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Aims and Scope

Turkish Journal of Colorectal Disease is an official journal of the Turkish Society of Colon and Rectal Surgery to provide epidemiologic, pathologic, diagnostic and therapeutic studies relevant to the management of small intestine, colon, rectum, anus and pelvic floor diseases. It was launched in 1991. Although there were temporary interruptions in the publication of the journal due to various challenges, the Turkish Journal of Colorectal Disease has been published continually from 2007 to the present. It is published quarterly (March, June, September and December) as hardcopy and an electronic journal at http://www.turkishjcrd.com/

The target audience of Turkish Journal of Colorectal Disease includes surgeons, pathologists, oncologists, gastroenterologists and health professionals caring for patients with a disease of the colon and rectum.

The Turkish name of the journal was formerly Kolon ve Rektum Hastalıkları Dergisi and the English name of the journal was formerly Journal of Diseases of the Colon and Rectum.

Turkish Journal of Colorectal Disease is indexed in **TÜBİTAK/ULAKBİM, Directory of Open Access Journals (DOAJ), British Library, ProQuest, Root Indexing, Idealonline, Gale/Cengage Learning, Index Copernicus, Turkish Citation Index, Hinari, GOALI, ARDI, OARE, J-GATE** and **TürkMedline.**

The aim of Turkish Journal of Colorectal Disease is to publish original research papers of the highest scientific and clinical value at an international level. Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions and congress/meeting announcements are released.

Turkish Journal of Colorectal Disease is an independent open access peer-reviewed international journal printed in Turkish and English languages. Manuscripts are reviewed in accordance with "double-blind peer review" process for both referees and authors. The Editorial Board of the Turkish Journal of Colorectal Disease endorses the editorial policy statements approved by the WAME Board of Directors. The journal is in compliance with the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors (NEJM 1997;336:309-315, updated 2001).

Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge. Open Access Policy is based on rules of Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/.

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Instructions for authors are published in the journal and at www.turkishjcrd.com

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Authors are responsible for the manuscripts they publish in Turkish Journal of Colorectal Disease. The editor, editorial board, and publisher do not accept any responsibility for published manuscripts.

If you use a table or figure (or some data in a table or figure) from another source, cite the source directly in the figure or table legend.

The journal is printed on acid-free paper.

Financial expenses of the journal are covered by Turkish Society of Colon and Rectal Surgery.

Editorial Policy

Following receipt of each manuscript, a checklist is completed by the Editorial Assistant. The Editorial Assistant checks that each manuscript contains all required components and adheres to the author guidelines, after which time it will be forwarded to the Editor in Chief. Following the Editor in Chief's evaluation, each manuscript is forwarded to the Associate Editor, who in turn assigns reviewers. Generally, all manuscripts will be reviewed by at least three reviewers selected by the Associate Editor, based on their relevant expertise. Associate editor could be assigned as a reviewer along with the reviewers. After the reviewing process, all manuscripts are evaluated in the Editorial Board Meeting.

Turkish Journal of Colorectal Disease's editor and Editorial Board members are active researchers. It is possible that they would desire to submit their manuscript to the Turkish Journal of Colorectal Disease. This may be creating a conflict of interest. These manuscripts will not be evaluated by the submitting editor(s). The review process will be managed and decisions made by editor-in-chief who will act independently. In some situation, this process will be overseen by an outside independent expert in reviewing submissions from editors.

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Amaç ve Kapsam

Türk Kolon ve Rektum Hastalıkları Dergisi, Türk Kolon ve Rektum Cerrahi Derneği'nin resmi dergisidir. Bu dernek; ince barsak, kolon, rektum, anüs ve pelvik taban hastalıkları gibi hastalıkların yönetimi ile ilişkili epidemiyoloijk patolojik, tanısal ve tedavi edici çalışmalar yapar. Derneğimiz 1991'de kurulmuştur. Çeşitli zorluklar nedeniyle geçici aksaklıklar olsa da Türk Kolon ve Rektum Hastalıkları Dergisi 2007'den bu yana aralıksız olarak basılmaktadır ve 3 ayda bir olmak üzere (Mart, Haziran, Eylül, Aralık) basılı dergi ve elektronik olarak (http://www.turkishjcrd.com/) yayımlanır.

Derginin hedef kitlesini; cerrahlar, patologlar, onkologlar, gastroenterologlar ve kolorektal hastalarına hizmet veren profesyoneller oluşturur. Derginin amacı; uluslararası düzeyde en yüksek bilimsel ve klinik değeri olan orijinal çalışmaları yayınlamaktır. Bunlara ek olarak derleme (review) makaleleri, olgu sunumları, teknik notlar, editöre mektuplar, editöryal yorumlar, eğitim yazıları ve kongre/toplantı duyuruları yer almaktadır.

Derginin Türkçe eski adı; Kolon ve Rektum Hastalıkları Dergisi ve İngilizce eski adı; Journal of Diseases of the Colon and Rectum'dur.

Kolon ve Rektum Hastalıkları Dergisi, **TÜBİTAK/ULAKBİM, Directory of Open Access Journals (DOAJ), British Library, ProQuest, Root Indexing, Idealonline, Gale/Cengage Learning, Index Copernicus, Türk Atıf Dizini, Hinari, GOALI, ARDI, OARE, J-GATE ve TürkMedline**'de indekslenmektedir.

Türk Kolon ve Rektum Hastalıkları Dergisi, İngilizce ve Türkçe olarak yayımlanan; bağımsız, hakemli, uluslararası bir dergidir. Eserler, hem hakemler hem de otörler tarafından "çift kör hakem denetimi (peer review)" yöntemi ile değerlendirilir. Türk Kolon ve Rektum Hastalıkları Dergisi'nin Editör Kurulu, World Association of Medical Editors (WAME) politikalarına bağlı olarak yürütülmektedir. Bu dergi, Uluslararası Tıp Dergisi Editörler Komitesi (NEJM 1997;336:309-315, updated 2001) tarafından bildirilen, biyomedikal dergilere gönderilen makalelerin uyması gereken standartlara uygunluk göstermektedir.

Açık Erişim Politikası

Bu dergi bilginin yer değiştirmesi ve toplum içinde bilgiye özgürce ulaşma olanağı sağlamak üzere açık erişime imkan vermektedir. Açık Erişim İlkesi "Budapeşte Açık Erişim Girişimi (BOAI)" http://www.budapestopenaccessinitiative.org/ kurallarına dayanmaktadır.

Derginin mali giderleri Türk Kolon ve Rektum Cerrahi Derneği tarafından karşılanmaktadır.

Yazarlar için Kılavuz

Yazarlar için kılavuz hem yayınlanan dergide hem de "http://www.turkishjcrd.com" web sayfasında bulunmaktadır.

Telif Hakkı Devri

Yazarlar Türk Kolon ve Rektum Hastalıkları Dergisi'nde yayınladıkları yazılardan kendileri sorumludurlar. Editör, editör kurulu ve yayıncı hiçbir sorumluluk kabul etmemektedir. Başka bir kaynaktan tablo ya da figür (veya tablo/figürden bir veri) kullandıysanız, direkt olarak tablo ya da figürü kaynak gösteriniz.

Dergi asitsiz kağıda basılmaktadır.

Derginin mali giderleri Türk Kolon ve Rektum Cerrahi Derneği tarafından karşılanmaktadır.

Editöryal Politika

Her yazının alınmasını takiben, bir kontrol listesi Editör Yardımcısı tarafından tamamlanır.

Editör yardımcısı, her yazıyı gerekli öğeleri sağladığı ve yazar kılavuzuna uyumu açısından kontrol eder, ardından editöre iletir. Editör değerlendirmesinin ardından her bir yazı için editör yardımcısı tarafından gözlemciler (reviewers) belirlenir. Genelde, her bir yazıyı ilgili uzmanlıkları göz önüne alınarak atanmış en az 3 gözlemci inceler. Yardımcı editör de diğer gözlemcilerle birlikte gözlemci olarak atanabilir. Gözlemci incelemesinin ardından yazılar editör kurul toplantısında değerlendirilir.

Türk Kolon ve Rektum Hastalıkları Dergisi'nin editör ve editör kurulu üyeleri aktif araştırmacılardır. Kendi araştırmalarının da Türk Kolon ve Rektum Hastalıkları Dergisi'nde yayınlanmasını pek ala arzu edebilirler. Bu durum çıkar sorunları doğurabilir. Bu yazılar, yazıyı yazan editör(ler) tarafından değerlendirilemez. Bu gibi durumlarda bu süreç, (editörlerin yazı başvurularında) yazıların uzman olan bağımsız kişiler tarafından incelenmesiyle aşılabilir.

Abonelik Bilgileri

Türk Kolon ve Rektum Hastalıkları Dergisi, Türk Kolon ve Rektum Cerrahisi Derneği üyelerine, Dünya'da ve Türkiye'deki kütüphanelere ücretsiz dağıtılmaktadır. Yayınlanmış tüm sayılar ücretsiz olarak şu linkte mevcuttur (http://www.turkishjcrd.com/).

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GENERAL INFORMATION

Turkish Journal of Colorectal Disease (TJCD) is the journal of Turkish Society of Colon and Rectal Surgery. The mission of the Journal is to advance knowledge of disorders of the small intestine, colon, rectum, anus and pelvic floor. It publishes invited review articles, research articles, brief reports and letters to the editor, and case reports that are relevant to the scope of the journal, on the condition that they have not been previously published elsewhere. Basic science manuscripts, such as randomized, cohort, cross-sectional, and case control studies, are given preference. Invited reviews will be considered for peer review from known experts in the area.

Manuscripts should be prepared according to ICMJE guidelines (www.icmje.org). All manuscripts are subject to editorial revision to ensure they conform to the style adopted by the journal. There is a double blind kind of reviewing system.

Reviewed and accepted manuscripts are translated from Turkish to English by the Journal through a professional translation service. Prior to printing, the translations are submitted to the authors for approval or correction requests, to be returned within 7 days. If no response is received from the corresponding author within this period, the translation is checked and approved by the editorial board.

Accepted manuscripts are published in both Turkish and English languages.

All manuscripts submitted to the Turkish Journal of Colorectal Disease are screened for plagiarism using the 'iThenticate' software. Results indicating plagiarism may result in manuscripts being returned or rejected.

Turkish Journal of Colorectal Disease does not charge any article submission or processing charges.

The abbreviation of the Turkish Journal of Colorectal Disease is "TJCD", however, it should be denoted as "Turk J Colorectal Dis" when referenced.

EDITORIAL POLICIES

All manuscripts will be evaluated by the scientific board for their scientific contribution, originality and content. Authors are responsible for the accuracy of the data. The journal retains the right to make appropriate changes on the grammar and language of the manuscript. When suitable the manuscript will be sent to the corresponding author for revision. The manuscript, when published, will become the property of the journal and copyright will be taken out in the name of the journal

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In the cover letter the authors should state if any of the material in the manuscript is submitted or planned for publication elsewhere in any form including electronic media. A written statement indicating whether or not "Institutional Review Board" (IRB) approval was obtained or equivalent guidelines followed in accordance with the Helsinki Declaration of 2013 update on human experimentation must be stated; if not, an explanation must be provided. The cover letter must contain address, telephone, fax and the e-mail address of the corresponding author.

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The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can create at http://orcid.org.

Online Submission

Only online submissions are accepted for rapid peer-review and to prevent delay in publication. Manuscripts should be prepared as word document (*.doc) or rich text format (*.rtf). After logging on to the web www. journalagent.com/krhd double click the "submit an article" icon. All corresponding authors should be provided a password and an username after providing the information needed. After logging on the article submission system with your own password and username please read carefully the directions of the system to provide all needed information in order not to delay the processing of the manuscript. Attach the manuscript, all figures, tables and additional documents. Please also attach the cover letter with "Assignment of Copyright and Financial Disclosure" forms.

Manuscript Preparation Guidelines

Turkish Journal of Colorectal Disease follows the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (International Committee of Medical Journal Editors: Br Med J 1988;296:401-5).

Upon submission of the manuscript, authors are to indicate the type of trial/research and statistical applications following "Guidelines for statistical reporting in articles for medical journals: amplifications and explanations" (Bailar JC III, Mosteller F. Ann Intern Med 1988;108:266-73).

Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA,

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Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Title Page

All manuscripts, regardless of article type, should start with a title page, containing:

The title of the article;

The short title of the article

The initials, names and qualifications of each author;

The main appointment of each author;

The name(s) of the institution(s) of each author;

The name and email address of the corresponding author;

Full disclosures of potential conflicts of interest on the part of any named author, or a statement confirming that there are no conflicts of interest;

The word count excluding abstract, references, tables, figures and legends;

The place and date of scientific meeting in which the manuscript was presented and it's abstract published in the abstract book, if applicable.

Article Types

Original Articles

This category includes original research including both clinical and basic science submissions. The work must be original and neither published, accepted, or submitted for publication elsewhere. Any related work, either SUBMITTED, in press, or published from any of the authors should be clearly cited and referenced.

All clinical trials must be registered in a public trials registry that is acceptable to the International Committee of Medical Journals Editors (ICMJE). Go to (http://www.icmje.org/faq.html). Authors of randomized controlled trials must adhere to the CONSORT guidelines, available at: www.consort-statement.org, and provide both a CONSORT checklist and flow diagram. We require that you choose the MS Word template at www.consort-statement.org for the flow chart and cite/upload it in the manuscript as a figure. In addition, submitted manuscripts must include the unique registration number in the Abstract as evidence of registration.

All authors are expected to abide by accepted ethical standards for human and animal investigation. In studies that involve human subjects or laboratory animals, authors must provide an explicit statement in Materials and Methods that the experimental protocol was approved by the appropriate institutional review committee and meets the guidelines of their responsible governmental agency. In the case of human subjects, informed consent, in addition to institutional review board approval, is required.

Original Articles should not exceed 3000 words (excluding abstract, references, tables, figures and legends) and four illustrations.

Original Articles should be organized as follows:

Abstract: The abstract must contain fewer than 250 words and should be structured as follows:

Aim: What was the purpose of the study?

Method: A brief description of the materials - patients or subjects (i.e. healthy volunteers) or materials (animals) - and methods used.

Results: What were the main findings?

Conclusion: What are the main conclusions or implications of the study?

Keywords: Below the abstract provide up to 6 key words or short phrases. Do not use abbreviations as keywords.

Introduction: State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

Materials and Methods: Describe your selection of the observational or experimental subjects clearly (patients or experimental animals, including controls). Provide an explicit statement that the experimental protocols were approved by the appropriate institutional review committee and meet the guidelines of the responsible governmental agency. In the case of human subjects, state explicitly those subjects have provided informed consent. Identify the methods, apparatus/product** (with manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known, describe substantially modified methods, including statistical methods, give reasons for using them, and evaluate their limitations;

Results: Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion: State the importance and significance of your findings but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with those of others. No new data are to be presented in this section.

Acknowledgments: Only acknowledge persons who have made substantive contributions to the study. Authors are responsible for obtaining written permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions. Begin your text of the acknowledgment with, "The authors thank…".

Authorship Contributions: The journal follows the recommendations of the ICMJE for manuscripts submitted to biomedical journals. According to these, authorship should be based on the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and

Drafting the work or revising it critically for important intellectual content; and

Final approval of the version to be published; and

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All other contributors to the paper should be credited in the 'Acknowledgments' section.

References: The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in parenthesis in superscript at the end of citation content or after the cited author's name. Use the form of "Uniform Requirements for manuscript abbreviations in Turk Bilim Terimleri" (http:/www.bilimterimleri.com).

Journal titles should conform to the abbreviations used in "Cumulated Index Medicus".

Journals; Last name(s) of the author(s) and initials, article title, publication title and its original abbreviation, publication date, volume, the inclusive page numbers.

Example: 1. Dilaveris P, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. Pacing Clin Electrophysiol 1999;22:1532-1538.

Book chapter; Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the extract cited.

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Example: 1. Schwartz PJ, Priori SG, Napolitano C. The Long QT Syndrome. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology. From Cell to Bedside. Philadelphia; WB Saunders Co. 2000:597-615.

Tables: All tables are to be numbered using Arabic numerals. Tables should always be cited in text in consecutive numerical order. For each table, please supply a table caption (title) explaining the components of the table. Identify any previously published material by giving the original source in the form of a reference at the end of the table caption. Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Figures: Figures should work under "Windows". Color figures or grayscale images must be at least 300 dpi. Figures using "*.tiff", "*.jpg" or "*.pdf" should be saved separate from the text. All figures should be prepared on separate pages. They should be numbered in Arabic numerals. Each figure must have an accompanying legend defining abbreviations or symbols found in the figure. Figures could be submitted at no additional cost to the author.

Units of Measurement and Abbreviations: Units of measurement should be in Systéme International (SI) units. Abbreviations should be avoided in the title. Use only standard abbreviations. If abbreviations are used in the text, they should be defined in the text when first used.

Permissions: Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Invited Review Articles

Abstract length: Not to exceed 250 words.

Article length: Not to exceed 4000 words.

Reference Number: Not to exceed 100 references.

Reviews should include a conclusion, in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. The study's new and important findings should be highlighted and interpreted in the Conclusion section. There should be a maximum of two authors for review articles.

Case Reports

Abstract length: Not to exceed 100 words.

Article length: Not to exceed 1000 words.

Reference Number: Not to exceed 15 references.

Case Reports should be structured as follows:

Abstract: An unstructured abstract that summarizes the case.

Introduction: A brief introduction (recommended length: 1-2 paragraphs).

Case Report: This section describes the case in detail, including the initial diagnosis and outcome.

Discussion: This section should include a brief review of the relevant literature and how the presented case furthers our understanding to the disease process.

References: See under 'References' above.

Acknowledgments.

Tables and figures.

Technical Notes

Abstract length: Not to exceed 250 words.

Article length: Not to exceed 1200 words.

Reference Number: Not to exceed 15 references.

Technical Notes include description of a new surgical technique and its application on a small number of cases. In case of a technique representing a major breakthrough one case will suffice. Follow-up and outcome need to be clearly stated.

Technical Notes should be organized as follows:

Abstract: Structured "as above mentioned".

Indications

Method

Comparison with other methods: advantages and disadvantages, difficulties and complications.

References, in Vancouver style (see under 'References' above).

Acknowledgments.

Tables and figures: Including legends.

Letters to the Editor

Article length: Not to exceed 500 words.

Reference Number: Not to exceed 10 references

We welcome correspondence and comment on articles published in Turkish Journal of Colorectal Disease. No abstract is required, but please include a brief title. Letters can include 1 figure or table.

Video Article

Article length: Not to exceed 500 words.

Reference Number: Not to exceed 5 references

Briefly summarize the case describing diagnosis, applied surgery technique and outcome. Represent all important aspects, i.e. novel surgery technique, with properly labelled and referred video materials. A standalone video vignette, describing a surgical technique or interesting case encountered by the authors.

Requirements: The data must be uploaded during submission with other files. The video should be no longer than 10 minutes in duration with a maximum file size of 350Mb and 'MOV, MPEG4, AVI, WMV, MPEGPS, FLV, 3GPP, WebM' format should be used. Documents that do not exceed 100 MB can be uploaded within the system. For larger video documents, please contact iletisim@galenos.com.tr All videos must include a narration in English. Reference must be used as it would be for a Figure or a Table. Example: ".....To accomplish this, we developed a novel surgical technique (Video 1)." All names and institutions should be removed from all video materials. Video materials of accepted manuscripts will be published online.

Letters to the Editor

Article length: Not to exceed 500 words.

Reference Number: Not to exceed 10 references

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This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

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The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism").

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The Turkish Journal of Colorectal Disease publishes abstracts of accepted manuscripts online in advance of their publication in print. Once an accepted manuscript has been edited, the authors have submitted any final corrections, and all changes have been incorporated, the manuscript will be published online. At that time the manuscript will receive a Digital Object Identifier (DOI) number. Both forms can be found at www.journalagent.com/krhd. Authors of accepted manuscripts will receive electronic page proofs directly from the printer, and are responsible for proofreading and checking the entire manuscript, including tables, figures, and references. Page proofs must be returned within 48 hours to avoid delays in publication.

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Yazarlara Bilgi

GENEL BİLGİ

Türk Kolon ve Rektum Hastalıkları Dergisi, Türk Kolon ve Rektum Cerrahisi Derneği'nin dergisidir. Derginin misyonu; ince bağırsak, kolon, rektum, anüs ve pelvik taban bozuklukları hakkındaki bilgiye katkı sağlamaktır. Dergi daha önce başka bir yerde yayınlanmamış olması koşuluyla, derginin kapsamı ile ilgili ve talep üzerine yazılan derleme makaleleri, araştırma makaleleri, kısa raporlar ve editöre mektuplar ve olgu sunumlarını yayınlamaktadır. Randomize, kohort, kesitsel ve vaka kontrol çalışmaları gibi temel bilim yazılarına öncelik verilir. Alanında bilinen uzmanlarca talep üzerine yazılan derlemeler dikkate alınacaktır.

Yazılar ICMJE yönergelerine göre (http://www.icmje.org/) hazırlanmalıdır. Tüm yazılar dergi tarafından benimsenen stile uygunluk sağlamak için editöryal kontrol ve düzeltmelere tabi tutulmaktadır. Derginin çift kör bir değerlendirme sistemi vardır. Değerlendirilen ve kabul edilen yayınlar Türkçeden İngilizceye veya İngilizceden Türkçeye derginin profesyonel çeviri hizmeti aracılığıyla tercüme edilir. Yayınlanmadan önce, çeviriler onay veya düzeltme istekleri için yazarlara gönderilir ve 7 gün içinde geri dönüş talep edilir. Bu süre içinde yanıt alınamazsa, çeviri kontrol ve yayın kurulu tarafından onaylanır.

Kabul edilen yayınlar hem Türkçe hem de İngilizce olarak yayınlanır.

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Türk Kolon ve Rektum Hastalıkları Dergisi, makale gönderme veya işlem ücreti adı altında herhangi bir ücret talep etmemektedir.

Türk Kolon ve Rektum Hastalıkları Dergisi'nin kısaltması "TJCD"dir, ancak, refere edildiğinde "Turk J Colorectal Dis" olarak kullanılmalıdır.

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Tüm makaleler bilimsel katkıları, özgünlük ve içerikleri açısından bilimsel komite tarafından değerlendirilecektir. Yazarlar verilerinin doğruluğundan sorumludurlar. Dergi gerekli gördüğü yerlerde dil ve uygun değişiklik yapma hakkını saklı tutar. Gereğinde makale revizyon için yazara gönderilir. Dergide basılan yayın derginin malı haline gelir ve telif hakkı "Türk Kolon ve Rektum Hastalıkları Dergisi" adına alınmış olur. Daha önce herhangi bir dilde yayınlanmış makaleler dergide yayınlanmak üzere kabul edilmeyecektir. Yazarlar bir başka dergide yayınlanmak üzere olan makaleyi teslim edemez. Tüm değişiklikler, yazar ve yayıncının yazılı izin alındıktan sonra yapılacaktır. Tüm makalelerin tam metinleri derginin www.journalagent.com/krhd web sitesinden indirilebilir.

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Açıklama bildirimi

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Makale Hazırlama Kuralları

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İnsan katılımcılı araştırma ve/veya hayvan deneyleri

Bilgilendirilmiş Onam

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Gecikmeyi önlemek ve hızlı hakemlik için sadece çevrim içi gönderimler kabul edilir. Yazılar word belgesi (*.doc) veya zengin metin biçimi (*.rtf) olarak hazırlanmalıdır. www.journalagent.com/krhd adresinde web oturumu açtıktan sonra "Makale gönder" ikonuna tıklayın. Tüm yazarlar, gerekli bilgileri sisteme girdikten sonra bir şifre ve bir kullanıcı adı alır. Kendi şifre ve kullanıcı adınız ile makale gönderme sistemine kayıt olduktan sonra yazının işleme alınmasında bir gecikme olmaması için gerekli tüm bilgileri sağlamak için sistemin yönergelerini dikkatlice okuyunuz. Makaleyi ve tüm şekil, tablo ve ek dökümanları ekleyiniz. Ayrıca üst yazı ve "Telif Hakkı ve Finansal Durum" formunu ve yazının tipine göre aşağıda belirtilen kılavuzların kontrol listesini ekleyiniz.

Makale Hazırlama Kuralları

Türk Kolon ve Rektum Hastalıkları Dergisi "Biyomedikal Dergilere Gönderilen Makaleler için Gerekli Standartları" izler. (International Committee of Medical Journal Editors: Br Med J 1988; 296: 401-5).

Yazarlar yayınlarını gönderirken, çalışmalarının türünü ve uygulanan istatistik yöntemlerini "Tıbbi Dergilere Gönderilen Makaleler için İstatistiksel Raporlama Rehberi"ne uygun olarak belirtmelidir (Bailar JC III, Mosteller F. Ann Intern Med 1988;108:266-73).

Araştırma makalesi, sistematik değerlendirme ve meta-analizin hazırlanması aşağıdaki çalışma tasarımı kurallarına uymak zorundadır; (CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group.

The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285:1987-91) (http://www.consort-statement.org/);

PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

Metin Biçimlendirme

Yazılar Word programı ile hazırlanarak teslim edilmelidir.

- Metin için normal, düz yazı tipi kullanın (örneğin, 10 punto Times Roman).

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- Alan fonksiyonları kullanmayın.

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- Tablo yapmak için diğer işlevleri değil, elektronik tablo fonksiyonunu kullanın.

- Dosyanızı .docx formatında (Word 2007 veya üstü) ya da .doc formatında (eski Word sürüm) kaydedin.

