunu[2](ID), Alper Karacan[3](ID), Volkan Öter[1](ID), Fehmi Çelebi[1](ID), Metin Ercan[1](ID), Erdal Birol Bostancı[1](ID)

[1] Clinic of General Surgery, Sakarya University Training and Research Hospital, Sakarya, Turkey
[2] Clinic of Hematology, Sakarya University Training and Research Hospital, Sakarya, Turkey
[3] Clinic of Radiology, Sakarya University Training and Research Hospital, Sakarya, Turkey
[4] Clinic of General Surgery, Health Science University Ankara City Hospital, Ankara, Turkey

ABSTRACT

Objective: Minimal invasive surgery is one of the most popular treatment approaches which is safe and effective in experienced hands in different clinical practices. In the present study, we aimed to evaluate the risks factors for conversion to open splenectomy and the performance of indirect hilum dissection technique.

Material and Methods: A total of 56 patients who underwent laparoscopic or robotic splenectomy for isolated spleen diseases were included into the study. Patients were divided into two groups as robotic or laparoscopic splenectomy (Group 1; n= 48) and conversion to open surgery (Group 2; n= 8). Patients were retrospectively evaluated according to clinical, biochemical, hematological and microbiological parameters and morbidity.

Results: No statistically significant difference was found between the groups in terms of age, gender, body mass index (BMI), ASA score, co-morbid disease, operation time, hospital stay, follow-up period, accessory spleen, diagnosis, international normalized ratio (INR), red cell distribution width (RDW), platelet distribution width (PDW), platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), reapplication, splenosis, surgical site infection, vascular thrombus and incisional hernia (p> 0.05). On the other hand, intraoperative splenic hilum hemorrhage and increased spleen size (p< 0.05) were higher in the conversion to open surgery group. In logistic regression analysis, intraoperative splenic hilum hemorrhage (B= 4.127) (OR= 61.974) (95% CI= 3.913-981.454) (p= 0.003) and increased spleen volume (B= 3.114) (OR= 22.509) (95% CI= 1.818-278.714) (p= 0.015) were found as risk factors for conversion to open surgery.

Conclusion: Intraoperative hemorrhage from the splenic hilum and increased spleen volume (> 400 cm^3) are risk factors for conversion to open splenectomy in patients undergoing elective robotic or laparoscopic splenectomy. Indirect splenic hilum dissection can decrease intraoperative hemorrhage and conversion to open surgery.

Keywords: Conversion to open surgery, indirect hilum dissection, laparoscopic splenectomy, robotic splenectomy

INTRODUCTION

Minimal invasive surgery (MIS) is feasible and safe with growing popularity in different clinical practices (1-5). Laparoscopic and robotic splenectomies are subgroups of MIS and have been increased due to good exposure of the surgical field, less bleeding, postoperative abdominal pain and shorter length of the hospital stay (6-8). Robotic or laparoscopic splenectomies (RLS) are performed usually for benign blood disorders, splenic cystic disease, and play a crucial role in the management of a many malignant lymphoproliferative disorders (9,10).

RLS, which is associated with good exposure, less bleeding, postoperative abdominal pain, shorter length of hospital stay and better cosmetic results, require expertise such as insertion of trocars and ports, proper dissection of hilar vessels, removing of the spleen due to uncontrolled intraoperative hemorrhage and conversion to open splenectomy (11-14). Many published studies have assessed the safety and practicability of RLS (12-17). Nevertheless, a few trials are reported regarding the risks factors of conversion to open splenectomy for RLS in the literature (18). In the present study, we aimed to evaluate the risk factors of conversion to open splenectomy for isolated splenic diseases in patients who underwent RLS.

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Corresponding Author
Mehmet Aziret
E-mail: mhmtaziret@gmail.com

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MATERIAL and METHODS

Patients and Ethics

This study was conducted in the general surgery department between September 2013 and August 2018. A total of 56 patients who underwent laparoscopic or robotic splenectomy for isolated spleen diseases including benign blood disorders, cystic and malignant diseases were included into the study. Patients were retrospectively evaluated in terms of age, gender, body mass index (BMI), co-morbidity, diagnosis, ASA score, splenomegaly or spleen volume, biochemical, hematological and microbiological parameters, morbidity and mortality. The Ethical Committee of the Sakarya University Education and Research Hospital approved the study protocol (71522473/050.01.04/2).

Study Design

Of the splenectomized 255 patients, 56 RLS cases were enrolled in the study. The patients were divided into two groups;

- Group 1: Patients with laparoscopic and robotic splenectomy (n= 48),

- Group 2: Patients with conversion from RLS to open splenectomy (n= 8).

The flow-chart of the study is illustrated in Figure 1. Blood samples were taken from all patients before laparoscopic or robotic splenectomy. Indication of RLS was considered after hematology and anesthesiology consultation.

Inclusion Criteria

- Patients who were resistant to medical treatment for isolated benign or malignant splenic diseases.

- Hematological disorders including idiopathic thrombocytopenic purpura (ITP) and hereditary spherocytosis, splenic cyst or splenic malignity.

- Patients with a platelet count higher than 50.000/lL.

- Patients with normal hemostatic parameters (PTZ/INR, aPTZ, etc.).

Exclusion Criteria

- Patients who could not be followed up

- Patients with abnormal coagulation tests, immunosuppression, sepsis

- Patients without isolated splenic disease

Vaccinations and Antibiotic Prophylaxis

Hemophilus influenza, meningococcal, and pneumococcal vaccinations were administered to all patients following the evaluation of the infectious disease clinic. Most of the patients (2/3 cases) were vaccinated after postoperative 14th day. Others were vaccinated at least two weeks before the surgery. An antibiotic prophylaxis was performed with intravenous 1 g cefazolin before anesthesia induction.

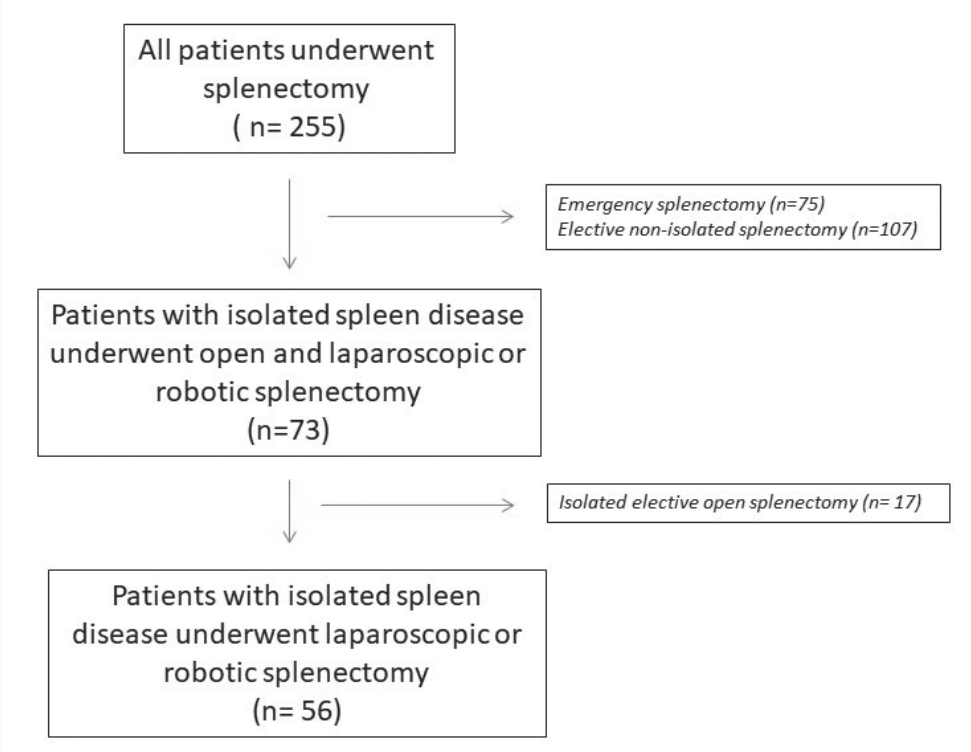

Figure 1. Flowchart of the study.

Indications for Splenectomy

ITP is the most common hematologic disorder for splenectomy. Splenectomy is usually performed only in cases in which corticosteroid therapy fails to achieve remission. A very important part of the operative procedure is the detection of accessory spleens. Accessory spleens or accidentally re-implanted splenic tissue may cause recurrent thrombocytopenia after splenectomy. Splenectomy is indicated when conservative treatment is ineffective in patients with hereditary spherocytosis (9).

Hodgkin's disease (lympho-granulomatosis) and non–Hodgkin's lymphomas are grouped together under the heading "malignant lymphomas". They develop primarily in lymphatic tissue, mostly in lymph nodes, and less than 1% occurs in the spleen (10). Splenectomy is performed for diagnosis and staging of the disease.

Perioperative Platelet Account, Identification of Accessory Spleen and Calculation of the Splenic Volume

Abdominal ultrasound (US) and computerized tomography (CT) scans were used preoperatively in all patients. Splenectomy was performed in patients with a platelet count higher than 50.000/lL. Fresh frozen plasma or platelet apheresis was given to increase the platelet count, if the platelet counts were less than 50.000/lL. All patients were screened with CT for accessory spleen. The accessory spleen was removed when it was detected during operation. Contrast-enhanced CT images of each spleen were obtained by scanning in the axial plane and were reformatted in sagittal-transverse planes. Splenic length, width, and thickness measurements were obtained. Length was measured along the long axis, from the dome to the tip of the spleen, in the sagittal plane. Width was the longest (straight) organ diameter in the transverse plane. Thickness was the distance between the center (inner) and peripheral (outer) surface, measured at the level of the splenic hilum on the transverse plane. This was identified on the section with the largest width. Splenic length, width, and thickness measurements were obtained by positioning electronic calipers manually on the image. To assess interobserver and intraobserver variability, three separate measurements of each distance (i.e., length, width, and thickness) were recorded by two separate independent observers, then an average for each observer was determined. Splenic volume was calculated using the standard clinical ellipsoid equation of length x width x thickness x 0.523 (normal volume range 107 to 314.5 cm^3) (11).

Operative Technique

Robotic splenectomy: The patients were positioned in a right modified lateral decubitus position under general anesthesia. A CO2 pneumoperitoneum of 12 mmHg was established using a Veress needle introduced through a between umbilicus and inferior arcus costarium positioned on the patient's left side. Four or five ports (three 8-mm robotic arms, 12-mm camera and 11-mm assistant) were inserted under direct vision, and localization of ports was similar to the placements in laparoscopic splenectomy. At first, docking of the robotic arms were performed, and then the dissection was performed with bipolar cautery scissors in the right hand and the Maryland forceps in the left hand. A 3rd arm of the robot was used for retraction of the spleen and other tissues. In some cases, an assistant port was inserted in case of hemoclip application when necessary. The peritoneal attachments, splenic ligaments and adjacent tissues were dissected with monopolary electro-cautery and bipolary electro-cautery. The splenic hilar vessels were dissected and ligated with hemo-lock clips. After hilum dissection, the operation underwent similar to the laparoscopic splenectomy (Figure 2).

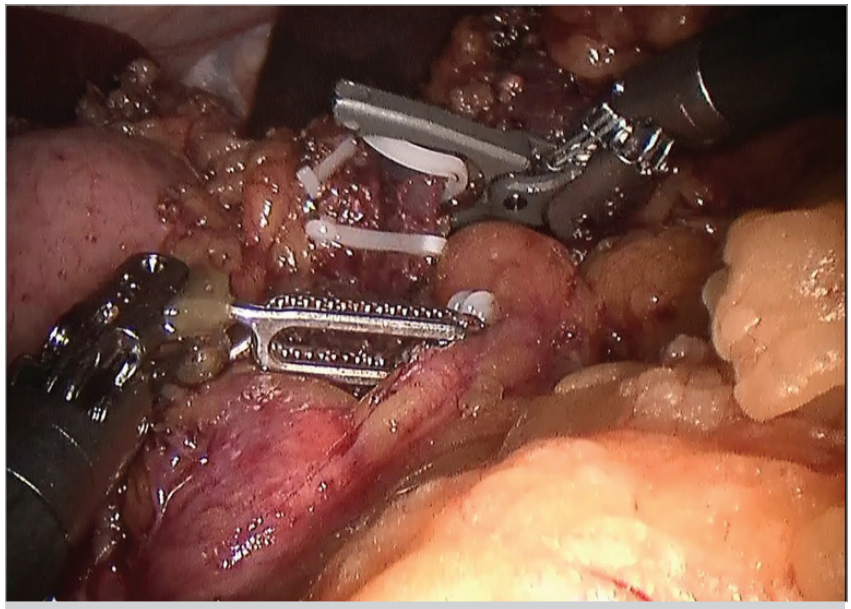

Figure 2. Robotic splenectomy during splenic hilum dissection.

Laparoscopic splenectomy: All patients were positioned in a right and lateral decubitus following general anesthesia. Prior to making the trocars insertion, a Foley catheter was inserted into the bladder. A three or four-port technique was used on all patients and different surgeons performed the laparoscopic or robotic splenectomies. A 10-mm port was inserted under the arcus costarium in midclavicular line using the Veres needle. Pneumoperitoneum was applied with carbon dioxide (CO_2), and intraabdominal pressure was fixed at 12 mmHg. Next, a 5-mm trocar was inserted into the epigastric area just inferior to the xiphoid process. A 10-mm trocar was inserted to the left upper quadrant under the direct 30º scope vision (Figure 3). The possibility of hemorrhaging or organ injury occurring in connection with trocar was controlled prior to performing the splenectomy. After the spleen was visible, it was controlled from the other adjacent organs or tissues. A 5-mm bipolar vessel sealer was used for the ligament of spleen dissection (splenocolic, splenophrenic and splenogastric). Once the base of the ligament of spleen dissection was performed, splenic hilum was revealed. The splenic vein and splenic artery were ligated using vascular clips under direct vision. In a few patients, these vascular tissues were sealed with 10-mm (Figure 4). Splenectomy specimen was placed in large retrieval bag. The spleen was extracted through the left upper quadrant port following smashing the spleen in the retrieval bag. After removing the spleen, the splenectomy area was washed with serum physiologic (0.9% sodium-chlo-

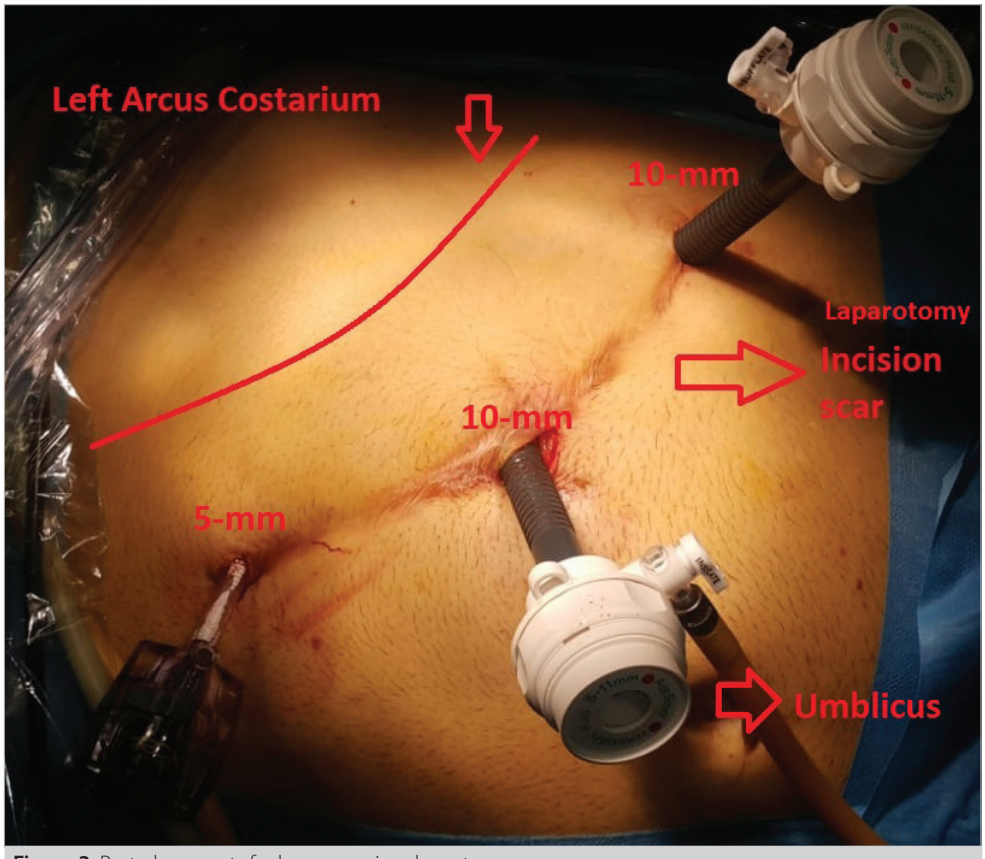

Figure 3. Port placements for laparoscopic splenectomy.

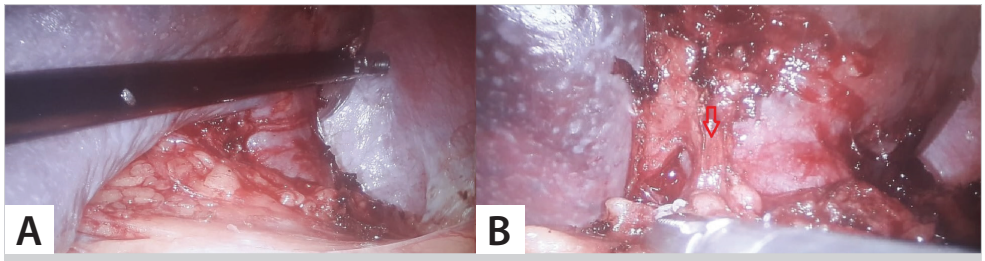

Figure 4. Indirect splenic hilum dissection; removing of the spleno-colonic and spleno-diapragmatic ligaments **(A)**, and splenic vascular plane after bilateral hilum dissection (arrow: splenic pedicle) **(B)**.

ride) and then aspirated. A drain was used in all patients for the purpose of controlling hemostasis. A mini-laparotomy (< 6 cm) was performed in the absence of large retrieval bag in left subcostal area.

Postoperative Care, Anticoagulation and Follow-up

In all patients, an intensive monitoring was provided at the early postoperative hours in terms of pulse, blood pressure, temperature and drains. After eight hours, hemoglobin, platelet count and INR were checked. Oral feeding and mobilization were started at the postoperative 8th hour. Drain was removed provided the drainage was less than 30 mL over 48 h. Most of the patients were discharged with low-molecular weight heparin (LMWH) of 0.4 IU/mL during the first 2 weeks of the postoperative period. The patients were followed up to ensure well healing of wounds and hemodynamic parameters in the first 1 month. After this period, patients who had hematological disease were followed up by hematology.

Statistical Analysis

Data analysis was performed by using IBM SPSS Statistics version 21.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not was determined by Shapiro-Wilk test. Continuous variables were shown as median (25^{th}-75^{th}) percentiles. Number of cases and (%) were used for categorical data. While mean differences between the groups were compared by Student's t test, Mann-Whitney U test was used for comparisons of the not normally distributed data. Categorical variables were analyzed by Continuity Corrected Chi-square or Fisher's exact test, where appropriate. The optimal cut-off points for spleen volume to assess conversion to open splenectomy were evaluated by receiver operating characteristics (ROC) analyses, calculating the area under the curve to give the maximum sum of sensitivity and specificity. Determining the best predictor(s) which affected both conversions to open surgery was evaluated by Multiple Logistic Regression Analyses. Any variable whose univariable test had a p value < 0.25 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Odds ratios, 95% confidence intervals and Wald statistics for each independent variable were also calculated. A p value less than 0.05 was considered statistically significant.

RESULTS

Perioperative Outcomes

Of the 255 patients, 56 cases were enrolled in the study, whereas 199 patients were excluded due to failing of the inclusion criteria. Fifty-one patients underwent laparoscopic and 5 patients underwent robotic splenectomy.

Mean age was 42.3 (± 15.5) years. Thirty-four (62.5%) patients were females and 21 (37.5%) patients were males. Mean BMI was 26.1 (± 5.5) kg/m^2. Median ASA score was 2 (min-max; 1-3). Median follow-up time was 25.2 (1-89) months. Most of the patients (39 patients, 69.6%) had steroid usage, and comorbidities were hypertension (14.2%), diabetes mellitus (14.2%), coronary artery disease or congestive heart failure (3.5%), chronic obstructive lung disease (3.5%) and others (cerebrovascular disease, depression, lymphoma) (5.3%), respectively. Median operation time of laparoscopic and robotic splenectomy was 172.5 (52-450) minutes. A statistical difference was not found in terms of age, gender, BMI, ASA, co-morbidity, operation time, follow up, length of the hospital stays and accessory spleen in two groups (p> 0.05) (Table 1).