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Tüm yazılar, makale türü ne olursa olsun, aşağıdakileri içeren bir başlık sayfası ile başlamalıdır:

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Makale Tipleri

Orijinal Makaleler

Bu kategori, klinik ve temel bilimde orijinal araştırmaları içerir. Yayın orijinal olmalı ve başka bir dergide yayınlanmış/gönderilmiş ya da kabul edilmiş olmamalıdır. Yazarlar, herhangi biri tarafından bir dergiye gönderilmiş, baskıda veya basılmış ilgili herhangi bir çalışmaya atıfta bulunmak istiyorlarsa açıkça atıfta bulunulmalı ve kaynak gösterilmelidir.

Tüm klinik çalışmalar, Uluslararası Tıp Dergisi Editörler Komitesince (ICMJE) kabul gören bir kayıt sistemine kayıtlı olmalıdır. Bunun için http://www.icmje.org/faq.html adresine müracaat edin. Randomize kontrollü çalışmaların yazarları da, www.consort-statement.org adresinden başvurulabilen CONSORT kılavuzuna uymalıdır ve yayınlarıyla birlikte CONSORT kontrol listesi ve akış diyagramı tebliğ edilmelidir. Akış şeması olarak www.consort-statement.org adresinde bulunan MS Word şablonunun kullanılması ve bunun yayının içinde bir alıntı veya bir figür olarak yerleştirilmesi gereklidir. Buna ek olarak, sunulan yayınlar her yayına spesifik verilen özel kayıt numarasını içermelidir.

Tüm yazarların, insan üzerindeki çalışmalar ve hayvan deneylerinde etik standartlara uymaları beklenmektedir. İnsan üzerindeki veya laboratuvar hayvanları içeren çalışmalarda, yazarların yayının Gereç ve Yöntem kısmında deney protokolünün ilgili kurumsal inceleme komitesi tarafından onaylandığını ve sorumlu devlet kurumu kurallarına uyduğunu açık bir dille açıklamaları gereklidir. İnsan üzerindeki çalışmalarda kurumsal inceleme kurulu onayına ek olarak, aydınlatılmış onam da bulunmalıdır.

Orijinal Makaleler (özet, kaynaklar, tablolar, rakamlar hariç) 3000 kelime ve dört figürü aşmamalıdır.

Orijinal Makaleler aşağıdaki gibi organize edilmelidir:

Özet: Özet 250 kelimeyi geçmemeli ve şunları içermelidir;

Amaç: Çalışmanın amacı nedir?

Yöntem: Kullanılan yöntem ve materyaller (örneğin hayvanlar) veya hastalar ya da konu (sağlıklı gönüllüler gibi) hakkında kısa bir açıklama içermelidir.

Bulgular: Ana bulgular nelerdir?

Sonuç: Çalışmanın ana sonuçları ve etkileri nelerdir?

Anahtar kelimeler: Özetin altında en az 3 anahtar kelime veriniz. Kısaltmaları anahtar kelime olarak kullanmayınız.

Giriş: Açık bir dille çalışmanın amaç ve gerekçesini belirtin ve çalışmanın arka planını açıklarken sadece en önemli kaynaklardan alıntı yapın.

Gereç ve Yöntem: Gözlemsel veya deneysel deneklerin (hastalar, deney hayvanları veya kontrol grupları dahil) seçim şeklini açıklayın. Deney protokolünün ilgili kurumsal inceleme komitesi tarafından onaylandığını ve ilgili devlet kurumu kurallarına uyduğunu açık bir dille açıklayın. İnsan çalışması durumunda, tüm şahısların aydınlatılmış onamlarının alındığını açık bir dille belirtin. Yöntem, cihaz ve ürünleri tanımlayın (Parantez içinde üretici firma adı ve adresi)** Uygulanmış olan tüm prosedürler, diğer çalışmacıların aynı deneyi tekrar edebilecekleri detay ve netlikte anlatılmalıdır. İstatistiksel yöntemler de dahil olmak üzere yerleşik ve yaygın olarak bilinen çalışma yöntemleri için kaynaklar belirtilmelidir. Yayınlanmış ancak yaygın olarak bilinmeyen yöntemler için ise kaynaklar ve kısa tanımlamalar verilmelidir. Kullanma sebepleri ve limitasyonları belirtilmelidir.

Bulgular: İstatistiksel yöntemlerle desteklenmiş bulgularınızı ayrıntılı olarak sunun. Şekil ve tablolar metni tekrar değil, takviye etmelidir. Verilerin hem metinde hem figür olarak verilmemesi gerekir. Metin veya figürden birisi olarak verilmesi yeterlidir. Sadece kendi önemli izlenimlerinizi belirtin. Kendi izlenimlerinizi diğerlerininkiyle karşılaştırmayın. Bu tür karşılaştırma ve yorumlar tartışma bölümünde yapılmalıdır.

Tartışma: Bulgularınızın önem ve anlamını vurgulayın ancak bulgular kısmında verilenleri tekrarlamayın. Fikirlerinizi yalnızca bulgularınızla kanıtlayabildiklerinizle sınırlı tutun. Bulgularınızı diğerlerininkiyle karşılaştırın. Bu bölümde yeni veriler bulunmamalıdır.

Teşekkür: Sadece çalışmaya ciddi katkılarda bulunmuş kişilere teşekkür edin. Yazarlar ismen teşekkür ettikleri herkesten yazılı izin almak zorundadır. Teşekkür kısmına "Yazarlar ….teşekkür eder" şeklinde başlayın.

Yazarlık ve Katkı Sağlayanlar: Dergi, biyomedikal dergilere gönderilen yayınlara yönelik ICMJE tavsiyelerini izler. Buna göre "yazarlık" aşağıdaki dört kritere dayalı olmalıdır:

Yazar;

- Yayının konsept veya dizaynına, çalışmanın verilerinin elde edilmesine, analizine ve yorumlanmasına önemli katkılar veren; ve

- İşi hazırlayan veya entellektüel içerik açısından eleştirel biçimde gözden geçiren; ve

- Yayınlanacak son şekli onaylayan; ve

- Çalışmanın her bir bölümünün doğruluğu ve bütünlüğü ile ilgili sorunları uygun bir şekilde inceleyen ve çözüm sağlayan sorumlu kişidir.

Bu şartların hepsini sağlamayan diğer tüm katılımcılar yazar değil, "Teşekkür" bölümünde anılması gereken katkı sağlamış kişilerdir.

Kaynaklar: Kaynakları 1'den başlayarak Arap rakamları ve alfabetik sıra ile verin. Kaynak numaraları cümle sonunda noktadan sonra üstte küçük rakamlar şeklinde (superscript) yazılmalıdır. Kısaltmalar için gerekli standartları http:/www.bilimterimleri.com adresinde bulunan Türk Bilim Terimleri Kılavuzu'ndan edinin.

Dergi başlıkları "Cumulated Index Medicus" kısaltmalarına uygun olmalıdır.

Dergiden: Yazar/yazarların soyadı ve adının ilk harfi, makale başlığı, dergi başlığı ve derginin özgün kısaltması, yayın tarihi, baskı, kapsayıcı sayfa numaralarını içermelidir.

Örneğin: 1. Dilaveris P, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. Pacing Clin Electrophysiol 1999;22:1532-1538.

Kitap Bölümü: Yazar/yazarların soyadı ve adının ilk harfi, bölüm başlığı, kitap editörleri, kitap başlığı, basım, yayın yeri, yayın tarihi, kapsadığı sayfa numaralarını içermelidir

Örneğin: 1. Schwartz PJ, Priori SG, Napolitano C. The Long QT Syndrome. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology. From Cell to Bedside. Philadelphia; WB Saunders Co. 2000:597-615.

Tablolar: Tüm tablolar Arapça sayılarla numaralandırılmalıdır. Tüm tablolardan metin içerisinde numara sırası ile bahsedilmelidir. Her tablo için tablonun içeriği hakkında bilgi veren bir başlık verin. Başka yayından alıntı olan tüm tabloları tablonun alt kısmında kaynak olarak belirtin. Tabloda dipnotlar tablonun altında, üst karakter olarak küçük harflerle verilmelidir. İstatistiksel anlamlı değerler ve diğer önemli istatistiksel değerler yıldız ile işaretlenmelidir.

Şekiller: Şekillerin "Windows" ile açılması gerekir. Renkli şekiller veya gri tonlu görüntüler en az 300 dpi olmalıdır. Şekiller ana metinden ayrı olarak "*.tiff", "*.jpg" veya "*.pdf" formatında kaydedilmelidir. Tüm şekil ayrı bir sayfada hazırlanmalı ve Arap rakamları ile numaralandırılmalıdır. Her şekilde kendisindeki işaret ve sembolleri açıklayan bir alt yazı olmalıdır. Şekil gönderme için yazardan hiçbir ek ücret alınmaz.

Ölçü Birimleri ve Kısaltmalar: Ölçü birimleri System International (SI) birimleri cinsinden olmalıdır. Kısaltmalardan başlıkta kaçınılmalıdır. Sadece standart kısaltmalar kullanın. Metinde kısaltma kullanılırsa ilk kullanıldığı yerde tanımlanmalıdır.

İzinler: Yazarlar yayınlarına önceden başka bir yerde yayınlanmış şekil, tablo, ya da metin bölümleri dahil etmek isterlerse telif hakkı sahiplerinden izin alınması ve bu izin belgelerinin yayınla beraber değerlendirmeye gönderilmesi gerekmektedir. Böyle bir belgenin eşlik etmediği her materyalin yazara ait olduğu kabul edilecektir.

Davetli (Talep üzerine yazılan) Derlemeler

Özet uzunluğu: 250 kelimeyi aşmamalıdır.

Makale uzunluğu: 4000 kelimeyi aşmamalıdır.

Kaynak sayısı: 100 kaynağı aşmamalıdır.

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Derlemeler, üzerine konuyla ilgili yeni bir hipotez ya da çalışma oturtulabilecek bir sonuç içermelidir. Literatür taraması metodlarını veya kanıt düzeyi yöntemlerini yayınlamayın. Derleme makaleleri hazırlayacak yazarların ilgili konuda önceden araştırma makaleleri yayımlamış olması gerekir. Çalışmanın yeni ve önemli bulguları sonuç bölümünde vurgulanır ve yorumlanmalıdır. Derlemelerde maksimum iki yazar olmalıdır.

Olgu Sunumları

Özet uzunluğu: 100 kelimeyi aşmamalıdır.

Makale uzunluğu: 1000 kelimeyi aşmamalıdır.

Kaynak sayısı: 15 kaynağı aşmamalıdır.

Olgu Sunumları aşağıdaki gibi yapılandırılmalıdır:

Özet: Olguyu özetleyen bir yapılandırılmamış özet (gereç ve yöntem, bulgular, tartışma gibi bölümlerin olmadığı).

Giriş: Kısa bir giriş (tavsiye edilen uzunluk: 1-2 paragraf).

Olgu Sunumu: Bu bölümde ilk tanı ve sonuç da dahil olmak üzere olgu ayrıntılı olarak anlatılır.

Tartışma: Bu bölümde ilgili literatür kısaca gözden geçirilir ve sunulan olgunun, hastalığa bakışımızı ve yaklaşımımızı nasıl değiştirebileceği vurgulanır.

Kaynaklar: Vancouver tarzı, (yukarıda 'Kaynaklar' bölümüne bakınız).

Teşekkür

Tablolar ve şekiller

Teknik Notlar

Özet uzunluğu: 250 kelimeyi aşmamalıdır.

Makale uzunluğu: 1200 kelimeyi aşmamalıdır.

Kaynak Sayısı: 15 kaynağı aşmamalıdır.

Teknik Notlar, yeni bir cerrahi tekniğin açıklanmasını ve az sayıda olguda uygulanmasını içermektedir. Büyük bir atılım/değişikliği temsil eden bir tekniğin sunulması durumunda tek bir olgu yeterli olacaktır. Hastanın takip ve sonucu açıkça belirtilmelidir.

Teknik Notlar aşağıdaki gibi organize edilmelidir:

Özet: Aşağıdaki gibi yapılandırılmalıdır:

Amaç: Bu çalışmanın amacı nedir?

Yöntem: Kullanılan yöntemlerin, hastalar ya da sağlıklı gönüllülerin veya hayvanların tanımı, malzemeler hakkında kısa bir açıklama.

Bulgular: Ana bulgular nelerdir?

Sonuç: Bu çalışmanın ana sonuçları ve etkileri nelerdir?

Endikasyonları

Yöntem

Diğer yöntemlerle karşılaştırılması: Avantaj ve dezavantajları, zorluklar ve komplikasyonlar.

Kaynaklar: Vancouver tarzı (yukarıda 'Kaynaklar' bölümüne bakınız)

Teşekkür

Tablolar ve şekiller; alt yazıları dahil

Video Makale

Makale Uzunluğu: 500 kelimeyi aşmamalıdır.

Kaynak Sayısı: 5 kaynağı aşmamalıdır.

Tanıyı, uygulanan cerrahi tekniği ve sonucu açıklayarak olguyu kısaca özetleyiniz. Uygun şekilde adlandırılmış ve referans edilmiş video materyalleri ile tüm önemli noktaları, örn; yeni cerrahi tekniği, belirtiniz. Materyaller, yazarların cerrahi tekniğini anlattıkları veya karşılaştıkları ilginç vakalardan oluşmalıdır.

Teknik Gereklilikler: Veriler, makale yükleme sırasında diğer dosyalarla birlikte eklenmelidir. Video süresinin 10 dakikayı geçmemesi kaydıyla dosya boyutu maksimum 350 MB olmalı ve 'MOV, MPEG4, AVI, WMV, MPEGPS, FLV, 3GPP, WebM' formatlarından biri kullanılmalıdır. 100 MB'yi aşmayan video dokümanları sisteme yüklenebilir. Daha büyük video dokümanları için lütfen iletisim@galenos.com.tr adresinden bizimle iletişime geçiniz. Tüm video seslendirmeleri İngilizce olmalıdır. Video atıfları, Şekil veya Tablo atıfları ile aynı biçimde kullanılmalıdır. Örneğin; "….Bunu gerçekleştirmek için, yeni bir cerrahi teknik geliştirdik (Video 1)." Video materyallerinde isim ve kurumlar yer almamalıdır. Kabul edilen makalelerin video materyalleri online yayınlanacaktır.

Editöre Mektuplar

Makale uzunluğu: 500 kelimeyi aşmamalıdır.

Kaynak Sayısı: 10 kaynağı aşmamalıdır.

Türk Kolon ve Rektum Hastalıkları Dergisi'nde yayınlanan makaleler hakkında yorumlar memnuniyetle kabul edilir. Özet gerekli değildir, ancak lütfen kısa bir başlık ekleyiniz. Mektuplar bir şekil veya tablo içerebilir.

Editöryal Yorumlar

Makale uzunluğu: 1000 kelimeyi aşmamalıdır.

Kaynak Sayısı: 10 kaynağı aşmamalıdır.

Editöryal yorumlar sadece editör tarafından kaleme alınır. Editöryal yorumlarda aynı konu hakkında başka yerlerde yayınlanmış yazılar hakkında fikir veya yorumlar belirtilir. Tek bir yazar tercih edilir. Özet gerekli değildir, ancak lütfen kısa bir başlık ekleyiniz. Editöryal gönderimler revizyon/gözden geçirme talebine tabi tutulabilir. Editörler, metin stilini değiştirme hakkını saklı tutar.

Etik

Bu dergi, bilimsel kayıtların bütünlüğünü korumayı tahhüt etmektedir. Yayın Etik Komitesi (COPE) üyesi olarak, dergi olası olumsuz davranışlarla nasıl başa çıkılacağı konusunda Yayın Etik Komitesi (COPE) kılavuzlarını takip edecektir.

Yazarlar araştırma sonuçlarını yanlış sunmaktan; derginin güvenilirliğine, bilimsel yazarlık profesyonelliğine ve en sonunda tüm bilimsel çabalara zarar verebileceğinden dolayı, sakınmalıdır. Araştırma bütünlüğünün sürdürülmesi ve bunun sunumu, iyi bilimsel uygulama kurallarını takip ederek başarılır. Bu da şunları içerir:

- Yazılı eser değerlendirilmek üzere eş zamanlı birden fazla dergiye gönderilmemelidir.

- Yazılı eser daha önceki bir eserin geliştirilmesi olmadıkça, daha önce (kısmen ya da tamamen) yayınlanmamış olmalıdır. [Metnin yeniden kullanıldığı imasından kaçınmak için tekrar kullanılabilir materyallerde şeffaflık sağlayın ("self-plagiarism""kişinin kendinden intihali")].

- Tek bir çalışma; sunum miktarını arttırmak için birçok parçaya bölünmemeli ve zaman içinde aynı ya da çeşitli dergilere gönderilmemelidir. (örneğin "salam-yayıncılık" "salamizasyon").

- Veriler, sonuçlarınızı desteklemek için fabrikasyon (uydurma) ya da manüple edilmiş olmamalıdır.

- Yazarın kendine ait olmayan hiçbir veri, metin veya teori kendininmiş gibi sunulmamalıdır (intihal). Diğer eserlerin kullanımı, (eserin birebir kopyalanması, özetlenmesi ve/veya başka kelimeler kullanarak açıklanmasını da içeren) ya telif hakkı korunacak şekilde izin alınarak ya da tırnak işareti içinde birebir kopyalanarak uygun onay ile kullanılmalıdır.

Önemli not; Türk Kolon ve Rektum Hastalıkları Dergisi intihal taramak için bir program (iThenticate) kullanmaktadır.

- Eser sunulmadan önce sorumlu makamlardan ve çalışmanın yapıldığı enstitü/kuruluşlardan-zımnen veya açıkça-onay alınmasının yanı sıra tüm yazarlardan açıkça onay alınmış olmalıdır.

- Sunulan eserde yazar olarak ismi olanların, bilimsel çalışmaya yeterince katkısı olmuş olmalıdır ve ortak mesuliyet ve sorumluluğu olmalıdır.

Bununla beraber:

- Yazarlık veya yazarların sıra değişiklikleri eserin kabulünden sonra yapılamaz

- Yazının revizyon aşamasında, yayın öncesi veya yayınlandıktan sonra yazar isim eklenmesi veya çıkarılması istemi; ciddi bir konudur ve geçerli sebepler olduğunda değerlendirilebilir. Yazar değişikliği gerekçesi; haklı gerekçeli, inandırıcı ve sadece tüm yazarların yazılı onayı alındıktan sonra; ve yeni/silinmiş yazarın rolü silme hakkında ikna edici ayrıntılı bir açıklama ile kabul edilebilir. Revizyon aşamasında değişiklik olması halinde, bir mektup revise edilmiş yayına eşlik etmelidir. Yayına kabul edildikten veya yayınlandıktan sonra değişiklik olması halinde, bu istek ve gerekli dökümantasyonun yayıncı yoluyla editöre gönderilmesi gerekmektedir. Gerek görüldüğünde bu isteğin gerçekleşmesi için daha fazla doküman talep edilebilir. Değişikliğin kabul veya red kararı dergi editörü insiyatifindedir. Bu nedenle, yayının gönderilmesi aşamasında yazar/yazarlar; gönderecekleri ilgili yazar grubunun isim doğruluğundan sorumludur.

- Yazarlardan sonuçların geçerliliğini doğrulamak amacıyla verilerin ilgili belgelerinin istenmesi halinde bu verileri göndermek için hazır bulundurulmalıdır. Bunlar, ham veri, örnekler, kayıt vb. şeklinde olabilir.

Görevi kötüye kullanma ya da suistimal şüphesi halinde dergi COPE yönergeleri izleyerek bir soruşturma yürütecektir. Soruşturmanın ardından, iddia geçerli görünüyorsa, yazara sorunu gidermek için bir fırsat verilecektir.

Usulsüzlük, şüphe seviyesinde kaldığında; dergi editörü aşağıdaki yollardan birine başvurabilir;

- Makale halen şüpheli ise, reddedilip yazara iade edilebilir.

- Makele online yayınlanmış ise; hatanın mahiyetine bağlı olarak ya yazım hatası olarak kabul edilecek ya da daha ciddi durumlarda makale geri çekilecektir.

- Hatalı yayın ve geri çekme durumlarında açıklayıcı not yayınlanır ve yazarın kurumu bilgilendirilir.

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İnsan ve Hayvan Araştırmaları

İnsan Hakları Beyannamesi

İnsan katılımlı araştırmalar; 1964 Helsinki Deklarasyonu'na ve sonrasında yayımlanan iyileştirici ilkelere uygun olmalıdır ve yazarlar tarafından kurumsal ve/veya ulusal etik kurul komitelerine başvurulup onay alınmış olduğu beyan edilmelidir.

Araştırmanın 1964 Helsinki Deklarasyonu veya kıyaslanabilir standartlara göre yürütülmesi ile ilgili şüphe durumunda, yazarlar bu durumun nedenlerini açıklamak zorundadır ve bağımsız etik kurulları veya diğer değerlendirme kurulları aracılığıyla şüphelerin giderilmesi gerekmektedir.

Aşağıda belirtilen durumlar yazı içerisinde "Kaynaklar" bölümünden önce yer almalıdır:

Etik Kurul Onayı: "Çalışmada insanlara uygulanan tüm prosedürler kurumsal ve ulusal araştırma kurullarının etik standartlarına, 1964 Helsinki Deklarasyonu'na ve sonrasında yayımlanan iyileştirici ilkelere uygun olmalıdır."

Retrospektif çalışmalarda, aşağıda belirtilen cümle yer almalıdır.

"Bu tür çalışmalarda yazılı onam gerekmemektedir."

Hayvan Hakları Beyannamesi

Araştırmalarda kullanılan hayvanların refahına saygı gösterilmelidir. Hayvan deneylerinde, yazarlar hayvanların bakımında ve kullanımında uluslararası, ulusal ve/veya kurumsal olarak oluşturulmuş kılavuzlara uymalıdır ve çalışmalar için kurumdaki veya çalışmanın yapıldığı veya yürütüldüğü merkezdeki (eğer böyle bir merkez varsa) Klinik Araştırmalar Etik Kurulundan onay alınmalıdır. Deneysel hayvan çalışmalarında "Guide for the care and use of laboratory animals http://oacu.od.nih.gov/regs/guide/guide.pdf doğrultusunda hayvan haklarını koruduklarını belirtmeli ve kurumlarından etik kurul onay raporu almalıdırlar.

Hayvanlar ile yürütülen çalışmalarda, aşağıda belirtilen durumlar yazı içerisinde 'Kaynaklar' bölümünden önce yer almalıdır:

Etik Kurul Onayı: "Hayvanların bakımı ve kullanımı ile ilgili olarak uluslararası, ulusal ve/veya kurumsal olarak oluşturulmuş tüm kılavuzlara uyulmuştur."

Eğer uygun bulunduysa (komitenin bulunduğu merkezde): "Hayvan çalışmalarında yapılan tüm uygulamalar kurumsal veya çalışmanın yürütüldüğü merkez tarafından belirlenmiş etik kurallara uyumludur."

Eğer makale insan ya da hayvan katılımlı bir çalışma değilse, lütfen aşağıda yer alan uygun durumlardan birini seçiniz:

"Bu makalenin yazarları insan katılımlı bir çalışma olmadığını bildirmektedir."

"Bu makalenin yazarları çalışmada hayvan kullanılmadığını bildirmektedir."

"Bu makalenin yazarları insan katılımlı veya hayvan kullanılan bir çalışma olmadığını bildirmektedir."

Bilgilendirilmiş Onam

Bütün bireyler ihlal edilemeyecek kişisel haklara sahiptir. Çalışmada yer alan bireyler, elde edilen kişisel bilgilere, çalışmada geçen görüşmelere ve elde edilen fotoğraflara ne olacağı konusunda karar verebilme hakkına sahiptir. Bundan dolayı, çalışmaya dahil etmeden önce yazılı bilgilendirilmiş onam alınması önemlidir. Bilimsel olarak gerekli değilse ve katılımcılardan (veya katılımcı yetkin değilse ebeveynlerinden veya velilerinden) basılması için yazılı onam alınmadıysa, katılımcılara ait detaylar (isimleri, doğum günleri, kimlik numaraları ve diğer bilgileri) tanımlayıcı bilgilerini, fotoğraflarını ve genetik profillerini içerecek şekilde yazılı formda basılmamalıdır. Tam gizlilik sağlanmasının zor olduğu durumlarda, bilgilendirilmiş onam formu şüpheyi içerecek şekilde düzenlenmelidir. Örneğin fotoğrafta katılımcıların göz kısmının maskelenmesi gizlilik açısından yeterli olmayabilir. Eğer karakteristik özellikler gizlilik açısından değiştirilirse, örneğin genetik profilde, yazar yapılan değişikliğin bilimsel olarak sorun oluşturmadığından emin olmalıdır.

Aşağıdaki ifade belirtilmelidir:

Bilgilendirilmiş Onam: "Çalışmadaki tüm katılımcılardan bilgilendirilmiş onam alınmıştır."

Eğer makalede katılımcıların tanımlayıcı bilgileri yer alacaksa, aşağıdaki ifade belirtilmelidir:

"Makalede kişisel bilgileri kullanılan tüm katılımcılardan ayrıca bilgilendirilmiş onam alınmıştır."