Median spleen volume was 285 (129-950) cm^3, and the conversion to open splenectomy group had significantly higher spleen volume than the laparoscopic and robotic splenectomy group (p= 0.01) (Table 1). Indications for splenectomy were ITP (67.8%), followed by splenic cyst (14.3%), lymphoma (7.1%), hereditary spherocytosis (5.3%) and splenic artery aneurysm or splenic infarct (5.3%), respectively. There was no difference in terms of diagnosis between the two groups (p> 0.05) (Table 2).

Median INR value was 0.95 (min-max; 0.75-1.38); platelet distribution width (PDW) was 17.9% (min-max; 16.0-24.8); red cell distribution width (RDW) was 16.7% (min-max; 14.4-29.7), platelet to lymphocyte ratio (PLR) was 106.8 (min-max; 13.6-510) and neutrophil to lymphocyte ratio (NLR) was 3.3 (min-max; 0.5-37.5), respectively (Table 3).

No statistically difference was found in terms of PDW, RDW, PLR, NLR, preoperative adhesion, robotic surgery and mini-laparotomy in two groups (p> 0.05) (Table 3). In our study, there were a total of 5 patients who underwent robotic splenectomy, and none of these patients had conversion to open splenectomy. There was no statistically significant difference in terms of the robotic surgery between the two groups. This result can be due to the increased concentration in the learning curve of robotic surgery and advanced surgeon's experience in laparoscopic surgery (p> 0.05). Sixteen (28.5%) patients underwent mini-laparotomy for removing of the spleen in the absence of large retrieval bag (Table 1 and 3).

Complications

Mortality did not occur during the first postoperative month. Most of the complications were minor complications including incisional hernia [5 (8.9%) patients], wound infection [3 (5.3%) patients], splenosis [1 (1.7%) patient], and readmission to hospital [8 (14.2%) patients]. Patients with readmission were hospitalized, and wound care was applied on 3 of them, another three underwent incisional hernia repair and 2 of patients received anticoagulant treatment for branch of the portal vein thrombosis (PBVT). Patients with PBVT were followed up in the outpatient clinic with LMWH followed by oral Warfarin. A non-abundant hemorrhage occurred in 9 (16%) patients. These patients were followed up and treated medically and carefully including erythrocyte suspension, fresh frozen plasma and vitamin K supple-

Table 1. Clinical and operative characteristics

	Total (n= 56)	Laparoscopic and robotic splenectomy (n= 48)	Conversion to open splenectomy (n= 8)	p
Age	42.3 ± 15.5	41.3 ± 14.5	48.1 ± 21.3	0.260†
Gender				0.235$
Male	21 (37.5%)	16 (33.3%)	5 (62.5%)	
Female	35 (62.5%)	32 (66.6%)	3 (37.5%)	
BMI (kg/m^2)	26.6 ± 4.1	26.7 ± 4.4	25.8 ± 2.6	0.573†
ASA				0.599¶
I	5 (8.9%)	4 (8.3%)	1 (12.5%)	
II	41 (73.2%)	37 (77%)	4 (50%)	
III	6 (10.7%)	4 (8.3%)	2 (25%)	
Steroid usage	39 (69.6%)	35 (72.9%)	4 (50%)	0.228$
Co-morbidity				
HT				
DM	8 (14.2%)	6 (12.5%)	2 (25%)	0.320$
CAD/CHF	8 (14.2%)	6 (12.5%)	2 (25%)	0.320$
COLF	2 (3.5%)	2 (4.1%)	-	> 0.999$
Others	2 (3.5%)	2 (4.1%)	-	> 0.999$
CVD, Depression, lymphoma	3 (5.3%)	3 (6.2%)	-	> 0.999$
Operation time	172.5 (52-450)	163 (52-450)	199 (90-349)	0.233¶
Length of hospital stay	5 (3-21)	5 (3-21)	7 (4-9)	0.378¶
Robotic splenectomy	5 (8.9%)	5 (10.4%)	-	> 0.999$
Laparoscopic splenectomy	51(71.5%)	43 (84.6%)	8 (15.6%)	0.159$
Follow up	25.2 (1-89)	22.6 (1-66)	22.8 (1-72)	> 0.999¶
Spleen volume	285 (129-950)	270 (129-950)	521 (212-695)	**0.01**¶
Accessory spleen				0.319$
No	37 (66%)	31 (64.5%)	6 (75%)	
Yes	13 (23.2%)	13 (27%)	-	

BMI: Body mass index, CAD: Coronary artery disease, CHF: Congestive heart failure, COLF: Chronic obstructive lung failure, CVD: Cerebrovascular disease, DM: Diabetes mellitus, HT: Hypertension, RA: Romatoid arthritis.
† Student's t test, ‡ Continuity Corrected Chi-square test, $ Fisher's exact test, ¶ Mann-Whitney U test.

Table 2. Comparison of groups in terms of diagnosis

	Total (n= 56)	Laparoscopic and robotic splenectomy (n= 48)	Conversion to open surgery (n= 8)	p value†
ITP	38 (67.8%)	33 (68.7%)	5 (62.5%)	0.703
Hereditary spherocytosis	3 (5.3%)	2 (4.1%)	1 (12.5%)	0.376
Splenic cyst	8 (14.2%)	7 (14.5%)	1 (12.5%)	> 0.999
Splenic artery aneurysm or infarct	3 (5.3%)	2 (4.1%)	1 (12.5%)	0.376
Malignancy	4 (7.1%)	4 (8.3%)	-	> 0.999

ITP: Idiopathic thrombocytopenic purpura.
† Fisher's exact test.

mentation. Major hemorrhage occurred during operation in 7 (12.5%) patients. Of the 16 patients (with perioperative bleeding patients), seven cases were converted to open splenectomy. An improved splenosis patient was followed up as outpatient with normal range platelet level. There was no difference in terms of readmission, splenosis, surgical side infection, incisional hernia and PBVT (p> 0.05). The rates of intraoperative hemorrhage were higher in conversion to open surgery group (p< 0.001) (Table 3). Moreover, the conversions to open surgery were associated with expertise of the surgical team because the number of conversions were 5 (8.9%) patients and 3 (5.3%) patients in the first half of study and second half of study, respectively.

Table 3. Alterations of biochemical parameters and complications in groups

	Total (n= 56)	Laparoscopic and robotic splenectomy (n= 48)	Conversion to open surgery (n= 8)	p value
INR	0.95 (0.75-1.38)	0.95 (0.80-1.38)	0.97 (0.75-1.1)	0.765†
PDW	17.9 (16.0-24.8)	17.8 (16.0-24.8)	18.4 (17.2-21.7)	0.550†
RDW	16.7 (14.4-29.7)	16.6 (14.7-29.7)	18.1 (15.4-20.8)	0.197†
PLR	106.8 (13.6-510.0)	100.7 (13-510)	130.5 (47-180)	0.404†
NLR	3.3 (0.5-37.5)	3.3 (0.4-37.5)	2.5 (0.8-6.9)	0. 242†
Adhesion	6 (10.8%)	4 (8.3%)	2 (25%)	0.200‡
Increased spleen volume (> 400 cm^3)	16 (20.8%)	10 (17.9%)	6 (75%)	0.005‡
Mini-laparotomy	16 (28.5%)	16 (33.3%)	-	0.089‡
Readmission	8 (14.2%)	6 (12.5%)	2 (25%)	0.329‡
Total complications				
Hemorrhage	16 (28.5%)	9 (18.7%)	7 (87.5%)	< 0.001‡
Incisional hernia	5 (8.9%)	3 (6.2%)	2 (25%)	0.104‡
Surgical side infection	3 (5.3%)	2 (4.1%)	1 (12.5%)	0.330‡
PMVT	2 (3.5)	2 (4.1%)	-	> 0.999‡
Splenosis	1 (1.7%)	1 (2%)	-	> 0.999‡

INR: International normalized ratio, NLR: Neutrophil lymphocyte ratio, PDW: Platelet distribution width, PLR: Platelet lymphocyte ratio, RDW: Red cell distribution width.
† Mann-Whitney U test, ‡ Fisher's exact test.

Table 4. Risk factors of conversion to open surgery

						95% CI for EXP(B)		
	B	S.E.	Wald	df	Exp(B)	Lower	Upper	p value
Intraoperative Hemorrhage	4.127	1.409	8.574	1	61.974	3.913	981.454	0.003
Spleen volume (> 400 cm^3)	3.114	1.284	1.284	1	22.509	1.818	278.714	0.015
Constant	5.465	1.516	12.992	1	.004			< 0.001

Risk Factors for Development of Complications

No significant difference was found between the patients converted to open splenectomy and those who had not according to age, gender, BMI, ASA, co-morbidity, operation time, follow up, length of the hospital stay and accessory spleen (p> 0.05).

Patients with conversion to open splenectomy had significantly higher splenic volume and splenic hilum hemorrhage than laparoscopic or robotic splenectomy group (p= 0.01 and p< 0.001; respectively).

ROC analysis for spleen volume to assess conversion to open splenectomy measurements revealed that the under-curve area was significant in distinguishing patients. The cut-off value for spleen volume to determine conversion to open surgery was 416 cm^3 with 87.5% sensitivity and 80% specificity. In univariate analysis, all variables identified as p< 0.25 were included as risk factors for multiple logistic regression model. Intraoperative hemorrhage and spleen volume (> 400 cm^3) were found as risk factors for conversion to open surgery. The rates of conversion to open splenectomy were correlated with increased intraoperative splenic hilum hemorrhage in patients undergoing laparoscopic and robotic splenectomy. When intraoperative hilum hemorrhage occurred, it was significantly associated with increased rate of conversion to open surgery with a risk of 61 times (B= 4.127) (OR= 61.974) (95% CI= 3.913-981.454) (p= 0.003). Moreover, a significant association was found between the rates of conversion to open splenectomy and increased spleen volume (B= 3.114) (OR= 22.509) (95% CI= 1.818-278.714) (p= 0.015) (Table 4).

DISCUSSION

This is the first study which assesses spleen volume for predicting the risk of conversion to open surgery. We found that a spleen volume higher than 400 cm^3 increases the risk of conversion to open surgery 22.5 times. Secondly, intraoperative hemorrhage from the splenic hilum has a 61-fold risk of conversion

to open surgery (p= 0.015 and p= 0.003, respectively). On the other hand, it was found that age, gender, BMI, ASA, co-morbidity, operation time, accessory spleen, INR, PDW, RDW, PLR, NLR, preoperative adhesion, and robotic surgery were not associated with conversion to open surgery (p> 0.05).

Minimal invasive surgery, whether robotic or laparoscopic, has become popular due to less postoperative abdominal pain, shortened length of hospital stay, and early return to normal daily activity (1-8). Robotic surgery surpasses laparoscopic technique by providing more articulation and maneuverability (7,8). RLS is frequently used for hematological disorders of the spleen such as ITP, hereditary spherocytosis, lymphoma and splenic cyst (9-11).

There are some risk factors for conversion to open surgery including intraoperative hemorrhage, massive splenomegaly (over 1 kg), a low platelet count, obesity, and adhesions. In the literature, conversion to open rates ranges from 0.7% to 30% (6,12-17). In the present study, conversion to open surgery rate was 14.2%, which is comparable with the literature (1,3,6,12-17). Here, it is known as 'difficult splenic hilum', occurrence of abundant bleeding due to hardly of dissection and lead to slippage of knots or clips in splenic hilum (18). In patient with difficult splenic hilum, there is lymphatic edema, lymphadenopathy, chronic infection or fibrotic bands at the splenic hilum increase the conversion rate. Vecchio et al. (18) suggest ligation of hilar vessels and branches by using intracorporeal sutures. Two approaches can be recommended for hilum dissection as the following: direct hilum dissection and indirect hilum dissection techniques. In the direct dissection technique; the splenic artery and vein are ligated before the dissection of the splenic hilum. However, massive hemorrhage may sometimes occur during the ligation of these vessels. On the other hand, the dissection starts in the indirect hilum dissection technique from the posterolateral region by dissection of the splenocolonic, splenophrenic and gastrosplenic ligaments towards the splenic hilum. Furthermore, if possible, we recommend a 360º circumferentially dissection for exactly revealing the splenic artery and vein, so surgeon can behave safely and easily before splenic hilum ligation (Figure 4a, 4b). Patients with malignancy, lymphoma, liver cirrhosis and chronic infections disease have always a difficult splenic hilum to dissection so a careful and sharp dissection should be performed to decrease the hemorrhage rate.

In these patients, Giza et al. (19) recommend robotic splenectomy over laparoscopic due to the ability of better articulation. Further, they have suggested sponges-assisted spleen retraction to avoid laceration during the indirect splenic hilum dissection technique. Splenic hilum dissection can be performed closely to the spleen to prevent injury of the pancreatic tail.

Another indication for conversion to open surgery is the enlarged spleen volume or splenomegaly because splenomegaly cannot allow adequate surgical exposure, suitable location of ports and maneuverability during the laparoscopic and robotic splenectomy which raises the risk of hemorrhage (20-23). On the other hand, despite longer operative time of laparoscopic splenectomy, Pattenden et al., Owera et al. and Silecchia et al. suggest laparoscopic splenectomy in patients with splenomegaly after an effective learning curve (15,24,25). Currently, with the advanced minimally invasive method, robotic splenectomy has been used for first training of robotic systems and routine clinical practice. Cavaliere et al. suggest robotic splenectomy due to less intraoperative bleeding for splenomegaly (26). On the other hand, Bodner et al. and Gelmini et al. have reported that robotic surgery is not cost-effective and the operation time is longer than in LS (27,28). We recommend indirect hilum dissection approach which can allow easy and safe vascular clipping. Thus, risk of intraoperative hemorrhage and conversion to open surgery is reduced with this technique.

The present study has some limitations. First, it is retrospective. Secondly, the sample size is small. On the other hand, this is the first study which measured the splenic volume to determine the risk of conversion to open surgery.

CONCLUSION

Intraoperative hemorrhage from the splenic hilum and a spleen volume > 400 cm^3 are risk factors for conversion to open splenectomy in patients undergoing minimal invasive surgery. Indirect splenic hilum dissection technique seems to be feasible in reducing bleeding from the splenic hilum.

Ethics Committee Approval: The Ethical Committee of the Sakarya University Education and Research Hospital approved the study protocol (71522473/050.01.04/2).

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ORİJİNAL ÇALIŞMA-ÖZET
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İntraoperatif splenik hilus kanaması ve splenomegali robotik ve laparoskopik splenektomiden açık cerrahiye geçişe etki eden risk faktörleridir

Mehmet Aziret[1], Bülent Koyun[1], Kerem Karaman[1], Cenk Sunu[2], Alper Karacan[3], Volkan Öter[1], Fehmi Çelebi[1], Metin Ercan[1], Erdal Birol Bostancı[1]

[1] Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Sakarya, Türkiye
[2] Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, Hematoloji Kliniği, Sakarya, Türkiye
[3] Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği, Sakarya, Türkiye
[4] Sağlık Bilimleri Üniversitesi Ankara Şehir Hastanesi, Genel Cerrahi Kliniği, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Minimal invaziv cerrahi tüm dünyada farklı klinik pratiklerde etkili ve güvenli popüler tedavi yöntemlerinden biridir. Bu çalışmada amacımız, robotik veya laparoskopik splenektomi (RLS)'den açık cerrahiye geçişe etki eden risk faktörlerini ve indirekt hilum diseksiyonu tekniğinin performansını ortaya koymaktır.

Gereç ve Yöntem: Çalışmaya izole dalak hastalıkları nedeniyle RLS splenektomi yapılan 56 hasta kabul edildi. Hastalar iki gruba ayrıldı; RLS yapılan hastalar (grup 1) (n= 48) ve açık cerrahiye geçilen hastalar (grup 2) (n= 8). Hastalar yaş, cinsiyet, beden kütle indeksi (BKİ), yandaş hastalık, tanı, ASA skoru, dalak çapı, biyokimyasal, mikrobiyolojik parametreler ve morbiditeler açısından retrospektif olarak değerlendirildi.

Bulgular: Yaş, cinsiyet, BKİ, ASA skoru, yandaş hastalık, operasyon süresi, hastanede kalış süresi, takip süresi, aksesuar dalak, tanı, Uluslararası Normalizasyon Oranı (INR), eritrosit dağılım genişliği (RDW), trombosit dağılım genişliği (PDW), trombosit-lenfosit oranı (PLR), nötrofil-lenfosit oranı (NLR), tekrar başvuru, splenozis, cerrahi alan infeksiyonu, vasküler trombüs ve insizyonel herni açısından gruplar arasında istatistiksel olarak farklılık yoktu (p> 0,05). Diğer taraftan, açık splenektomiye geçilen grupta intraoperatif splenik hilustan kanama ve dalak çapı istatistiksel olarak daha fazlaydı (p< 0,05). Multivaryant analizde açığa geçişe etki eden faktörler; intraoperatif hilustan kanama (B= 4,127) (OR= 61,974) (%95 GA= 3,913-981,454) (p= 0,003) ve artmış dalak çapı (> 400 cm3) (B= 3,114) (OR= 22,509) (%95 GA= 1,818-278,714) (p= 0,015) olarak tespit edilmiştir.

Sonuç: İntraoperatif splenik hilustan kanama ve artmış dalak çapı (> 400 cm^3) elektif RLS'den açık splenektomiye geçişe etki eden risk faktörleridir. İndirekt splenik hilum diseksiyonu intraoperatif kanama ve açık cerrahiye geçişi azaltabilir.

Anahtar Kelimeler: Açık cerrahiye konversiyon, indirekt hilum diseksiyonu, laparoskopik splenektomi, robotik splenektomi

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ORIGINAL ARTICLE
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General surgery specialism in Turkey: Work power currently, continuity at quality and quantity

Ahmet Çınar Yastı[1](ID), Ahmet Deniz Uçar[2](ID), Murat Kendirci[3](ID)

[1] Health Sciences University, General Surgery, Ankara, Turkey
[2] Bozyaka Education and Research Hospital, General Surgery, Izmir, Turkey
[3] Hitit University, General Surgery, Corum, Turkey

ABSTRACT

Objective: As one of the oldest and main branches of medicine, process of General Surgery speciality training is long, expensive and difficult. Along with the principle of using limited sources wisely, there is a need for national forward planning in order to keep the number of General Surgery specialists in the proper level and in the proper quality. This study is made for the assurement of training quality specialists and for the sustainability in the best conditions after determining of the number of general surgeons, work force, and working conditions.

Material and Methods: The number of General Surgery specialists (professors, associate professors, specialists or General Surgery subspecialists) and assistants who actively work in our country from the end of 2017 in the public sector, private sector, and university hospitals, is examined. These numbers were subjected to cross evaluation according to the provinces, academic titles and number of assistants. The estimated ratio of the existing number of General Surgery specialists to upcoming five and ten years were calculated according to the data of Turkish Statistical Institute.

Results: From the end of 2017, 3957 General Surgery specialists are actively working in 1031 of 1499 health facilities. Four hundred and forty of them are titled as professors, 324 of them are titled as associate professors. For every 25 thousand people, there exist 1.22 surgeons. Ten years ago, this ratio was calculated as 1.27. The number of assistans, which was 1005 ten years ago, is decreased to 768 today, but the increase of the number of specialists is 409.

Conclusion: The number of General Surgeons in our country is above the ideal ratio, which is one for 25 thousand people. In case rate of increase of the number of General Surgeons for the last 10 years continues, when the decrease of population growth rate is considered, there will be an uncontrolled increase in the number of surgeon per 25 thousand people. Just as the distribution of General Surgery specialists -whether or not having an academic title- is not balanced, the number of instructor per assistant is also excessive.

Keywords: Surgery, work power, quality, quantity

INTRODUCTION

One of the fundamental objectives of Turkish Surgical Association (TSA), as a professional body, is to advance the profession in every sense. Keeping the number of general surgery specialists at an ideal ratio is a parameter that could directly affect quality. Along with the studies carried out by TSA on general surgery manpower, the most extensive report on employment has been published by Terzi et al. using data from 2007 (1). As a result of the meetings with the Ministry of Health and Board of Specialty in Medicine held in light of this report, a decrease in the number of residents employed for general surgery specialty has been resorted.