DEĞERLENDİRME SÜRECİ

Türk Kolon ve Rektum Hastalıkları Dergisi'ne gönderilen tüm yazılar, sisteme yüklendikten sonra ilk önce editöryal kurul tarafından derginin amaç ve hedeflerine uygunluk ve temel şartları sağlama yönünden değerlendirilecektir. Yazılar, konusunda uzman dergi hakemlerine değerlendirilmek üzere gönderilecektir. Tüm kabul edilen yazılar yayımlanmadan önce, istatistik ve İngiliz dili konusunda uzman editörler tarafından değerlendirilecektir. Sayfaların ilk gözden geçirilmesinden sonra, hakem yorumları ön karar vermek için Editör'e gönderilecektir. Bu aşamada, ilk değerlendirmede bulunanların düşüncesi doğrultusunda, yazı kabul edilebilir, reddedilebilir veya yazıda düzeltme yapılması istenebilir. İlk değerlendirme sonrasında değerli bulunan makaleler için genellikle düzeltme istenir. Düzeltilen makaleler ilk karardan sonraki 2 ay içerisinde tekrar dergiye gönderilmelidir. Süre uzatmaları yardımcı editörden 2 aylık süre bitmeden en az 2 hafta önce talep edilmelidir. Türk Kolon ve Rektum Hastalıkları Dergisi tarafından, 2 aylık düzeltme süresi sona erdikten sonra, yazı kabul edilmeyecektir. Düzeltme yapılan yazılar sisteme tekrar yüklendikten sonra değerlendirilmek üzere (genellikle ilk değerlendirmeyi yapan hakeme) gönderilecektir. Sonuç olarak yayımlanma kararı verildikten sonra, baskı öncesi Teknik Editör tarafından son kez değerlendirilecektir ve iletişim kurulacak olan yazara gözden geçirme ve son düzenlemeleri yapmak üzere işaretlenmiş bir nüshası elektronik ortamda gönderilecektir.

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Revize edilmiş bir versiyonu gönderirken yazar, yorumcular tarafından ele alınan her konuyu ayrıntılı olarak açıklamalı ve nokta nokta ayrıntılı olarak "yorumlara yanıt" sunmalıdır ve ardından belgenin açıklamalı kopyası bulunmalıdır (her yorumcunun yorumu nerede bulunabilir, yazarın cevap ve satır numaraları gibi yapılan değişiklikler).

Bunun yanı sıra ana revize yazı, kabul mektubu tarihinden itibaren 30 gün içinde teslim edilmelidir. Yazının revize edilmiş versiyonunun tanınan süre içinde verilmemesi durumunda, revizyon seçeneği iptal edilebilir. Yazar(lar) ek sürenin gerekli olduğunu düşünüyorsa, ilk 30 günlük süre bitmeden, uzatmayı talep etmelidir.

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REVIEW

Transanal Advancement Flap Repair: The Current Gold Standard for Cryptoglandular Transsphincteric Perianal Fistulas

Transanal İlerletme Flep Tekniği: Kriptoglandüler Transsfinkterik Perianal Fistüllerde Güncel Altın Standart

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ABSTRACT

Transanal advancement flap repair has been considered as a treatment modality for transsphincteric perianal fistulas for over a century. Several systematic reviews have shown that this technique is effective in 80 percent of cases with a minimal and predictable effect on continence. The use of thicker flaps has been shown to increase the rate of recovery, but also to increase the rate of continence impairment. Unfortunately, there are few modifiable factors that seem to affect recovery. These include smoking cessation and weight loss. There is no evidence to support the use of diverting stomas. The placement of setons as part of a standardized treatment regimen is not supported by the literature. It is unadvisable to combine flap repair with other techniques.
Keywords: Endorectal, fistula, fistula in ano, transanal advancement flap, transsfincteric

ÖZ

Transanal ilerletme flep tekniği, yüz yıldan fazla süredir transsfinkterik perianal fistüller için bir tedavi yöntemi olarak görülmüştür. Çeşitli sistematik derlemeler, bu tekniğin kontinans üzerinde minimal ve öngörülebilir bir etki ile olguların yüzde 80'inde etkili olduğunu göstermiştir. Daha kalın fleplerin kullanımının iyileşme oranını artırdığı, ancak aynı zamanda kontinans bozulma oranını da artırdığı gösterilmiştir. Ne yazık ki, iyileşmeyi etkileyebilecek az sayıda değiştirilebilir faktör vardır. Sigarayı bırakma ve kilo verme bunların arasında sayılabilir. Saptırıcı stomaların kullanımını destekleyen herhangi bir kanıt yoktur. Standart tedavi rejiminin bir parçası olarak setonların yerleştirilmesi literatür tarafından desteklenmemektedir. Flep onarımını diğer tekniklerle birleştirmek tavsiye edilmez.
Anahtar Kelimeler: Endorektal, fistül, anal fistül, transanal ilerletme flebi, transsfinkterik

Introduction

Historic Considerations

To the best of our knowledge, transanal advancement flap repair (TAFR) for perianal fistulas was first described by Elting.[1] Interestingly, he stated that "while the treatment of practically every other surgical malady has been improved in the past few decades, the treatment of fistula in ano remains about where it was twenty years ago, and the general results of such treatment are but little if any more satisfactory than they were then". Interestingly, a few surgeons would be surprised if this statement was expressed today. Throughout the years, many modifications have been made to the technique, originally described by Elting.[1] Nonetheless, most authors have published their techniques under a similar name ("endorectal" or "transanal" advancement flap). Elting.[1] described a large series of 96 patients with perianal fistula. The surgery was successful in all cases and he described fecal incontinence in only four cases (4%). Several small series were published throughout the 20th century, but the first

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large series in recent years was published by Aguilar et al.[2] Interestingly, like Elting.[1] he described a very dissimilar flap design to the flap most authors have described in the past 20 years. We have published our technique extensively in earlier reports.[3,4]

Effectiveness of Technique

Even though the reported recovery rate of TAFR varies widely, ranging from 30% to 100%, most author surgeons state an approximately 2/3 improvement rate for their patients. As with many techniques, the reported initial recovery rates are very high. The large series by Aguilar et al.[2] in the 1980s described an almost perfect recovery rate of 98%. This high recovery rate motivated many others to start utilizing the technique in order to improve the outcome of fistula surgery. Unfortunately, other authors failed to reproduce these results. Decreased success rates were published in the 1990s, reporting more realistic recovery rates varying between 68 and 87%.[4,5,6] In an excellent review of 35 studies including over 2000 patients, Soltani and Kaises[7] presented a weighted average recovery rate of 80.8% for cryptoglandular fistulas. A later similar review by Balciscueta et al.[8] found a similar pooled rate of recurrence of 21%, although it included several large-scale new studies and ignored low-quality studies. Due to these findings, we think that the expected recovery rate of TAFR is around 80%.

Impact on Fecal Continence

Interestingly, the first series at the end of the 20th century hardly entail detailed reports of the impact on fecal continence. The series of Aguilar et al.[2] described an impairment of continence in approximately 10% of cases, whereas Schouten et al.[4] reported a significantly higher rate of impaired continence of 35%. It is unclear why exactly patients who undergo TAFR may encounter impaired continence. Although the external anal sphincter is preserved in all patients, they frequently experience minor effects on fecal continence. Although overt fecal incontinence is rare, minor impairment is a frequent finding. Aguilar attributed this effect to the inclusion of circular muscle fibers in the flap.[2] Zimmerman et al.[9] postulated that the use of the Parks retractor was a major contributing factor. This phenomenon was also described by other authors.[10] It is difficult to draw meaningful conclusions on this subject; however, there are some indications in the literature that the use of this retractor is a major contributing factor to fecal continence impairment. It is rare for published results of flap repair to contain detailed information about the effect on fecal continence. However, authors describing the use of different retractors (such as Hill-Ferguson, Eisenhammer or Scott retractors) reported a rate of impaired continence varying between 0 and 12%, whereas authors who used the Parks retractor reported a rate of impaired continence varying between 28 and 40%.[4, 11,12,13,14,15] Moreover, in our early study, we compared the use of the Parks retractor to the use of the Scott retractor, and we found a statistically significant difference both in Rockwood Fecal Incontinence Severity index and postoperative anal resting pressure.[9] Finally, the rate of impaired continence in our patients decreased from 35% to 4% after discontinuation of the use of Parks retractor.[4,16] The review of Soltani and Kaiser[7] calculated a weighted average incontinence rate of 13%. In conclusion, approximately one in 10 patients will encounter impaired continence after this surgery. The inclusion of circular muscle fibers and the use of Parks retractor may play a major contributing role in this regard.

Aspects of Surgical Technique

Type of Flap

The original description of the technique (as described by both Elting[1] and Aguilar et al.[2]) encompasses the creation of an elliptical (or even straight?) flap as opposed by more recent authors, who create a more rhomboid flap. The main difference between these techniques is the vertical incisions on the lateral sides of the flap (Figure 1). These authors do not describe why they chose different types of flap design. Most likely, training or trainers may play a role in this. Not all authors have described their exact choice of flap type; therefore, it is impossible to draw any meaningful conclusions into the benefit of one flap type over the other. Yellinek et al.[17] performed an interesting study in which they compared the results of a heterogeneous group of fistula repairs (including many different types and etiologies of fistulas) by a rather large group of six colorectal surgeons who rarely performed advancement flap repair (about two procedures per surgeon per year). They compared patients with a rhomboid flap to patients with an elliptical flap. They concluded that there was no difference between these two groups of patients in terms of recovery. On theoretical grounds, it can be advocated that elliptical flaps allow better blood supply to the tip of the flap due to the absence of corners, however, the literature does not support this belief

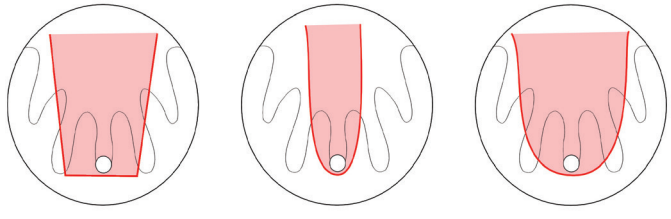

Figure 1. a) Elliptical flap incision, b) rhomboid flap incision. Red line depicts incision, red shaded area depicts submucosal dissection limits

sufficiently, so we recommend that one should not choose the type of flap on the grounds of expected improved recovery.[17] In our experience, when a relatively large part of the distal end of the flap has to be excised (due to suppuration), a rhomboid flap is usually indicated in order to achieve a tension-free closure.

Shape of Flap

Over the last two decades, various different shapes have been described, including wide-angular flaps (Figure 2a), relatively narrow round flaps (Figure 2b), and relatively wide round flaps (Figure 2c).[4,12,18] It is rare for authors to describe the reason for their choice of flap shape. Moreover, most often flap shape has to be deduced from schematic drawings supplied with the article. Therefore, it is impossible to draw meaningful conclusions about the preferred shape of the flap.

Thickness of Flap

More robust research has been performed on the optimal thickness of the flap. Different methods have been described over time ranging from the formation of pure mucosal flaps to the use of full thickness rectal wall. Both prospective and retrospective investigations were performed. The difference in approach was first identified by the Dubsky et al.[19] Their retrospective review suggested an improvement in recovery rates without higher rates of impaired continence after full mobilization of the rectal wall. Khafagy et al.[20] performed a prospective analysis and randomized flap designs consisting of mucosa and submucosa with (Group 1) or without (Group 2) inclusion of circular muscle fibers. They noticed a statistically significant difference between these two groups in terms of recurrence in favor of full thickness flaps. The recovery rate in Group 1 was 90%, whereas only 60% recovered in Group 2. Even though there was a minor difference in terms of impairment of continence (0% vs. 10%) in favor of Group 2, this difference did not reach statistical significance. Balciscueta et al.[8] investigated this issue by performing a systematic review and meta-analysis. This group meticulously investigated reports on full and partial thickness flaps and their influence on recovery and fecal continence. They identified not two but three types of flaps, namely mucosal, partial thickness and full thickness flaps. Some criticism on this classification is warranted in our opinion, since many reports do not offer detailed descriptions of their technique. Moreover, most reports are retrospective and many describe surgeries by different surgeons, making full standardization of technique unlikely. Nonetheless, this systematic review elegantly shows an explicit suggestion that there is a strong correlation between the increasing thicknesses of the flap and improved recovery rates. It is noteworthy that they also showed a higher rate of continence impairment after the use of thicker flaps, even though statistical significance was not reached. Intuitively, it is easy to accept that thicker flaps may lead to both high recovery rates and poorer continence. It is however not entirely clear why it affects continence. Khafagy et al.[20] performed anorectal manometry and did not identify differences between the effects of the two techniques on resting- or squeeze pressure. It is likely that all intra-anal surgery will have an effect on anorectal continence; however, it may be minor. As stated before, selective use of retractors may play a role. Also, some surgeons advocate that the type of anesthesia (resulting in different levels of pelvic relaxation) may play a role. No objective data about this issue are available. Sensibility of the anal verge may be impaired after formation of advancement flap, possibly deteriorating fecal continence in some patients. More extensive dissection when creating thicker flaps may contribute to this. In conclusion, it seems clear that creating advancement flaps that encompass circular fibers, or even the full thickness of the rectal wall will lead to higher recovery rates at the cost of a seemingly higher rate of (minor) continence impairment. We advocate the use of thicker flaps where possible, while recognizing the fact that individualized flap design, based on the pathology and anatomy of the patient is mandatory.

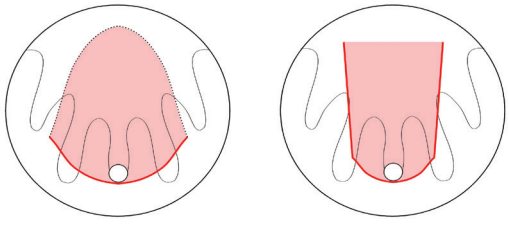

Figure 2. a) Wide angular rhomboid flap, b) narrow round rhomboid flap, c) wide round rhomboid flap. Red line depicts incision, red shaded area depicts submucosal dissection limits

Addition of Accessory Techniques (Or the "Icarus Syndrome")

An interesting phenomenon observed in many different types of fistula surgeries is the desire of individual authors to combine different treatment modalities in order to improve the outcomes of said treatment. Regrettably, these additions dilute the available data on operative techniques, often before their exact role is clarified. Moreover, authors often attempt to improve their own imperfect results when compared to initial reports without reporting the imperfect results, thereby inadvertently inflating the publicly available results. Ellis and Clark[21] published a small series of 60 patients who underwent anocutaneous or mucosal advancement flap repair, and in half of these patients, an attempt was made to improve the outcomes by adding obliteration of the external tract with fibrin glue. A contrary effect was noted. The authors concluded that the study failed to improve outcome,

but interestingly they did not consider that obliteration of the tract with fibrin glue might also have a negative effect. Interestingly, not only were the outcomes of the flap repair poorer than expected, the recovery rates were also much worse than those initially published for fibrin glue treatment (75 to 81%).[22,23] Other authors have also attempted to augment the putcomes of flap repair by obliterating the external fistula tract. Several authors reported small series of combined treatment of TAFR and fistula plugs, yielding varying results (recovery rates between 25-75%).[24,25,26.] These outcomes are unimpressive compared to series reporting the outcome of plug alone.[27] An attempt by our group to augment outcomes of flap repair by obliterating the external fistula tract using BioGlue® was discontinued after including eight patients in a pilot study and noticing adverse events (severe pain and/or abscess formation) in seven patients. Wilhelm et al.[28] published their large series of patients who underwent laser-assisted fistula treatment (LAFT). Fifty-three patients underwent LAFT in combination with mucosal advancement flap repair. Primary recovery was achieved in 35 patients (67%). This recovery rate does not seem to differ from the reported recovery rates of Giamundo et al.[29] through LAFT alone (without the addition of a flap repair).[30] Finally, the outcomes of flap repair has also been attempted to be augmented by additional ligation of the intersphincteric fistula tract (LIFT). van Onkelen et al.[31] disappointingly described that recovery was observed in only 21 patients (51%) out of 41 patients. Again, this recovery rate was lower than expected in the TAFR as well as what has been reported in studies using LIFT alone (a reported pooled recovery rate of 71%).[32] These findings are summarized in Figure 3. In conclusion, it should be noted that, to date, no additional treatment to TAFR has ever shown improved results, both when compared to the expected results of TAFR as well as to the expected results of the augmentative procedure. In our opinion, attempts at augmenting the well-investigated and predictable results of TAFR should be undertaken with extreme caution and should only be attempted when a very solid theoretical basis for the expected improvement of outcomes can be formulated. Furthermore, these attempts should be considered experimental and can only be undertaken within studies, after careful and detailed patient informed consent and shared decision making where applicable.

Factors Contributing to Successful Recovery

Several studies have investigated which factors contribute to recovery or failure of TAFR (Table 1). Upon reviewing these different factors, it is clear that there is no consensus on which factors can predict failure. Besides, different authors used different definitions and aspects of complexity to describe the fistulas they treated.

Fistula-related Factors

Even though several authors have investigated the effect of horseshoe extensions on the recurrence rate, only van Onkelen et al.[33] found a statistically significant negative effect of the presence of horseshoe extensions. Intuitively, one would easily understand that this factor is effective. However, other authors did not identify fistula complexity as a negative contributing factor.

Patient-related Factors

Several patient-related aspects are clearly not negative predictors. Several authors have investigated the effect of gender, age, previous seton drainage, alcohol consumption and diabetes and found no association with negative outcome. Thus, the available evidence suggests that these factors do not play a role. However, several factors are matter for debate. First, we identified smoking as a negative predictive factor.[34] We also showed a statistically significant effect of the number of cigarettes smoked per day on the recovery rate. This finding was confirmed by Ellis and Clark[35] Moreover, we showed a decreased blood flow using laser doppler flowmetry in transanal advancement flaps in smokers.[36] However, this factor has been extensively investigated by several other authors who did not identify smoking as a negative predictor. Interestingly, a later study by our own group also did not find a significant difference between smokers and non-smokers. It is unclear why this difference occurred. Possibly, patient counseling (concerning smoking cessation) after the initial publication played a role. A similar debate exists about obesity. Obesity was identified as an independent negative predictor of outcome

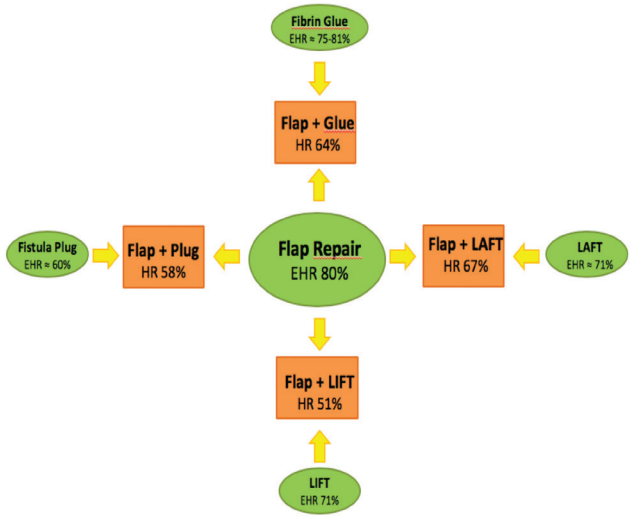

Figure 3. The impact of augmentative additional procedures have never shown to be beneficial

EHR: Expected healing rate, HR: Healing rate, LAFT: Laser assisted fistula treatment, LIFT: Ligation of the intersphincteric fistula tract

by 2 research groups (Table 1)[37,38] but was discredited by three others.[33,36,39] In our opinion, TAFR can be considerably more challenging in obese patients, so there may definitely be a rationale behind this factor. Unfortunately, due to conflicting evidence as well as the difficulty of intervening, this factor does not seem to be a worthwhile modifiable factor. In conclusion, after extensive research over the past 15 years, no undisputed realistically modifiable factors seem to exist. The one possible exception is the smoking status of the patient. Even if the value of this negative predictive factor was debated, a dose-response relation was shown and a pathophysiologic basis was demonstrated. Moreover, this factor is modifiable (it is often possible for patients to discontinue smoking perioperatively). In our opinion, it would be helpful to inform patients about their smoking behavior and advise them to quit smoking. If the fistula repair will not be performed on short notice, weight loss may be considered as well.

Effect of Covering Ostomy

Sonoda et al.[40] compared patients who underwent flap repair with and without a covering colostomy in a heterogeneous retrospective group of patients. Sixty-four patients underwent TAFR with a covering stoma, resulting in a recovery rate of 72%. Twenty-five patients had a covering colostomy. In these patients, TAFR was only 60% successful. Even though this difference was not statistically significant, and it seems likely the more challenging cases may have been offered a stoma, this study did not suggest an advantage of a covering stoma. Similar findings were reported by Mizrahi et al.[41] even though they had only three patients who had a covering ostomy.

The "Seton Paradox"

Interestingly, as stated before, none of the authors who investigated the role of preoperative seton drainage showed a statistically significant higher recovery rate in patients in whom a seton was placed before undergoing TAFR. Our group has reported on this subject several times throughout the years (Figure 4).[33,34,42] Even though these investigations have led us to refrain from prior seton placement more frequently (Figure 4), still a considerable percentage of patients will undergo seton drainage before TAFR either in the referring hospital or because of excessive inflammation on preoperative magnetic resonance imaging. Paradoxically, this suggests that the most difficult cases will

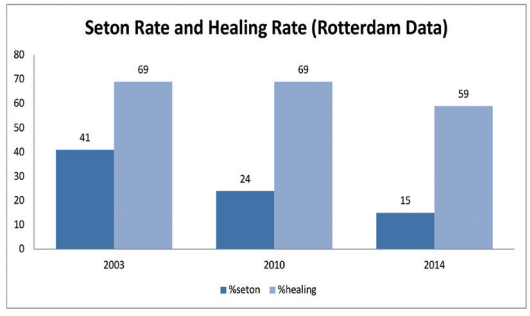

Figure 4. The Rotterdam data concerning prior seton drainage and healing

Table 1. The results of investigations conducted by different authors about the value of different contributing factors

			Contributing Factor								
Author	**Year**	**n**	**Age**	**Gender**	**Prior surgery**	**Fistula complexity**	**Prior seton**	**Smoking**	**Alcohol**	**Diabetes**	**Obesity**
Sonoda et al.[40]	2002	48	No	N/A	Yes**	No	Yes	N/A	N/A	N/A	N/A
Mizrahi et al.[41]	2002	41	No	No	No	N/A	N/A	N/A	N/A	N/A	N/A
Zimmerman et al.[9]	2003	105	No	No	No	No	No	Yes	No	N/A	No
Ellis and Clark[21]	2006	95	No	No	Yes	N/A	N/A	Yes	N/A	N/A	N/A
van Koperen et al.[14]	2008	54	No	No	No	N/A	No	No	N/A	N/A	N/A
Schwandner[37]	2011	220	No	N/A	No	No	No	No	N/A	No	Yes
van Onkelen et al.[33]	2014	252	No	No	No	Yes*	No	No	No	No	No
Boenicke et al.[38]	2017	61	No	No	Yes**	No	No	No	No	No	Yes
Bessi et al.[39]	2018	53	No	No	Yes***	No	N/A	No	N/A	N/A	No

*Horseshoe extension, **Prior abscess drainage, ***Two fistula drainages, ⁺Same research group, different time span
N/A: Not applicable

be prone to undergo seton drainage. Remarkably, not only the recovery rate in these patients was not higher than in patients without prior seton drainage, some authors have found it to be lower.[40] Seton placement prior to TAFR is a well-accepted treatment regimen. Many surgeons advocate seton placement as an important preparatory step before flap repair. Due to the reasonable use of setons, good results can be obtained in the more complex group of patients. In addition to the conclusion that the benefit of previous seton drainage has not been proven and therefore questionable, it is very hard to draw meaningful conclusions from the available literature. In our opinion, seton placement may still be part of an adequate treatment plan. A thorough curettage followed by placement of a comfortable seton may reduce the amount of active inflammation and thereby minimize the size of external wounds at a later time. However, there should be a good reason for seton placement. The placement of setons as part of a standardized treatment regimen is not supported by the literature in our opinion.

In conclusion, TAFR is a well-investigated technique that yields good results in the treatment of perianal cryptoglandular fistulas. It may be expected that 80% of fistulas will recover after TAFR. The effect on fecal continence is predictable and will affect about 13% of patients. We advocate the use of thicker flaps, where possible. There are few modifiable factors that seem to affect recovery. Smoking cessation and weight loss may be considered. There is no evidence to support the use of diverting stomas. The placement of setons as part of a standardized treatment regimen is not supported by the literature. It is unadvisable to combine flap repair with other techniques.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D.E.Z., K.G., D.K.W., Concept: D.D.E.Z., K.W.A.G, D.K.W., J.S., Design: D.D.E.Z., Data Collection or Processing: D.D.E.Z., Analysis or Interpretation: D.D.E.Z., Literature Search: D.D.E.Z., Writing: D.D.E.Z., K.W.A.G., J.S.

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RESEARCH ARTICLE

Evalution of the Patients with Colon Polyps in Terms of *Helicobacter pylori* with Sydney Criteria

Kolon Polibi Saptanan Hastaların Sydney Kriterleri Eşliğinde *Helicobacter pylori* Açısından İrdelenmesi

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ABSTRACT

Aim: Colorectal cancer (CRC) is one of the leading three cancers with high mortality. Colon polyps are precursors for CRC development. *Helicobacter pylori* is known to increase the risk of gastric cancer by intestinal metaplasia (IM) and glandular atrophy (GA), there are studies suggesting that it increases the risk of CRC by various mechanisms. Sydney criteria have been developed to provide a standardized approach to histopathological changes in gastric mucosa caused by *H. pylori*. The aim of this study was to evaluate *H. pylori* according to the Sydney criteria in patients with colon polyps and to contribute to the literature.

Method: The study cohort included a control group (n=231) with normal colonoscopy findings and a patient group (n=600) who underwent upper gastrointestinal endoscopy and colonoscopy on the same day and had hyperplastic polyps, adenomatous polyps and malignant polyps. Age, gender, complications during endoscopy, number and localization of polyps, and histopathological results of gastric and colon biopsies were analyzed. The relationship between *H. pylori*, IM and GA and colon polyps were investigated with logistic regression model.

Results: *H. pylori* was present in 609 (73.3%) of 831 patients. There was no statistically significant relationship between coexistence of *H. pylori* + IM and hyperplastic polyp and adenomatous polyp (p>0.05). It was found that IM did not increase the risk of CRC without *H. pylori* (p=0.15). There was a statistically significant relationship between CRC and *H. pylori* + IM (p=0.03). GA was detected in 70 patients (8.4%), and there was a statistically significant relationship between the presence of GA and CRC, regardless of the presence of *H. pylori* (p<0.05).

Conclusion: The results of the study showed that the coexistence of *H. pylori* and IM did not increase the risk of colon hyperplastic polyps, adenomatous polyps, but increased the risk of malignant polyps. There was also a statistically significant relationship between colon malignant polyps in the presence of GA regardless of the presence of *H. pylori*. In the light of the data obtained in the study, patients with *H. pylori* and IM and patients with GA should be followed up more closely for malignant colon polyps.

Keywords: *Helicobacter pylori*, Sydney criteria, colon polyps, glandular atrophy, intestinal metaplasia

ÖZ

Amaç: Kolorektal kanserler (KRK) yüksek mortaliteyle seyreden ilk 3 kanserden biridir. Kolon polipleri KRK gelişimi için prekürsordür. *Helicobacter pylori*'nin intestinal metaplazi (İM) ve glandular atrofi (GA) ile mide kanseri riskini arttırdığı bilinmekte olup ve çeşitli mekanizmalarla KRK riskini artırdığına dair çalışmalar mevcuttur. *H. pylori*'nin gastrik mukozada meydana getirdiği histopatolojik değişikliklere standart bir yaklaşım getirmek için Sydney kriterleri geliştirilmiştir. Amacımız kolon polibi saptanan hastalarda Sydney kriterleri eşliğinde *H. pylori*'yi irdeleyip literatüre katkıda bulunmaktır.

Yöntem: Çalışmaya kolonoskopisi normal olan kontrol grubu (n=231) ile birlikte üst gastrointestinal endoskopisi ve kolonoskopisi aynı gün yapılıp histopatolojisinde hiperplastik polip, adenomatöz polip ve malign polip saptanan hastalar (n=600) dahil edildi. Hastaların yaşı, cinsiyeti, endoskopi sırasındaki komplikasyonlar, polip sayısı ve lokalizasyonu, mide ve kolon biyopsilerinin histopatolojik sonuçları analiz edildi. *H. pylori*, İM ve GA'nın kolon polipleri ile ilişkisi lojistik regresyon modeli ile incelendi.

Bulgular: Çalışmada 831 hastanın 609'unda (%73,3) *H. pylori* mevcuttu. *H. pylori* ve İM birlikteliğinde hiperplastik polip ve adenomatöz polip arasında istatistiksel olarak anlamlı ilişki saptanmamıştır (p>0,05). İM'nin *H. pylori* olmaksızın KRK riskini artırmadığı saptanmış olup (p=0,15), *H.*

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pylori + İM birlikteliği ile KRK arasında istatistiksel olarak anlamlı ilişki saptanmıştır (p=0,03). Hastaların 70'inde (%8,4) atrofi saptanırken, *H. pylori* olup olmadığı fark etmeksizin, GA mevcudiyeti ile KRK arasında istatistiksel olarak anlamlı ilişki saptanmıştır (p<0,05).

Sonuç: Çalışma sonucunda *H. pylori* ve İM ile birlikteliğinde kolon hiperplastik polibi, adenomatöz polibi riskini arttırmadığını ancak malign polip riskini artırdığı saptandı. Ayrıca GA mevcudiyetinde, *H. pylori* varlığı fark etmeksizin, kolon malign polipleri arasında istatistiksel olarak anlamlı bir ilişki bulunmaktadır. Çalışmada elde edilen veriler ışığında *H. pylori* ve İM mevcut olan hastalar ile GA mevcut olan hastalar malign kolon polibi açısından daha yakın takip edilmelidir.

Anahtar Kelimeler: *Helicobacter pylori*, Sydney kriterleri, kolon polipleri, glandular atrofi, intestinal metaplazi

Introduction

Colorectal cancers (CRC) are one of the leading three common cancers in the world with high mortality.[1] The environmental and genetic factors play a role in the pathogenesis of CRC and 95% of CRC develop sporadically. Environmental factors play a role in sporadic forms, but not genetic factors.[2] The precursor of the sporadic form is mostly adenomatous polyps; and rarely, CRC may also develop from hyperplastic polyps.[3] *Helicobacter pylori* was detected in 1983 by Marschall and Warren[4] in the gastric epithelium of patients with chronic active gastritis. This microorganism is gram (-), spiral-shaped and produces urease enzyme, and is involved in the etiology of diseases such as chronic gastritis, peptic ulcer, gastric carcinoma and gastric mucosa-associated lymphoid tumor.[5,6] The Sydney criteria were established in 1990, allowing us to histopathologically evaluate the response of gastric mucosa to *H. pylori*. In 1990, Sydney criteria were developed by a group of pathologists to provide a standardized approach to the histopathological changes caused by *H. pylori* in the gastric mucosa. In the revised criteria in 1994, chronic inflammation, neutrophil activity, glandular atrophy (GA), intestinal metaplasia (IM) and *H. pylori* intensity are evaluated and graded.[7] Although *H. pylori* is known to increase the risk of gastric cancer through IM and GA, recent studies have also demonstrated its association with neurodegenerative diseases and ischemic heart disease.[8] *H. pylori* is one of the agents causing more than 90% of cancers related to infections.[9] In addition, there are studies showing that *H. pylori* increases the risk of CRC, as well as studies showing that it does not, and there is no definite consensus.[10,11,12] The aim of our study was to evaluate the patients with colon polyps together with *H. pylori* according to Sydney criteria and to contribute to the literature.

Materials and Methods

The patients who underwent upper gastrointestinal system (GIS) endoscopy and colonoscopy in the general surgery and gastroenterology departments of 4 public hospitals in Ordu province between January 2014 and August 2018 were analyzed retrospectively. In this study, age, gender, complications during endoscopy (bleeding, perforation), number of polyps, localization of polyps (cecum, ascending colon, transverse colon, descending colon, sigmoid, rectum and anal canal), and histopathological results of stomach and colon biopsies were analyzed. Patients who underwent colonoscopic polypectomy and who had mucosal biopsy from the antrum, corpus, fundus or duodenum during simultaneous upper gastrointestinal endoscopy were included in this study. Patients under 18 years of age, patients with malignancy, inflammatory bowel disease, familial adenomatous polyposis, patients with suboptimal colon examination, patients with missing colon or gastric biopsy results, and patients who did not undergo endoscopy on the same day were excluded. The control group consisted of patients who underwent upper GIS endoscopy and had normal colonoscopy findings. Patient data were obtained from hospital data processing system and patient archive system.

Endoscopy procedures were performed by general surgery and gastroenterology specialists under sedation. Gastric biopsy contents were obtained from the corpus, antrum and suspicious localizations by the clinician performing the endoscopy. Colonoscopic polypectomy was performed piece-by-piece or totally by using forceps and snare. Polyps that could not be removed colonoscopically were either referred to a more advanced center or removed by surgical intervention. Colon and gastric pathology specimens were examined in the pathology laboratory of the hospital. Gastric specimens were evaluated histopathologically according to Sydney criteria for the presence of *H. pylori*, neutrophil activity, chronic inflammation, IM and GA.[7] Pathological evaluation was between 0 and 3 (0. none, 1. mild, 2. moderate, 3. severe) for *H. pylori*, neutrophil activity, and chronic inflammation criteria, and as -/+ (-: negative, +: positive) for IM and GA. Colon specimens were classified as non-neoplastic (hyperplastic) and neoplastic (tubular, tubulovillous, villous, intramucosal carcinoma, adenocarcinoma) histopathologically. Patients with normal colonoscopy were named as control group, patients with hyperplastic polyp as hyperplastic group, patients with neoplastic adenomatous polyp as adenoma group, and patients with malignancy as malignancy group. Patients with both hyperplastic polyps and adenomatous polyps

were included in the adenoma group, while patients with both adenomatous polyps and malignant polyps were included in the malignancy group. In addition, patients with intramucosal carcinoma histopathology were included in the malignancy group.

The study was carried out in accordance with the Helsinki Declaration 2008 principles. Descriptive statistics for continuous variables included mean, minimum and maximum values, and categorical variables were expressed as numbers and percentages. Chi-square test was used to compare categorical variables. Mann-Whitney U test was used for comparison of continuous data. One-way ANOVA was used for the correlation of Sydney criteria, including *H. pylori* intensity, activation and inflammation. Logistic regression analysis was used to compare the relationship between IM and GA, and CRC. P<0.05 was considered statistically significant. SPSS (IBM SPSS for Windows, Ver.24) statistical package program was used for analysis.

Results

The mean age of 831 patients in our study was 58.85±10.95 (range, 26-88) years. Of the patients, 333 (40.1%) were female and 498 (59.9%) were male. There was no statistically significant difference between the groups in terms of age and gender (p>0.05). Colon polyps were detected in 600 (72.2%) patients, and no colonic polyps were detected in 231 (27.8%) patients in the control group. The total number of polypectomy was 971 and the mean number of polyps per colonoscopy was 1.55. There were no complications in 816 patients (98.2%) during colonoscopy, while bleeding was seen during polypectomy in 15 patients (1.8%). Bleedings stopped spontaneously without any intervention. There was no perforation during colonoscopy and no complication occurred during upper GIS endoscopy. The number of polypectomy performed during colonoscopy was minimum one and maximum eleven. Polyps could not be excised by colonoscopy in 24 patients. While 23 patients required surgical intervention, one patient underwent colonoscopic polypectomy in the advanced center. The histopathological results of these patients were adenocarcinomas in 18 patients, villous adenoma in five patients and tubulovillous adenoma in one patient. The number of polyps according to colonic localization was as follows: 37 (3.8%) in cecum, 72 (7.3%) in ascending colon, 136 (15.1%) in transverse colon, 97 (10%) in descending colon, 356 (35%) in sigmoid colon, 273 (27.7%) in rectum and 15 (1.5%) in anal canal. Hyperplastic polyps were detected in 200 (24.1%), adenomatous polyps in 371 (44.6%) and malignant polyps in 29 (3.5%) patients. Eight of the malignant polyps were interpreted as intramucosal carcinoma and 21 of them were as colonic adenocarcinoma. There was no statistically significant relationship between histopathology and localization of polyps (p>0.05). Data regarding age, gender, number of polyps, localization and histopathology of the patients are given in Table 1. *H. pylori* was positive in 609 patients (73.3%), while negative in 222 patients (26.7%). *H. pylori* negativity/positivity ratio according to groups was

Table 1. Data on age, gender, number of polyps, localization and histopathology

Variables	Group 1 (n=231) (control)	Group 2 (n=200) (hyperplastic)	Group 3 (n=371) (adenoma)	Group 4 (n=29) (malignant)	Total (n=831)	p
Age (min-max)	56.97±10.48 (31-79)	58.16±11.11 (30-78)	60.54±10.69 (26-88)	61.97±11.92 (39-86)	59.03±10.89 (26-88)	0.139*
Gender						
Female	105	71	144	13	333	0.169**
Male	126	129	227	16	498	
Polyp localization						
Cecum		7	26	3	36	
Ascending colon		15	54	2	71	
Transverse colon		25	105	3	133	
Descending colon		24	69	2	95	
Sigmoid colon		117	227	8	352	>0.05*
Rectum		119	140	11	270	
Anus		9	5	-	14	
Total		316	626	29	971	

Min: Minimum, Max: Maximum, *Mann-Whitney U test was used, **Chi-square test was used

as follows: 65/166 in Group 1, 52/148 in Group 2, 100/271 in Group 3, and 5/24 in Group 4. There was no statistically significant relationship between *H. pylori* positivity and colon polyps (p=0.65). When the intensity of *H. pylori* was examined, *H. pylori* was negative in 215 patients (25.9%), (+) in 367 patients (44.2%), (++) in 231 patients (27.8%) and (+++) in 18 patients (2.2%). There was no statistically significant relationship between *H. pylori* intensity and neoplastic status of colon polyps (p=0.65). Activation values of gastric biopsies were negative in 125 patients (15%), (+) in 400 patients (48.1%), (++) in 1261 patients (31.4%) and (+++) in 45 patients (5.4%). Inflammation values were negative in 14 patients (1.7%), (+) in 410 patients (49.3%), (++) in 344 patients (41.4%) and (+++) in 63 patients (7.6%). According to the Sydney criteria, no significant correlation was found between *H. pylori* intensity, activation and inflammation and colon polyp neoplasms (p=0.65, p=0.99, p=0.31, respectively). The neoplastic data and statistical data of the patients according to chi-square test of IM, GA and colon polyps are shown in Table 2. Although the relationship between IM and CRC patients was significant (p=0.003), Table 3 shows that IM was not a single risk factor in the presence of *H. pylori* and GA when evaluated by multiple logistic regression analysis. When the relationship between colon polyps and the presence of *H. pylori*, IM and GA were examined together, the data of the multiple logistic regression analyzes are shown in Table 3.

In the study, it was shown in Table 2 that IM was found to be proportionally high in patients compared to GA, and it was found that GA decreased proportionally less than IM in patients with CRC and that IM was more homogeneous in all patients than GA. Data showing the distribution between GA, IM and CRC is shown in Figure 1. In logistic regression analysis, when the IM and GA values of *H. pylori* negative patients were examined, no statistically significant relationship was found between CRC and IM (p=0.15), and a significant relationship was found between CRC and GA (p=0.041).

Discussion

CRCs are an important cause of morbidity and mortality in the world, accounting for 9% of the incidence of cancer.[13] Although multiple factors play a role in colon cancerogenesis, environmental factors constitute 95% of this rate.[14] *H. pylori* is a microorganism that is found in about 50% of the population and the rate increases to 80% in developing countries.[15] *H. pylori* is a type of bacteria classified as Group 1 carcinogen and is in the same category as smoking and asbestos.[16] The high rate of environmental factors in CRC and the fact that *H. pylori* is carcinogenic and common in the population has led to the necessity to investigate *H. pylori* in the etiology of CRC. In addition, in recent studies, the cultivation of some *H. species* in the colon mucosa of patients with inflammatory bowel disease has

Table 2. Neoplastic information of colon polyps with intestinal metaplasia and atrophy parameters of Sydney criteria

Variables	Group 1 (n=231) (control)	Group 2 (n=200) (hyperplastic)	Group 3 (n=371) (adenoma)	Group 4 (n=29) (malignant)
Intestinal metaplasia				
Present	35	29	58	11
Absent	196	171	313	18
Atrophy				
Present	8	16	37	9
Absent	223	184	334	20

Table 3. Data regarding colon polyps and presence of hyperplastic polyps, intestinal metaplasia and atrophy

	HP OR (95% CI)	p*	T OR (95% CI)	p*	TV OR (95% CI)	p*	V OR (95% CI)	p*	M OR (95% CI)	p*
HP	0.95 (0.66-1.36)	0.76	1.12 (0.81-1.53)	0.50	0.88 (0.51-1.51)	0.63	2.78 (0.59-13.13)	0.20	0.66 (0.24-1.77)	0.40
Intestinal metaplasia	0.85 (0.52-1.41)	0.53	0.85 (0.55-1.31)	0.46	1.07 (0.54-2.12)	0.84	1.48 (0.19-11.46)	0.71	1.86 (0.72-4.86)	0.20
Atrophy	1.02 (0.53-1.96)	0.96	1.35 (0.77-2.37)	0.30	1.76 (0.79-3.94)	0.17	7.87 (0.98-63.06)	0.06	3.57 (1.29-9.89)	0.02

OR: Odds ratio, HP: Hyperplastic polyp, T: Tubular polyp, TV: Tubulovillous polyp, V: Villous polyp, M: Malignant polyp, CI: Confidence interval, *Logistic regression analysis was applied

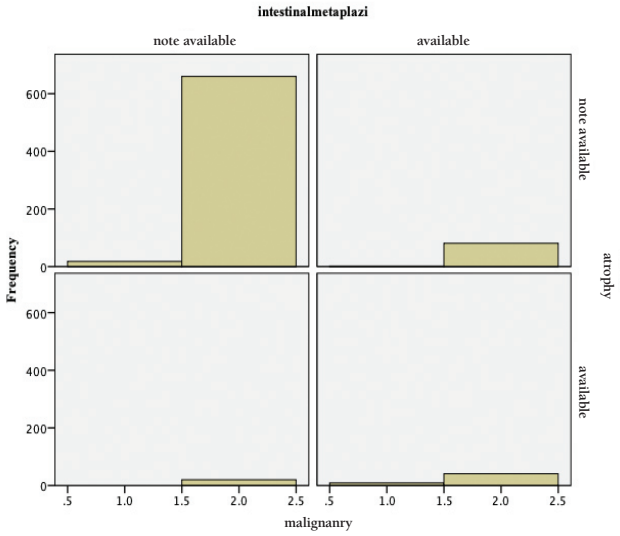

Figure 1. Information showing the distribution between glandular atrophy, intestinal metaplasia and colorectal cancer

aroused more interest between *Helicobacter species* and colon pathologies.[17,18] *H. pylori* diagnosis can be made with non-invasive and invasive diagnostic methods and histological method, which is the gold standard method, was used in our study.[19] This diagnostic method also gave us the advantage of examining the Sydney criteria with colon polyps, except for *H. pylori* intensity. Buso et al.[20] and Fujimori et al.[21] found no significant relationship between the presence of *H. pylori* and CRC in women. We think that these clinical results are caused by gynecological hormones. In our study, no significant relationship was found between female gender and colon hyperplastic and adenomatous polyps, and adenocarcinoma. Fujimori et al.[21] and Brim et al.[22] found no significant relationship between the localization of *H. pylori* and colorectal neoplastic polyps. In our study, we did not find any significant relationship between *H. pylori* and the localization of hyperplastic, adenomatous and malignant polyps. *H. pylori* has a virulence factor called cytotoxin-associated gene A (Cag-A), which can cause ulcers and cancer. There are studies stating that this factor is colonized in the gastric mucosa and leads to hypergastrinemia through long-term inflammation and leads to the risk of CRC.[23] In a prospective study, Strofilas et al.[24] examined gastrin and Cag-A levels in 93 CRC patients, and found no significant relationship between CRC and *H. pylori*. Zhao et al.[25] revealed a significant relationship between *H. pylori* and CRC in patients analyzed by Anti-*H. pylori* immunoglobulin G. In a case-control study by Wang et al.[26], a significant relationship was found between Cag-A levels and CRC in 27 patients. They also found that the risk of tubular and villous adenomas was associated with increased Cag-A levels. In our study, a non-serological histological method was used for the diagnosis of *H. pylori* and the result of our study was not consistent with the study of Wang et al.[26] Sonenberg and Genta[27] examined simultaneous gastric and colon biopsies of 156.000 patients and found a significant relationship between *H. pylori* and hyperplastic polyps, adenomatous polyps, villous adenomas, and CRC. However, considering active gastritis patients as a result of upper GIS endoscopy pathology as *H. pylori* (+) was a limitation of this study.[28] In our study, patients diagnosed as *H. pylori* histologically were included in the study.

There are studies showing that chronic gastritis caused by *H. pylori* triggers a series of events in gastric carcinogenesis known as GA-IM-dysplasia-cancer sequence.[29] In addition, there are studies stating that IM leads to bacterial overgrowth in colon and contributes to CRC.[30] Therefore, IM associated with *H. pylori* may increase colorectal carcinogenesis. Yan et al.[31] found that IM increases CRC. In our study, a statistically significant relationship was found between IM and the risk of CRC in the presence of *H. pylori*. Considering the *H. pylori*-associated cancer sequence,[29] we can explain the fact that the risk of CRC does not increase in the group of patients with IM who do not have *H. pylori*, although GA occurs before IM. Prolonged exposure to *H. pylori* increases gastrin levels.[32] Hypochlorhydria caused by long-lasting hypergastrinemia and chronic GA may disrupt acid-sensitive microflora and increase the risk of CRC.[32] In addition, increased hypergastrinemia in GA cases may lead to increased intraluminal ammonia and increased systemic inflammation, which can trigger intracellular tumor mechanisms.[25] Lee et al.[33] found that *H. pylori* and especially *H. pylori* positivity in patients with GA increased the risk of CRC. Gastrin has a trophic effect on epithelial cell growth and proliferation that may contribute to colorectal carcinogenesis, which is likely to increase the risk of CRC.[34] In a prospective study, Thorburn et al.[34] found that increased serum gastrin levels increased the risk of CRC. Kikendall et al.[35] found that increased serum gastrin level did not increase the risk of CRC. In our study, patients with GA had significant *H. pylori* positivity and a significant correlation was found between GA level and CRC. In addition, increased risk of CRC in patients with GA without *H. pylori* suggests the possibility that hypergastrinemia may be the precursor of CRC other than *H. pylori*. Limitations of the study include retrospective nature and the inability to question environmental factors such as obesity and smoking, which may increase the risk of CRC in patients. The advantages of the study include the diagnosis of *H. pylori* by histological diagnosis, which is the gold standard, the inclusion of hyperplastic polyps other than neoplastic colon polyps and the examination of

Sydney criteria together with colon polyps. As a result of the study, it was determined that *H. pylori* did not increase the risk of colon hyperplastic polyps, adenomatous polyps, but increased the risk of malignant polyps in association with IM. In the presence of GA, there is also a statistically significant relationship between colon malignant polyps regardless of the presence of *H. pylori*. In the light of the data obtained in this study, patients with GA and patients with *H. pylori* and IM should be followed-up more closely for malignant colon polyps.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Ordu University Faculty of Medicine (approval no: 2019-19, date: 7/2/2019).

Informed Consent: Informed consent form was obtained from patients for surgical intervention and subsequent care, necessary permissions were obtained for the use of their data.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.A., Concept: Ç.A., Ö.Ö., Design: Ç.A., Data Collection or Processing: Ç.A., Ö.Ö., Analysis or Interpretation: Ç.A., Ö.Ö., Literature Search: Ö.Ö., Writing: Ç.A.

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RESEARCH ARTICLE

Utility of Methylene Blue Guided Limberg Flap on Long-term Recurrence in Adult Chronic Pilonidal Disease

Erişkin Kronik Pilonidal Sinüs Hastalığında Metilen Mavisi Kılavuzluğunda Uygulanmış Limberg Flepli Hastaların Uzun Dönem Nüks Açısından Değerlendirilmesi

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ABSTRACT

Aim: Pilonidal sinus is a chronic intermittent disease, usually involving the sacrococcygeal area. This study was undertaken to compare the long-term results of peroperative methylene blue use in patients with pilonidal disease who underwent Limberg flap technique with and without methylene blue application.

Method: Patients who underwent Limberg flap for pilonidal sinus surgery between January 2014 and November 2018 were divided into two groups: methylene blue-guided surgery (group 1) and unguided surgery (group 2). Data of the patients were collected from the files, and the long-term recurrence data of the patients were obtained by one-to-one phone calls and outpatient controls at 36 months. Age and body mass index (BMI) were also evaluated. BMI of the patients was categorized as 18.1-20.0 kg/m^2, 20.1-22.5 kg/m^2, 22.6-25.0 kg/m^2, 25.1-27.5 kg/m^2, 27.6-30.0 kg/m^2 and >30.1 kg/m^2.

Results: Methylene blue was performed in 62 of 100 patients who underwent Limberg flap procedure and there was one recurrence in both groups. Methylene blue application did not have an effect on long-term recurrence (p=0.98). BMI groups and recurrence were analyzed regardless of methylene blue use, and BMI greater than 27.5-30.0 kg/m^2 was statistically significant in the development of recurrence in long-term results (p=0.040).

Conclusion: Although it is considered as an integral part of pilonidal sinus surgery, there is no superiority of methylene blue guided surgery on long-term recurrences.

Keywords: Pilonidal disease, Limberg flap, methylene blue, long-term

ÖZ

Amaç: Pilonidal sinüs aralıklı olarak iyileşen ve genellikle sakrokoksigeal alanı tutan kronik bir hastalıktır. Bu çalışma, pilonidal hastalığı bulunan ve ameliyat esnasında metilen mavisinin kulanıldığı ve kullanılmadığı Limberg flep uygulanmış hastalardaki uzun dönem sonuçlarını karşılaştırmak için yürütülmüştür.

Yöntem: Pilonidal sinüs nedeniyle Ocak 2014- Kasım 2018 arası Limberg flep uygulanmış olan hastalar metilen kılavuzluğunda cerrahi uygulanmış (grup 1) ve uygulanmamış (grup 2) olarak ayrıldılar. Hasta bilgileri dosyalarda edinilip, uzun dönem nüksler hastalıklarının 36. ayında bire bir telefon görüşmeleri ve poliklinik kontrolleri ile sağlandı. Yaş, beden kitle indeksi (BKİ) ayrıca takip edildi. BKİ, 18,1-20,0 kg/m^2, 20,1-22,5 kg/m^2, 22,6-25,0 kg/m^2, 25,1-27,5 kg/m^2, 27,6-30,0 kg/m^2 and >30,1 kg/m^2 olarak katogorize edildi.

Bulgular: Limberg flep uygulanmış olan 100 hastadan 62'sine metilen mavisi uygulanmış olup, her iki grupta da birer nüks olgusu mevcuttu. Uzun dönem nükslerde metilen mavisi kılavuzluğunda cerrahinin nükse etkisi görülmedi (p=0,98). BKİ ve nüks arasında metilen mavisi kullanımından bağımsız olarak yapılan incelemede, BKİ'nin 27,5-30,0 kg/m^2'den büyük olduğu kişilerde nüks gelişiminin istatiksel olarak daha fazla olduğu görüldü (p=0,040).

Sonuç: Pilonidal sinüs cerrahisinin ayrılmaz bir parçası olarak düşünülse de uzun dönem nüksler üzerinde metilen mavisi kılavuzluğunda yapılan cerrahilerin herhangi bir üstünlüğü yoktur.

Anahtar Kelimeler: Pilonidal hastalık, Limberg flep, metilen mavisi, uzun dönem

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Introduction

Pilonidal sinus is a chronic intermittent disease that usually involves the sacrococcygeal area and commonly affects young and middle-aged male patients.[1] There are several techniques described for the treatment of this disease and Limberg flap is one of the most preferred techniques because of its low complication rate and acceptable long-term results.[2] There are disagreements on the utility of methylene blue-guided surgery in sacrococcygeal pilonidal sinus disease. In this study, we retrospectively evaluated 100 patients who were operated using Limberg flap technique with and without methylene blue in order to determine the effectiveness of methylene blue in long-term results.