There has been a worldwide debate ongoing for many years on whether the deficit in the number of surgeons, the irregularity of their distribution or both poses a problem. The basic reason for the debate is the fact that an agreement has still not been made on the number of general surgeons per population. To this end, a scientifically precise conclusion has not been reached despite the numerous studies conducted by various bodies and institutions, only recommendations have been put forth over general approval. In manifold studies from the USA, while one surgeon has been foreseen to a population of 25.000, a better performance has been claimed to be achieved with a surgeon/population ratio of 6/100.000, and 3/100.000 has been defined as the critical value (2,3). Giddings determined the ratio as 1/50.000 in a study conducted for England and Ireland in 1993 and noted that

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Corresponding Author
Ahmet Çınar Yastı
E-mail: cinaryasti@gmail.com

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this ratio should be urgently lowered to the ratio of 1/30.000. In the upcoming years, studies from the UK reported a ratio between 1/20.000 and 1/40.000 (4).

Although surgeon per population is normal according to the population of the country, distribution irregularities constitute an issue in practice. While there can be more surgeons found in densely populated areas than needed, the number of surgeons found in rural areas is either below the number needed or even none (3,5). This situation is similar in developed and developing countries (1,5,6).

The discipline of general surgery is one of the specialties comprising the cornerstone of the healthcare system. In this sense, *the surgeon pool must be constantly improved in quality and carefully planned in quantity*. This study aimed at investigating the current status alongside the effect of 2007 data on 2017 and carrying out a prospective projection.

MATERIAL and METHODS

Approval was received from the Ethics Board of University of Health Sciences Izmir Bozyaka Education and Research Hospital. All healthcare institutions employing general surgery specialists all around Turkey were included into the study. Even though a number had not been given for Turkey in previous studies, a rate of one general surgery specialist per a population of 25.000 was accepted as a scale. Basic parameters supporting the specialist pool generating the general surgery workforce were thoroughly examined accepting as the number of physicians retiring from the profession and the number of those brought in the profession, in other words the number of residents being trained. General calculations and distributions were analyzed by determining cluster areas and those with deficits.

RESULTS

Current Status in the General Surgery Residency Training Program in Turkey

General surgery specialty has one of the longest professional training periods with a total of 11 years including 6 years of medical school and 5 years of residency. Following the 6-year medical school education, the candidates successful in the Examination for Specialty in Medicine held by Student Selection and Placement Center are placed into the specialties they have preferred. Those successful in this examination are trained in university hospitals or in states hospitals affiliated to universities. Training curriculum of general surgery in our country is prepared and determined by the Board of Specialty in Medicine. Resident Report Cards prepared accordingly are followed by the person in charge of training or by the head of the department of the relevant institution. Predicating on this report card including all necessary qualifications residents should be able to acquire during their training period, assessment and follow-up of their efficiency and competence in designated fields are ensured. Each specialist candidate is obliged to conduct a residency thesis at the end of the training period. The specialist candidate, whose thesis is found successful, is subject to a two-phase examination. First phase is a practical one where the candidate performs a surgery as the first surgeon under the supervision of a jury and replies to the questions asked. Oral examination evaluating their theoretical knowledge constitutes the second phase. The candidate found successful following this two-phase examination earns the right to receive the title of general surgery specialist.

Residency training is full of difficulties without a doubt. General surgery resident training in the world and in our country is bound to change, development and transformation in parallel to the developments in medicine (6). Due to the fact that it is not the main objective of this study and report, this important matter that should always be on the front burner will not be further scrutinized in this study.

Following the mandatory state service, the physician who has received the title 'general surgery specialist' can work as a private senior physician, senior physician in state/private hospitals, or as a senior physician participating in academic career studies in training institutions of university/affiliated state hospitals.

Institutions Giving Specialty Training in General Surgery

General surgery specialty training de facto continues in a total of 93 inpatient healthcare facilities in our country. University hospitals comprise 51.7% of these units where residents are present and training still continues as of the time of the study (Table 1).

Status of General Surgery Specialist Teachers

Table 2 demonstrates the number of professors, associate professors and specialist physicians on the basis of provinces and

Table 1. The distribution of institutions providing specialty training (93) and the presence of teachers with academic titles

Type of the institution offering training	Presence of academics		Total	
	None	Present	n	%
Ministry of health	4	41	45	(48.4)
University	0	46	46	(49.5)
Private institution	0	2	2	(2.2)
Total	4	89	93	(100)

also the number of residents on the basis of provinces. While the total number of professors in Turkey was 440, the top three provinces were found respectively as Istanbul (n= 148), Ankara (n= 94) and Izmir (n= 22). These three provinces, with a total of 264 professors, contain 60% of the professors in Turkey. On the other hand, these three provinces only constitute 33% of the country's population. There are no professors in 34 provinces and there is only one each in 10.

The total number of associate professors in our country was found as 324, and Istanbul (n= 89), Ankara (n= 71) and Izmir (n= 32) again comprise the top three provinces with the highest number of associate professors. While there are no associate professors in 38 provinces, there is only one each in 14 (Table 2). One hundred and twenty-one of the 237 surgeons with academic titles in Istanbul work for training clinics and 116 of them work for institutions that do not offer general surgery training. Overall in Turkey, a total of 221 surgeons with academic titles do not participate in training, and 175 (79.19%) work for private institutions, 11 for hospitals of the Ministry of Health and 35 in private institutions that do not have any training programs. 52.4% of the surgeons (116/221) that do not participate in training reside in Istanbul.

One professor and one associate professor are found in 6 provinces in our country. There are 20 residents in these 6 provinces in total and their distribution is as Van (n= 8), Batman (n= 0), Balikesir (n= 4), Kutahya (n= 4), Mugla (n= 3), and Amasya (n= 1). On the other hand, in 4 provinces with only one associate professor, there are three residents in total [Rize (n= 2), Erzincan (n= 1)] (Table 2).

When the number of specialists without any academic title is considered, these three provinces house 1223 specialists, and the ranking is as Istanbul (n= 772), Ankara (n= 258) and Izmir (n= 193). 38% of the general surgery specialist pool consisting 3193 specialists in Turkey are found in these three provinces comprising 33% of the population. In other words, 62% of the general surgery specialists without any academic title serve 67% of the Turkish population. While there are no provinces without a general surgery specialist, this number is 9 and lower than 9 in 25 provinces (Table 2).

While total number of residents in Turkey is 768, 433 (56%) of these are found in Istanbul (n= 223), Ankara (n= 149) and Izmir (n= 61), which make up of 33% of the population (Table 2).

When institutions with residents and those that provide residency training are scrutinized, it was seen that there were 4 surgical clinics without professors and associate professors. Moreover, it was also found that there were 5 surgical clinics without any professors that provided training with one associate professor (Table 2).

19.3% of a total of 3957 general surgeons have academic titles with 440 professors and 324 associate professors. In a general overview, the rate of general surgery specialists with academic titles (n= 764) and general surgery residents (n= 768) is close to 1:1.

General Surgery Specialist Pool in Turkey and Resident Support

General surgery specialist pool: As of April 2017, there are health institutions with 1498 beds. Eight hundred and seventy-eight (58.6%) of these are hospitals affiliated with the Ministry of Health and university hospitals constitute only 4.5% (Table 3).

The number of general surgery specialists in Turkey has been found as 3957 as of April 2017. General surgeons provide services in 1031 healthcare facilities in total, i.e. there is at least one general surgery specialist in 1031 healthcare facilities. Eight of the 467 hospital without a surgical specialist are university hospitals and these hospitals receive consultation services (Istanbul University Cardiology Institute, Ankara Baskent University Ayas Physical Therapy and Rehabilitation Center, Istanbul Medipol University Healthcare Training and Practice Center, Istanbul University Oncology Institute, Ankara Hacettepe University Medical School Ihsan Dogramaci Pediatric Hospital, Ankara Hacettepe University Medical School Oncology Hospital, Kars Kafkas University Healthcare Research and Practice Senter, Marmara University Neurologic Sciences Institute) (Table 4).

While 497 (48.2%) of the 1031 hospitals where general surgeons work is affiliated with the Ministry of Health, the private sector constitutes 46% of the hospitals employing general surgery specialists with 474 hospitals. Besides, patients are treated in only 60 (5.8%) university hospitals in the department of general surgery (Table 4).

Of the 3957 general surgery specialists employed in the indicated 1031 hospitals, 440 are professors and 324 are associate professors, and the number of actively working general surgery specialists without an academic title was found as 3193. A total of 2467 general surgery specialists are employed in institutions that do not offer training.

At the time of the study, a total of 938 hospitals that do not offer residency training but employ at least one general surgery specialist and 2467 general surgery specialists employed in these hospitals were probed into. Four hundred and seventy-two of the 938 healthcare facilities where service not training was taken as a basis belonged to the private sector and constituted 50.3% of the facilities with bed in which surgeons provided treatment (Table 5). Table 5 shows the 14 (1.5%) university hospitals that do not offer training but provide treatment.

In 120 of the 938 healthcare facilities that do not offer training, a total of 221 general surgeons with academic titles are employed and 83% of the 120 healthcare facilities comprise the private sector (Table 6). One hundred and twenty (15.7%) of the existing 764 general surgeons with academic titles work in the private sector. While 543 of the existing 764 general surgeons with academic titles provide residency training de facto, 221 physicians work in institutions that do not provide training. While the rate

Table 2. Provincial distribution of professors, associate professors and specialists and residents in general surgery specialty training program

Province	Professor	Associate professor	Specialist	Resident	Total
Adana	15	15	92	24	122
Adiyaman	0	0	17	1	17
Afyonkarahisar	1	0	19	5	20
Agrı	0	0	13	0	13
Amasya	1	1	7	1	9
Ankara	94	71	258	149	421
Antalya	12	11	105	27	128
Artvin	0	0	5	0	5
Aydin	5	2	45	4	52
Balikesir	1	1	44	4	46
Bilecik	0	0	4	0	4
Bingol	0	0	6	0	6
Bitlis	0	0	8	0	8
Bolu	2	2	18	5	22
Burdur	0	0	9	0	9
Bursa	10	3	119	18	132
Canakkale	2	1	29	3	32
Cankiri	0	0	4	0	4
Corum	3	0	16	3	19
Denizli	6	5	33	7	44
Diyarbakir	5	7	37	11	49
Edirne	2	5	20	12	27
Elazig	4	5	23	8	8
Erzincan	0	1	7	1	8
Erzurum	4	2	20	10	26
Eskisehir	6	0	45	8	51
Gaziantep	7	4	58	11	69
Giresun	0	2	13	0	15
Gumushane	0	0	5	0	5
Hakkari	0	0	8	0	8
Hatay	2	5	54	5	61
Isparta	3	0	21	10	24
Mersin	5	4	63	6	72
Istanbul	148	89	772	222	1009
Izmir	22	32	193	61	247
Kars	0	0	7	0	7
Kastamonu	0	0	9	0	9
Kayseri	5	1	51	17	57
Kirklareli	0	1	16	0	17
Kirsehir	2	0	12	1	14
Kocaeli	10	4	83	13	97
Konya	12	10	76	28	98

Table 2. Provincial distribution of professors, associate professors and specialists and residents in general surgery specialty training program (continue)

Province	Professor	Associate professor	Specialist	Resident	Total
Kutahya	1	1	21	4	23
Malatya	7	7	35	13	49
Manisa	5	3	54	5	62
Kahramanmaras	1	2	39	5	42
Mardin	0	0	17	0	17
Mugla	1	1	49	3	51
Mus	0	0	7	0	7
Nevsehir	0	0	8	0	8
Nigde	0	0	9	0	9
Ordu	0	0	30	0	30
Rize	0	1	11	2	12
Sakarya	2	3	37	10	42
Samsun	3	6	65	7	74
Siirt	0	0	7	0	7
Sinop	0	0	5	0	5
Sivas	6	2	19	6	27
Tekirdag	2	2	52	4	56
Tokat	2	0	18	3	20
Trabzon	7	5	28	10	40
Tunceli	0	0	3	0	3
Sanliurfa	1	0	42	3	43
Usak	1	2	12	0	15
Van	1	1	31	8	33
Yozgat	2	0	9	2	11
Zonguldak	4	1	16	5	21
Aksaray	0	0	10	0	10
Bayburt	0	0	2	0	2
Karaman	0	0	8	0	8
Kirikkale	2	1	7	3	10
Batman	1	1	17	0	19
Sirnak	0	0	10	0	10
Bartin	0	0	4	0	4
Ardahan	0	0	3	0	3
Igdir	0	0	5	0	5
Yalova	0	0	14	0	14
Karabuk	2	0	11	0	13
Kilis	0	0	5	0	5
Osmaniye	0	1	19	0	20
Duzce	0	0	10	0	10
Total	440	324	3193	768	3931

Table 3. Distribution of healthcare institutions with beds in Turkey

Type of Institution	n	%
Ministry of Health	878	58.6
University	68	4.5
Private institution	552	36.8
Total	1498	100

Table 4. Distribution of healthcare institutions with beds that employ general surgery specialist

Type of institution	General surgeon presence		Total
	None	Present	
Ministry of Health	381	497	878
University	8	60	68
Private	78	474	552
Total	467	1031	1498

Table 5. Distribution of institutions with beds having a healthcare-service hospital objective that employ general surgery specialist but do not offer training

Type of Institution	n	%
Ministry of Health	452	48.2
University	14	1.5
Private	472	50.3
Total	938	100

Table 6. Number of general surgeons with academic titles working in hospitals that do not offer training

Type of institution	None	Present	Total
Ministry of Health	444	8 (6.7%)	452
University	2	12 (10%)	14
Private	372	100 (83.3%)	472
Total	818	120 (100%)	938

of surgeons with academic titles in 472 private institutions of the 938 service hospitals is 21.2% (100/472), this rate is 1.8% in hospitals affiliated with the Ministry of Health (8/452) and 85.7% in university hospitals (12/14).

General surgery specialty resident support: The vacancies opened for general surgery specialty between 2007-2017 in Turkey and the number of specialists given for these years were 1258 and 931, respectively. Three hundred and twenty-seven physicians completing their 6-year university education and then gaining the privilege to general surgery residency with the examination resigned from the general surgery department by not completing the residency. The commencement and completion rate of the general surgery training program was found as 74%.

When the status of the residents receiving training at the present time is evaluated, there are a total of 768 residents, of whom 433 (56.38%) receive training in three provinces [Ankara (n= 149), Istanbul (n= 223) and Izmir (n= 61)]. In the evaluation of the number of teachers per residents, the rate was found as 5.0 in a private hospital where 5 teachers and one resident were employed during the collection of data; however, the resident was found to have left this institution during the research carried out for the interpretation of the data. This resident was excluded not to corrupt data soundness. Following this, 2 teachers per resident were found only in two healthcare institutions. These two institutions are Amasya University Sabuncuoglu Serefeddin Training and Research Hospital and Kirsehir Ahi Evran University Kirsehir Training and Research Hospital. It has been found as of the study date that there are no teachers in Adiyaman, Erzurum, Kocaeli and Mogadishu training clinics. A total of 543 physicians with academic titles provide training for 768 residents and the

teacher per resident mean was found as 0.71(543/768) for Turkey. Following the omission of the general surgeons with academic careers employed in institutions that do not offer training from the pool of 746 general surgeons with academic titles in Turkey, the number of teachers per resident was found as 119/149=0.798 for Ankara, 121/222=0.545 for Istanbul and 48/61=0.786 for Izmir. The same number was found as 255/336=0.758 for other provinces. Table 7 presents the number of residents under training according to years. In the last ten years, 2162 physicians have completed or are still continuing their residency training.

Besides the general surgery specialty, a central examination is performed for all specialties. Tables 8 and 9 show the preferences and scores related to these exam results. The fact that score averages of those placed in a specialty program but did not complete or even did not start the program are higher than those that started and continued a program is another important matter to be approached in a study.

Changes in the General Surgery Specialist Pool on the Basis of Provinces

As of April 2017, the number of specialists working de facto in Turkey is 3957. While the number of general surgery specialists in the last ten years increased by a number of 409 specialists, redundant physician number according to 1/25.000 rate was found as 725 (Table 10). The highest redundancy numbers of general surgeons were found in Istanbul and Ankara, and the highest vacancies were found in Sanliurfa and Diyarbakir, respectively (Table 10). As of 2017, surgeon rate for Turkey according to 1/25.000 rate was found as 1.22/25.000. Regarding the ideal rate, there is still a 22% surgeon redundancy in Turkey.

DISCUSSION

The history of surgical association in Turkey dates back to 1929 when the Turkish Surgical Society was founded. Following the 1980 military coup that shut down all associations, it was founded as the National Surgical Association in 1982 and named as Turkish Surgical Association in 1997. Since its establishment, studies in all related fields have been conducted for the improvement of surgery in every sense.

"Employment", which did not have any priority in the studies of the association due to lack of physicians nationwide in the past years, has become an important issue by putting forth the need to keep the pool of general surgeons in an appropriate balance with the newly founded educational institutions. This balance constitutes two major elements. The first is the ideal number of general surgeons for the country's population and the second is the provision of the appropriate distribution of the appropriate number of general surgeons regarding population according to the number of surgeons foreseen for unit population. In order to obtain all, it is mandatory to plan the number of surgeons retiring and the number of those joining the profession at a balance paying regard to the population of the country. Studies on general surgery manpower started with a report by Sayek at al. in 1990 (7). Afterwards, these studies continued with

Table 7. Number of residents accepted for residency training with the central examination according to years

Years	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
n	256	312	288	106	133	163	147	139	196	200	222

Table 8. Clinical score average according to the status of attendancy to residency training

Status of residency	2017 Spring		2017 Fall	
	Number of candidates	Average clinical score	Number of candidates	Average clinical score
Continues residency training	638	52.92	517	51.92
Resigned while continuing residency training	163	53.62	77	52.33
Had not started a program though placed in a residency	292	54.20	447	51.56
Total	1093		1041	

Table 9. Resident vacancies opened for general surgery specialty in the Examination for Specialty in Medicine and the number of specialty physicians in the last ten years

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Vacancies	256	312	288	106	133	163	147	139	196	200	222	2162
Number of specialty physicians	153	212	200	212	178	213	153	208	122	98	137	1733

Table 10. Number of surgeons that should have been found in 2007 and 2007 according to provinces and the current number as of 2017 and rate of redundancy

			A	B	B – A	C	C – B
Provinces According to licence plate	**Population 2007**	**Population 2017**	**1/25.000 2007**	**1/25.000 2017**	**1/25.000 Based difference**	**Current surgeon number 2017**	**Redundancy 2017**
Adana	2.006.650	2.216.475	80.3	88.7	8	122	33
Adiyaman	582.762	615.076	23.3	24.6	1	17	-8
Afyonkarahisar	701.572	715.693	28.1	28.6	1	20	-9
Agri	530.879	536.285	21.2	21.5	0	13	-8
Amasya	328.674	329.888	13.1	13.2	0	9	-4
Ankara	4.466.756	5.445.026	178.7	217.8	39	423	205
Antalya	1.789.295	2.364.396	71.6	94.6	23	128	33
Artvin	168.092	166.143	6.7	6.6	0	5	-2
Aydin	946.971	1.080.839	37.9	43.2	5	52	9
Balikesir	1.118.313	1.204.824	44.7	48.2	3	46	-2
Bilecik	203.777	221.693	8.2	8.9	1	4	-5
Bingol	251.552	273.354	10.1	10.9	1	6	-5
Bitlis	327.886	341.474	13.1	13.7	1	8	-6
Bolu	270.417	303.184	10.8	12.1	1	22	10
Burdur	251.181	264.779	10.0	10.6	1	9	-2
Bursa	2.439.876	2.936.803	97.6	117.5	20	132	15
Canakkale	476.128	530.417	19.0	21.2	2	32	11
Cankiri	174.012	186.074	7.0	7.4	0	4	-3
Corum	549.828	528.422	22.0	21.1	-1	19	-2
Denizli	907.325	1.018.735	36.3	40.7	4	44	3
Diyarbakir	1.460.714	1.699.901	58.4	68.0	10	49	-19
Edirne	396.462	406.855	15.9	16.3	0	27	11
Elazig	541.258	583.671	21.7	23.3	2	32	9
Erzincan	213.538	231.511	8.5	9.3	1	8	-1
Erzurum	784.941	760.476	31.4	30.4	-1	26	-4
Eskisehir	724.849	860.620	29.0	34.4	5	51	17
Gaziantep	1.560.023	2.005.515	62.4	80.2	18	69	-11
Giresun	417.505	437.393	16.7	17.5	1	15	-2
Gumushane	130.825	170.173	5.2	6.8	2	5	-2
Hakkari	246.469	275.761	9.9	11.0	1	8	-3
Hatay	1.386.224	1.575.226	55.4	63.0	8	61	-2
Isparta	419.845	433.830	16.8	17.4	1	24	7
Mersin	1.595.938	1.793.931	63.8	71.8	8	72	0
Istanbul	12.573.836	15.029.231	503.0	601.2	98	1009	408
Izmir	3.739.353	4.279.677	149.6	171.2	22	247	76
Kars	312.205	287.654	12.5	11.5	-1	7	-5
Kastamonu	360.366	372.373	14.4	14.9	0	9	-6
Kayseri	1.165.088	1.376.722	46.6	55.1	8	57	2