Materials and Methods

This study was approved by the local ethics committee (approval no: 326). The patients who underwent Limberg flap for pilonidal sinus surgery between January 2014 and November 2018 were evaluated. The patients were divided into two groups as patients managed by methylene blue-guided surgery (group 1) and unguided surgery (group 2). The data of the patients were collected from the files, and the recurrences of the patients were followed-up with one-to-one phone calls and outpatient clinic controls after telecommunications at 36th month. Age and body mass index (BMI) were also evaluated. BMI of the patients was categorized as 18.1-20.0 kg/m^2, 20.1-22.5 kg/m^2, 22.6-25.0 kg/m^2, 25.1-27.5 kg/m^2, 27.6-30.0 kg/m^2 and >30.1 kg/m^2. Since the aim of the study was to evaluate the long-term results of the patients, early clinical conditions and complications were overlooked and not followed-up. The patients with missing data, patients with acute pilonidal disease and patients younger than 18 years were excluded.

Statistical Analysis

The data analysis was performed using SPSS for Windows, version 22 (SPSS, Chicago, IL, USA). The normality of the distribution of continuous variables was determined by Kolmogorov-Smirnov test. The data were reported as mean ± standard deviation for parametric tests or as median and range for non-parametric tests, where applicable. The differences between the data from the groups were compared with Student's t-test or One-way ANOVA test, where appropriate. The categorical data were analyzed using Pearson's chi-square or Fisher's exact test, where appropriate. Multiple logistic regression analysis was used to assess the differences between groups in terms of age, gender, BMI and methylene blue. A p value less than 0.05 was considered statistically significant.

Results

Eighty-six patients were excluded due to inability to make contact or missing data. The remaining 100 patients who underwent Limberg flap reconstruction were divided as patients managed by methylene blue-guided surgery (group 1) and unguided patients (group 2). Demographic variables are shown in Table 1. Methylene blue was applied to 62 patients. There were 2 recurrences (2%) and were equally distributed in group 1 and group 2, indicating that methylene blue application had no effect on long-term recurrence outcomes (p=0.98). These two patients with recurrences had a BMI over 27.5 kg/m^2. BMI groups and recurrence were analyzed regardless of methylene blue use, and BMI greater than 27.5-30.0 kg/m^2 was statistically significant in the development of recurrence in long-term results (p=0.040).

Discussion

Pilonidal sinus disease is a common surgical disease that mostly involves the young population. There are several treatment modalities, including simple incision and drainage, deroofing, marsupialization, excision and primary closure or rhomboid excision with Limberg flap procedure.[3] Unfortunately, none of the existing surgical options is perfect. The ideal treatment should eradicate the disease, minimize the risk of recurrence, and be associated with low morbidity and short recovery time. Many studies have reported a recurrence rate of 7-42% following excision and primary closure; however, a recurrence rate of approximately 3% was reported following Limberg flap repair.[2] Other authors also advocate the benefits of this technique as being effective with a low complication rate, shorter time to return to normal activity, and shorter hospitalization.[4] In order to standardize the long-term results of this study, we preferred to evaluate the patients operated with this technique due to its low rate of recurrence. Methylene blue-guided surgery is

Table 1. Demographic variables according to body mass index distribution and age

Age, years		**25 (18-67)**
Male/female ratio		**9/1**
BMI groups (n)	18.1-20.0 kg/m^2	2
	20.1-22.5 kg/m^2	23
	22.6-25.0 kg/m^2	26
	25.1-27.5 kg/m^2	25
	27.6-30.0 kg/m^2	12
	>30.1 kg/m^2	12

BMI: Body mass index

the most adopted and preferred technique for the treatment of pilonidal disease.[5] Many surgeons use the dye in order to prevent recurrence due to inadequate excision. There are opponents of this approach advocating unreliableness of methylene blue to help with adequate excision. Doll et al.[6] followed up the patients who were operated for chronic pilonidal disease with and without methylene blue guidance. The recurrence rates after a mean of 14.9 years were 19% in patients operated with methylene blue guidance and 24% among those without methylene blue (p=0.35). These results are convincing the unreliableness of methylene blue to prevent recurrence of the disease in chronic pilonidal disease. In acute pilonidal disease, methylene blue was found to be useful in preventing recurrences.[6] Idiz et al.[5] evaluated the specimens excised with and without the guidance of methylene blue with microscopic assessment parameters, and found that the application of methylene blue in pilonidal disease surgery may cause inadequate excision of the diseased area. These two results give the same opinion as the findings in our study.

In conclusion, although we consider it as an integral part of pilonidal sinus surgery, methylene blue-guided surgery has no benefit on the long-term recurrence rates of chronic disease.

Ethics

Ethics Commitee Approval: The study was approved by the Adana City Training and Research Hospital Ethics Committee (project no: 326).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.P., Concept: A.K., Design: S.Ç., Data Collection or Processing: A.K., Analysis or Interpretation: S.Ç., Literature Search: A.P., Writing: A.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

Comparison of Laparoscopic Embedding Technique and Other Techniques for Appendiceal Stump Closure

Apendiks Güdüğünün Kapatılmasında Laparoskopik Gömme Tekniğinin Diğer Tekniklerle Karşılaştırması

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ABSTRACT

Aim: Acute appendicitis is the most common surgical emergency worldwide. Laparoscopic appendectomyis widely used in acute appendicitis. In our study, we aimed to investigate the efficacy and safety of laparoscopic embedding technique.

Method: Patients who underwent laparoscopic embedding technique for appendiceal stump between July 2017 and December 2018 were included in the study. Acute appendicitis was diagnosed by physical examination, laboratory tests, ultrasound and computed tomography scan. Dissection of the mesoappendix was performed with a bipolar tissue sealing system, and then the appendix radix was ligated using intracorporeal knotting technique and inverted into the cecum with a suture. The patients were evaluated in terms of age, gender, body mass index (BMI), rate of conversion, operative time, postoperative complications and length of hospital stay.

Results: The mean age was 34.81±1.88 years and the mean BMI was 27.51±5.44 kg/m^2. The mean operative time was 61.93±17.67 minutes. Thirty-two patients had complicated appendicitis and 39 patients had uncomplicated appendicitis. In patients with uncomplicated appendicitis, four patients developed surgical site infection and two patients had ileus; whereas two patients developed ileus and three patients developed surgical site infection in complicated appendicitis cases. The mean length of hospital stay was 38.92±25.90 hours.

Conclusion: Laparoscopic embedding technique is easy, simple, safe, fast and effective for acute appendicitis and will become the method of choice in securing the base of the appendix in complicated appendicitis.

Keywords: Laparoscopic appendectomy, acute appendicitis, appendiceal stump

ÖZ

Amaç: Akut apandisit tüm dünyada en sık görülen cerrahi acil durumdur. Laparoskopik apendektomi akut apandisit ameliyatlarında yaygın olarak kullanılmaktadır. Apendiks güdüğünün kapatılmasında birçok teknik kullanılmıştır. Çalışmamızda, laparoskopik gömme tekniğinin etkinlik ve güvenilirliğini araştırmayı amaçladık.

Yöntem: Temmuz 2017-Aralık 2018 tarihleri arasında akut apandisit için apendiks güdüğünün kapatılmasında laparoskopik gömme yöntemi kullanılan hastalar dahil edildi. Fizik muayene, laboratuvar testleri, ultrason ve bilgisayarlı tomografi muayenesi ile akut apandisit tanısı kondu. Mezoapendiksin diseksiyonu bir LigaSure cihazı ile yapıldı ve daha sonra apendiks radiks intrakorporeal düğümleme tekniği ile bağlandı ve bir keseli dikiş ipliği ile çekuma ters çevrildi. Hastalar yaş, cinsiyet, vücut kitle indeksi (VKİ), dönüşüm oranı, ameliyat süresi, ameliyat sonrası komplikasyonlar ve hastanede kalış süresi açısından incelendi.

Bulgular: Yaş ortalaması 34,81±1,88 idi; ortalama VKİ 27,51±5,44 kg/m^2 idi. Ortalama ameliyat süresi 61,93±17,67 dk idi. Otuz iki hastada komplike apandisit, 39 hastada komplike olmayan apandisit vardı. Komplike olmayan apandisitli hastalarda, 4 hastada cerrahi alan enfeksiyonu ve 2 hastada ileus gelişti; komplike apandisit olgularında 2 hastada ileus, 3 hastada cerrahi alan enfeksiyonu gelişti. Ortalama hastanede kalış süresi 38,92±25,90 saat idi.

Sonuç: Laparoskopik gömme tekniği akut apandisit için kolay, basit, güvenli, hızlı ve etkilidir ve komplike apandisitte appendiks tabanının güvenliğinde tercih edilen yöntem olacaktır.

Anahtar Kelimeler: Laparoskopik apendektomi, akut apandisit, apendiks güdüğü

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Introduction

Appendicitis is a common condition affecting the population of all ages; however, it usually affects young and healthy people. Appendicitis accounts for approximately 25% of patients admitted to emergency surgery clinics and >40% of all emergency laparotomies.[1,2] Laparoscopic appendectomy (LA) was first described by Semm.[3] Compared to open appendectomy (OA), LA caused less pain, faster return to normal activities, better cosmetic outcomes and shorter hospital stay.[4,5] The most common concern regarding LA is the closure of the appendiceal stumps. The most important reason is that it can affect the outcome in terms of infectious complications. However, evidence and studies in the literature reveal conflicting results.[6,7] Therefore, the optimal closure type of the appendiceal stumps is still under discussion. Endoloop, endostapler, metal endoclip, Hem-O-Lok clip and intracorporeal ligation were used to close the appendiceal stumps.[2,7,8,9,10,11] Complicated appendicitis (CA) means a gangrenous and/or perforated appendix that can lead to abscess formation and peritonitis. The laparoscopic grading system (LGS) of acute appendicitis (AA) was first described by Gomes et al.[12] It should be kept in mind that appendix base necrosis, which is the most common reason for procedure failure in some patients, is the most important factor in the closure of the appendix in most studies.[9,10,11] The most common complications after LA are of infectious origin, especially postoperative intraabdominal abscess (POIAA) formation. It has been emphasized that appendiceal stump leakage may be an important factor in POIAA formation.[13] In this study, we aimed to investigate the efficacy and safety laparoscopic intracorporeal knotting (ICK) and purse string suture (PSS) in AA.

Materials and Methods

This retrospective study was conducted by two surgeons experienced in laparoscopic surgery in a 100-bed training and research hospital in İstanbul between February 2017 and October 2018. We retrospectively examined 71 patients with AA who underwent LA. AA was diagnosed by abdominal ultrasound (45 patients) or computed tomography (26 patients). The diameter of the appendix was measured by ultrasound or computed tomography. The LA techniques selected were the surgeon's own preference. Seventy-one patients who underwent laparoscopic ICK and PSS were included in the study. Patients with sepsis and shock were not included. Informed consent was obtained from all patients before surgery. LGS of AA was used to grade the disease (Table 1).[12] Age, gender, height, weight, body mass index (BMI) and comorbid diseases of the patients were recorded. Operative time, complications, appendix diameter, drainage, C-reactive protein, white blood cell count, length of hospital stay, and time of enteral feeding were recorded. Postoperative complications such as trocar site infection, bleeding, stump leakage, ileus and POIAA were recorded. This study was approved by Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval no: 2018-22, Date: 03.12.2018). The surgeries were performed by a left-handed surgeon and an assistant (laparoscopy technician). All patients were given general anesthesia. After general anesthesia induction, a temporary Foley catheter and an orogastric tube were inserted to prevent visceral injury, and they were removed before the patient recovered from anesthesia. A 1 cm skin incision was performed under the umbilicus and the abdominal cavity was accessed with a Veress needle. A 14 mmHg CO_2 pressure was generated for pneumoperitoneum and a 10 mm trocar was inserted in the intraperitoneal cavity. After inserting a 30°, 10 mm optical camera through the umbilical trocar, a 10 mm trocar and a 5 mm trocar were placed under direct vision in the left lower quadrant and suprapubic region, respectively. The patients were positioned at an angle of 15 degrees in the Trendelenburg position on the left. Diagnostic investigation was performed and AA was confirmed (Figure 1). Dissection

Table 1. Laparoscopic grading system of acute appendicitis according to macroscopic inflammatory findings

Grade	Laparoscopic findings
Grade 0	Normal looking appendix
Grade 1	Hyperemia and edema
Grade 2	Fibrinous exudate
Grade 3A	Segmental necrosis
Grade 4A	Abscess
Grade 4B	Regional peritonitis
Grade 5	Diffuse peritonitis

From Gomes et al.[12]

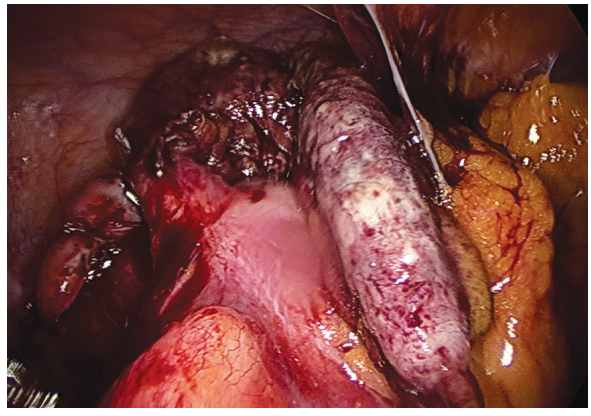

Figure 1. View of complicated acute appendicitis

of the mesoappendix was performed with a 5 mm or 10 mm bipolar tissue sealing system (LigaSure® Valleylab, Boulder, CO) as close as possible to minimize at least a portion of the dissection. The appendix base is exposed to the appendix base with 2/0 vicryl and is secured by ICK (Figure 2). The standard node type used was a square knot with two turns in the first shot and one turn in the last two. Following appendectomy, a sample was removed from the sample bag in the left lower quadrant. If there was no localized haze accumulation in the pelvic region, irrigation was preferred according to irrigation only. Atraumatic 3/0 silk with PSS was passed. The appendix stump was embedded in the cecum of the knot (Figure 3a, b). After the control of bleeding in cases of non-appendicitis, the operation was stopped. The fascia was closed with 2/0 vicryl and the skin was closed with 4/0 intracutaneous vicryl suture. All patients, except those who had nausea or vomiting, began to take oral intake at the 4th hour postoperatively. Diclofenac sodium (75 mg twice daily, intramuscular) was administered for the treatment of postoperative pain and was replaced with naproxen sodium (550 mg twice daily, per oral) after oral administration. The patients were followed up 30 days after the operation. All findings of the applications for dressing changes and sutures and postoperative complications were recorded.

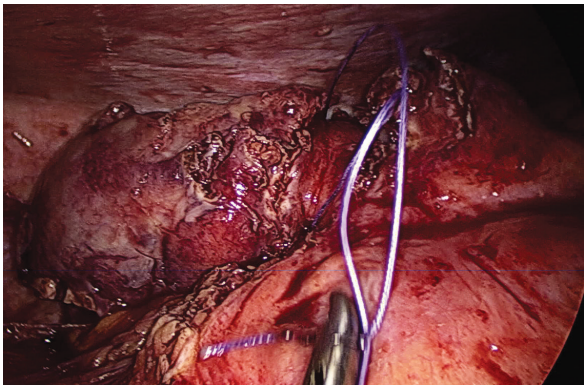

Figure 2. Appendiceal stump closure by intracorporeal knotting technique in grade 3a complicated acute appendicitis

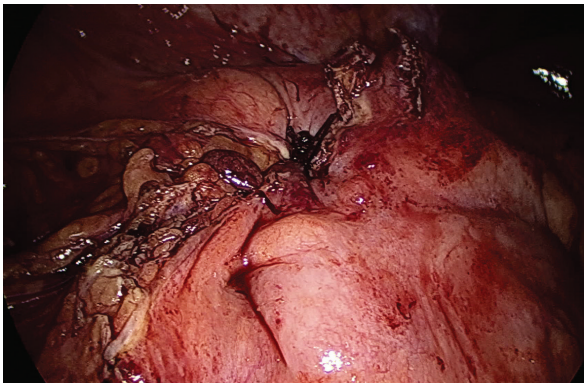

Figure 3a. Atraumatic 3-0 silk suture from the base of the cecum

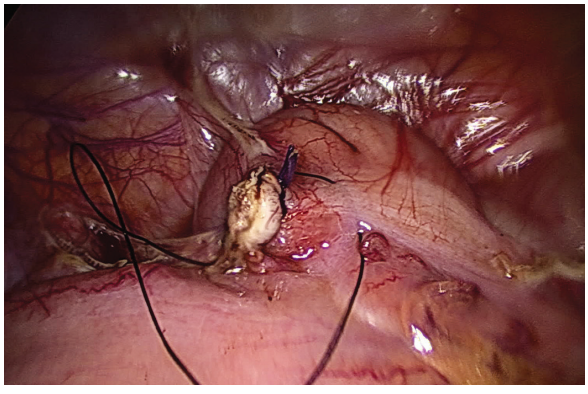

Figure 3b. The appendix stump was embedded in the cecum

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation or range, whereas categorical variables, such as number of patients, were expressed as a percentage.

Results

The appendiceal stump closure by ICK and PSS was viable in 71 (100%) patients who underwent LA for AA. Seventy one (25 female, 46 male) patients were included. The mean age was 34.81±12.88 years and the mean BMI was 27.51±5.44 kg/m^2. Forty four patients were American Society of Anesthesiologists (ASA) 1, 21 patients were ASA 2, and 6 patients were ASA 3 (Table 2).

The mean operative time was 67.64±16.26 minutes (Table 2). The mean length of hospital stay was 38.92±25.9 hours. The hospital stay was longer in cases of CA (50.56±30.64 hours) (Table 3).

Table 2. Patient demographic data

Variable	Patients (n=71)
Age, year	34.81±12.88
Gender (female/male), n	25/46
BMI, kg/m^2	27.51±5.44
ASA 1/2/3, n	44/21/6
WBC, 10^3/mm^3	14.618±3833
CRP	7.36±5.83
Appendix diameter, mm	10.24±2.4
Uncomplicated appendectomy, n (%)	39 (54.92)
Complicated appendectomy, n (%)	32 (45.08)

Values are presented as mean ± standard deviation, n: number of patients

BMI: Body mass index, ASA: American Association of Anesthesiology score, WBC: White blood cell count, CRP: C-reactif protein

According to laparoscopic grading in acute CA, nine patients were grade 3A, eight patients were grade 3B, six patients were grade 4A, five patients were grade 4B and four patients were grade 5. The mean time spent in LA for complicated degrees of AA was 74.93±15.16 minutes. Drainage was placed in three cases with uncomplicated appendicitis (UCA) and four cases with CA due to minimal hemorrhage in Douglas pouch. After surgery, four patients developed ileus and recovered with surgical treatment. Surgical site infections were wound infection in five patients (7.04%) and POIAA (1.4%) in one patient (5.08%). A 5 cm abscess was detected in the Douglas in one patient. The abscess was evacuated with an ultrasound-guided catheter. All other patients recovered completely (Table 3).

Discussion

AA is one of the most common causes of acute abdominal pain, with an annual incidence of 250.000 patients in the United States and 50.000 patients requiring emergency surgical intervention in the United Kingdom.[14] AA is a common surgical emergency with an incidence of 1.17 per 1000 patients, with a lifetime incidence of 8.6% in women (6.7%) and also in men (6.7%). LA has the advantage of reducing the need for analgesics, shorter hospital stay, early return to work, better cosmetic results and lower wound infection rate.[4,5] The laparoscopic technique also provides a clear view of the entire abdominal cavity in case of acute abdomen. Although LA has become a common method for the treatment of AA in recent years, its role in patients with CA remains controversial. Some reports have suggested that LA may be associated with higher rates of intraabdominal infection in the treatment of CA.[15,16] Improper closure of the appendix stump is an important step during appendectomy as it may cause serious postoperative complications. Endostapler,[7,10,17,18] endo ligature (endoloop),[7,8,18] metal endoclips,[2,11,19,20,21] bipolar endocoagulation, polymeric endoclips (hem-o-log clip)[9,10,22] and intracorporeal suture[2,3,23] are used for the closure of the appendix stump in LA.[24] Complications of appendicitis are very important in patients with CA. The classification of appendicitis is also very important. To facilitate this, Gomes et al.[12] classified macroscopic, laparoscopic technical difficulties according to peroperative macroscopic appearance (Table 1). In this classification, grade 3b is particularly important. However, there are very few reports about stump leakage in the literature.[13] In a clinical prospective randomized study by Tagguchi et al.[13] four appendiceal stump leakages were detected with endostapler in CA cases. Gomes et al.[12] used a CA metal clip application to close the stump. In the study, a metal clip was successfully applied in 118 of 131 cases. In this study, it was impossible to apply metal clips in 12 grade 3b (appendix base necrosis) cases. In these cases, the appendix stump was connected to the laparoscopic suture or laparotomy with open technique.[12] In other studies, we do not know the reason, whether it was because of the lack of stump leakage or other reasons. In our study, eight cases among 32 patients with CA were diagnosed laparoscopically as grade 3b. They were treated with PSS. No re-operation was required in any case. The mean operative time in UCA cases was 61.93±17.67 minutes, the lowest compared with the other four studies,[24,25,26] but similar to those reported by Ates et al.[2] and Gonenc et al.[23] (Table 4). The mean working time for complicated degrees of AA during LA was compared with four other similar studies (n=32) (Table 5). The mean operative time in CA cases was 74.93±15.16 minutes. The operative time was lower in the studies by Ay et al.[27] and Gomes et al.[11] compared to previous studies (Table 5).

Table 3. Surgery data

Variable	Uncomplicated appendectomy	Complicated appendectomy	Total
Operative time, minute	61.93±17.67	74.93±15.16	67.64±16.26
Hospital stay, hours	29.38±16.18	50.56±30.64	38.92±25.9
Oral diet, day	1.26 (1-2)	1.43 (1-3)	1.34 (1-3)
Drainage (+)	3 (7.69%)	32 (100%)	35 (49.29%)
Complication	4 (10.25%)	6 (18.75%)	10 (14.08%)
Ileus	2 (5.125%)	2 (6.25%)	4 (5.63%)
Trocar site infection	2 (5.125%)	3 (9.375%)	5 (7.04%)
Intraabdominal abscess	0	1 (3.125%)	1 (1.4%)
Appendix stump leakage, n	0	0	0
Bleeding, n	3	4	7

Values are presented as mean ± standard deviation or median (range), n: number of patients

The surgical technique used in the study by Ay et al.[27] was similar to our technique and they closed the appendiceal stump with ICK. In our technique, in addition to stump security, the appendix is buried into the stump cecum and embedded by using PSS. This explains our longer working hours. In the study of Ay et al.[27] no adequate data were presented for CA grade 3b cases. They emphasized that they failed using metal clips method by Gomes et al.[12] in grade 3b cases to close the stump and that they preferred laparotomy or additional methods in these cases. In a randomized clinical study conducted by Taguchi et al.[13] four cases of stump leakage were found in the closed appendiceal stump with the technique of bipolar endocoagulation in CA cases. The operative time in the studies by Taguchi et al.[13] and Quezada et al.[28] was longer than in our study. In our study, patients with an abscess had a longer operative time, which may explain the presence of appendiceal inflammatory processes, aspiration of abscess formation, irrigation, and a more difficult operation. LA has been proven to be a safe procedure in the management of UCA.[3,12] However, there are controversial data about the indications of laparoscopy in relation to the rate of POIAA in CA.[12,13,14,15,16,17] It may be reasonable to assume that the presence and proliferation of peritonitis may be a risk factor for POIAA, and therefore, necrotic perforated appendicitis in the intraabdominal space may have a lower risk of POIAA than cases complicated by peritonitis.[3,12,14,16,17,28] Another issue discussed is that abundant irrigation of the abdominal cavity with 0.9% saline solution is shown as one of the causes of abscess development.[3] In a clinical study performed by Katkhouda et al.[17] the examination of the Douglas, irrigation, aspiration and the use of endobags removed abscesses and necrotic fragments from cavities and reduced the frequency of POIAA from 2.4% to 0.4%. The frequency of intraabdominal infection and percutaneous drainage under abdominal ultrasound in our study was similar (3.1%) (Table 3). None of the patients required reoperation and all had a smooth recovery. In this context, the treatment of the appendix stump using laparoscopic ligation and PSS technique is considered as a safe and effective alternative.

In some cases, it may be necessary to switch from LA to OA. The need for laparotomy may be 0% to 39.7%.[4,5,16,17,18,26,28] Laparotomy causes adhesions, local perforation, diffuse peritonitis, appendix base necrosis, retrocecal position, bleeding, appendicular tumor and inability to identify iatrogenic lesions.[27,28,29,30] In our study, none of the 71 patients required laparotomy. Four patients with developed paralytic ileus responded to medical treatment. In CA and UCA cases with varying degrees, laparoscopic ligation and closure of the appendix stump with PSS is a safe and

Table 4. Mean operative time spent during laparoscopic appendectomy for uncomplicated acute appendicitis from four similar studies (n=39)

Mean operative time in uncomplicated laparoscopic appendectomy		
Study or subgroup	Mean ± SD*	n
Ates et al.[2]	62.81±15.4	30
Gonenc et al.[23]	61.9±27.1	46
Kiudelis et al.[25]	79.6±21.1	40
Aziret et al.[26]	76.7±17.5	36
Our study	61.93±17.67	39

*Mean ± standard deviation, n: sample number of each series

Table 5. Mean operative time spent during laparoscopic appendectomy for complicated acute appendicitis from four similar studies (n=32)

Mean operating time in complicated laparoscopic appendectomy		
Study or subgroup	**Mean ± SD***	**n**
Ay et al.[27]	54±48.85	28
Quezada et al.[28]	150±45	76
Taguchi et al.[13]	84.6±34.57	42
Gomes et al.[11]	67.4±28.1	131
Our study	74.93±15.16	32

*Mean ± standard deviation, n: sample number of each series

effective procedure. In CA with appendix base necrosis, it is recommended to use other stump closure techniques.