Table 10. Number of surgeons that should have been found in 2007 and 2007 according to provinces and the current number as of 2017 and rate of redundancy (continue)

			A	B	B – A	C	C – B
Provinces According to licence plate	**Population 2007**	**Population 2017**	**1/25.000 2007**	**1/25.000 2017**	**1/25.000 Based difference**	**Current surgeon number 2017**	**Redundancy 2017**
Kirklareli	333.256	356.050	13.3	14.2	1	17	3
Kirsehir	223.170	234.529	8.9	9.4	0	14	5
Kocaeli	1.437.926	1.883.270	57.5	75.3	18	97	22
Konya	1.959.082	2.180.149	78.4	87.2	9	98	11
Kutahya	583.910	572.256	23.4	22.9	0	23	0
Malatya	722.065	786.676	28.9	31.5	3	49	18
Manisa	1.319.920	1.413.041	52.8	56.5	4	62	5
Kahramanmaras	1.004.414	1.127.623	40.2	45.1	5	42	-3
Mardin	745.778	809.719	29.8	32.4	3	17	-15
Mugla	766.156	938.751	30.6	37.6	7	51	13
Mus	405.509	404.544	16.2	16.2	0	7	-9
Nevsehir	280.058	292.365	11.2	11.7	0	8	-4
Nigde	331.677	352.727	13.3	14.1	1	9	-5
Ordu	715.409	742.341	28.6	29.7	1	30	0
Rize	316.252	331.041	12.7	13.2	1	12	-1
Sakarya	835.222	990.214	33.4	39.6	6	42	2
Samsun	1.228.959	1.312.990	49.2	52.5	3	74	21
Siirt	291.528	324.394	11.7	13.0	1	7	-6
Sinop	198.412	207.427	7.9	8.3	0	5	-3
Sivas	638.464	621.301	25.5	24.9	-1	27	2
Tekirdag	728.396	1.005.463	29.1	40.2	11	56	16
Tokat	620.722	602.086	24.8	24.1	-1	20	-4
Trabzon	740.569	786.326	2.6	31.5	2	40	9
Tunceli	84.022	82.498	3.4	3.3	0	3	0
Sanliurfa	1.523.099	1.985.753	60.9	79.4	19	43	-36
Usak	334.115	364.971	13.4	14.6	1	15	0
Van	979.671	1.106.891	39.2	44.3	5	33	-11
Yozgat	492.127	418.650	19.7	16.7	-3	11	-6
Zonguldak	615.890	596.892	24.6	23.9	-1	21	-3
Aksaray	366.109	402.404	14.6	16.1	1	10	-6
Bayburt	76.609	80.417	3.1	3.2	0	2	-1
Karaman	226.049	246.672	9.0	9.9	1	8	-2
Kirikkale	280.234	278.749	11.2	11.1	0	10	-1
Batman	472.487	585.252	18.9	23.4	5	19	-4
Sirnak	416.001	503.236	16.6	20.1	3	10	-10
Bartin	182.131	193.577	7.3	7.7	0	4	-4
Ardahan	112.721	97.096	4.5	3.9	-1	3	-1
Igdir	181.866	194.775	7.3	7.8	1	5	-3

Table 10. Number of surgeons that should have been found in 2007 and 2007 according to provinces and the current number as of 2017 and rate of redundancy (continue)

			A	B	B – A	C	C – B
Provinces According to licence plate	**Population 2007**	**Population 2017**	**1/25.000 2007**	**1/25.000 2017**	**1/25.000 Based difference**	**Current surgeon number 2017**	**Redundancy 2017**
Yalova	181.758	251.203	7.3	10.0	3	14	4
Karabuk	218.463	244.453	8.7	9.8	1	13	3
Kilis	118.457	136.319	4.7	5.5	1	5	0
Osmaniye	452.880	527.724	18.1	21.1	3	20	-1
Duzce	323.328	377.610	12.9	15.1	2	10	-5
Total	70.586.256	80.810.525	2823.5	3232.4	409	3957	725

A: 2007 need with 1/25.000 population rate, B: 2017 need with 1/25.000 rate, C: The current number of specialists as of 2017 in that province, C – B: The difference between the number of surgeons needed and the currently employed surgeons as of 2017.

those by Başkan and Terzi (1,8). A report prepared by 2007 data was published the very last (1). This study will be valuable for evaluating the studies conducted in 2007 and making predictions for subsequent years.

It is important in the planning of general surgery manpower that physicians graduating from medical school receive training in the field of general surgery. Along with replacing those that retire from the profession, meeting the surgeon need according to the increasing population is directly related to the number of physicians accepted for training. As of April 2017, residency training in general surgery is being given in a total of 93 healthcare facilities with beds in Turkey.

Beside 60% of all professors work in Istanbul, Ankara and Izmir and the rate of these provinces in the Turkish population is 33%, it is significant that there are no professors in 34 provinces (41.9%) of the 81 provinces and that there is only one professor in ten provinces. In the evaluation of associate professors, 59% of the associate professors are found in these three provinces, there are no associate professors in 38 provinces and there is only one associate professor in 14 (17.3%) provinces. 56.26% (432/768) of the residents currently in training are found in these three provinces. Teacher rate per resident for these three provinces is 1.77, which is more than twofold of the average in Turkey. However, the fact that general surgeons with academic titles do not work for training clinics prevent the rise to these rates. With the calculations made following the exclusion of the surgeons with academic titles that do not participate in training, Istanbul becomes prominent as the province where residency training is conducted with the least teachers, having received a score under the average of Turkey and the average of these three provinces.

In the 2004 study of our association, while there were 52 clinic chiefs, 255 professors, 76 associate professors, 76 assistant professors, 22 lecturers, 68 deputy chiefs, and 48 chief residents nationwide, the number of specialists without an academic title was given as 323 and the number of residents was found as 943. The calculation performed using the data of the study revealed that the number of teachers per resident was 0.54 (510/943) (8). Only the numbers of three provinces were provided in the 2007 study. Professor and associate professor were not scrutinized for the training and research hospitals of these provinces and the number was given only for university hospitals. Again, since the number of residents was not given in the 2007 study, an assessment regarding the number of residents could not be performed (1). It was presented in the 2007 report that there were 182 professors, 53 associate professors, 27 assistant professors, 11 lecturers, 30 specialists, and 244 residents in Ankara, Istanbul and Izmir (1). While the number of professors of these three provinces increased 82, the number of associate professors increased 139.

Comparing the study by Baskan et al. in 2004, it can be seen that the number of teachers per residents has increased. However, it would be wrong to interpret and explain this picture with the increase in teachers. The report of Terzi and colleagues has put forth that *there is no deficiency in the number of general surgery specialists in Turkey but there is a problem with their distribution* (1). In order not to create an abundancy of general surgery specialists, meetings with the institutions indicated an arrangement that would decrease the number of general surgery residency positions in the Examination for Specialty in Medicine. In the end, *the number of teachers per residents was positively increased by correcting two parameters*.

This matter will not be thoroughly addressed since it is not the aim of the present study. However, matters like how many teachers should be present in a training institution and what should be done in the absence of a teacher must be investigated. Moreover, due to the fact that the aim of the present study is to assert the sufficiency of the number of general surgery specialists nationwide, to evaluate the reflection of the work carried out pursuant

to the 2007 study and to present the distribution of specialists, matter of academics-teacher-the sufficiency of the training institution will not be discussed in this study.

83% of the institutions where physicians with academic titles work is private ones. We are of the opinion that the physicians working in these private institutions prefer the private sector owing to the fact that working conditions are more appealing that those of the training institutions. *The deterioration of both physical, legal and social conditions of the general surgeons incline them to work for private institutions*. The same goes for many Western and Eastern countries, not just Turkey (4,6,9,10). A similar situation like the shift to the private sector from academy is observed in the specialty preference of the physicians graduating from medical school (11,12). The 2017 spring exam results of the Examination for Specialty in Medicine reveal that while 50% of the candidates received 47 points and higher in Basic Medical Sciences Test (BMST), a 10% fraction received 81.25 points and higher. In the Clinical Medical Sciences Test of the same examination, 50% of the candidates scored 54 points and higher. This number indicates that clinical sciences are taught more commonly and the top 10% starts with a score of 75 and increases. In other words, 40% of the candidates succeeded with a score between 54-75. Correct answer to 34 surgery related questions was 15.51 and was lower than internal medicine (21.91/40). The fact that 1093 candidates qualifying for clinical medical branches re-took the examination is of serious concern and scrutiny (Table 8). In the Spring 2017 examination, General Surgery was preferred by 114 physicians, the average score obtained was 52.53 and among 35 clinical specialties, General Surgery ranked the 30th (11).

In the order of preference for the 2017 fall examination, general surgery was preferred by 113 physicians and ranked 29th among 35 clinical specialties with an average score of 55.33 (12). In both periods, the number one medical branch preferred with the highest score average was Dermatological and Venereal Diseases (11,12). Similar to other countries, *the preferability priority of general surgery as a specialty regresses in Turkey*. Along with the investigation of the reluctance of medical school graduates to general surgery, the reasons behind the physicians starting residency to leave the profession should also be examined (Table 9). Between 2007 and 2017 327 physicians left without completing their residency training and the completion rate in reference to the vacancies opened was 74%. The reasons for not completing the residency period and leaving the program for this 26% of the physicians must be reviewed, their rationale must be corrected and the profession should be made more appealing. Since there are no studies conducted on this matter, as a personal opinion, the authors of this article believe that economic and social conditions as well as the inappropriate working hours can be the reasons for leaving the program. Furthermore, another reason for the reluctancy towards general surgery may have its roots in the recently effectuated malpractice applications that do not have any grounded basis. Another matter to be kept in mind is the lack of concrete steps taken towards "violence against physicians", which leads to a decrease in the demand on the profession. Alarms are ringing for Turkey as regards general surgery since it ranked 29th and 30th among 35 specialties and physicians leave the residency period at a rate of 26%. Following the completion of this article, significant studies will be commenced before the Ministry of Health and related institutions.

General Surgery Specialist Pool in Turkey and Resident Support

In the 2004 study of our association, the number of actively working specialists was not provided. In 2009, Terzi and colleagues reported 3594 actively working specialists nationwide.

As of April 2017, 58.6% of the healthcare institutions with beds are affiliated with the Ministry of Health (Table 3). Practical problems occur when the Ministry of Health bothj determines policies in the health management of the country and turn it into service. When red tape is considered in the public offices despite valid reasons contained within, processes advance slowly and are delayed or even cancelled in many phases. Whereas, the private sector can act faster taking into account the profit/loss rate. Besides that, it is obvious that there are difficulties in public offices because of personnel regime and bureaucratic rules and practices in decision-making. It is known that the public office cannot do planning as easily as the private sector since civil servants have a responsibility of representing the state and the state has a responsibility of serving its citizens. In the meantime, as of April 2017, the number of general surgery specialists in Turkey is 3957 and the number of healthcare facilities giving service is 1031.

More surgeons treat patients in more hospitals affiliated with the Ministry of Health. When the number of surgeries is added to the calculation, the sector that provides the most and the quality of the provided service will be revealed. For, the type of surgeries is as significant as the number of surgeries performed. A study investigating the type and number of surgeries performed by the general surgery clinics of healthcare institutions and training hospitals should be carried out with a thorough research.

The number of specialists without an academic title working in the designated 1031 hospitals was found as 3193. With the exclusion of the specialists working in training hospitals, 2467 general surgery specialists were found to be working in 938 healthcare institutions that act as a health-service hospital. 50.3% of these healthcare facilities whose essence is to serve are private institutions. In 120 of these 938 healthcare facilities that do not offer training employ general surgeons with academic titles, and 83% (100/120) of the health-service hospitals employing surgeons with academic titles belong to the private sector (Table 6). 28.93% of the 764 general surgeons with academic titles work without

contributing to the training of residents. The reasons behind the 175 surgeons with academic titles to work in the private sector should be investigated. It is a known fact that general surgery specialty necessitates going through a difficult training period and using public resources substantially. Training academics that would offer their expertise in training residents is a much longer, more troublesome and costly process. Even though it is not in the scope and aim of this study, the fact that 28.93% general surgery specialty teachers are actively working outside training institutions should be investigated for professional reasons. There is a need for serious and practical projects and applications to keep these teachers of outmost significance in universities or affiliated training hospitals.

When the status of the residents currently under training is assessed, there are 768 residents in total and of these, 430 (55.9%) are located in Ankara (n= 149), Istanbul (n= 222) and Izmir (n= 61). The number of teachers per residents is 119/149=0.798 for Ankara, 121/222=0.545 *for Istanbul* and 48/61=0.786 for Izmir. This number was found as 255/336=0.758 for other provinces. Out of the 1258 medical school graduates accepted for training between 2007 and 2012, the number of those completing the training period and joining the pool of general surgeons between 2012 and 2017 was 931. Compared to the vacancies opened, 25.99% of the residents (327 residents) left the program. It is obvious that close evaluation of the working conditions and the status of the professionals actively engaged in the profession is highly effective in this situation. However, there is no study from our country regarding this issue. Studies from Taiwan to Ireland have indicated that there is a reluctancy towards not just general surgery but to other surgical departments as well (6,10). As stated in the previous report, working conditions that are not meliorated, physical and psychological violence against physicians, unrighteous outcomes of the malpractice regulation that mostly aggrieves the physicians are unquestionably effective. A study scrutinizing this matter should be carried out urgently and necessary measures should be taken. Otherwise, general surgery will rank lower in the Examination for Specialty in Medicine and there may even be vacancies that are not selected (11,12). In fact, the rate of dropping out of residency training, which is 25.99%, appears as vacated placements (Table 9). The renouncement of placements decreases the success chance of further projections.

Projection with 2007 Data and Its Comparison with 2017

Terzi and colleagues emphasized in their study with 2007 data that there was no need of general surgeons in our country but the need to arrange their distribution was paramount. In the study, 1.27/25.000 surgeons were present in Turkey. A 2011 study conducted in the USA revealed that there were problems with both the number and the distribution of surgeons. For instance, in District of Colombia, there were 31.08 general surgeons per 100.000 population (7.77/25.000) but in Nevada, this number was 6.55 (1.63/25.000) (9). When the change in the rate of general surgeons per 100.000 population was evaluated on the basis of states, it was seen that the number of surgeons was diminished in all states except 7.

In a study investigating surgeon distributions, it has been reported that in comparison to family physicians, the distribution of general surgeons is more irregular (5).

"Critical" scarcity limit for the number of general surgeons has been reported in various studies as 0.75/25.000 and 1/25.000 is regarded as the minimum and 1.5/25.000 is regarded as the ideal number of general surgeons (3,13). When hospital service area is considered for the USA again, it is seen that 28% of the hospitals employ 0.75 or lesser general surgeons per 25.000 population.

There is not an exact rate for the United Kingdom. It was noted that the goal should be 1/30.000 when there was 1/50.000 surgeon before. When the targeted rate was exceeded due to the failure in planning, ideal number was set as 1/20.000 and a balance was tried to be accomplished (4). Despite this, the number and distribution of general surgeons is still problematic in England and Ireland (4).

The basic reason for the irregularity in the distribution of general surgeons in the USA is the malpractice suits executed without adequate descriptions and having uncontrolled sub-specialty. Wages policy has also been effective in this situation. A 10% wage differential was brought to the surgeons in the USA; however, this policy which was put forth without considering the infrastructure and capabilities of the hospitals they worked in has brought along the fact that these surgeries with wage differential could not be performed in desired places (5). In short, unless social rights besides the environment and conditions are made more inviting, these places cannot be made appealing with financial support and these surgeons cannot be forced to operate in these places. Again in our country, the concept of "specialized surgeries" has been defined to increase the interest towards surgery and to make financial regulations and physicians performing these surgeries have been tried to gain the upper hand. These surgeries, for the general surgery specialty, have become lacking, insufficient in number and turned out to be surgeries that cannot be performed in many hospitals, just as the example seen in the USA. In short, we can see that there was no field success achieved with the scores of the Examination for Specialty in Medicine and with the presence of a 26% rate of drop out residents.

Besides, it has been noted that the work environment and work quality of the surgeons should be meliorated. General surgery planning should be made as a team. What is intended here is that there should be sufficient number of clinical allied health personnel and support personnel as well as surgical nurse, anesthesiologist and support personnel. Same-day surgery should be given special care and priority so that it can have a positive effect on patient cycle. Another point is made to the danger of

sub-branching in our country. It is recommended that a single and corresponding data system be used by all state hospitals. The working hours, shifts and working conditions of general surgery specialists and residents must be improved.

Improvement can be seen in the number of shifts and working conditions for city hospitals taking into consideration the number of residents, and their results will be evaluated in the upcoming ten years.

In conclusion, the number of general surgeons and the rate of medical school graduates preferring general surgery are decreasing due to the indicated similar incorrect policies (6,10). In our country, preference priority of general surgery in the Examination for Specialty in Medicine has unfortunately ranked lower in our country.

The Effect of 2007 Projection on 2017

It was clearly stated in 2007 that the number of general surgery specialists in our country was 1.27 per 25.000 population. Along with this number, it was also noted that there was a problem with the distribution of the surgeons and not with the quantity. It was reported that an arrangement in the distribution of the surgeons would compensate the relative deficiency in regions lacking surgeons. The population of Turkey rose 10.224.269 from 2007 and 2017. Parallel to this increase, the pool of general surgeons also increased by 363 persons. If it were ideal, 408 surgeons would be added to the pool based on the ideal rate of 1/25.000. Whereas in reality, the general surgeon pool of Turkey was found as 1.27 per 25.000 in a calculation considering the number to be 1 surgeon per 25.000 population in 2007. While this number points that there are 1.27 surgeons per 25.000 population, as a result of the planning made and the diminished general surgery resident number, the number of general surgeons was decreased to 768 from 1005 but the ideal increase in the number of specialists was 363 not 408, the ideal quantity. In the end, general surgery specialist inflation was prevented by dropping the number to 1.22 from 1.27 and positive result was received for its improvement.

According to the data of the Turkish Statistical Institute, population growth rate continues with decreasing acceleration. According to calculations, the expected population for 2022 and 2027 is 83.540.076 and 86.776.550, respectively. Reaching its highest limit in 2050 with a population of 93.475.575, the population is expected to decrease following this year (14). The number of surgeons per 25.000 with a total of 3957 surgeons is 1.22. In the event of preserving the current number of residents and if the increase in the number of general surgeons supposedly stays the same (363 surgeons), it can be concluded that 4139 and 4320 surgeons will be achieved in 2022 and 2027, respectively, which means that there will be 1.2386 and 1.2445 surgeons per 25.000 in 2022 and 2027, respectively. It is concluded by preserving the current increase in the number of surgeons and the decrease in the population growth rate that the number of surgeons that showed a decrease in the past 10 years will go through a period of increase again. In this case, it is without doubt that a decrease in the number of residents is mandatory. Physician workload is excessive in General Surgery training clinics and reducing the number of residents may not be welcomed by the teachers in these clinics. The fact that city hospitals will bring the dispersed general surgery training clinics in big provinces and provide a more fruitful and efficient workforce can eliminate these concerns.

CONCLUSION

General surgery training is difficult, expensive and troublesome. Suitable teachers and persistence are mandatory in quality general surgery training. There is a need for urgent arrangements to ensure that teachers stay in training institutions. These urgent arrangements for Turkey are necessary due to the fact that significant number of teachers leave, residents in substantial numbers leave the training program and general surgery is among the least preferred specialties. Working conditions of the general surgeons must be improved, economic concerns must be eliminated and their lawful rights and protection must be provided. This is the best possible way to keep the general surgeon pool in balance both in number and in quality.

The results of this study will be shared with the Ministry of Health and other related institutions, and effort will be shown to make the necessary improvements.