Ethics

Ethics Committee Approval: Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 03.12.2018-22).

Informed Consent: Informed consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.D., E.G., Concept: M.E.G., T.D., E.G., Design: M.E.G., Data Collection or Processing: T.D., E.G., Analysis or Interpretation: M.E.G., Literature Search: E.G., Writing: T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

Mucinous Neoplasms of the Appendix: Our Clinical Experience and Review of the Literature

Apendiks Musinöz Neoplazmları: Klinik Deneyimimiz ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Aim: Neoplastic lesions of the appendix are very rare and most of them are incidentally detected during appendectomy. In this study, we aimed to evaluate the clinicopathological features and applied treatments of the patients who were operated in our clinic and diagnosed as appendiceal mucinous tumor (ApMT) in the light of the literature.

Method: The data and appendectomy specimens of the patients who were operated in our clinic between January 2011 and December 2016 and who were diagnosed as ApMT were retrospectively evaluated. Age, gender, clinical findings, diagnostic methods, histopathological diagnosis and subsequent treatments were evaluated.

Results: Six of the patients were male and four were female. The mean age was 48.6 years (range, 28-85). Nine patients were operated for acute abdomen and one patient was operated electively. Ultrasonography was performed in four patients and computed tomography was performed in six patients preoperatively. Pathological examination revealed simple mucocele in eight patients, mucinous adenoma in one patient and mucinous cystadenoma in one patient. Two patients had appendiceal diverticulum and two patients had diverticulitis associated with acute appendicitis, two patients had appendix perforation and three patients had periapendicular abscess. All patients underwent appendectomy for ApMT.

Conclusion: ApMT is a rare tumor of the appendix that may be benign or malignant. Patients may present with symptoms of acute appendicitis as well as unspecific symptoms. Although preoperative diagnosis is difficult, it helps to minimize complications. Care should be taken to prevent appendix rupture and peritoneal mucus contamination during surgery.

Keywords: Mucocele, appendicitis, appendectomy, pseudomyxoma peritonei

ÖZ

Amaç: Apendiksin neoplastik lezyonları oldukça nadir görülen ve çoğunluğu apendektomi esnasında insidental olarak saptanan lezyonlardır. Bu çalışmada kliniğimizde opere edilen ve apendiks musinöz tümör (ApMT) tanısı konulan olguların klinikopatolojik olarak incelenerek uygulanan tedavilerin literatür eşliğinde değerlendirilmesi amaçlandı.

Yöntem: Ocak 2011-Aralık 2016 tarihleri arasında kliniğimizde opere edilen ve ApMT tanısı konulan hasta dosyası ve apendektomi piyeslerine ait sonuçlar retrospektif olarak incelendi. Hastaların yaş, cinsiyet, klinik bulgular, tanı yöntemleri, histopatolojik tanı ve sonraki tedavileri değerlendirildi.

Bulgular: Hastaların 6'sı erkek, 4'ü kadın olup yaş ortalaması 48,6 (28-85 aralığında) idi. Dokuz hasta akut batın bulguları ile ve 1 hasta elektif olarak opere edilmiş idi. Tanısal yöntem olarak 4 hastada ultrasonografi ve 6 hastada bilgisayarlı tomografi uygulanmış idi. Patolojik değerlendirmede 8 hastada basit mukosel, 1 hastada musinöz adenom ve 1 hastada musinöz kistadenom mevcut idi. İki hastada akut apandisite eşlik eden apandiks divertikülü ve iki hastada divertikülit; iki hastada apendiks perforasyonu; üç hastada ise periapendiküler apse mevcut idi. Tüm hastalarda ApMT için apendektomi işlemi uygulanmış idi.

Sonuç: ApMT apendiksin benign veya malign olabilen nadir bir tümörüdür. Hastalar akut apandisit bulguları yanı sıra belirgin olmayan semptomlar ile başvurabilir. Preoperatif tanı zor olmasına rağmen komplikasyonları en aza indirmede yardımcıdır. Cerrahi esnasında apendiks rüptürünü ve peritoneal mukus kontaminasyonunu önlemek için dikkatli olunmalıdır.

Anahtar Kelimeler: Mukosel, apandisit, apendektomi, psödomiksoma peritonei

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Introduction

The neoplastic lesions of the appendix (NLA) are very rare and the majority of them are incidentally noticed during appendectomy. Although NLA are seen at approximately 1%, it is accepted that the rate of unpredictable pathological anomalies is up to 5%, especially due to unexamined lesions.[1] Appendiceal mucinous tumors (ApMT), also called appendiceal mucocele, are rare NLA and are found incidentally during surgery, routine radiological evaluations or colonoscopic examination. Accumulation of mucoid material within the lumen of the appendix leads to obstructive enlargement of the appendix.[2] ApMT are more common in women and over the age of 50, and they constitute 8% of NLA and 0.3-0.7% of all appendix pathologies.[3,4] They have four histopathological subtypes namely simple or retention mucoceles, mucoceles with local or diffuse villous hyperplastic epithelium, mucinous adenoma/cystadenoma and malignant mucinous cystadenocarcinomas. Clinical findings include right lower quadrant pain, palpable mass in the right lower quadrant, colic pain in case of obstruction or invagination, gastrointestinal bleeding, anemia, genitourinary symptoms, acute abdomen, and sepsis in case of rupture of the cyst. Because the findings are nonspecific, they are rarely diagnosed during radiological, sonographic, or endoscopic procedures.[3,4] On the other hand, most cases are asymptomatic until diagnosis is made intraoperatively or during postoperative histopathological examination.[4] The recommended treatment for ApMT is surgery and the surgical method should be determined according to tumor size, the presence of local or diffuse peritoneal mucus, appendix perforation, surgical margin status and histological type of tumor.[5] Appendectomy is sufficient in benign ApMT, and cecum resection or right hemicolectomy is recommended in the presence of spread to neighboring bowel segments, regional lymphadenopathy, pseudomyxoma peritonei (PMP) or malignancy.[5] In this study, we aimed to evaluate the clinicopathological examination of the patients who were operated in our clinic and diagnosed as ApMT in the light of the literature.

Materials and Methods

The medical records and the results of appendectomy specimens of ten patients who underwent emergency surgery with the diagnosis of acute appendicitis or elective surgery with other diagnoses in our clinic between January 2011 and December 2016 were retrospectively analyzed. Informed consent was obtained from all patients in the study. Age, gender, clinical findings, diagnostic methods, histopathological diagnoses and subsequent treatments were evaluated.

Results

Six of the patients were male and four were female. The mean age was 48.6 years (range, 28-85). Physical examination records revealed right lower quadrant pain and direct rebound findings on physical examination in nine patients. One patient was electively operated. Ultrasonography (US) was performed in four patients and computed tomography (CT) was performed in six patients as a diagnostic method, and both diagnostic methods were used in one patient who was operated electively. Pathological examination revealed simple mucocele in eight patients, mucinous adenoma in one patient and mucinous cystadenoma in one patient. One of the patients with simple mucocele was consulted to general surgery clinic due to periapendicular adhesions while undergoing total abdominal hysterectomy + bilateral salpingo-oopherectomy for endometrial adenocarcinoma, and she had appendectomy. The patient with detected mucinous cyst adenoma was operated for acute abdomen and right ovarian hemorrhagic cyst adenoma rupture was detected. Two patients had appendiceal diverticulum and two patients had diverticulitis associated with acute appendicitis, two patients had diverticulitis, two patients had appendix perforation and three patients had periapendicular abscess. Open appendectomy was performed in all patients (Tables 1, 2).

Discussion

ApMT, which is rarely reported in the literature and is usually incidentally detected, is more common between the ages of 50 and 69 years, although it occurs at any stage of life.[6,7] Regarding the gender distribution, there are

Table 1. Demographic data of patients

Mean age (years)	**48.6 (range, 28-85)**
Gender	6 M, 4 F
Type of admission	Acute abdomen (9) Elective surgery (1)
Diagnostic method	US (4)/CT (6) CT/US (1)
Pathological diagnosis	Simple mucocele (8) Mucinous adenoma (1) Mucinous cystadenoma (1)
Accompanying Appendix diverticulum (n)	2
Abscess, perforation	2/2
Surgical procedure	Appendectomy (10)

M: Male, F: Female, CT: Computed tomography, US: Ultrasonography

Table 2. Gender, age, pathologic diagnosis, clinical diagnosis, surgical procedure and accompanying findings of the patients

Patient ID	Gender	Age	Pathologic diagnosis	Clinical diagnosis	Surgical procedure	Accompanying findings
1	M	40	Simple mucocele	Acute appendicitis	Open appendectomy	-
2	F	70	Mucinous adenoma	Perforated appendicitis	Open appendectomy	-
3	F	85	Simple mucocele	Acute appendicitis	Open appendectomy	-
4	M	62	Simple mucocele	Perforated appendicitis	Open appendectomy	Abscess, diverticulum
5	M	60	Simple mucocele	Acute appendicitis	Open appendectomy	Abscess, diverticulitis
6	M	28	Simple mucocele	Acute appendicitis	Open appendectomy	Abscess, diverticulitis
7	M	28	Simple mucocele	Acute appendicitis	Open appendectomy	Abscess, diverticulum
8	M	29	Simple mucocele	Acute appendicitis	Open appendectomy	-
9	F	43	Mucinous cystadenoma	Hemorrhagic serous ovarian cystadenoma	Open appendectomy/right ovarian cyst excision	-
10	F	41	Simple mucocele	Endometrial adenocarcinoma	TAH/BSO/open appendectomy	-

F: Female, M: Male, ID: Identify, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo oferectomy

inconsistencies in the literature, and some studies report a higher incidence in women, while others report a similar incidence in both genders.[5,7] In our study, the mean age of the patients was 48.6 years (range, 28-85) and was close to the lower limit of the age range reported in the literature. The male-female ratio was 2/3 and a total of three male patients had simple mucocele detected in 20s. ApMT are divided into 4 pathological types according to their epithelial characteristics:

- Simple or retention mucoceles; they are usually caused by obstruction of the root of the appendix with fecalitis or inflammatory adhesion. It is characterized by normal epithelial structure and slight luminal dilatation up to 1 cm.
- Mucoceles containing local or diffuse villous hyperplastic epithelium; luminal dilatation is mild and constitutes 5-25% of mucoceles.
- Mucinous adenoma/cystadenoma; is the most common group and constitutes 63-84% of the cases. This group usually has some degree of epithelial atypia and villous adenomatous changes. There is significant distention in the lumen (up to 6 cm). It is benign and does not carry a risk of recurrence.
- Malignant mucinous cystadenocarcinomas; constitute 11-20% of the cases. Glandular stromal invasion, desmoplastic reaction and/or the presence of epithelial cells in peritoneal implants are observed. Luminal dilatation is very high.[8]

Most patients with ApMT are asymptomatic and may exhibit different clinical findings.[9] Acute or chronic pain in the right iliac fossa is the most common symptom. Sometimes a palpable mass may be detected on physical examination.[4] The symptoms observed in the presence of malignant mucocele are weight loss, general condition disorder and presence of intraabdominal masses; however, acute pain in the right iliac fossa is more common in benign mucoceles.[6] In our study, nine patients showed clinical findings of acute appendicitis at admission and one of them had mucinous cyst adenoma associated with right ovarian cyst rupture. Mucinous cystadenoma is located in the benign part of the pathological spectrum and does not carry a risk of recurrence. Mucinous cystadenocarcinoma with stromal invasion and intraperitoneal spread is similar to ovarian mucinous cystadenocarcinoma with high lymph node involvement and liver metastasis and low survival rate.[9] In our study, simple mucocele was detected in eight patients, mucinous adenoma in one patient and cyst adenoma in one patient. No mucinous cystadenocarcinoma was detected. One case was operated electively for endometrial adenocarcinoma and concurrent appendiceal simple mucocele was detected. Advances in diagnostic methods, especially in abdominal US and CT, have increased the possibility of preoperative diagnosis of mucoceles.[6] Cysts of different echogenicities can be identified in relation to the amount of mucus on US.

Multiple echogenic foci in the dilated appendix may reveal multiple echogenic layers that give the appearance of onionskin layers that may be pathognomonic for the mucocele.[10] In the US, an appendix with a diameter of 15 mm and above has a sensitivity of 83% and a specificity of 92% for mucocele.[11] On the other hand, appendiceal mucocele is a round, thin-walled cystic mass with a capsular structure in CT. Calcification is detected in 50% of the cases and the presence of nodules in the mucocele wall suggests cyst adenocarcinoma.[12] Malignancy is rarely detected under 2 cm. In addition, cystadenoma/cystadenocarcinoma is detected more frequently in large mucoceles (6 cm or more) and a higher rate (20%) of perforation is observed.[13] The presence of acid on CT is a nonspecific finding and may be observed in PMP. Since the mucin-producing cells in PMP are weakly adhesive, they can easily be displaced by peristaltic movements and adhere to immobile areas. Douglas/rectovesical pouch, right and left subphrenic areas, and liver and spleen surfaces are the most common sites.[14] Colonoscopy should also be performed preoperatively to exclude the presence of colorectal neoplasia in all patients with suspected appendiceal mucocele.[15] Colonoscopy shows a "volcano sign" in which the appendix orifice is located in the middle of a prominent bump surrounded by a normal mucosa or a yellowish lipoma-like submucosal mass.[16] Mucosal biopsies are usually reported as normal.[15] Biochemical tests may also be used in the diagnosis of ApMT. High levels of carcinoembryonic antigen (CEA) may be seen in cystadenocarcinomas, but this antigen is not routinely evaluated in ApMT because the CEA levels in cystadenomas are rarely high. Preoperative evaluation may include tumor markers such as alpha-fetoprotein and carsinoma antigen 19-9 as well as CEA.[17] In our study, US was performed in four patients and CT was performed in five patients who underwent emergency surgery, and the imaging findings were reported consistent with acute appendicitis. ApMT was not suspected preoperatively in any patients, and therefore colonoscopy was not performed and tumor markers were not examined. Right hemicolectomy is often performed in the treatment of suspected malignancy in preoperative imaging or when malignant mucocele is detected during frozen examination.[5] Although right hemicolectomy is the standard treatment modality in malignant ApMT, recent studies suggest that the presence of a mucocele with a solid surgical margin is an indicator of good prognosis and disease-free survival.[7] Gonzalez-Moreno and Sugarbaker[18] reported in 501 patients with appendiceal epithelial neoplasia that right hemicolectomy was not superior to appendectomy in terms of survival. However, the authors suggested that right hemicolectomy is required in the presence of need for complete excision of a primary tumor or complete cytoreduction, lymph node involvement revealed by histopathological examination of the appendix or ileocolic lymph nodes, and the presence of a non-mucinous neoplasia identified by histopathological examination. The choice of open or laparoscopic surgery in ApMT is controversial.[19] Laparotomy is the best option if the mass is large and resection is difficult. On the other hand, laparoscopic methods have become popular in the last decade and many authors have suggested that laparoscopic method is a safe choice in ApMT surgery.[5] However, since the distribution of mucus or epithelial cells in the peritoneal space is associated with poor prognosis, rupture and peritoneal contamination should be avoided. For this purpose, the appendix should be pulled to a minimum during laparoscopy, low levels of pneumoperitonium pressure should be provided and the bag should be used when removing the excised material.[5] In addition, the presence of any mucinous fluid in the abdomen should be carefully examined. There is consensus that appendectomy is sufficient in the treatment of non-ruptured benign appendix mucoceles.[20] In our study, all patients underwent open appendectomy. Since no malignancy was reported pathologically, the surgical procedure was satisfactory. Two cases where the appendix was ruptured during surgery were at 26th and 28th months and are still being followed up. Follow-up was not recommended in other cases. PMP occurs only in a small proportion of mucinous neoplasms. It is characterized by peritoneal spread and implant formation due to iatrogenic or spontaneous rupture of mucocele during appendectomy or due to mucinous cystadenoma/cystadenocarcinoma.[5] Although clinically more severe, it has a slowly progressive course, often accompanied by nonspecific abdominal symptoms. The most common symptom is acute or chronic pain in the right lower quadrant.[21] The disease is progressive in both cases when the ruptured primary mass and mucinous cells spreading along the peritoneal surfaces are benign or malignant. Since PMP usually develops as a complication of ovarian and appendix masses, PMP should be suspected in the history of appendectomy.[21] Although ovaries were considered to be the most common primary organ in the past, recent studies based on immunohistochemical analysis and molecular biology have shown that ovary is a rare source of PMP and that lesions previously called "ovarian borderline mucinous tumors" are typically metastatic lesions of the appendix.[21] PMP treatment varies due to the rarity of the disease and slow progression of the disease.[22] Current treatment strategies of PMP include careful monitoring and continuous observation; enlarged cytoreductive surgery alone or with

hyperthermic intraoperative peritoneal chemotherapy and early postoperative intraperitoneal chemotherapy.[19] In a study based on Sugarbaker's peritonectomy procedure, cytoreductive surgery with intraperitoneal hyperthermic perfusion allowed complete removal and this combined treatment proved its efficacy in terms of increased long-term survival and better regional control of the disease.[23] However, other studies support that fluorouracil-based adjuvant systemic chemotherapy should be the standard treatment for appendix-related PMP patients.[24] When surgery is not required immediately, patients can be monitored with CT scans, tumor markers, laboratory tests and physical symptoms, and the time of surgery can be planned. Since the risk of developing colonic adenocarcinoma in these patients is 6 times higher than in the general population, patients should be followed by colonoscopy.[25] In addition, screening of solid organs, such as kidney and lung, should be performed in malignant ApMT cases. No PMP was detected in any patient in our study. In conclusion, ApMT is a rare tumor of the appendix that can be benign or malignant. Patients may present with signs of acute appendicitis as well as non-significant symptoms. Although preoperative diagnosis is difficult, it is highly helpful in determining the correct treatment method and minimizing intraoperative and postoperative complications. Ultrasound and CT may be helpful in preoperative diagnosis: however, sometimes it is accompanied by colon cancer and may be detected incidentally during colonoscopy. ApMT treatment is open or laparoscopic appendectomy. Treatment options for malignancy include right hemicolectomy. Since PMP is a feared complication, appendix rupture and peritoneal mucus contamination should be avoided during surgery.

Ethics

Ethics Committee Approval: The study was approved by the Recep Tayyip Erdoğan University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2019/21).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., M.K.Ç., A.P., Concept: G.D., S.K., Design: S.K., A.Ö., Data Collection or Processing: M.K.Ç., A.P., Analysis or Interpretation: G.D., A.P., Literature Search: G.D., A.Ö., Writing: G.D.

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RESEARCH ARTICLE

Peritoneal Disease Severity Score Predicts the Prognosis of Peritoneal Metastasis of Colorectal Origin: A 10-year Longitudinal Analysis of a Single-center Experience

Peritoneal Yüzey Hastalığı Şiddet Skorunun Kolorektal Kansere Sekonder Peritoneal Metastazlı Hastalarda Prognozu Öngörme Gücü: Tek Merkezin 10 Yıllık Deneyimi

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ABSTRACT

Aim: Peritoneal Surface Disease Severity score (PSDSS) has been used in the evaluation of patients who are scheduled for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastasis of colorectal origin (PMCO). The aim of this study was to evaluate the validity of PSDSS in predicting prognosis in patients who underwent CRS + HIPEC for PMCO at our center.

Method: Demographic data, operation data, histopathological features, perioperative morbidity and mortality, and oncologic follow-up data were obtained retrospectively from the database and analyzed. Peritoneal carcinomatosis index (PCI) values were calculated from preoperative computed tomographies. PSDSS was calculated by evaluating clinical symptoms, PCI and histology of primary tumor. Two PSDSS groups were formed: PSDSS 1 and 2 groups as low PSDSS group, and PSDSS 3 and 4 groups as high PSDSS group.

Results: Sixty-one patients, including 36 females (59%) and 25 males (41%), with PMCO who underwent CRS and HIPEC were included in the study. Forty-four patients were enrolled to the low PSDSS group and 17 patients were enrolled to the high PSDSS group. Three patients (3.2%) died during the perioperative period. Twenty-one patients (34.4%) had perioperative complications. The mean follow-up was 35.0±23.2 months. During the follow-up period, 36 patients (59%) had recurrence and 44 patients (72.1%) died. The mean survival was 46.5±5.5 months, and 1-,3- and 5-year survival rates were 85%, 47% and 21%, respectively. There was no correlation between low and high PSDSS groups in terms of morbidity and recurrence (p=0.486 and p=0.385, respectively). Mortality was more frequent in high PSDSS group (94% vs 63%; p=0.024). The mean survival of patients in the low PSDSS group was significantly longer than in the high PSDSS group (57.2±6.7 months vs 16.5±2.6 months; p=0.001).

Conclusion: The findings of this study demonstrated the validity of PSDSS in predicting prognosis in patients with PMCO who were scheduled for CRS and HIPEC.

Keywords: Colorectal cancer, peritoneal metastasis, peritoneal carcinomatosis, Peritoneal Surface Disease Severity score, hyperthermic intraperitoneal chemotherapy

ÖZ

Amaç: Kolorektal kansere ikincil peritoneal metastaz (KRKPM) nedeniyle sitoredüktif cerrahi (SRC) ve hipertermik karın içi kemoterapi (HİPEK) uygulanacak hastaların değerlendirilmesinde, Peritoneal Yüzey Hastalığı Şiddet skoru (PYHŞS) kullanılmaya başlanmıştır. Bu çalışmanın amacı merkezimizde KRKPM nedeniyle SRC + HİPEK uygulanan hastalarda PYHŞS'nin prognozu öngörmedeki geçerliliğini değerlendirmektir.

Yöntem: Hastaların demografik bilgileri, operatif veriler, histopatolojik özelllikler, perioperatif morbidite ve mortalite bilgileri, onkolojik izlem verileri prospektif olarak doldurulan veri tabanının retrospektif incelenmesi ile elde edildi. Hastaların preoperatif dönemdeki bilgisayarlı tomografilerinden peritoneal karsinomatozis indeks (PKİ) değerleri hesaplandı. PYHŞS klinik semptomlar, PKİ ve primer tümörün histolojisi değerlendirilerek

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hesaplandı. Dört PYHŞS grubu oluşturuldu: PYHŞS 1 ve 2 grupları, düşük PYHŞS grubu; PYHŞS 3 ve 4 grupları ise yüksek PYHŞS grubu olarak katmanlandırıldı.

Bulgular: SRC ve HİPEK uygulanmış 61 KRKPM'li hasta [36 kadın (%59), 25 erkek (%41)] çalışmaya dahil edildi. Kırk dört hasta düşük PYHŞS grubuna, 17 hasta yüksek PYHŞS grubuna eklendi. Üç hasta (%3,2) perioperatif dönemde eksitus oldu. Yirmi bir hastada (%34,4) perioperatuvar komplikasyon görüldü. Ortalama izlem süresi 35,0±23,2 ay idi. Takip süresinde 36 hastada (%59) rekürens görüldü, 44 hasta (%72,1) eksitus oldu. Ortalama sağkalım süresi 46,5±5,5 ay olup. Bir, üç ve 5 yıllık sağkalımlar sırasıyla %85, %47 ve %21 olarak saptandı. Morbidite ve rekürens gelişimi ile düşük ve yüksek PYHŞS grupları arasında ilişki saptanmadı (sırasıyla p=0,486 ve p=0,385). Mortalite yüksek PYHŞS grubunda daha sık görüldü (%94'e karşı %63; p=0,024). Düşük PYHŞS grubundaki hastaların ortalama sağkalımı, yüksek PYHŞS grubundakilere göre anlamlı olarak daha uzun bulundu (57,2±6,7 aya karşı 16,5±2,6 ay; p=0,001).

Sonuç: Bu çalışmadaki bulgular, KRKPM'li hastaların SRC ve HİPEK planlanan hasta grubunda PYHŞS'nin prognozu öngörmede geçerliliğini göstermiştir.

Anahtar Kelimeler: Kolorektal kanser, peritoneal metastaz, peritoneal karsinomatozis, Peritoneal Yüzey Hastalığı Şiddet skoru, hipertermik karın içi kemoterapi

Introduction

Approximately 10% of patients with colorectal carcinoma develop peritoneal metastasis (PM).[1] While the mean survival of this patient group was 7 months by conventional treatments[2], 5-year survival rate is increased to 20-45% with the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to the cytoreductive surgery (CRS) technique described by Sugarbaker.[3,4] Peritoneal cancer index (PCI) is the most commonly used prognostic indicator in patients diagnosed with PM of colorectal origin (PMCO).[5,6] The biggest accepted deficiency of the PCI is that it can only be calculated during surgical exploration.[7] Complete CRS cannot be performed in 25% of patients who underwent surgery due to PMCO.[8] Patient selection is very important for achieving high survival with acceptable morbidity in patients with advanced stage cancer who will undergo both high-cost and high-risk surgical procedures such as CRS and HIPEC, so patients need to be graded according to the severity of the disease in the preoperative period. Pelz et al.[9] defined a new staging system called Peritoneal Surface Disease Severity score (PSDSS), which is calculated by using the clinical symptoms of patients, the extent of carcinomatosis and primary histopathology. In single and multicenter studies, this staging system has been shown to be effective in predicting prognosis in patients with PMCO.[6,9,10,11,12,13] The aim of this study was to evaluate the validity of PSDSS in prognosis in patients who underwent CRS and HIPEC for PMCO at our center.

Materials and Methods

Between 2005 and 2015, 291 patients underwent CRS and HIPEC at our clinic. The primary tumors of these patients were colorectal cancer in 93 patients (32%), ovarian cancer in 73 patients (25%), appendix cancer and pseudomyxoma peritonei in 33 patients (11%), and primary cancers of the peritoneum and peritoneal malignant mesothelioma in 35 patients (12%). Sixty-one patients with PMCO, including 36 women (59%) and 25 men (41%), were included in the study. Extra-abdominal metastasis, widespread small bowel involvement, extensive portal pedicle invasion, plaque-like small bowel mesentery involvement, extensive involvement in the pancreaticoduodenal region, bilateral ureter invasion, extensive and deep involvement of pelvic wall and major abdominal vessel invasion were accepted as contraindication for CRS and HIPEC. Patients without complete cytoreduction (CC) CC-2, CC-3, patients without preoperative computed tomography (CT) scans or CT scans with poor quality, and patients who died during the perioperative period (0-90 days or postoperative hospital stay) were not included in the study. According to these criteria, 32 patients (34.4%) were excluded from the study. The reasons for exclusion from the study were CT-related problems in 21 patients (22.5%), perioperative mortality in 3 patients (3.2%), and incomplete cytoreduction in 8 patients (8.7%). Complications were graded according to Clavien-Dindo (C-D) classification. Grade 1-2 complications were classified as minor and grade 3-4 complications were classified as major.[14] Demographic data, operative data (operative time, cytoreduction status), histopathological features, and perioperative morbidity and mortality data were obtained by retrospectively examining the database. Oncologic follow-up data (intraabdominal recurrence and/or distant metastasis) and date of death of patients were obtained from hospital database and national population registration system. PCI scores obtained by evaluation of preoperative CT scans of the patients were calculated by three radiologists experienced in abdominal radiology who were unaware of the operative and follow-up data. Approval was obtained from the non-invasive local ethics committee for the study. PSDSS was calculated by evaluating the clinical symptoms, PCI score and histology of the primary tumor as defined in the study of Pelz et al.[9] and four PSDSS groups were formed according to the scores of the patients. (Table 1). PSDSS 1 and 2 groups were

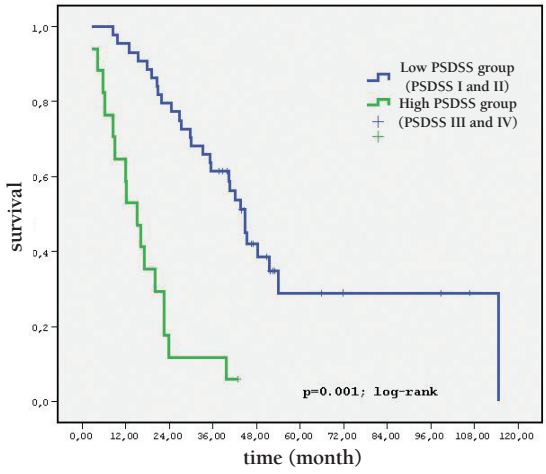
evaluated as low PSDSS group, and PSDSS 3 and 4 groups as high PSDSS group.

Statistical Analysis

SPSS 22 (SPSS, Chicago, Ill) was used for all statistical analyzes. Chi-square test was used for comparison of categorical variables and Student-t test was used for comparison of numerical variables. The time from surgery to death was considered as mean survival. "Kaplan-Meier estimator (K-M)" was used to calculate overall survival rates, and "log-rank test" was used to compare the differences between survival curves. P<0.05 was considered statistically significant.

Results

The mean age of the 61 patients included in the study was 53.3±14.1 years (53.5±14.6 years for female patients and 53.1±13.6 years for male patients). Twenty-seven patients (44%) had synchronous and 34 (56%) had metachronous PM. At the time of the surgery, none of the patients had distant metastases. When the patients were classified according to their symptoms, there were no symptoms in 8 patients (13.1%), mild symptoms in 42 patients (68.8%) and severe symptoms in 11 patients (18.1%). PCI scores obtained by examining preoperative CT scans were <10 in 25 patients (41%), between 10-20 in 25 patients (41%) and >20 in 11 patients (18%). According to histopathological results, five patients (8.2%) had well-differentiated carcinoma and node (N) N0 lymph N involvement, 52 patients (85.2%) had moderately differentiated carcinoma and N1-N2 lymph N involvement, and four patients (6.6%) had poorly differentiated or signet ring cell carcinoma. The mean PSDSS was 7.9±4.07 (range, 2-17). According to these data, four patients (6.6%) were included in the PSDSS 1 group, 40 patients (65.6%) were included in the PSDSS 2 group, four patients (6.6%) were included in the PSDSS 3 group, and 13 patients (21.3%) were included in the PSDSS 4 group. The demographic and clinical data of the patients are summarized in Table 2. The mean operative time of the patients was 328.9±129.7 (range, 125-720) minutes. Eleven patients (18%) were followed up in the intensive care unit (ICU) postoperatively. The mean ICU stay was 1.4±0.6 days, and the mean postoperative hospital stay was 15.1±10.3 days. A total of 21 patients had (34.4%) perioperative complications, including minor (C-D grade 1-2) complications in eight patients (13.1%) and major (C-D grade 3-4) complications in 13 patients (21.3%). The



Graphic 1. Kaplan-Meier curves of low and high Peritoneal Surface Disease Severity score (PSDSS) groups. Mean survival in low PSDSS group (PSDSS 1 and 2): 57.2±6.7 months, mean survival in high PSDSS group (PSDSS 3 and 4): 16.5±2.6 months

PSDSS: Peritoneal Surface Disease Severity score

Table 1. Calculation of Peritoneal Surface Disease Severity score and formation of groups

Clinical symptoms	PCI	Histopathological features
No symptoms=0 point	PCI <10=1 point	Well or moderately differentiated and N0=1 point
Mild symptoms=1 point	10< PCI <20=3 points	Moderately differentiated and N1/N2=3 points
Severe symptoms=6 points	PCI >20=7 points	Poorly differentiated or signet ring cell tumor=9 points
PSDSS is graded according to the total score of these three components		
PSDSS score	**PSDSS Group**	
2-3	1	
4-7	2	
8-10	3	
>10	4	

PSDSS: Peritoneal Surface Disease Severity score, PCI: Peritoneal cancer index, N: Node

Mild symptoms: <10% weight loss, mild abdominal symptoms, asymptomatic ascites,

Severe symptoms: >10% weight loss, unremitting pain, bowel obstruction, symptomatic ascites

Table 2. Demographic, clinical and oncologic follow-up data of patients

		Low PSDSS (PSDSS 1-2) (n=44)	High PSDSS (PSDSS 3-4) (n=17)	p
Age, mean		53.7±12.8	52.5±17.4	0.803
Gender	Male	18	7	0.604
	Female	26	10	
Synchronous disease		17	10	0.250
Metachronous disease		27	7	
Mean PCI score		11.02±3.9	17.71±8.0	0.001
Operative time, minutes		296.4±101.6	343.1±139.3	0.212
Need for ICU		7 (15.9%)	4 (23.5%)	0.481
Length of ICU stay, days		1.2±0.4	1.7±0.9	0.09
Length of hospital stay after surgery, days		13.9±10.2	18.1±10.1	0.386
Complication	All complications	14 (31.8%)	7 (41.2%)	0.555
	Minor (C-D 1-2)	6 (13.6%)	2 (11.7%)	0.656
	Major (C-D 3-4)	8 (18.2%)	5 (29.5%)	
Recurrence		24 (54.5%)	12 (70.6%)	0.385
Mortality		28 (63.6%)	16 (94.1%)	0.024
Mean survival time, months		57.21±6.7	16.55±2.6	0.001

PSDSS: Peritoneal Surface Disease Severity score, PCI: Peritoneal cancer index, ICU: Intensive care unit, C-D: Clavien-Dindo classification

mean follow-up was 35.0±23.2 (range, 3.2-114.7) months. Recurrence (distant metastasis in six patients, intraabdominal recurrence in 14 patients, intra-abdominal recurrence and distant metastasis in 16 patients) was observed in 36 patients (59%). During the follow-up, 44 patients (72.1%) died. The mean survival was 46.5±5.5 months (K-M), with 1-, 3- and 5-year survival rates of 85%, 47%, and 21%, respectively (K-M). There was no statistically significant difference between low and high PSDSS groups in terms of operative time, postoperative ICU follow-up, ICU stay and hospital stay (p=0.212; independent Samples t-test, p=0.481; chi-square test, p=0.09; independent Samples t-test, p=0.386; independent Samples t-test, respectively). There was no statistically significant relationship between morbidity and recurrence and low and high PSDSS groups (p=0.486 and p=0.385, respectively; chi-square test). During the follow-up, 94.1% of the patients in the high PSDSS group died, while 63.6% of the patients in the low PSDSS group died (p=0.024; chi-square test). The mean survival of patients in the low PSDSS group was significantly longer than in the high PSDSS group [57.2±6.7 months vs. 16.5±2.6 months (C-M)] (p=0.001; log-rank test) (Graphic 1). Postoperative follow-up data of the patients are summarized in Table 2.

Discussion

The aim of CRS in PMCO is the resection of locally advanced primary disease and peritoneal metastatic foci without leaving macroscopic disease, and the goal of complementary HIPEC is to treat potential microscopic residues after macroscopic eradication. Perioperative mortality decreased to 5% and morbidity decreased to 23-45% in patients undergoing CRS and HIPEC for PMCO due to increased surgical technical experience, improvement of perioperative complex cancer care conditions, and more conscious multi-disciplinary approach on toxicity, nutrition and infection.[15,16] In our series, perioperative mortality was 3.2% and morbidity was 34.4%. Despite all these improvements, CRS and HIPEC treatment have a relatively high mortality and morbidity risk, requiring high cost and center experience. The selection of patients to perform this marathon complex surgery is one of the most important issues. In 2008, a consensus report containing eight radiological and clinical variables was published to achieve complete cytoreduction in patients with PMCO,[17] which recommended the surgical treatment of patients with an Eastern Cooperative Oncology group (ECOG) performance score ≤2, but all variables except the ECOG performance score are related to the spread of malignant disease. It has

been shown in many studies that histology of the primary tumor is also important; especially the presence of signet ring cell carcinoma has been shown to be a marker of poor prognosis.[18,19] PCI is most commonly used for the evaluation of the extent of carcinomatosis, another component of PSDSS described by Pelz et al.[9] In a study by Elias et al.[20] in a series of 523 patients with PMCO, they stated a PCI ≥17 as a predictor of poor prognosis. Similarly, Goéré et al.[21] stated a PCI ≥20 as a predictor of poor prognosis in their study of 180 patients. There are publications that detected a negative correlation between survival and PCI as in these studies,[22,23] and there is also a study of 50 patients reported that PCI is more effective than PSDSS in predicting prognosis.[6] PCI values used to evaluate PSDSS are obtained by examining preoperative abdominal contrast enhanced CT scans. There is no consensus on the sensitivity and specificity of contrast-enhanced CT in assessing the extent of peritoneal implants in patients with PMCO. In the initial studies in the literature, over 90% sensitivity was reported in lesions over 5 cm, this rate decreases below 25% in implants below 5 mm.[24] Also, except for implant size, the type of the lesion (nodular or plaque), location (inside the intestine loop, solid organ neighborhood, etc.) and the experience of the radiologist affect CT sensitivity.[25] In studies involving experienced radiologists in large-scale centers, it was shown that there was a high correlation between intraoperative PCI values and preoperative PCI values, but it was found that PCI values calculated by CT in the preoperative period were lower than the intraoperative PCI values.[26,27,28] In our study, a study conducted as a specialty thesis in medicine also showed a high correlation between intraoperative and preoperative PCI values, but lower preoperative PCI scores were calculated compared to intraoperative PCI scores.[29] In the light of this information, it can be said that the PCI value calculated by CT scans can be used safely considering that it may be a little low. In our study, the mean operative time of the patients in the low PSDSS group was shorter than the patients in the high PSDSS group (296 minimum vs 343 minimum), and those patients with better overall performance status needed less postoperative ICU follow-up (16% vs 23%) and they were discharged sooner after surgery (14 days vs 18 days), but there was no statistically significant difference between these values. There was also no statistical significance between perioperative complications between the groups. In the literature, there are no studies evaluating the relationship between PSDSS and these parameters in patients with PMCO, and statistical significance may be seen between these parameters in larger patient groups. In a series of 40 patients who underwent CRS and HIPEC for PMCO, Pelz et al.[9] reported that the mean survival of the PSDSS 4 group was worse and that the inclusion in the PSDSS 4 group was a poor prognostic marker. In a study of 56 patients undergoing CRS and HIPEC due to PMCO published in 2010, Chua et al.[11] showed that PSDSS was an independent prognostic marker for survival. In a multicenter study published in 2014, 1013 patients diagnosed with PMCO who underwent CRS and HIPEC in 609 patients were examined and PSDSS was found to be effective in predicting median survival.[12] In a series of 49 patients with heterogeneous primers by Yoon et al.[13] Thirty three patients were treated with CRS and HIPEC, and PSDSS 3 and 4 were reported to be associated with unresectability. There are also studies reporting that PSDSS is effective in predicting survival in patients undergoing CRS due to ovarian and appendix mucinous neoplasm.[30,31] In our study, supporting the literature, it was found that the patients in the low PSDSS group had longer mean survival, and that PSDSS was effective in predicting overall mortality. The potential limitations of our study are inclusion of data from a single center, a relatively limited number of patients and retrospective analysis of these data. In conclusion, the findings of this study supports that PSDSS is a valid, easy to apply and non-invasive scoring system that can be used safely in the selection and evaluation of patients with PMCO before CRS and HIPEC.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Local Ethics Committee (approval number: 2017/25-36).

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., C.A., A.E.C., I.B.A., C.A., F.O., S.S., N.Ç.A., Concept: S.S., C.A., A.E.C., F.O., S.S., N.Ç.A., Data Collection or Processing: C.A., N.Ç.A., S.S., A.E.C., I.B.A., C.A., Analysis or Interpretation: C.A., S.S., I.B.A., C.A., F.O., S.S., N.Ç.A., Literature Search: C.A., N.Ç.A., S.S., A.E.C., I.B.A., C.A., Writing: C.A., S.S., N.Ç.A., A.E.C., I.B.A., C.A., F.O., S.S.

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RESEARCH ARTICLE

Surgical Treatment of Recurrent Colorectal Cancer: Short and Long Term Outcomes

Nüks Kolorektal Kanserde Cerrahi Tedavi: Kısa ve Uzun Dönem Sonuçlar

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ABSTRACT

Aim: The aim of this study was to investigate the effect of surgical margin positivity on short- and long-term outcomes in patients undergoing recurrent colorectal cancer surgery.

Method: Demographics, parameters related to primary tumor and previous surgery, recurrent tumor characteristics and perioperative features and long-term outcomes were compared between groups (R0 vs. R1) according to surgical margin positivity.

Results: Of 57 patients who underwent surgery for recurrent colorectal cancer, 49 patients (86%) in whom curative resection was achieved were included in the study. Eleven (22.4%) cases had surgical margin positivity (R1) on pathological examination. Demographics, primary tumor localization, tumor stage, time to recurrence, adjuvant oncological treatments were comparable between R0 and R1 groups. Although the surgical procedures performed differed according to the location of the recurrent lesion, they were proportionally similar between the groups. The operative time, the amount of intraoperative bleeding, the need for transfusion, and the length of hospital stay were similar (p>0.05 for each variable). There were 17 (44.7%) and four (36.4%) postoperative complications in the R0 and R1 groups, respectively, but no difference was observed between the groups. Regional recurrence rate was 18.9% (n=7) in R0 group and 27.3% (n=3) in R1 group, respectively (p=0.675). Overall survival rates of R0 and R1 patients at 1, 3 and 5 years were 78.4% vs. 81.8%, (p=0.754), 43.2% vs. 36.4%, (p=0.720) and 27.0% vs. 27.3% (p=0.866), respectively.

Conclusion: Complications are higher after recurrent colorectal cancer surgery. This study emphasizes that microscopic surgical margin positivity (R1) may not adversely affect short- and long-term outcomes in patients operated for recurrent colorectal cancer, and that local recurrence rates of these cases may be similar to those with complete resection (R0).

Keywords: Recurrence, colorectal cancer, R0 resection, survival, complication

ÖZ

Amaç: Nüks kolorektal kanser cerrahisi uygulanan hastalarda cerrahi sınır pozitifliğinin erken ve geç dönem sonuçlarını üzerine etkisini incelemektir.

Yöntem: Nüks kolorektal kanser tanısıyla ameliyat edilen hastalarda cerrahi sınır pozitifliği durumuna göre demografik veriler, ilk hastalık ve operasyon bilgileri, nüks hastalık ve tedavi verileri ile uzun dönem sonuçları kıyaslandı.

Bulgular: Nüks kolorektal kanser nedeniyle ameliyat edilen 57 hastanın küratif amaçlı rezeksiyonun başarıldığı 49'u (%86) çalışmaya dahil edildi. Bu olguların 11'inde (%22,4) patoloji raporlarında cerrahi sınır pozitifliği (R1) saptandı. R0 ve R1 grupları demografik veriler, ilk tümörün yerleşim ve evresi ile nükse kadar geçen süre, uygulanan onkolojik tedaviler açılarından istatistiki farklılık göstermiyordu. Uygulanan cerrahi işlemler nüks lezyonun yerleşimine göre farklılık göstermekle beraber oransal olarak gruplar arasında benzerdi. Operasyon süresi, ameliyat sırasında kanama miktarı, transfüzyon ihtiyacı ve miktarı ile hastanede kalış süreleri benzerdi (her bir değişken için p>0,05). R0 ve R1 gruplarında %44,7 (n=17) ve %36,4 (n=4) oranlarında postoperatif komplikasyon izlendi, ancak gruplar arasında farklılık gözlenmedi. R0 ve R1 gruplarında yer alan hastalarda yeniden bölgesel tekrarlama oranları %18,9 (n=7) ve %27,3 (n=3) idi (p=0,675). Hastaların 1, 3 ve 5 yıllık genel sağkalım oranları (%78,4 vs. %81,8, p=0,754; %43,2 vs. %36,4, p=0,720 ve %27,0 vs. %27,3, p=0,866) idi.

Sonuç: Nüks kolorektal kanser ameliyatı sonrası komplikasyon oranları yüksektir. Bu çalışma nüks kolorektal kanser tanısı ile ameliyat edilen hastalarda mikroskobik cerrahi sınır pozitifliğinin (R1) erken ve geç dönem sonuçları olumsuz olarak etkilemeyebileceğini ve bu olguların lokal tekrarlama oranlarının tam rezeksiyon başarılan (R0) olgulara benzer olabileceğinin altını çizmektedir.

Anahtar Kelimeler: Nüks, kolorektal kanser, R0 rezeksiyon, sağkalım, komplikasyon

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Introduction

Colorectal tumors are among the first three most common cancers that cause mortality in both women and men in our country. The treatment of the disease is multidisciplinary, but surgery constitutes an important stage of treatment. Regional recurrence can be seen after colorectal cancer surgery, whether applied for curative or palliative purposes. Although steps have been taken to develop and standardize neoadjuvant therapies and surgical techniques to reduce this risk, local recurrence rates after colon and rectal cancer surgeries have been reported to be 5-19% and 3-33%, respectively.[1,2] The chance of re-reoperation is limited in such recurrences and is only possible in 13-30% of all cases. There are many studies on the surgical technique that can be performed in case of local recurrence and their outcomes.[3,4,5,6,7,8,9,10,11,12] The surgery varies greatly due to many variables such as the location of the tumor, affected organs, presence or absence of metastases and accompanying diseases of the patient. This complicates both the measurement and demonstration of perioperative outcomes and does not allow comparison of different treatment modalities. However, it is believed that following oncological surgical principles provides a significant survival advantage. Two separate analyzes showed that median survival was prolonged from 5 months in patients without treatment to 7 and 15 months with radiotherapy.[4,13] However, many studies have shown that the median survival time increases to 33 to 59 months and the 5-year survival rate increases to 30 to 54% if recurrent disease is completely excised.[4,14] Surgical procedures performed to obtain this survival advantage are more radical interventions than primary tumor surgery due to unavailability of laparoscopic surgery, entering the previously operated abdomen, the need for multiple organ resections, and the need for neoadjuvant/adjuvant therapies. Therefore, intraoperative and early postoperative morbidity rates are higher. Some studies have reported perioperative complication rates between 15% and 68%, and have reported that early mortality reaches 3%.[3,6,7,14,15,16,17,18] Especially in rectal cancer surgery, surgical margin positivity is an important problem and its relationship with local recurrence has been known for a long time.[19] On the other hand, due to the nature of the disease and the difficulty of surgery, it is not possible to achieve surgical margin negativity in the case of recurrence as much as primary disease surgery.[3,5,6,10,12,20,21,22,23,24,25] The effect of microscopic surgical margin on recurrence in these patients has not been elucidated. The aim of this study was to evaluate the short- and long-term outcomes of surgery in patients with recurrent colorectal cancer who were operated in our clinic and to compare the outcomes of patients with microscopically negative and positive surgical margins.

Materials and Methods

Study Design and Inclusion Criteria

All patients who are operated at Dr. Lütfi Kırdar Kartal Training and Research Hospital, Clinic of General Surgery are enrolled in a prospective database. The study was conducted by retrospectively reviewing this database for all patients who were operated for recurrent colorectal cancer between 2004 and 2012. Patients with less than 5 years from surgery to data analysis were excluded to examine long-term outcomes. The potential for surgery was evaluated by carcinoembryogenic antigen, colonoscopy, thoracic and abdominal computed tomography, abdominal and pelvis magnetic resonance imaging, and positron emission tomography computed tomography in recent years. Preoperative pathologic diagnosis was obtained in suspected patients or in patients in whom endoscopic biopsy could be done. The entire treatment process was managed by a multidisciplinary council, and the applicability of surgery and the need for neoadjuvant/adjuvant treatments were decided by this council. Palliative surgeries in cases with metastasis other than resectable liver metastases were excluded from the study. The main criterion for surgical indications was the removal of the entire disease with potential negative surgical margins. All surgical procedures were performed or supervised by a single colorectal surgeon (M.O.).

Definitions

Recurrent colorectal cancer was defined as tumor recurrence at the surgical resection site or due to dissemination of the disease during surgery without causing carcinomatosis. Following complete removal of the tumor, surgical margin >1 mm was defines as R0, 1 mm or closer was defined as R1, and remaining macroscopic tumor after surgery or perioperative evaluation of the tumor as unresectable was defined as R2.

The Analyzed Variables and Groups

The following data were compiled: demographic data, data from the first surgery (tumor location, tumor, lymph node, metastases stage, surgical margins, operation performed, shape and center, preoperative and/or postoperative chemo/radiotherapy status), surgical procedures for recurrence (type and duration of surgery, intraoperative hemorrhage, perioperative blood transfusion rate and amount of transfusion, postoperative complications, mortality and length of hospital stay) and long-term outcomes (follow-up time, local recurrence and distant metastasis rates, overall survival). Patients were divided into two groups as R0 and R1. The R2 group was also evaluated, identified, but comparison was made between groups R0 and R1.

Statistical Analysis

SPSS 20.0 for Windows (IBM Corp. Released in 2011. Armonk, NY: IBM Corp) was used to analyze the data. Categorical data were expressed as number and percentage, and numerical data as mean ± standard deviation or median (range). The distribution between the groups was evaluated by Kolmogorov-Smirnov test. The numerical data with normal distribution were compared using Student's t-test and non-normally distributed data were compared using Mann-Whitney U test. Categorical data were compared using chi-square test (Pearson or Fisher's exact test). The overall survival rates of the groups were compared using Kaplan-Meier method.