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ORİJİNAL ÇALIŞMA-ÖZET
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Türkiye'de Genel Cerrahi Uzmanlığı: İş Gücünde Güncel Durum, Nitelik ve Nicelikte Sürdürülebilirlik

Ahmet Çınar Yastı[1], Ahmet Deniz Uçar[2], Murat Kendirci[3]

[1] Sağlık Bilimleri Üniversitesi, Genel Cerrahi Anabilim Dalı, Ankara, Türkiye
[2] Bozyaka Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye
[3] Hitit Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Çorum, Türkiye

ÖZET

Giriş ve Amaç: Tıbbın en eski ve ana dallarından birisi olan Genel Cerrahi uzmanlığı eğitimi, uzun, pahalı ve zahmetli bir süreçtir. Kısıtlı kaynakların akılcı kullanımı ilkesi yanında bir meslek olarak Genel Cerrahinin uzmanı sayısının olması gereken seviyede ve kalitede tutulabilmesi için ileriye dönük ulusal planlamalara ihtiyaç vardır. Bu çalışma ülkemizdeki Genel Cerrah hekim iş gücü, sayısı, dağılımı ve çalışma koşullarının tespitini takiben kaliteli uzman yetiştirilmesi ve en iyi şartlarda sürdürülebilirliğinin temini için yapılmıştır.

Gereç ve Yöntem: Ülkemizde 2017 yılı sonu itibarı ile kamu, özel sektör ve üniversite tıp fakülteleri hastanelerinde faal olarak çalışan Genel Cerrahi uzmanı (profesör, doçent, uzman veya genel cerrahi yan dal uzmanı) ve asistan (araştırma görevlisi) sayıları irdelenmiştir. Bu sayılar illere, akademik unvanlara ve asistan sayılarına göre çapraz değerlendirmelere tabii tutulmuştur. Türkiye İstatistik Kurumu nüfus verilerine ve tahminlerine göre halihazırda Genel Cerrah sayılarının nüfusa oranları, önümüzdeki beş ve 10 yılda gerçekleşecek tahmini oranları hesaplanmıştır.

Bulgular: Ülkemizde 2017 yılı sonu itibarı ile 1499 sağlık tesisinin 1031'inde 3957 Genel Cerrahi uzmanı aktif çalışmaktadır. Bunların 440'ı profesör, 324'ü doçent unvanlıdır. Her 25 bin kişiye 1,22 cerrah düşmektedir. Bu oran 10 yıl önce 1,27 olarak bulunmuştu. On yıl önce 1005 olan asistan sayısının günümüzde 768'e düşmüş olmasına rağmen uzman sayısı 409 artış göstermiştir.

Sonuç: Ülkemizde Genel Cerrah sayısı ideal oran olan 25 bin kişiye bir sayısının üzerindedir. Nüfus artış hızındaki azalma dikkate alındığında, son 10 yıldaki Genel Cerrah artış hızının korunması durumunda 25 bin kişiye düşen cerrah sayısında kontrolsüz bir şekilde artış olacaktır. Ülkemizde akademik unvanlı olsun olmasın Genel Cerrahi uzmanı dağılımı dengeli olmadığı gibi asistan başına düşen eğitici sayısı da fazladır.

Anahtar Kelimeler: Genel cerrahi, iş gücü, kalite, kantite

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ORIGINAL ARTICLE
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Thymoquinone reduces ischemia and reperfusion-induced intestinal injury in rats, through anti-oxidative and anti-inflammatory effects

Ali Parlar[1](ID), Seyfullah Oktay Arslan[2](ID)

[1] Department of Medical Pharmacology, Adiyaman University School of Medicine, Adiyaman, Turkey
[2] Department of Medical Pharmacology, Ankara Yildirim Beyazit University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: The aim of the present study was to investigate the effect of thymoquinone on ischemia/reperfusion (I/R) injury at 150 min or/and 24 h of reperfusion in male Wistar Rats.

Material and Methods: The therapeutic value of thymoquinone on cellular damage caused by reactive oxygene species or inflammatory processes during intestinal ischemia/reperfusion was investigated using pharmacological function studies on smooth muscle contractile responses of acetylcholine (Ach) and KCl, along with myeloperoxidase activity, malondialdehyhde, glutathione and cytokine levels such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β in serum and ileum tissue of rats. Thymoquinone was administered at a dose of 50 mg/kg orally for three times: 30 min, 24 h and 48 h prior to the surgical procedure. Soon after reperfusion timing (150 min or 24 h), the contractility traces to KCl and acetylcholine of the ileum smooth muscle were recorded through isolated organ bath.

Results: Pretreatment with thymoquinone reversed the disrupted contractility of the ileum smooth muscle at the 24 h reperfusion. Increased malondialdehyde and depleted glutathione levels and high myeloperoxidase activity determined in the ileum I/R tissue returned to reasonable amounts by pretreatment of Thymoquinone, which attenuated malondialdehyde quantity, restored glutathione level and inhibited myeloperoxidase activity. In addition, both serum and tissue TNF-α and IL-1β activities were modulated by thymoquinone at 24 h of intestinal I/R.

Conclusion: The results indicate that thymoquinone may have therapeutic value due to its immunomodulating, radical scavenging and/or antioxidant effects in intestinal I/R injury including oxidant damage mechanisms.

Keywords: Thymoquinone, intestinal ischemia and reperfusion, ileum smooth muscle contractility, cytokines, oxidative injury

* The research was discussed at the fifth International Congress of Turkish Society of Pharmacology, 2013, Antalya, Turkey.

INTRODUCTION

Ischemia due to insufficient blood supply to tissues results in cellular function failure; however, reperfusion exacerbates the ischemic damage more. Actually, the intestinal tissue is quite sensitive to ischemia/reperfusion (I/R) through mesenteric artery. Cellular damages during surgical procedures or pathological conditions including bowel transplantation, acute mesenteric ischemia, abdominal aortic aneurysm, and shock are remarked as the main causes of intestinal I/R injury. Increased protein extravasations, disruption of mucosal barrier, decreased contractile activity, and impairment of gut motility are clearly observed with intestinal I/R (1). The activation of inflammatory cells such as polymorphonuclear leukocytes leads to fast exagreation of the onset of inflammatory reaction. Previous studies have shown that in the pathologenesis of I/R, there is an increase in the amounts of reactive oxygen and nitrogen species, cytokines, endotoxins, and neutrophils (2-4). Several studies have also demonstrated that neutrophils, adhesive molecules and endothelial cells are responsible for serious and deleterious cellular inflammatory dysfunction caused by intestinal I/R injury (3,4). It is well known that the produced reactive oxygen or nitrogen species and oxidative damage are the main responsibles of cell death and organ dysfunction in intestinal I/R (3,5).

Thymoquinone (TQ; 2-isopropyl-5-methyl-1,4-benzoquinone) is a therapeutically active chemical structure of the essential and fixed oil obtained from Nigella sativa

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Corresponding Author
Seyfullah Oktay Arslan
E-mail: soarslan@gmail.com

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seeds. Recently, data have addressed on its in vivo and in vitro pharmacotherapeutic effects (6). Its antioxidant, anti-inflammatory or immunmodulatory actions have been revealed in several disease models (7-11), as well as in gastric ulcer caused by I/R (9). Moreover, TQ has been shown to inhibit the accumulation of inflammatory cells in bronchial alveolar fluid (BALF) and lung tissue (12). In a study of Tas et al., TQ has been found to cause decreased levels of malondialdehyde (MDA) in ischemia-reperfusion injury while increasing the level of glutathione (GSH) (13). A recent study reveals that TQ reverses cytokine increases such as tumor necrosis factor (TNF)-α and interleukin (IL)s caused by I/R in both serum and intestinal tissue (13).

For all reasons, it is to prove the hypothesis that the antioxidant and antiinflammatory role of TQ in I/R injury will reduce injury of intestinal ischemia reperfusion. Therefore, this research was planned to reveal the effect of TQ on intestinal I/R.

MATERIAL and METHODS

Animals

This study was conducted with forty-eight male Wistar-albino rats weighing 200-250 g in Experimental Research Section of Duzce University. The approval of the animal ethical committee of Duzce University was taken with the number: 2011/009.

Thymoquinone Treatment

All chemicals used in the study was obtained from Sigma (USA) and was prepared with 1% Tween 80 to be administered orally. TQ (50 mg/kg of body weight per day) or gavage canula (1 mL) was given orally once a day for 3 days before surgery and 30 min before surgical procedures (n= 8). The dose of TQ was administered as done by El-Abhar et al. in their study (14).

Experimental Protocols of Induction of Ischemia/Reperfusion in Intestinal Tissue

Intestinal I/R was performed as described previously (3). Briefly, under sodium thiopental anaesthetize midline laparotomy was performed, the small intestine was gently naked with humid sterile gauze to block dehydration. After I/R was performed through the occlusion of superior mesenteric artery with a 30-minute schedule using microvascular clamp, ileum was perfused by 150 min. Loss of pulsation and coloration in the bowel was observed in the ischemia period. To let blood flow to the intestines, the clamp was opened gently at the end of 30 minutes. In the experimental protocol, groups were divided as follows:

I. Sham group (n= 16): The rats underwent laparotomy, without ischemia/reperfusion, remained open until the ischemia/reperfusion period or after 30 minutes of follow-up, the abdominal wall was sutured.

II. I/R-vehicle group without any treated (n= 16): First, the superior mesenteric artery was occluded with clamp for 30 min and then ischemia was started. Immediately 150 minutes or 24 h reperfusion was performed and this procedure was also done for the I/R-vehicle after vehicle was given.

III. I/R and TQ-treated group (n= 16): Animals subjected to ischemia/reperfusion were preadministered with TQ as described above.

Animals were divided into 2 series for 150 min and 24 h reperfusion studies (n= 8). Bioochemical analyses were only measured at 24 h.

Preparation of the Terminal Ileum and Contractile Studies in Intestinal Tissue

The aim of this process was to evaluate the contractile activity of the ileal longitudinal muscle in isolated ileal segments in organ bath (Commant Iletisim Co, Ankara, Turkey). A 15-mm length terminal ileum tissue fragment was cleaned and immediately suspended in an isolated organ bath with a Krebs solution involving KCl 4.7, $NaHCO_3$ 24.88, $MgSO_4$ 1.16, KH_2PO_4 1.18, $CaCl_2$ 2.52, NaCl 118, and glucose 11.1 in mM. Longitudinal segments of the ileum smooth muscle were calibrated during 60 min at 2 g force in organ bath filled with Krebs solution regularly fed with a gas mixture of 5% CO_2 and 95% O_2 at 37°C. Following the 2 g tension equilibration, spontaneous activity, 30 mM KCl, and cumulative acetylcholine (Ach) contractility were recorded.

In order to measure cytokines, myeloperoxidase (MPO), glutathione (GSH), and malondialdehyde (MDA) activity, harvested blood and then tissues were immediately removed and cleaned with buffer solution and stored at -80°C deep freeze.

MDA Determination in the Intestinal Tissue

MDA levels were detected using a method described by Casini et al. based on thiobarbituric acid reaction (15).

Determine of GSH Levels in Intestinal Tissue

The method described by Ellman was used to determine the level of GSH in intestinal tissue (16).

Determinationt of MPO Activity in Ileum Homogenate

The method described by Bradley et al. was used to determine the amount of myeloperoxidase (MPO), which is an indicator of migration of the neutrophils to the inflammed tissue (17).

Determination of TNF-α and IL-1β Activities in Serum and Intestinal Tissue

In both serum and tissue, the activity of TNF-α and IL-1β was measured by following the instructions in the manufacturer's guideline papers (abcam ab100770, ab100768, respectively, Istanbul/Turkey).

Statistical Analysis

Statistical analysis was performed using a Kruskal-Wallis test, followed by a post hoc Bonferroni test to estimate the differences between groups. A two-way ANOVA with multiple post hoc

comparisons performed with the Bonferroni test was used to determine the differences between the 150 min and 24 h series.

RESULTS

Ileal Longitudinal Muscle Contractility

As seen in Figure 1 with original traces, the cumulative dose of Ach (10-8-10-3 M) produced concentration-dependent contraction on isolated ileum in the sham, I/R-vehicle and TQ at 24 h after ischemia procedure. Contraction response of the cumulative dosing of Ach in the TQ group was almost as much as the response of the sham group at 24 h after ischemia while the cumulative effect of Ach in the 150-minute reperfusion group was not statistically significant. In 150 min reperfusion periods, statistical significance was not significant in the 150-minute reperfusion pediods as shown in Table 1 and Figure 2.

There were statistical differences between I/R-vehicle and sham groups in the Ach contraction responses both at 150 min (Figure 2A) and 24 h (Figure 2B) of the reperfusion periods. The inhibition of Ach-induced contraction due to I/R was reversed by TQ for the responses to 10-6 M-10-3 M Ach at 24 h ($p< 0.05$, $p< 0.0001$), however, this effect of TQ was not observed at 150 min of reperfusion (Table 1). Therefore, biochemical analyses were only measured at 24 h.

At 24 h of reperfusion, the depressed response of KCl-induced contractions in the TQ treated I/R-vehicle group was reversed and a similarity was seen in the sham control group (Figure 3).

The ameliorating affects of TQ on the Ach and KCl contractile responses of the intestinal I/R tissue were observed only at 24 h of reperfusion even though there was no gain at 150 min of reperfusion (Table 1). Moreover, there was a statistical difference between the 150 min and 24 h reperfusion periods at 30 mM KCl when comparing TQ groups with each other.

MDA Levels in the Intestinal Tissue at the 24 h of Reperfusion

As shown in Figure 4A and Table 2, in the I/R-vehicle group, MDA level in the ileum homogenate was observed significantly higher than the Sham group at 24 h of reperfusion. Pre-treatment of a 50 mg/kg dose of TQ significantly inhibited out the content of MDA.

GSH Levels in the Intestinal Tissue at the 24 h of Reperfusion

As illustrated in Figure 4B and Table 2, GSH levels in the intestinal homogenate of the I/R-vehicle animals were observed significantly lower than the sham group at 24 h of reperfusion. Pre-treatment with a 50 mg/kg dose of TQ, however, significantly improved the decreased quantity of GSH in theTQ pre-administered I/R-vehicle group, with a significantly higher GSH level.

MPO Activity in the Intestinal Tissue at the 24 h of Reperfusion

Figure 4C shows that the statistical significances were found between I/R-vehicle and sham groups and between TQ and I/R-vehicle groups at 24 h of reperfusion (Table 2).

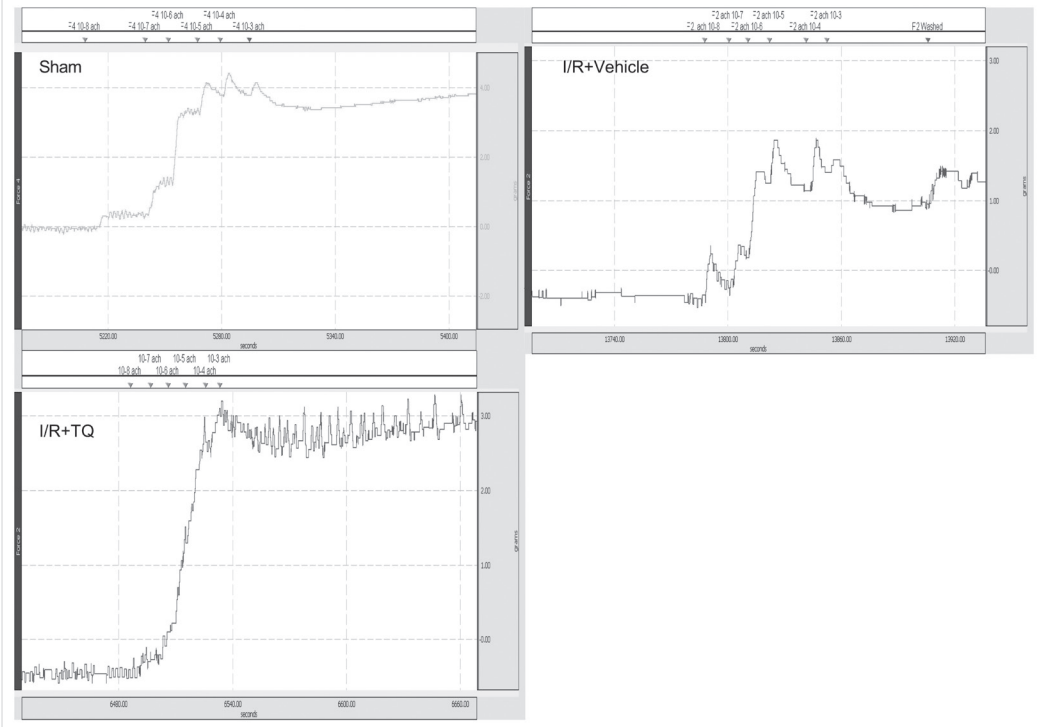

Figure 1. The original trace of the samples in isolated organ bath from groups sham, I/R-vehicle and thymoquinone groups.

Table 1. Maximum contraction effects of Ach on the sham, I/R+vehicle and thymoquinone groups of an isolated rat ileum

Ach Con.	Reperfusion periods (min; h) (n= 8)	Sham	I/R+vehicle	Thymoquinone	p1	p2
10^{-8}	150	24.23 ± 5.61	13.54 ± 6.85	18.46 ± 7.44	> 0.999	> 0.999
10^{-8}	24	24.33 ± 5.13	11.92 ± 6.09	18.46 ± 7.44	0.3632	> 0.999
10^{-7}	150	36.08 ± 4.77	16.46 ± 5.19**	23.15 ± 5.91	0.0067	> 0.999
10^{-7}	24	36.17 ± 4.92	14.96 ± 4.31**	26.15 ± 5.91	0.0002	0.8749
10^{-6}	150	64.34 ± 3.98	19.64 ± 6.13***	30.27 ± 8.41	< 0.0001	> 0.999
10^{-6}	24	64.33 ± 3.87	21.28 ± 6.46***	38.08 ± 7.44$^{\#}$	< 0.0001	0.0108
10^{-5}	150	85.00 ± 5.40	24.15 ± 11.34***	38.46 ± 10.05	< 0.0001	0.3016
10^{-5}	24	85.33 ± 4.89	30.02 ± 9.62***	54.67 ± 10.50$^{\#\#\#}$	< 0.0001	< 0.0001
10^{-4}	150	93.10 ± 4.88	28.26 ± 8.01***	45.15 ± 9.56	< 0.0001	0.0506
10^{-4}	24	93.04 ± 4.73	37.58 ± 7.56***	65.15 ± 9.56$^{\#\#\#}$	< 0.0001	< 0.0001
10^{-3}	150	95.12 ± 4.89	31.33 ± 6.68***	48.08 ± 11.34	< 0.0001	0.0562
10^{-3}	24	95.11 ± 4.82	39.88 ± 4.80***	68.08 ± 11.41$^{\#\#\#}$	< 0.0001	< 0.0001
KCl (30 mM)	150	99.49 ± 8.37	42.43 ± 17.46***	54.57 ± 15.20$^{\&}$	0.0003	> 0.999
KCl (30 mM)	24	99.63 ± 10.34	50.70 ± 16.60**	86.24 ± 15.55$^{\#}$	0.0011	0.0126

Data are expressed as mean ± SD (n= 8). p1: p value between I/R and Sham control groups, p2: p value between TQ and I/R groups. ##: p< 0.01, ***, ###; p< 0.001, $^{\&}$ Sign between 150 min and 24 h reperfusion, p< 0.05.

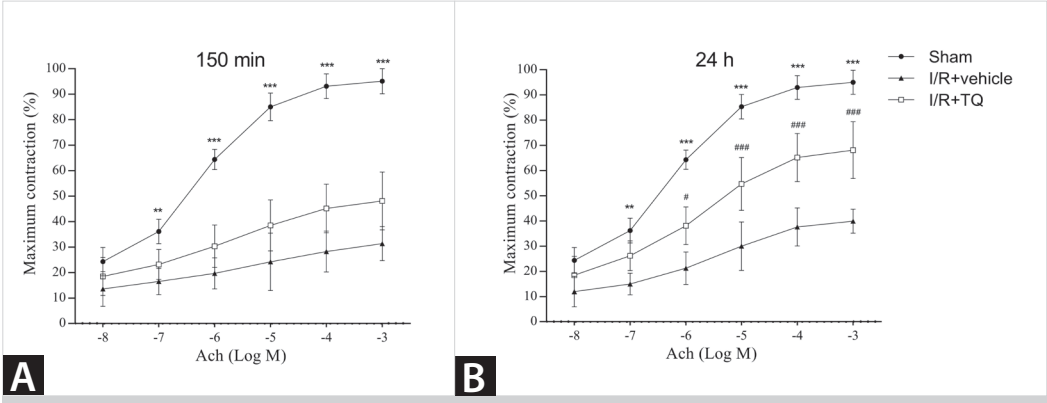

Figure 2. Maximum contraction effects of Ach on the sham (●), I/R-vehicle (▲) and TQ (□) groups of an isolated rat ileum. Data are presented as mean ± SD (n= 8). ** p< 0.001, and *** p< 0.0001 vs. I/R-vehicle groups, # p< 0.05 and ### p< 0.0001 vs. I/R-vehicle groups.

Level of TNF-α in Serum and Intestinal Tissue at the 24 h of Reperfusion

As shown in Figure 5A and 5B, in the I/R-vehicle group, the TNF-α levels in serum and ileum homogenate were observed significantly higher than the Sham group at 24 h of reperfusion. Pre-treatment of a 50 mg/kg dose of TQ significantly inhibited out the levels of TNF-α in the serum and tissue homogenate.

IL-1β Assay in Serum and Intestinal Tissue at the 24 h of Reperfusion

The other criteria of the size of the I/R-induced ileum injury is the determination of IL-1β levels in the serum and ileum tissue. As illustrated in Table 2, when the I/R-vehicle groups and sham groups were compared in terms of IL-1β levels in both the serum and ileum homogenate, the increase in all of these parameters in the I/R-vehicle groups was statistically different. There was a statistically significant difference when compared to a 50 mg/kg dose of TQ group with I/R-vehicle group in the serum (Figure 5C) and tissue homogenate (Figure 5D).

DISCUSSION

The results of the present research revealed that intestinal I/R resulted in a depressed ileum contractile responses to KCl, unspecific K ion channels related to contractility, and Ach, an excitatory neurotransmitter that effects by cholinergic induction in the smooth muscle cells of the digestive system. TQ administra-

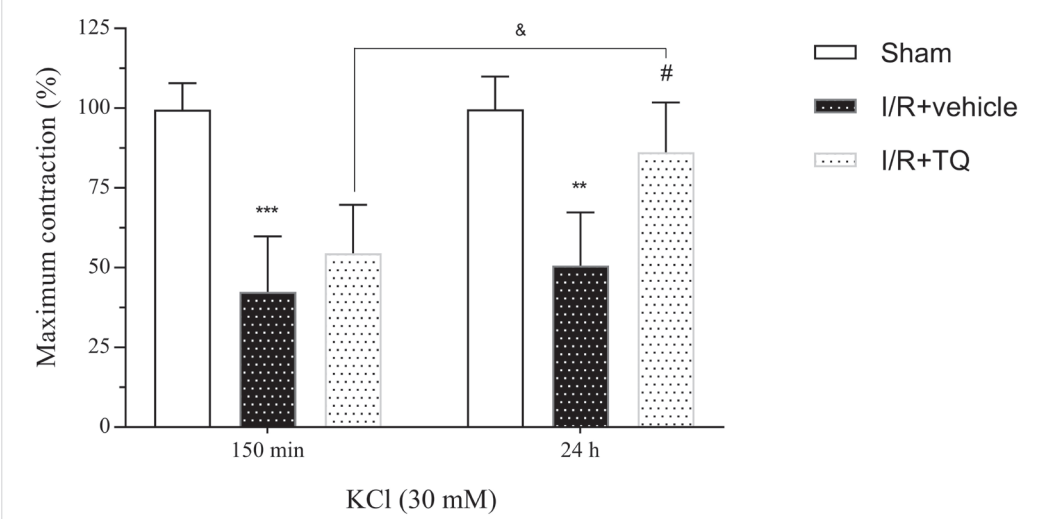

Figure 3. The response of resveratrol to 30 mM KCl in intestinal muscle in the I/R model. TQ was tested at 50 mg/kg dose once a day throughout 3 days before surgery. Data are expressed as mean ± SD. Statistically significant differences were found when comparing the I/R + vehicle with the sham group (*** p< 0.0001, 150 min; ** p< 0.001, 24 h reperfusion; n= 8). Statistically significant differences were only found at 24 h of reperfusion when comparing the TQ group with the I/R + vehicle groups (p< 0.05; n= 8; 24 h reperfusion). There was a statistical difference between the 150 min and 24 h reperfusion periods at 30 mM KCl when comparing TQ groups with each other (& p< 0.05).

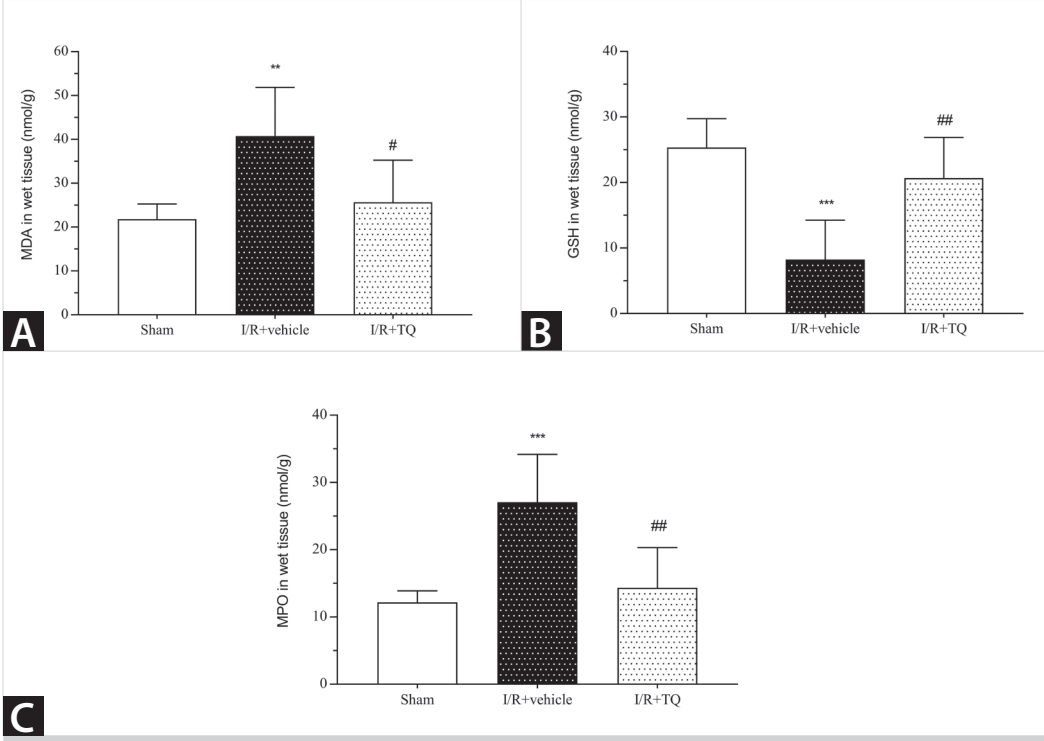

Figure 4. The effects of TQ on MDA, GSH and MPO levels in the ileum tissue. Effect of TQ on MDA (A) activity, GSH (B) and MPO (C) levels in ileum I/R injury rats. Data collected from 8 animals are expressed as means ± SD; ** p< 0.001 indicate differences between I/R-vehicle and sham; # p< 0.05, and ## p< 0.001, I/R-TQ indicate differences between I/R-TQ and I/R-vehicle groups.

Table 2. Comparison of oxidative stress and cytokine levels between the groups

Ach Con.	Reperfusion periods (min; h) (n= 8)	Sham	I/R+vehicle	I/R+TQ	p1	p2
MDA (nmol/g) in tissue	24	21.83 ± 3.43	40.75 ± 11.13**	25.67 ± 9.63$^{\#}$	0.0057	0.0272
GSH (nmol/mg) in tissue	24	25.33 ± 4.41	8.25 ± 6.01***	20.67 ± 6.22$^{\#\#}$	0.0003	0.0048
MPO (nmol/mg) in tissue	24	12.17 ± 1.72	27.08 ± 7.09***	14.33 ± 5.98$^{\#\#}$	0.0008	0.0031
TNF-α (pg/mL) in serum	24	749.67 ± 97.45	2955.12 ± 880.22***	1650.41 ± 417.37$^{\#\#}$	< 0.0001	0.0056
TNF-α (pg/g) in tissue	24	52.70 ± 5.50	107.50 ± 23.47***	64.40 ± 20.38$^{\#\#}$	0.0003	0.0029
IL-1β (pg/mL) in serum	24	258.83 ± 42.37	1127.33 ± 230.34***	597.17 ± 75.03$^{\#\#}$	< 0.0001	0.0027
IL-1β (pg/g) in tissue	24	6.78 ± 0.24	15.86 ± 3.63***	7.48 ± 2.50$^{\#\#\#}$	< 0.0001	0.0001

Data are expressed as mean ± SD (n= 8). p1: p value between I/R-vehicle and sham groups, ** p< 0.001, *** p< 0.0001. p2: p value between I/R-TQ and I/R-vehicle groups, # p< 0.05 ## p< 0.01, ### p< 0.001.
Data are presented as mean ± Standard Deviation (SD; n= 8). ** p< 0.001, and *** p< 0.0001 vs. sham groups; # p< 0.05, ## p< 0.001, and ### p< 0.0001 vs. I/R-vehicle groups.

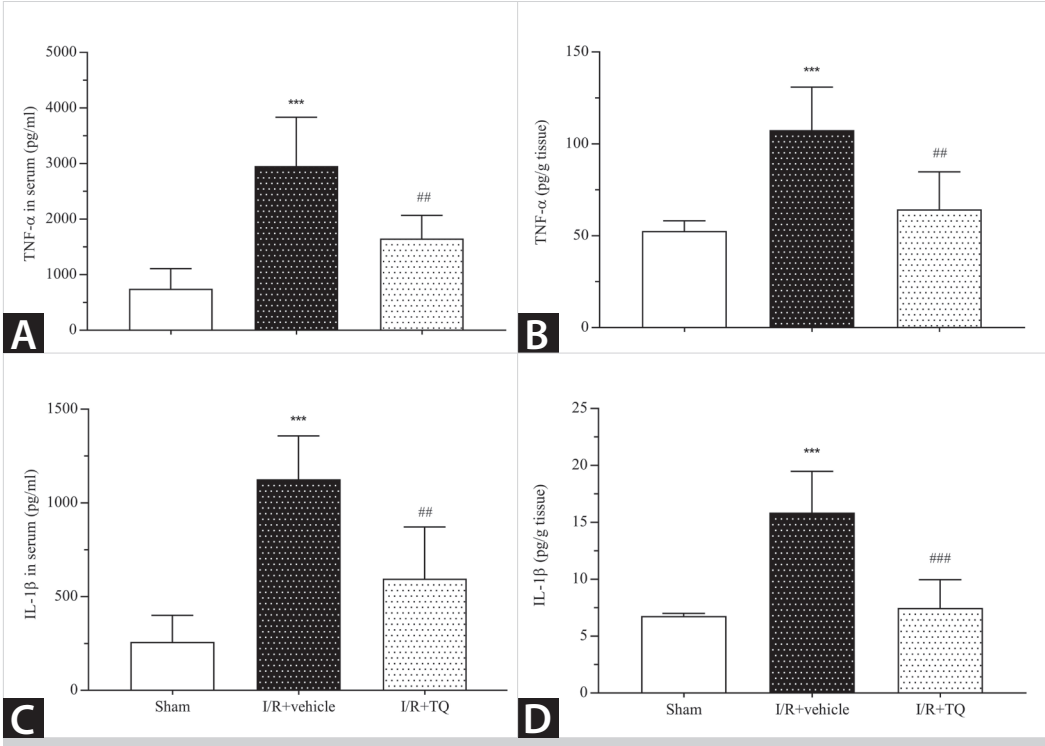

Figure 5. The effects of TQ on TNF-α and IL-1β in serum and ileum tissue. Effect of TQ on TNF-α level in serum (A) and ileum tissue (B), IL-1β activity in serum (C) and tissue (D). Data collected from 8 animals are expressed as means ± SD (pg/mL in serum; pg/g in wet tissue); *** p< 0.0001 indicate differences between I/R-vehicle and sham; ## p< 0.001 and ### p< 0.0001 indicate differences between I/R-TQ and I/R-vehicle groups.

tion was noticed ameliorate the distrupted contractile responses at 24 h after I/R, whereas it seemed to have no improvement at 150 min of I/R.

The ileum contraction response due to I/R damage of intestinal tissue is significantly impaired (3). Inflammatory mediators, ROS, leukocyte migration, and events in the immune processes can trigger the contractile chaos of the smooth muscle induced by I/R. It is known that I/R causes endothelium integrity, endothelial dysfunction, and failure in the oxydant defence mechanisms (2,3,5). In order to understand the therapeutic effect of TQ in intestinal I/R injury well, markers of oxidative stress and inflammation such as MDA, GSH, MPO and TNF-α activities in the ileum tissue were investigated. The results indicated that stimulated cytokine, neutrophilic inflammation and oxidative events play a role in I/R-induced intestinal damage. Fortunately, pretreatment

of animals with TQ restored intestinal dysfunction, reduced elevated MDA, MPO, TNF-α levels and reversed the depleted intestine GSH levels at I/R 24.

One of the unpredictive result was that we did not observe the reverse effect of distrupted contractily at the 150th min of reperfusion, while it was significantly decreased at the 24 h of reperfusion by TQ administration. Actually, a dose of 50 mg/kg/bw of TQ was chosen according to a previous paper (13,14). That dose may be insufficient to carry out a therapy for acute I/R injury. Another limitation about our research protocol may be the oral route of application of TQ to animals. In several investigations, unlike us, the application of antioxidant agent has been intravenous infusion just before ischemia (5). On the other hand, active TQ in the body can affect the liver due to its inactive biotransformation tract (18). Therefore, future studies are needed to plan the application routes of TQ in pathogenesis of I/R injury in detail.

The results of the present study on smooth muscle functions revealed that intestinal I/R injury was appreciably reduced by TQ preapplication. According to the literature, oxidant stress is a basic mechanism on inflammation and pathogenesis in intestinal I/R injury (13). This study revealed that increased MDA levels reversed with three times TQ administration prior to I/R surgery operation. In addition, GSH has non-enzymatic antioxidant structures of cells to protect against to oxidant processes (13,19). TQ elevated the deppressed GSH level of intestinal cells. These results indicate that TQ has attributed to the upregulation of endogenous cellular antioxidant systems during the progress of subacute I/R injury. MPO activity is often discussed to show the extent of inflammation in intestinal tissues subjected to I/R injury. Our study revealed that the increased MPO activity inhibited with three times TQ administration prior to I/R surgery operation.

Recent studies have revealed that the suppression of overproduction of pro-inflammatory cytokines including TNF-α and IL-1β occurs in exaggerated immunity or inflammation of disease models such as asthma, rheumatic arthritis, cancers, neurodegenerative diseases, cardiotoxicity, and etc. by TQ (12,20-24). Our results showed that TQ administration inhibits both ileum tissue and plasma TNF-α and IL-1β expressions in intestinal I/R injury. Cytokine production ring can occur due to the migration of polymorphonuclear leukocytes to the injured tissue.

Some limitations of this study are about other probable effect mechanisms of TQ on I/R injured tissue pathogenesis. One mechanism of TQ may be that it enhances the expression of endothelial nitric oxide synthase and increases nitric oxide levels, potent antioxidant which reacts with toxic molecular radicals, along with down-regulated nitric oxide synthase expression (25). TQ may have improved effects on endoplasmic stress and mitochondrial dysfunction and anti-apoptotic effects through activation of autophagy in damaged cells following numerous I/R models (13,26-29).

CONCLUSION

Our results confirm that TQ has antioxidant and aniinflammatory activities in the prevention and therapy of intestinal I/R injury. However, for clinical use, the dose, effect, and safety of TQ must be investigated by clinical phase studies in healthy volunteers or patients with numerous diseases. Finally, the results of the current study clearly reveal the role of oxidative damage in the immuno-pathophysiology of intestinal I/R injury, and in fact, TQ can be useful as a prophylactic and therapeutic agent in intestinal I/R injury.

Ethics Committee Approval: The approval of the animal ethical committee of Duzce University was taken with the number: 2011/009.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.O.A.; Design - S.O.A., A.P.; Supervision - S.O.A.; Resource - A.P.; Materials - A.P.; Data Collection and/or Processing - S.O.A., A.P.; Analysis and/or Interpretation - A.P.; Literature Search - S.O.A.; Writing Manuscript - S.O.A.; Critical Reviews - S.O.A., A.P.

Conflict of Interest: The authors declare that they have no conflict of interests.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (1): 96-104

Timokinon, bir antioksidan ve antienflamatuvar etki ile bağlantılı olarak sıçanlarda iskemi ve reperfüzyonun neden olduğu bağırsak hasarını azaltır

Ali Parlar[1], Seyfullah Oktay Arslan[2]

[1] Adıyaman Üniversitesi Tıp Fakültesi, Tıbbi Farmakoloji Anabilim Dalı, Adıyaman, Türkiye
[2] Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, Tıbbi Farmakoloji Anabilim Dalı, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, erkek wistar sıçanlarında timokinonun iskemi/reperfüzyon (I/R) yaralanmasına 150 dakika veya 24 saat reperfüzyon üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: Timokinonun reaktif oksijen türlerinin veya bağırsak iskemisi/reperfüzyonunda inflamatuvar süreçlerin neden olduğu hücresel hasar üzerindeki terapötik değeri, asetilkolinin (Ach) ve KCl'nin düzgün kas kasılma yanıtları, malondialdehit ile birlikte düz kas kasılma yanıtları üzerinde farmakolojik fonksiyon çalışmaları kullanılarak incelendi. Sıçanların serumları ve ileum dokularında tümör nekroz faktörü (TNF)-α ve interlökin (IL)-1β gibi glutatyon ve sitokin seviyeleri de incelendi. Timokinon 50 mg/kg dozda cerrahi işlemden 30 dakika önce, işlem sonrası 24. saatte ve işlem sonrası 48. saatte olmak üzere oral yoldan üç kez uygulandı. Reperfüzyon zamanlamasından kısa bir süre sonra (150. dakika veya 24. saat), KCl'ye bağlı kontraktilite izleri ve ileum düz kas asetilkolin izole organ banyosuna kaydedildi.

Bulgular: Timokinon ile ön tedavi, 24 saat reperfüzyonda ileum düz kasının bozulmuş kasılma kontraktilitesini tersine çevirmiştir. Artan malondialdehit ve tükenmiş glutatyon seviyeleri ve ileum I/R dokusunda belirlenen yüksek miyeloperoksidaz aktivitesi, malondialdehit miktarını azaltan, glutatyon seviyesini eski haline getiren ve miyeloperoksidaz aktivitesini önleyen timokinon ön tedavisi ile makul miktarlara getirilmiştir. Ek olarak, hem serum hem de doku TNF-α ve IL-1β aktiviteleri 24 saatlik intestinal I/R'de timokinon ile modüle edilmiştir.

Sonuç: Timokinonun, oksidan hasar mekanizmaları içeren bağırsak I/R yaralanmasında immünomodüle edici, radikal temizleyici ve/veya antioksidan etkileriyle terapötik değere sahip olabileceğini gösterir.

Anahtar Kelimeler: Timokinon, bağırsak iskemi ve reperfüzyon, ileum düz kas kasılması, sitokinler, oksidatif yaralanma

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ORIGINAL ARTICLE
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Obesity and appendicitis: Laparoscopy versus open technique

Ömer Vefik Özozan[1](ID), Cem Emir Güldoğan[2](ID), Emre Gündoğdu[2](ID), Mehmet Mahir Özmen[2](ID)

[1] Department of General Surgery, Istinye University Hospital, Liv Hospital Bahcesehir, Istanbul, Turkey
[2] Department of General Surgery, Istinye University Hospital, Liv Hospital Ankara, Ankara, Turkey

ABSTRACT

Objective: The clinical results of obese patients who have undergone open or laparoscopic appendectomy, whether one technique is superior to the other is still not clearly known.In our study, we compared the clinical results of obese patients operated with laparoscopic or open technique for acute appendicitis.

Material and Methods: We performed retrospective analyses of patients operated for acute appendicitis between the dates of July 2016 and July 2019 at Istinye University Faculty of Medicine Bahcesehir Liv Training and Research Hospital and Liv Hospital Ankara. Of the 241 patients whose height and weight information was accessible, 57 had a body mass index of 30 kg/m^2 or higher. Eighteen of these patients underwent open surgery while the other 39 underwent laparoscopic surgery. The primary result criterion was complication ratio. Secondary criteria were operation time and length of hospital stay.

Results: Upon comparison of laparoscopic and open techniques in terms of intraoperative-postoperative complications (p= 0.01), operation time (p= 0.02) statistically significant differences were found between the groups. However the mean length of hospital stay (p= 0.181) was similar in both groups.

Conclusion: In obese appendicitis patients, the laparoscopic technique proved to be superior to the open technique in criteria such as perioperative-postoperative complications, operation time, and etc. Length of hospital stay was determined to be similar between the groups.

Keywords: Appendicitis, obesity, body mass index, laparoscopic appendectomy, open appendectomy

INTRODUCTION

Laparoscopic techniques have been more and more preferred to open surgical techniques due to reasons such as less post-operative pain, faster return to daily life and activities, and cosmetic advantages (1,2). Laparoscopic appendectomy (LA) was first described in 1983 (3). Lesser risk of intraoperative complication, fever surgical site infections and shortened hospital stays stand out in obese patient groups operated with laparoscopic techniques (4,5). Medical literature related to appendectomy also shows superiority of laparoscopy especially in terms of wound site infections, postoperative recuperation period and out-of-hospital costs. That said, the literature also shows a correlation between laparoscopy and certain situations such as increased ratio of intra-abdominal abscess and increased hospital costs (6). In obese patients, due to the abdominal wall being thicker, difficulty may be encountered in revealing the surgical field, performing surgical techniques and wound related situations. Laparoscopy overcomes these issues and creates the belief that laparoscopy is better than open appendectomy (OA) for appendicitis. While some research shows that LA is a safe and efficient treatment method for both acute and perforated appendicitis, some others show that the open technique is superior (7-9). That said, when the data is limited to the obese population, the discussion whether there is a difference remains. Our objective is to determine whether there is a difference between OA and LA for patients grouped according to their body mass indexes (BMI).

MATERIAL and METHODS

We retrospectively examined the patients who underwent an operation for acute appendicitis at our institutions between the dates of July 2016 and July 2019.

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Corresponding Author
Cem Emir Güldoğan
E-mail: drguldogan@gmail.com

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Patient Selection

We separated patients with clinical appendicitis diagnosis into two groups, LA and OA. We followed up on the patients during their hospital stay and for 2 weeks after their discharge at the out-patient clinic. All patients were 16 or above (Figure 1).

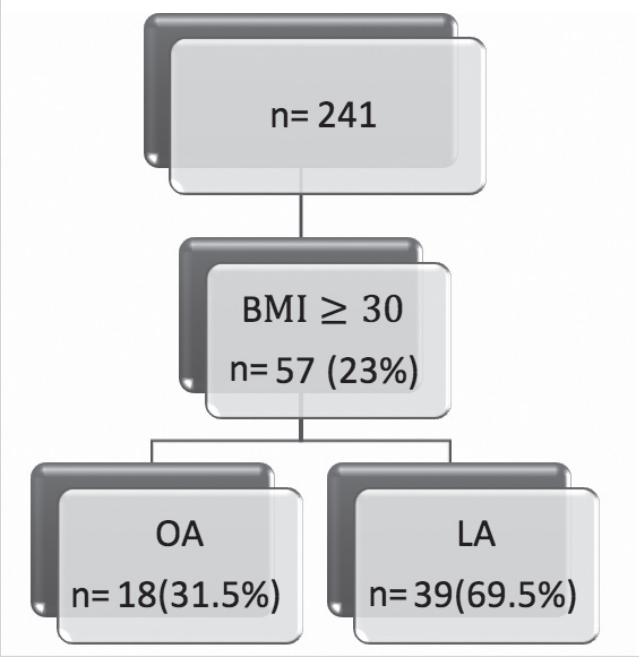

Figure 1. Body mass index (BMI) of 23% of the 241 patients was at or above 30 kg/m^2. In 18 of these patients (31.5%) open appendectomy (OA) was performed, and laparoscopic appendectomy (LA) was performed on the other 39 (69.5%).

Data

We examined the demographic data (age, sex), preoperative data [white blood cell (WBC), diagnosis], operation details (operation type, duration) and post-operative period (complications, length of hospital stay) of the patients.

Subgroup Analysis

We divided the patients into 3 subgroups according to their BMI's: BMI of lower than 25 kg/m^2, BMI between 25-30 kg/m^2 (overweight) and BMI of 30 kg/m^2 or above (obese).

Result Criteria

The primary criterion was complication ratio. Secondary criteria were operation time and length of hospital stay.

Statistical Methodology

We used SPSS 17. version. Data ranges were presented with median and percantages values. To compare the ratios of statistical significance, we used Mann-Whitney U test. Values with a p value of less than 0.05 were deemed statistically significant.

Ethics committee approval was received for this study from the Ethics Committee of Istinye University (No. 2019/1951) and Liv Hospital Ankara (No. 2019/006).

RESULTS

Both groups were similar in age (OA= 33, LA= 31, p= 0771), sex (OA= 61% male, LA= 52% male, p= 0.724) and presented with clinical appendicitis (confirmed with pathology p= 0.165) (Table 1). A statistically significant difference in favor of the laparoscopic group was observed in the ratio of complications between the open and laparoscopic groups categorized according to their BMIs (p= 0.01) (Table 2). No mortality occurred over the course

Table 1. Demographics and pathologies of the obese patients grouped according to types of operation

	OA (n= 18)	LA (n= 39)	p
Sex	61% male	52% male	0.724
Age (range)	33 (17-48)	31 (18-59)	0.771
Pathology (%)			
Normal	7%	4%	0.165
Acute	29%	61%	
Perforated/Gangrenous	64%	35%	

OA: Open appendectomy, LA: Laparoscopic appendectomy.

Table 2. Complications according to types of operation

	OA	LA
Wound site infection	3	-
Left inferior epigastric artery injury		1
Ileus	1	
Peritoneal findings	1	
Intra-abdominal abscess-hematoma	3	1

OA: Open appendectomy, LA: Laparoscopic appendectomy.

Table 3. Results

	OA (n= 18)	LA (n= 39)	p
Complications (patient count)	8	2	0.01
Operation time (minutes)	61 (40-119)	45 (29-134)	0.02
Mean length of hospital stay: days (range)	2 (1-6)	2 (1-5)	0.181

OA: Open appendectomy, LA: Laparoscopic appendectomy.

of this study. Upon comparison of the laparoscopy group to the open technique group, operation time of the laparoscopy group was observed to be shorter (p= 0.02). No statistically significant difference was observed in the length of hospital stay of the groups (p= 0.181) (Table 3).

DISCUSSION

Comparison discussions between OA and LA continues with numerous papers. There are some meta-analyses that go over this subject in the literature. In a meta-analysis dated 2004 where 54 studies were analyzed, LA was shown to result in distinctly fewer wound infections, less pain and shorter hospital stay; however a correlation was shown between it and higher cost with an increased risk of prolonged operation time and intra-abdominal infections. The conclusion was that LA is the better option for patient groups consisting of working population, young women and obese people (6). In another meta-analysis, similarly, LA procedure was reported to result in a higher probability of intra-abdominal abscess while also being superior in terms of wound infections and length of hospital stay. The analysis recommended to avoid LA in perforated and gangrenous appendicitis cases (10). In a double-blind, prospective, randomized study dated 2005 comparing LA and OA, no superiority of one procedure to the other was observed other than a better quality of life at the 2nd week after operation for the LA group (1). As for our study, we performed analyses to demonstrate whether the two procedures created different results among the patients grouped up according to their BMIs. Our study demonstrated that the laparoscopic approach was more advantageous for obese patients in terms of complications and operation time. Previous studies conducted regarding obese patient groups have not been as comprehensive as the ones conducted among the general population (11-14). In another retrospective study, length of hospital stay and wound recuperation period were shown to be superior for obese patients that underwent laparoscopic appendectomy than their counterparts who underwent operations where the open technique was used (15). Varela et al. have also reached similar conclusions such as lower complication rates and costs for morbidly obese people. Many studies that reach the opposite conclusion have also been published. Ricca et al. have found LA to result in significantly longer operation time and higher costs (12,16). Towfigh et al. have found no significant difference between the laparoscopic and open approaches in terms of length of hospital stay or complication ratio (17). The reason for the varying results may also be the experiences of the teams studying obese patients. Operation times and wound side infection ratios may potentially be affected, and when it comes to discharging a patient, the initiative of clinical discretion may also affect the length of hospital stay. Factoring in the variables tied to the operating surgeon, the surgical techniques also need to be standardized. Appendectomy is generally a short-lasting operation that is performed with a small incision (4-6 cm). Some studies show that the McBurney incision is superior to the median line incision in terms of pain, complications and wound site healing (18). When compared to other open techniques, OA results in less operation site pain and shorter hospital stays for pain management (19,20). In addition, in the literature, a higher rate of trocar site hernia is reported in appendectomies performed with a single port compared to LAs (21). The parameter that affects the length of hospital stay of appendectomy patients is the severity of the infection encountered during the operation. Post-operative antibiotherapy of the patients with ruptured or gangrenous appendicitis may also prolong hospital stay. The risk of complications caused by prolonged operation times of obese patients such as atrial fibrillation, pulmonary embolism, deep vein thrombosis (DVT) and rhabdomyolysis are not disregarded (22-26). In patients with a BMI of over 40 kg/m^2, while the risk of atrial fibrillation may increase by 50%, the risk of DVT or pulmonary embolism may increase by up to 3 times. In many studies, laparoscopy and obesity have been shown as independent factors for prolonged operation times (27-29). However, in our study, we recorded significantly shorter operation times in obese patients who underwent LA. We also observed the superiority of LA over OA in terms of complication frequency.

Limitations of the Study

One of the limitations of this study may have been ensuring that the operations would be performed by surgeons with high experience of operating on obese people. It must not be overlooked that the operation time, post-operative follow-up and treatment processes and even the decisions given regarding the patients' discharge may be affected by the said experience. In addition, 44 obese appendicitis patients were a rather small sample size for observation.

CONCLUSION

According to our data, technically, we recommend LA to obese patients, however, we are of the opinion that it should be shaped

according to clinical conditions and the discretion and experience of the surgeon.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Istinye University (No. 2019/1951) and Liv Hospital Ankara (No. 2019/006).

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.V.Ö., C.E.G.; Design - Ö.V.Ö., C.E.G.; Supervision - M.M.Ö.; Data Collection and/or Processing - Ö.V.Ö., C.E.G., E.G.; Analysis and/or Interpretation - Ö.V.Ö., E.G.; Literature Review - C.E.G.; Writing Manuscript - Ö.V.Ö.; Critical Reviews - M.M.Ö.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (1): 105-109

Obezite ve apandisit: Laparoskopi ile açık teknik karşılaştırılması

Ömer Vefik Özozan[1], Cem Emir Güldoğan[2], Emre Gündoğdu[2], Mehmet Mahir Özmen[2]

[1] İstinye Üniversitesi Hastanesi, Liv Hospital Bahçeşehir, İstanbul, Türkiye
[2] İstinye Üniversitesi Hastanesi, Liv Hospital Ankara, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Açık veya laparoskopik apendektomi yapılan obez hastaların klinik sonuçlarına göre, yöntemlerin birbirine üstünlüğünün olup olmadığı hala net olarak bilinmemektedir. Çalışmamızda akut apandisit nedeniyle laparoskopik veya açık yöntemle opere edilen obez hastaların klinik sonuçları karşılaştırıldı.

Gereç ve Yöntem: Temmuz 2016-Temmuz 2019 tarihleri arasında, İstinye Üniversitesi Liv Hospital Bahçeşehir ve Liv Hospital Ankara hastanelerinde akut apandisit nedeniyle opere edilen hastaların retrospektif analizleri yapıldı. Boy ve kilosuna ulaşılabilen 241 hastanın 57'sinde beden kütle indeksi 30 kg/m^2 veya daha fazla idi. Bu hastaların 18'ine açık cerrahi, 39'una laparoskopik cerrahi uygulandı. Primer sonuç ölçütleri komplikasyon oranlarıydı. İkincil sonuçlar ameliyat süresi ve hastanede kalış süresi idi.

Bulgular: Laparoskopik ve açık yöntem perioperatif-postoperatif komplikasyonlar (p= 0,01) ve operasyon süresi (p= 0,02) açısından kıyaslandığında gruplar arasında istatistiksel olarak anlamlı farklılıklar bulunmuştur. Ancak hastanede hastanede yatış süresi açısından gruplar arasında anlamlı fark yoktur (p= 0,181).

Sonuç: Apandisit nedeniyle opere edilen obez hastalarda, laparoskopik yöntem ile opere edilen grupta açık yönteme kıyasla daha az perioperatif-postoperatif komplikasyonlar, daha kısa operasyon süresi gibi üstünlüklerin olduğu gözlendi. Gruplar arasında hastanede yatış süresinin benzer olduğu tespit edildi.

Anahtar Kelimeler: Apandisit, obezite, beden kütle indeksi, laparoskopik apendektomi, açık apendektomi

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CASE REPORT
Turk J Surg 2020; 36 (1): 110-112

Solid pseudopapillary tumor of the pancreas: A case report

Hikmet Aktaş[1](ID), Özgen Işık[1](ID), Remzi Emiroğlu[1](ID)

[1] Clinic of General Surgery, Acibadem Bursa Hospital, Bursa, Turkey

ABSTRACT

Solid pseudopapillary tumor (SPT) of the pancreas is an uncommon pathological condition. It is classified as low-grade malignant neoplasm, but aggressive disease can be seen when the tumor size is larger than 5 cm, microscopic malignant features and local invasion are present. Resection of the mass with clear margins is the procedure of choice. However, lymph node dissection may be necessary in large tumors.

Keywords: Pancreas, pseudopapillary tumor, malignancy

INTRODUCTION

Solid pseudopapillary tumor of the pancreas (SPT) is a rare entity commonly seen in young women (1). Only 1 to 2% of all pancreatic neoplasms are consisted of SPTs (1,2). Although it was classified as an epithelial low-grade malignant neoplasm by World Health Organization in 2010, there are several cases reported in the literature with malignant metastatic features (1-3). Complete surgical resection is the preferred treatment option for SPT of the pancreas.

This study aimed to present a young woman who underwent distal pancreatectomy and splenectomy for SPT of the pancreatic tail.

CASE REPORT

A 41-year-old woman with a mass located at the pancreas tail that was detected on routine abdominal ultrasonography was admitted to the outpatient clinic. Abdominal CT scan showed a solid mass of 10 cm in diameter (Figure 1a). Tumor marker (carcinoembriogenic antigen and Ca 19.9) levels were in normal range. There was not an evidence of distant metastasis in preoperative imaging studies of the abdomen and thorax. The patient underwent open distal pancreatectomy and splenectomy on October 10, 2014 (Figure 1b). Postoperative recovery was uneventful, and the patient was discharged on postoperative day 4.

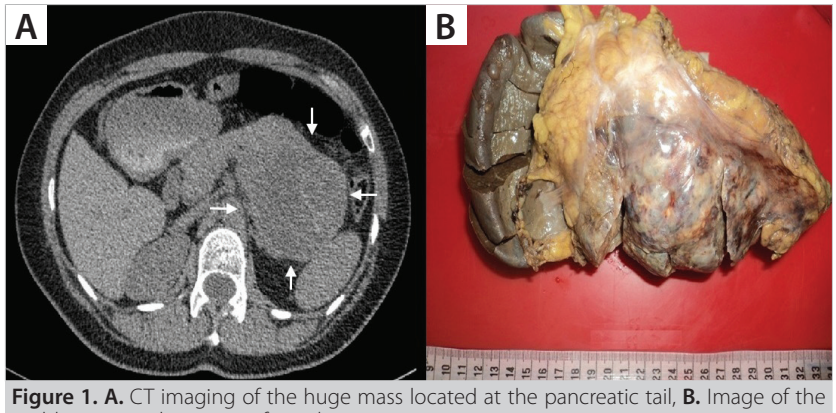

Figure 1. A. CT imaging of the huge mass located at the pancreatic tail, **B.** Image of the en-bloc resected specimen from the posterior aspect.

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Corresponding Author
Özgen Işık
E-mail: ozgen006@yahoo.com

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Pathological examination of the specimen revealed SPT of the pancreatic tail with low mitotic activity. Surgical margins were clear, and none of the 21 lymph nodes were metastatic. A decision was made to proceed with a 3-month follow-up interval during the first year of surgery. The patient was doing well with no evidence of recurrence or distant metastasis during the routine office visit on postoperative month 6. An informed consent was obtained from the patient presented in this report.

DISCUSSION

Solid pseudopapillary tumor of the pancreas is an uncommon pancreatic mass, and its origin is still debatable (2). Most data on this tumor consists case reports and small case series. During the past few years, several studies investigating the natural history and malignant potential of SPT were published (1,2).

Solid pseudopapillary tumors of the pancreas are seen as encapsulated masses with well-defined borders including both solid and cystic components in CT scan. MRI may provide more detailed information about tissue characteristics such as hemorrhage, cystic degeneration, and necrosis (4). Differential diagnosis of SPT includes pancreatic pseudocysts, endocrine neoplasms, pancreatoblastoma, and acinar cell carcinoma (5).

Perineural and vascular invasion, invasion of the surrounding tissues, tumor diameter larger than 5 cm have been reported to be associated with increased malignant potential (1). Additionally, tumor size larger than 8 cm, presence of microscopic poor prognostic factors, and stage IV disease (distant metastasis or peritoneal implants) have been determined as predictive factors of recurrence (2). SPT has been reported to metastasize to the peritoneum, liver, and lymph nodes. Formal lymph node dissection in addition to the resection of the tumor is recommended for patients with large tumors (1). In our patient, the only risk factor of poor prognosis was the tumor size.

Resection of the mass with clear margins is the procedure of choice for SPT. Distal pancreatectomy with or without splenectomy is enough for the management of the lesions located at the pancreatic tail. Laparoscopic spleen preserving resection for distal pancreatic tumors may be feasible when the tumor size is small (6). Minimally invasive laparoscopic resection for pseudopapillary tumor of the pancreas offers better short-term benefits than open surgery, such as shorter length of hospital stay and earlier toleration of the oral diet with comparable morbidity rates and long-term outcomes (5). Unfortunately, laparoscopic technique could not be utilized and preservation of the spleen was not feasible in this case due to the huge size of the mass.

Since it is a low-grade malignancy and surgical resection of the tumor is the only curative option, data regarding the impact of adjuvant chemotherapy on the outcomes are limited and controversial. However, systemic multimodal treatment may benefit when metastatic disease is present (7).

CONCLUSION

Solid pseudopapillary tumor of the pancreas may be in aggressive behavior when the tumor size is large, microscopic malignant features and local deep invasion exist. Resection of the tumor with clear margins, and lymph node dissection for tumors larger than 5 cm seems to be the best surgical strategy in the management of SPT's. Post-operative follow-up strategy should be personalized based on the presence of risk factors. Routine imaging of the abdomen during follow-up may be helpful in patients with aggressive tumors.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.E.; Design - R.E.; Supervision - R.E.; Resource - R.E.; Materials - H.A., Ö.I., R.E.; Data Collection and/or Processing - H.A., Ö.I.; Analysis and/or Interpretation - H.A., Ö.I.; Literature Search - H.A., Ö.I.; Writing Manuscript - H.A., Ö.I.; Critical Reviews - R.E.

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

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OLGU SUNUMU-ÖZET
Turk J Surg 2020; 36 (1): 110-112

Pankreasın solid psödopapiller tümörü: Bir olgu sunumu

Hikmet Aktaş[1], Özgen Işık[1], Remzi Emiroğlu[1]

[1] Acıbadem Bursa Hastanesi, Genel Cerrahi Kliniği, Bursa, Türkiye

ÖZET

Pankreasın solid psödopapiller tümörü (SPT) nadir görülen bir patolojidir. Düşük malignite potansiyeli bulunan bir neoplazm olarak sınıflandırılır, fakat tümör çapı 5 cm'den büyükse, mikroskobik malignite özellikleri mevcutsa ve lokal invazyon varsa hastalık agresif seyredebilir. Kütlenin güvenli cerrahi sınırlar ile rezeksiyonu tercih edilen prosedürdür. Ancak büyük tümörlerde lenf nodu diseksiyonu gerekebilir.

Anahtar Kelimeler: Pankreas, psödopapiller tümör, malignite

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CASE REPORT
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Endometriosis within the inguinal hernia sac

İsmail Zihni[1](ID), Oktay Karaköse[1](ID), Kazım Çağlar Özçelik[1](ID), Hüseyin Pülat[1](ID), Hasan Erol Eroğlu[1](ID), Kemal Kürşat Bozkurt[2](ID)

[1] Department of General Surgery, Suleyman Demirel University School of Medicine, Isparta, Turkey
[2] Department of Pathology, Suleyman Demirel University School of Medicine, Isparta, Turkey

ABSTRACT

Endometriosis is characterized by the presence of histologically normal endometrial tissue outside the uterine cavity. Endometriotic implants are usually located in the pelvic organs, but they have been described in almost every location of the female body. It may also be present after cesarean section or other gynecological operations. In this study, we reported a rare case of endometriosis located in an indirect inguinal hernia sac.

Keywords: Endometriosis, hernia sac, inguinal canal

INTRODUCTION

Endometriosis is a clinical problem often seen in females of child-bearing age and generally causes dysmenorrhea, dyspareunia, menstrual irregularity and infertility. Although primarily located in the ovaries, the sacro-uterine ligament, rectovaginal septum and pelvic peritoneum, it may also be seen rarely in the vulva, vagina, appendix, stomach, liver, thorax, bladder, umbilicus and the inguinal canal (1,2). In the general population, the incidence of endometriosis is estimated to be 1-8%. The frequency of endometriosis seen incidentally during any gynaecological intervention in the reproductive years is 15-20% (3). It is known that endometriosis can be determined during caesarean, hysterectomy, myomectomy, in the episiotomy line following birth, in the trochar location after laparoscopy and especially following pelvic gynaecological operations related to the uterus and endometrium. Its frequency following caesarean has been reported as 0.03-0.4%, which supports mechanical transplantation theory (4-7). The case presented here is of a patient with an uncommonly located endometriosis within an indirect inguinal hernia pouch, which was determined following caesarean operation.

CASE REPORT

A 31-year-old female patient presented with complaints of pain and swelling in the right inguinal area. The complaints had been ongoing for approximately 1 year, and the pain and swelling increased undertaking strenuous labour. It was learned that the patient had given birth by caesarean section 2 years previously. Physical examination determined a right-sided inguinal hernia. On ultrasonography examination, a cystic structure, 21 x 12 mm in size, was seen within the hernia pouch in the right inguinal canal. The decision was made as to operate on the patient, who was informed of the surgical technique and gave a written informed consent. With this diagnosis, the patient was admitted for surgery and the indirect inguinal hernia pouch, together with the 2cm cystic mass within, were excised and Lichtenstein herniorrhaphy was applied. No complications occured and the patient was discharged on postoperative day 1. Histopathologic examination of the mass reported it as endometriosis externa (Figures 1 and 2). At the 1-month follow-up gynaecological examination, the patient was determined as normal.

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Corresponding Author
İsmail Zihni
E-mail: ismailzihni@gmail.com

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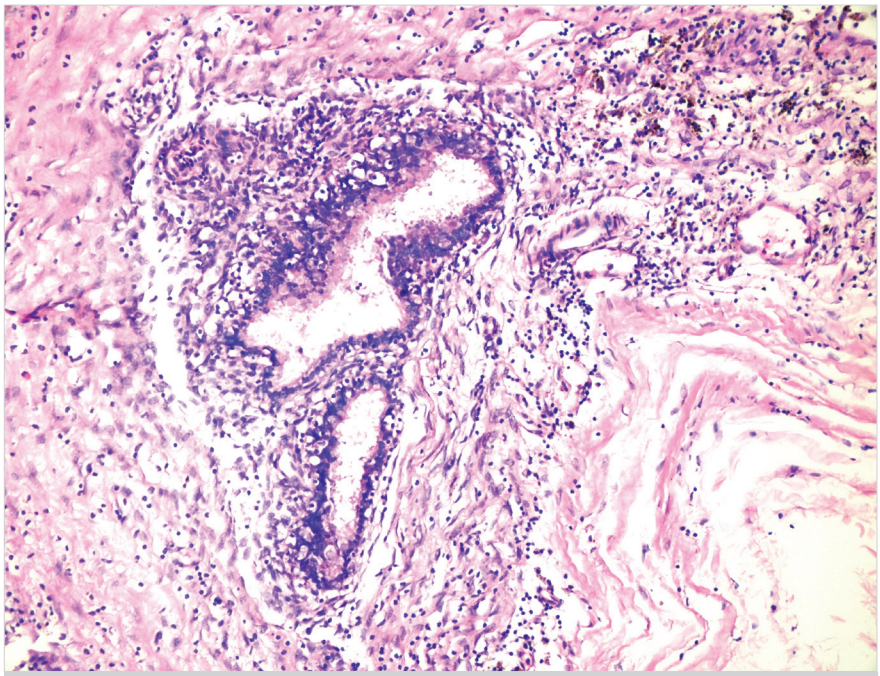

Figure 1. Endometrial glands and hemosiderin-laden macrophages in soft tissue (HE, x200).

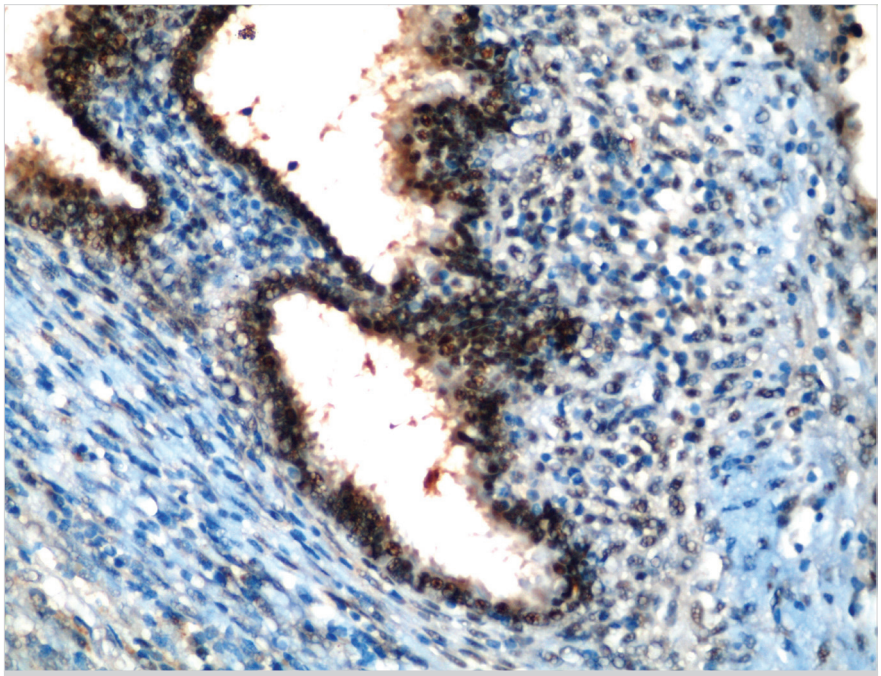

Figure 2. Immunohistochemical estrogen receptor positivity in endometrial glands (ER, x400).

DISCUSSION

Endometriosis was first described by Von Reclinghausen in 1885 as a functional endometrial tissue outside the uterine cavity (8). Cases of endometriosis outside the pelvis, including the abdominal wall, comprise less than 1% of all endometriosis cases. The most likely explanation of abdominal wall endometriosis is iatrogenic origin during surgery. The relationship between abdominal wall endometriosis and gynaecological operations was first determined by Aimakhu et al. in 1975 (9). Location in the abdominal wall is determined most frequently below the incision scar, in the umbilicus, within the rectus muscle, in the inguinal canal and rarely in an inguinal hernia pouch (10). Right side is more com-

mon when endometriosis is within an inguinal hernia pouch. In the case presented here, endometriosis was determined within a right side inguinal hernia pouch. The reason for right side dominance is that intraperitoneal circulation is clockwise and there is the effect of gravity (11).

The most common symptom of endometriosis is menstrual pain, sensitivity, swelling and a (Palpating? perceiving ? a mass) mass. However, these symptoms may not always be evident, as in the case presented here. Uterus surgery, particularly caesarean section operations are a significant risk factor for the development of endometriosis. Similarly, in the current case, who was still in her reproductive period, there was a history of caesarean operation 2 years previously. It has been reported that time elapsing from surgery to clinical presentation of endometriosis may range from 45 days to 20 years (12).

To reduce to a minimum the risk of endometriosis developing from mechanical transportation, it is recommended at the final stage of uterine surgery procedures, that the gloves, needles, suture materials and sponges are changed and removed from the operation area and contact with the wound area should reduced to a minimum. In caesarean operations, before closing the incision line, cleaning with high-flow saline solution is thought to be of benefit (13).

Endometriosis in an inguinal hernia pouch is more often encountered by general surgeons than gynaecologists. As it is a rare occurrence, the diagnosis is extremely difficult. It has been reported in many series that patients with a diagnosis of incarcerated inguinal hernia have been operated on by general surgeons (14). In these rarely seen cases, it may be helpful if there is a patient history of swelling in the inguinal area, especially during menstruation or a history of uterine surgery. However, definitive diagnosis is generally made after histopathological examination (10).

CONCLUSION

Herniorrhaphy is one of the most frequently performed operations by general surgeons. Although rare within a hernia pouch, endometriosis should be kept in mind and considered.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

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OLGU SUNUMU-ÖZET
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İnguinal herni kesesinde endometriyozis

İsmail Zihni[1], Oktay Karaköse[1], Kazım Çağlar Özçelik[1], Hüseyin Pülat[1], Hasan Erol Eroğlu[1], Kemal Kürşat Bozkurt[2]

[1] Süleyman Demirel Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Isparta, Türkiye
[2] Süleyman Demirel Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Isparta, Türkiye

ÖZET

Endometriyozis; histolojik olarak normal endometriyal dokunun, rahim içi boşluğunun dışında bulunmasıdır. Genellikle pelvik organlarda görülmekle birlikte, kadın vücudunda her yerde bulunabilir. Sezaryen ya da diğer jinekolojik operasyonlar sonrasında görülebilmektedir. Biz burada, indirekt inguinal fıtık kesesi içine yerleşmiş, nadir bir endometriyozis olgusunu sunduk.

Anahtar Kelimeler: Endometriyozis, fıtık kesesi, inguinal kanal

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LETTER TO THE EDITOR
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Routine histopathological examination of gallbladder specimens after cholecystectomy: Is it time to change the current practice?

Banu Karapolat[1] (ID)

[1] Clinic of General Surgery, Kanuni Training and Research Hospital, Trabzon, Turkey

Dear Editor,

Recently, we have read with great interest the article by Benkhadoura et al. entitled "Routine histopathological examination of gallbladder specimens after cholecystectomy: Is it time to change the current practice?" published in the "Turkish Journal of Surgery" (1). First, I congratulate the authors for this successful study and would like to mention some points regarding their article.

It is stated in the article that other than 4 (0.11%) cases that had preoperative or intraoperative diagnosis of malignity, gallbladder carcinoma was not diagnosed through histopathological examination in any of the 3423 gallbladder specimens after cholecystectomy. Therefore, the authors defend that not sending gallbladder specimens to pathology, which were taken from the areas with very low incidence of gallbladder carcinoma in patients who had no prior diagnosis of malignity, would be a safe and more cost-effective practice that would reduce the workload of the pathologists and that it does not appear to compromise patient outcome.

Postcholecystectomy syndrome can be defined as a syndrome where the symptoms such as right upper quadrant pain, dyspepsia, vomiting, and jaundice that had been present in some of the patients who underwent cholecystectomy start to occur again and the causes of which may include formation of residual gallbladder and residual cystic duct stump stone, recurrent/retained common bile duct stone and cystic duct stump remnant. In a cholecystectomy study involving 5820 patients conducted by El Nakeeb et al., residual gallbladder and residual cystic duct stump stone have been found in 21 patients and all patients have undergone open or laparoscopic completion cholecystectomy to relieve symptoms and avoid complications (2). In another study conducted by Shirah et al., postcholecystectomy syndrome has been encountered in 272 patients out of 1374 (incidence 19.8%) who had cholecystectomy due to gallstone diseases. From these patients, 26 (9.6%) has had recurrent common bile duct stone, 22 (8.1%) had retained common bile duct stone and 11 (4%) had cystic duct stump remnant. Endoscopic retrograde cholangiopancreatography, endoscopy, papillotomy, stone extraction and stenting have been administered to 48 of these patients with recurrent/retained common bile duct stone, the small retained stones have been removed endoscopically in 4 patients with cystic duct stump remnant, and the stumps have been shortened by way of laparoscopic repair in the 7 remaining patients (3). Since same symptoms usually recur in such patients and new invasive interventions or cholecystectomy are administered to them once again, a question like "Have they not removed my

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Corresponding Author
Banu Karapolat
E-mail: banukarapolat@hotmail.com

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gallbladder in my first operation?" may come to the minds of these patients. This thought will not only weaken their beliefs in the surgical team, but also cause a number of medicolegal problems to arise. For these reasons, we think that sending the removed gallbladder specimens to histopathological examination after cholecystectomy will constitute an evidence of the procedure performed during the operation and will prevent possible medicolegal problems.

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LETTER TO THE EDITOR
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Fertility and breast cancer: Recommendations of the 2019 Izmir Consensus Conference

Mehmet Ali Koçdor[1] (ID), Erbil Doğan[2] (ID), Işıl Kasapoğlu[3] (ID), Bahadır Güllüoğlu[4] (ID), Davut Güven[5] (ID), Nuh Zafer Cantürk (ID), Ahmet Zeki Işık[7] (ID), Sevilay Altıntaş[8] (ID), Mustafa Emiroğlu[9] (ID), Kemal Atahan[10] (ID), Funda Göde[7] (ID), Cemal Posacı[2] (ID), Öner Menteş[11] (ID), Bahadır Saatli[2] (ID), Muzaffer Sancı[12] (ID), Sefa Kurt[2] (ID), Mehmet Özeren[12] (ID), Abut Kebudi[13] (ID), Gürkan Uncu[3] (ID), Murat Celiloğlu[2] (ID)

[1] Department of General Surgery, Dokuz Eylul University School of Medicine, Izmir, Turkey
[2] Department of Obstetrics and Gynecology, Dokuz Eylul University School of Medicine, Izmir, Turkey
[3] Department of Obstetrics and Gynecology, Uludag University School of Medicine, Bursa, Turkey
[4] Department of General Surgery, Marmara University School of Medicine, Istanbul, Turkey
[5] Department of Obstetrics and Gynecology, Ondokuz Mayis University School of Medicine, Samsun, Turkey
[6] Department of General Surgery, Kocaeli University School of Medicine, Kocaeli, Turkey
[7] Department of Obstetrics and Gynecology, MedicalPark Izmir Hospital, Izmir, Turkey
[8] Department of Medical Oncology, Antwerp University Hospital, Antwerp, Belgium
[9] Clinic of General Surgery, Tepecik Training and Research Hospital, Izmir, Turkey
[10] Department of General Surgery, Katip Celebi University School of Medicine, Izmir, Turkey
[11] Corapcioglu Medikal Danismanlik, Ankara, Turkey
[12] Clinic of Obstetricas and Gynecology, Tepecik Training and Research Hospital, Izmir, Turkey
[13] Department of General Surgery, Okan University School of Medicine, Istanbul, Turkey

Dear Editor,

The most important expectation of a healthy young woman is to have a healthy pregnancy. No matter how strong she is psychologically, diverging from pregnancy expectation is a very difficult situation to accept for an infertile woman aside from being concerned of her life with cancer or probable cancer diagnosis (1). Current data suggests that breast cancer is not generally a contra-indication for pregnancy and/also pregnancy does not have a negative impact on the prognosis of breast cancer in patients with no existing local and systemic diseases and completed their standard treatments (2,3). Therefore, pregnancy expectation is quite natural in breast cancer cases which subsist a disease-free survival expectation.

The 2019 Symposium of Turkish Society of Reproductive Medicine (TSRM) was held together with the Turkish Senology Academy (SENATURK) under the theme of "Fertility and Breast Cancer" in Izmir, in May 18th-19th, 2019. Gynecologists specialized in fertility, general surgeons specialized in breast cancer and numerous family physicians participated actively to the meeting. Intended for family physicians, "Basic Concepts in Infertility", "The Role of Family Physician from Infertility to Birth" and "Critical Points of Breast Diseases in First Step" courses were performed with intense interest on the first day of the meeting.

The second day, the most comprehensive onco-fertility symposium based on breast cancer was performed for the first time in our country. The conferences titled "Breast Radiology-Suspicious Lesion Follow-up in Pregnancy", "Risk Consulting in Hereditary Breast Cancer Cases", "Risk Reducing Breast Surgery" and "The Role of Breast Surgeon in Planning Pregnancy" were performed in the Breast Cancer for Gynecologists Session. "Current Situation on Freezing and Transplantation of the Over Tissue", "Endometrial Follow-up During the Adjuvant Hormonal Treatment",

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Corresponding Author
Mehmet Ali Koçdor
E-mail: mehmet.kocdor@deu.edu.tr

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"Systemic Treatment of Breast Cancer in Infertile Women", "Preservation Modalities for Fertilization During the Chemotherapy", "Urgent Ovulation Induction Before Chemotherapy" and "Current Situation in Oocyte cryopreservation" were performed in the Preservation of Fertility in Oncological Cases Session. It appeared within these conferences that laboratories and technical infrastructure are available in many centers in Turkey, in which all contemporary applications intended for providing and preserving fertility in oncological cases are being performed successfully. These two disciplines performed a consensus panel in order to determine the principles peculiar to our country at the end of these conferences with critical subjects. The following articles were determined as basic principles by considering all the scientific data collected to date.

RECOMMENDATIONS, CONCENSUS ARTICLES

1. All fertile breast cancer survivors have the right to plan pregnancy and give healthy birth, except for the systemic disease and apparent low life expectation cases as the cure is in question -though the rates may differ-.
2. Patients should be informed that they have a pregnancy chance by the breast physician, especially at the diagnosis period, for the breast cancer cases aged forty and below. These cases should absolutely be questioned and recorded for their pregnancy expectations and wishes.
3. Breast cancer cases having the wish and expectation of pregnancy should be guided to the infertility clinic instead of standard gynecology clinics scarcely at the diagnosis period.
4. In cases showing BI-RADS 5 lesion in their breast radiograms and at the same time in pregnancy, expectations should be subjected to preparations in aspects of planning the fertility method and completing the related analyses and investigations until the histopathologic diagnosis is reached.
5. In mutation carriers with high breast cancer risk, in cases with strong family history or high risk histopathology in their biopsies, risk reducing surgery should be suggested before planned pregnancy if possible. As for the low level over reserve cases, risk reduction procedures may be shifted post embryo/oocyte cryopreservation.
6. When pregnancy consists in highly risked cases as stated in article 5, it cannot be terminated unless the family demands for it. However, these cases should be close-monitored by the breast surgeon and an experienced radiologist. This observation is continued post birth period and risk reducing procedures are suggested to the patient after the non-long-term of lactation.
7. Chemotherapy agents are gonadotoxic in variable ratios. However, considering pregnancy expectation, standard systemic treatment protocols including endocrine treatment cannot be changed. Embryo/oocyte cryopreservation before chemotherapy is the first choice for potential pregnancy for cases with a pregnancy wish. Embryo/oocyte cryopreservation before the planned standard treatment scheme has a critical importance due to the decrease in over reserve and permanent amenorrhea contingency, and cases should be encouraged towards this aspect. Pregnancy contingency with transferred embryos is almost equal to normal population in the light of current data (4).
8. Over suppression with GnRH analogs during chemotherapy is not an alternative application to embryo/oocyte cryopreservation. However, there is no objection in applying it independently from the estrogen receptor state of the breast tumor in order to preserve the ovary functions.
9. Ovulation induction and embryo/oocyte cryopreservation should be performed URGENTLY right from the histopathologic diagnosis by the infertility clinic within the protocols framework determined by TSRM. Transfer timing is determined multidisciplinarily upon the opinions of Fertility – Breast clinic, considering the special/biological condition and the cure/progression state of the patient after systemic treatment is completed. Pregnancy decision of the patient and her family is the main determinant unless there is a disease case showing progression.

CONCLUSION

All young, early breast cancer patients should be informed of their pregnancy chances provided that the current standard treatments are completed; and if desired, urgent oocyte stimulation and embryo/oocyte cryopreservation processes should be completed before systemic chemotherapy. However, this special condition should be carried out in cooperation with fertility clinics and general surgery clinics where intense breast tumor surgeries are performed.

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