Results

Fifty-seven patients [mean age=54.7±11.9 years, 35 male (61.4%)] who met the specified criteria and were operated for recurrent colorectal cancer were included in the study. Complete surgical resection failed in eight (14.0%) of these patients and these patients were considered as R2 resection group. No resection was performed in five patients (8.8%) in this group, and macroscopic residual tumor remained due to partial palliative resection in three patients (5.3%) who underwent tumor resection, subtotal colectomy and small bowel resection. This group of patients was excluded from further analysis and the remaining 49 patients [mean age=56.5±11.2 years, 30 male (61.2%)] were accepted as the subject of the study. Demographic data and data of the primary tumor were similar in these cases. Forty-one patients (83.7%) were operated for primary tumors in other centers. Twenty seven patients (71.1%) in the R0 group and 11 patients (100%) in the R1 group received chemotherapy and/or radiotherapy before or after their first surgery (p=0.050) (Table 1). The median time to recurrence in groups R0 and R1 was 28.5 (range=2-143) and 2 (range=6-70) months, respectively (p=0.581). Neoadjuvant chemo/radiotherapy was applied after recurrence in four patients [three patients (7.9%) in R0 and one patient (9.1%) in R1 groups, p=0.767]. Colon resections were higher in the R0 group (n=16, 42.1%) and rectal resections were higher in the R1 group (n=6, 54.5%), but this difference did not lead to a significant difference (p=0.337) (Table 2). The rate of need for additional organ resection was 61.2% (30/49) throughout the study and was similar between the groups. The most commonly resected organs were similar in the R0 and R1 groups. In the R0 group, four patients (10.5%) underwent synchronous metastasectomy (p=0.562). Intraoperative bleeding, operative time, intraoperative and postoperative blood transfusion requirements and hospital stay were similar in both groups (Table 2). Postoperative complications were observed in 21 cases (42.9%) and complication rates were similar between the groups (p=0.737) (Table 3). Early mortality was observed postoperatively in three patients (5.3%) who underwent R0 resection. The causes of mortality were as follows: hemorrhagic shock due to intraoperative blood loss on the day of surgery, treatment-refractory uncompensated pulmonary edema on postoperative day 2 and treatment-refractory sepsis due to anastomotic leakage on postoperative day 23. The median follow-up period was 35 (range=7-146) months in group

Table 1. Demographic and primary tumor data

	Group R0 (n=38)	Group R1 (n=11)	p
Age	56.9±11.8	54.9±9.2	0.610
Gender (female/male)	16 (42.1)/22 (57.9)	3 (27.3)/8 (72.7)	0.492
Primary tumor location			
Right colon	2 (5.3)	0	
Transverse colon	2 (5.3)	0	0.532
Left colon	16 (42.1)	3 (27.3)	
Rectum	18 (47.4)	8 (72.7)	
Primary TNM stage*			
1	7 (20.6)	1 (10.0)	
2	15 (44.1)	6 (60.0)	0.783
3	11 (32.4)	3 (30.0)	
4	1 (2.9)	0	
Neoadjuvant/adjuvant CT ± RT	27 (71.1)	11 (100)	0.050

*Histopathological data of primary tumor of four patients with R0 resection and one patient with R1 resection could not be reached, TNM: Tumor, lymph node, metastases, CT: Chemotherapy, RT: Radiotherapy

Table 2. Variables of recurrence surgery

	Group R0 (n=38)	Group R1 (n=11)	p
Type of surgery			
Colon resection	16 (42.1)	2 (18.2)	
Right/extended right	3 (7.9)	0	
Left/extended left	2 (5.3)	0	
Subtotal/total	11 (28.9)	2 (18.2)	
Rectal resection	15 (39.5)	6 (54.5)	
Anterior/inferior anterior resection	8 (21.1)	1 (9.1)	0.337
Abdominoperineal resection	5 (13.2)	4 (36.4)	
Pelvic exenteration	2 (5.3)	1 (9.1)	
Tumor/lymph node resection	7 (15.8)	1 (9.1)	
Additional organ resection	25 (65.8)	5 (45.5)	0.298
Bladder	7 (18.4)	3 (27.3)	0.673
Ureter	6 (15.8)	2 (18.2)	0.999
Prostate	2 (5.3)	3 (27.3)	0.068
Vagina	5 (13.2)	1 (9.1)	0.999
Uterus	5 (13.2)	1 (9.1)	0.999
Over	4 (10.5)	1 (9.1)	0.999
Small intestine	11 (28.9)	2 (18.2)	0.703
Stomach	4 (10.5)	0	0.562
Distal pancreas	3 (7.9)	0	0.999
Spleen	5 (13.2)	0	0.574
Kidney	4 (10.5)	0	0.562
Abdominal wall	7 (18.4)	0	0.325
Coccyx	1 (2.6)	0	0.999
Intraoperative bleeding	874.2±959.7	633.3±484.8	0.474
Intraoperative transfusion			
Quantity (units)	1 (0-7)	1 (0-2)	0.488
Rate	20 (52.6)	5 (50.0)	0.999
Postoperative transfusion			
Quantity (units)	0 (0-13)	0 (0-1)	0.074
Rate	13 (37.1)	1 (10.0)	0.137
Total transfusion			
Quantity (units)	2 (0-15)	0.5 (0-3)	0.124
Rate	23 (62.2)	5 (50.0)	0.496
Length of hospital stay	7 (0-70)	10 (4-24)	0.366

Table 3. Postoperative complications

	Group R0 (n, %)	Group R1 (n, %)	p
Clavien-Dindo Classification			
Grade 1	6 (15.8)	2 (18.2)	
Grade 2	2 (5.3)	1 (9.1)	0.928
Grade 3	7 (18.4)	1 (9.1)	
Grad 5	3 (7.9)	0	
Infective problems	9 (23.7)	0	0.098
Wound site infection	3 (7.9)	0	0.999
Evisceration	4 (10.5)	0	0.562
Intraabdominal abscess	3 (7.9)	0	0.999
Urinary fistula	3 (7.9)	1 (9.1)	0.999
Ileus	3 (7.9)	2 (18.2)	0.311
Nonsurgical problems	2 (5.3)	1 (9.1)	0.542
Bleeding	1 (2.6)	0	0.999
Enteric fistula	1 (2.6)	0	0.999
Total	17 (44.7)	4 (36.4)	0.737

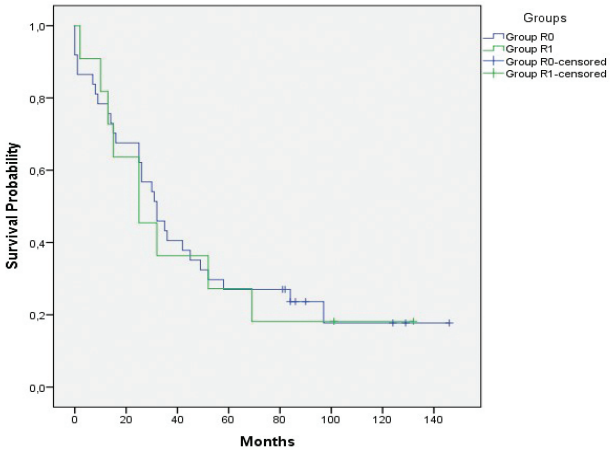

Figure 1. Kaplan-Meier analysis: overall survival rates

R0 and 25 months (range=2-132) in group R1 (p=0.922). During this period, the local recurrence rates in the R0 and R1 groups were 18.9% (n=7) and 27.3% (n=3), respectively (p=0.675). Overall survival rates of the patients at 1, 3 and 5 years (78.4% vs. 81.8%, p=0.754, 43.2% vs. 36.4%, p=0.720 and 27.0% vs. 27%, 3, p=0.866) were similar (Figure 1).

Discussion

In recurrent colorectal cancers, surgery has difficulties and success rates are lower than in primary cancers. It is known that surgery in accordance with oncologic rules provides a survival advantage in these patients, but the factors affecting the success of these complex operations have been studied less.[3,6,8,11,16,22,24] It is not known whether surgical margin negativity, which has been shown to be effective in primary tumors, is necessary in recurrent cancer patients due to tumor character and surgical difficulty. The aim of this study was to define the surgical characteristics of recurrent colorectal cancer patients and to determine the effect of microscopic surgical margin positivity on short- and long-term outcomes.

There are many data suggesting that the recurrence rate of colorectal cancer is higher in male gender.[4,5,7,10,16,20] In this series, more patients were male. However, no difference was found between R0 and R1 groups. In spite of all previous examinations and evaluations in recurrent colorectal cancer patients, it is not uncommon to detect the disease as unresectable during surgery. In a recent systematic review of nine studies including patients (n=950) operated for recurrent colon cancer, it was found that R2 resection rates in the series ranged from 7.1% to 62.9% (median=22.6%).[26] The results are similar for rectal cancer. In another review specifically addressing this issue, R2 resection rates were reported to be between 2% and 48% (median=14%).[9] In our series, the probability of failure of R0 or R1 resection was 14%. In five out of eight patients, it was decided not to perform any resection during surgery and the possibility of

a possible complication was minimized. We think that the main reason for this group of patients to be at an acceptable rate is related to the routine discussion of patients in multidisciplinary councils before surgery. Surgery for recurrent colorectal cancer includes larger areas of resection. In a previous study from our clinic, multiple organ resections were required in 25% of patients with primary colorectal cancer due to suspicion of T4 tumor, but the pathological T4 rate was found to be 8.8%.[27] However, due to its nature, recurrent cancers are significantly more likely to require multivisceral resection. In a single center study examining local and regional recurrences, 100 out of 744 patients underwent surgery, and 42 (42%) required multiple organ resections.[3] In the presented series, this rate was 62.2%. The most commonly affected organs were the urinary system and small intestine. In our unit, primary T4 tumors or recurrent tumors that tend to exhibit environmental invasion due to its nature are most preferred for en block resection. This method may be advantageous in terms of tumor spread. On the other hand, large resections may increase postoperative risks. In some series, complication rates have been reported as 50% and mortality rates as 10%.[10,21,23,28,29] In our series, postoperative complications were observed in 21 cases (42.9%) and the complication rates between the groups were similar. Overall mortality rate was 6.1% (n=3). According to our opinion, recurrence operations are procedures that should be performed in reference centers because of technical difficulties, multidisciplinary approach and high postoperative complication rates. Survival results are not excellent, even if tumor resection has been successfully performed in patients with recurrent colorectal cancer. Although 5-year survival rate is reported as 90% in some small series, a recurrence rate of 25% and a 50% survival rate are reported for 3 years, even in cases where R0 is achieved.[26,30] In a review of the results of recurrent rectal cancer surgery, recurrence rates were reported to be between 4% and 54%, and 5-year survival rates between 9 and 39%, even after curative surgery.[9] Similar recurrence and survival rates were determined in our series. It has long been known that it is a vital requirement to achieve surgical margin negativity, especially during resection of primary tumors located in the rectum.[19] For recurrent tumors, whether R0 and R1 resection really makes a difference is controversial. In a recent study involving mostly recurrence of colon cancer, survival differences between R0 and R1 resections could not be demonstrated.[21] Another review reported that survival rates after R0 resection were significantly better than R1 resection.[26] In our series, it is observed that the application of R1 resection is not a disadvantage in terms of both local recurrence and survival. This is an important finding in our opinion because these data make a further step unnecessary if more aggressive surgery is required to achieve the R0 limit, especially in patients with microscopic positivity. If these findings are confirmed by other series, it may be effective in determining the strategy during surgery and in the decision of the surgeon. This study has many limitations. The most important limitation is the problem posed by retrospective compilation of the data, despite the prospective recording of the data. The small number of the study population reduces the reliability of many inferences and raises doubts for statistically insignificant comparisons. The long study time renders the effects of the accumulation of experience and practical changes in the study results uncertain. Despite all of this, the study can be considered as efficient in terms of shedding light on the results of a rare surgical procedure.

Conclusion

In conclusion, surgery is difficult and often requires multiple organ resections in patients with recurrent colorectal cancer. This significantly increases the possibility of postoperative complications. Recurrence and survival results are not excellent in patients. However, R1 resection may not adversely affect the short- and long-term outcomes. Decision-making of such patients should be performed in multidisciplinary settings and performed by experienced surgeons.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ö., N.O., Concept: N.O., Design: M.Ö., Data Collection or Processing: N.O., Analysis or Interpretation: N.O., Literature Search: N.O., MÖ., Writing: N.O., MÖ.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

Effects of Calcium Dobesilate on Colonic Anastomosis Healing: An Experimental Study

Kalsiyum Dobesilatın Kolon Anastomoz İyileşmesi Üzerine Etkileri: Deneysel Bir Çalışma

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ABSTRACT

Aim: Anastomotic leakage in colon anastomosis (CA) increases morbidity and mortality. Calcium dobesilate (CaD) has angioprotective, antioxidant, lymphatic flow enhancing-and neuroprotective effects. Despite these capillary and cellular effects, there is no data in the literature regarding the effects of CaD on CA healing.

Method: Fifty Wistar-albino rats were randomly divided into five groups. All rats underwent CA after transverse colon transection. CaD was not administered to the control group (Group 1). CaD was administered to the experimental groups (Groups 2, 3, 4 and 5) intraperitoneally or by gavage at doses of 50 or 100 mg/kg/day. CaD was given as a single dose daily during postoperative five days. Bursting pressure values (BPV) and hydroxyproline values (HV) were measured. At the end of histopathological evaluation, polymorphonuclear leukocytes (PNLS), mononuclear leukocytes (MNLS), neovascularization (VS) and collagen fibers (CFS) were scored.

Results: CaD increased BPV and HV in experimental groups. We found a decrease in PNLS, MNLS, VS, and an increase in CFS in experimental groups. These increases seemed to be related to the administration doses of CaD. The decreases in PNLS, MNLS and VS were much more evident in Groups 4 and 5 than the other groups. There was no significant difference in terms of VS between experimental groups.

Conclusion: We found that CaD not only decreased the pathological parameters of inflammation, but also increased the strength of CA mechanically and biochemically. Although VS reduction seemed to have negative outcomes on CA, we know that CaD inhibits over-expression in angiogenesis. As a result, these effects of CaD appear to be dose-dependent rather than the administration methods.

Keywords: Calcium dobesilate, colon anastomosis, bursting pressure, hydroxyproline, antiangiogenesis, collagen fibers

ÖZ

Amaç: Kolon anastomozu (CA) sonrası gelişen anastomoz kaçağı morbidite ve mortaliteyi artırır. Kalsiyum dobesilate (CaD) anjiyoprotektif, antioksidan, lenfatik kan akımını artırıcı ve nöroprotektif etkilere sahiptir. Bu kapiller ve hücresel sahadaki etkilerine rağmen CaD'nin, CA iyileşmesi üzerine etkileri hakkında literatürde veri yoktur.

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Yöntem: Elli adet Wistar-albino sıçan, eşit sayıda ve rastlantısal olarak beş gruba ayrıldı. Tüm sıçanlara transvers kolon transeksiyonu sonrasında CA yapıldı. Kontrol grubuna (Grup 1) CaD uygulanmadı. Deney gruplarına (Grup 2, 3, 4 ve 5), periton içi ya da gavajla ve 50 ya da 100 mg/kg/gün dozlarında CaD uygulandı. CaD, günlük tek doz ve ameliyat sonrası 5 gün verildi. Patlama basınç değerleri (BPV) ve hidroksiprolin değerleri (HV) ölçüldü. Sonunda histopatolojik değerlendirmede (HPE), polimorfonükleer lökositler (PNLS), mononükleer lökositler (MNLS), yeni damar oluşumu (VS) ve kollajen lifler (CFS) skorlandı.

Bulgular: Kalsiyum dobesilat, deney gruplarında BPV ve HV artırdı. Biz deney gruplarında PNLS, MNLS, VS'de azalma, CFS'de ise artış saptadık. Bu artış, ilacın uygulama dozu ile ilişkili gibi görünmektedir. Çalışma gruplarında HPE'de PNLS, MNLS ve VS azalmaktadır ama CFS artmaktadır. Grup 4, 5 PNLS, MNLS ve VS'lerinde saptanan azalma, diğer gruplardan belirgindi. Deney grupları arasında, VS açısından fark yoktu.

Sonuç: Biz, CaD'nin sadece patolojik olarak enflamasyon parametrelerini azaltmakla kalmadığını aynı zamanda mekanik ve biyokimyasal olarak CA'nın gücünü artırdığını saptadık. VS azalması, CA iyileşmesinde olumsuz sonuçlar doğuracak gibi görünmesine rağmen, biz CaD'nin angiogenesisde oversupresyonun inhibe ettiği biliyoruz. Sonuçta, CaD'nin bu etkileri, uygulama şeklinden ziyade doz bağımlı gibi görünmektedir.

Anahtar Kelimeler: Kalsiyum dobesilat, kolon anastomozu, patlama basıncı, hidroksiprolin, antianjiogenezis, kollajen lifler

Introduction

Colon resection (CR) can be performed due to various emergency or elective pathologies. The anatomical integrity of gastrointestinal tract after resection is usually achieved by an anastomosis. Histologically, colonic anastomosis (CA) healing process can be divided into stages, and these stages of the healing in CA are substantially similar to the wound healing stages anywhere in the body.[1,2,3,4,5,6,7,8] The most important factor in anastomotic healing is collagen, which constitutes the stretching force of submucosal connective tissue.[9] The stage with highest risk for anastomotic leakage (AL) is the inflammation stage.[3] AL following a CR is still considered a serious problem for surgical care and has an incidence between 3% and 19%.[2,10] This estimate includes asymptomatic AL with an incidence as high as 50%.[11] In case of AL, the duration of hospitalization is doubled and perioperative mortality is tripled compared to the normal healing process of CA.[2] Many factors affect the healing of CA.[2] Pre-operative colon mechanical cleansing, antibiotic prophylaxis, healthy tissue for anastomosis, surgical technique, indication for surgery (elective or emergency), radiotherapy, hypothermia, advanced age, presence of systemic diseases (obesity, jaundice, anemia, diabetes, chronic renal failure, cirrhosis, malignancies, etc.), nutritional status of the patient (malnutrition, alcoholism and smoking), immune status of the patient, medical prescriptions used by the patient, sepsis and shock are some of these factors.[3,7,10,12,13,14,15] Calcium dobesilate (CaD) (Doxium® 500 mg capsule, Abdi İbrahim İlaç Sanayi ve Ticaret A.Ş, İstanbul, Turkey) is a synthetic agent, which has shown its efficacy at capillary level and which has vasoprotective effects.[16,17,18,19,20] In the experimental studies, it has been shown that CaD has a neuroprotective activity and is an antiangiogenesis in diabetic neuropathy.[21,22] CaD, reduces the over-expression of endothelin-1, intracellular adhesion molecule-1, vascular endothelial growth factor (VEGF) from retinal endothelial cells in diabetic retinopathy and prevents alterations on leukocyte adhesion.[21,23] CaD eliminates detrimental effects of reactive oxygen species (ROS).[24,25,26] CaD increases the nitric oxide synthase activity of capillary endothelial cells and regulates the formation of basal membrane collagen network.[16,19,25] It also regulates the capillary membrane resistance that reduces capillary hyper-permeability and fragility.[18,27] It reduces platelet aggregation and prevents thrombus formation.[25,28,29] Moreover, it also inhibits hyaluronidase, which is responsible for the fragmentation of the matrix mucopolysaccharides in the capillary basal membrane.[16,18,30] CaD reduces transcapillary escape of albumin from peripheral circulation.[18] The antioxidant properties of CaD are attributed to its scavenger activity in lipid peroxidation caused by ROS. It also inhibits the release of inflammatory cytokines, such as platelet activating factor (PAF).[17] Notwithstanding these capillary and cellular effects, there is no data available in the current literature regarding the effects of CaD on healing of CA.

Materials and Methods

Animal Model and Treatment Protocol

The current study was performed using 10-12 week-old male Wistar rats (n=50) weighing 225±25 g. The rats were housed in a temperature-controlled room (20-22 °C) and 55-60% humidity with 12-h light-dark cycles. All rats were fed a standard rodent chow (20% protein, 6% cellulose, 2% fat in 100 g of chow) and given water ad libitum. After an adaptation period of one week, the experimental animals were randomly divided into four experimental groups as Groups 2, 3, 4 and 5, and one control group as Group 1. The treatments were as follows: only CA was performed in Group 1 (n=10); CA was performed and CaD was administered intraperitoneally 50 mg/kg/day in Group 2 (n=10); CA was performed and CaD was administered by gavage at a dose of 50 mg/kg/day in Group 3 (n=10); CA was performed and CaD was administered intraperitoneally 100 mg/kg/day in Group 4 (n=10) and CA was performed and CaD was administered by gavage at a dose of 100 mg/kg/day in Group

5. The design of the experimental groups and control group is shown in Figure 1. An excipient of 0.9% sodium chloride was used for the preparation of various concentrations of CaD for intraperitoneal applications and distillated water was used as the adjuvant for various concentrations of CaD for gavage applications. After 12 hours post-operatively, CaD was administered to the experimental Groups 2, 3, 4 and 5) for five days (Figure 1). All experimental studies were conducted in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised in 1978). The ethical protocol of the current research was approved by Ethics Committee of İstanbul University, İstanbul, Turkey. Institutional Review Board (IRB) (number: 2006/ 30826).

Surgical Procedure

The rats were anesthetized by an intramuscular injection of ketamine hydrochloric acid (HCL) 50 mg/kg (Ketalar®, Eczacıbaşı Pharmaceuticals Marketing, Lüleburgaz, Turkey) and xylazine HCL 10 mg/kg (Rompun® 2%, Bayer, Leverkuesen, Germany). We made a midline incision to expose the transverse colon, which was divided about midway. Integrity was restored with an inverted one-layer end-to-end anastomosis consisting of six or eight interrupted sutures of 6/0 polypropylene (Prolene®; Ethicon, İstanbul, Turkey). The abdomen was closed in two layers with a continuous 3/0 silk suture for the fascia and skin. All rats underwent re-laparotomy at the end of the 5th day and all of them were sacrificed with high-dose ether anesthesia.

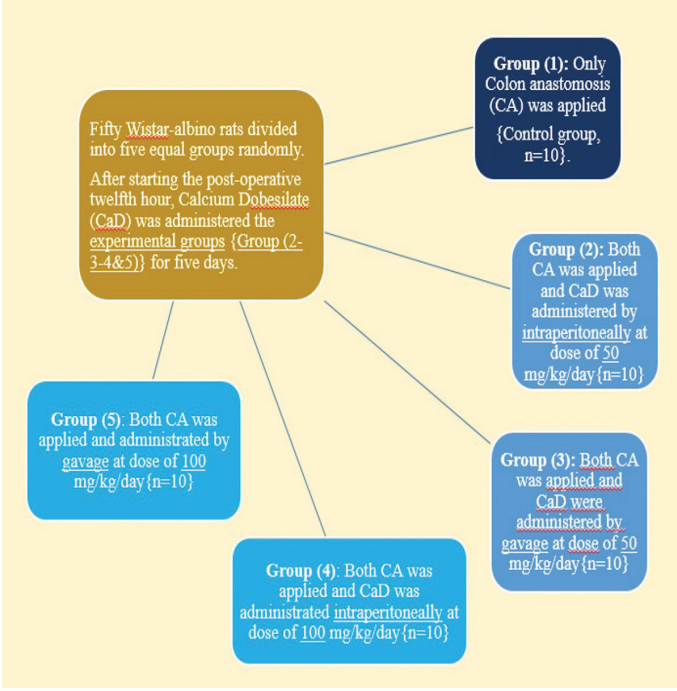

Figure 1. Design of the experimental groups and control group
CA: Colon anastomosis, CaD: Calcium dobesilate

Bursting Pressure Measurements

Bursting pressure value (BPV) was measured *ex vivo*. After re-laparotomy on the fifth postoperative day, anastomotic colonic segments were resected and bursting pressures were measured. The distal end of colon was ligated using a 3/0 silk suture and a catheter was secured into the proximal end and fixed to the bursting pressure apparatus as described elsewhere.[3,31] Through this catheter, the bowel was infused with a continuous flow of air at a rate of 3 mL/min using an infusion pump [Perfuser E (type 871112), B. Braun Meisingen a 6 device]. BPV was defined as the value recorded at the point of an air leakage or gross rupture, and it was noted in mmHg. The site of leakage or rupture during the bursting pressure measurement occurred at the anastomosis area in all rats.

Preparation of Tissue Homogenates

After anastomotic BPV measurement, one centimeter of the colonic segment including the anastomosis site was resected from each subject and half of the specimen was fixated in 10% formaldehyde for histopathological examination. The other half was used in tissue homogenate extraction to determine hydroxyproline levels (HV). The extracted tissues were rinsed in ice-cold PBS (0.02 mol/L, pH 7.0-7.2) to remove excess blood thoroughly and weighed before homogenization. Tissues were minced and homogenized in 6N HCL. The homogenates were then centrifuged at 1.500 x g (or 5.000 rpm) for 15 minutes. Removed supernatant samples were stored at -20 to -80 °C until the assay time for hydroxyproline.

Estimation of Tissue Hydroxyproline Concentrations

The chemicals used for the hydroxyproline assay were of the highest analytical grade available. All of the chemicals were purchased from Sigma-Aldrich (St Louis, MO, USA). All reagents were stored at +4 °C and brought to room temperature 20 minutes prior to the usage. Tissue HV were assessed by using the Bergman & Loxley method.[32] The analytic principle of the assay was colorimetric measurement of the colored complex formed with p-dimethylaminobenzaldehyde of pyrrolle after the oxidation of hydroxyl pyroline to pyrrole compound with chloramine T using a spectrophotometer (Shimadzu UV 1601, Tokyo, Japan) at 560 nm. The absorbance of trans-4-hydroxy-L-proline standards was used for the standard curve drawing. Hydroxyproline concentrations were expressed as mg/g of tissue-wet weight.

Histopathological Evaluation

After the samples fixed in 10% formalin solution for 24 hours, they were processed with standard paraffin technique and stained with hematoxylin and eosin. The samples were

then examined under a light microscope. The parameters were evaluated with help of the modified Ehrlich & Hunt scoring scale including polymorphonucleated cells (PNL), mononuclear cells (MNL), neovascularization and collagen fibers (CF). Scores ranged from 0 to 4 as: score 0 (-)=no evidence, score 1 (+)=occasional evidence, score 2 (++)=light scattering, score 3 (+++)=abundant evidence, and score 4 (++++)=confluent fibers or cells.[9,33,34,35]

Statistical Analysis

Categorical variables were presented in percentages and continuous variables were expressed as mean ± standard deviation. Repeated measures ANOVA, Post-hoc tests, Tukey-Kramer test and chi-square test were used to analyze statistical differences between the groups regarding BPV, HV and histopathological evaluation. A p value less than 0.05 was considered significant.

Results

Bursting Pressure Values

Anastomotic BPVs of Group 2 and 3 were significantly higher compared to Group 1 ($p<0.05$). There was no significant difference between Group 2 and 3 in terms of BPV (Figure 2). BPVs of Group 4 and 5 were significantly higher compared to Group 1, 2 and 3 ($p<0.05$). The comparison between Group 4 and Group 5 showed no significant difference (Figure 2). Table 1 shows anastomotic BPVs (mmHg) and HV (mg/g) according to groups.

Hydroxyproline Values

HVs of Group 2 and 3 were significantly higher compared to Group 1 ($p<0.05$). There was no significant difference between Group 2 and 3 in terms of HV (Figure 3). HV of Group 4 and 5 were significantly increased when compared to Group 1, 2 and 3 ($p<0.05$). The comparison between Group 4 and Group 5 showed no significant difference (Figure 3).

Histopathological Evaluation

Polymorphonuclear Leukocyte Infiltration Scores (PNLS)

Group 1 showed a significant increase in scores 2 and 3 ($p<0.05$). There was no statistically significant difference between Group 1, Group 2 and Group 3 ($p>0.05$). Group 4 and 5 showed a significant increase in scores 1 and 2 ($p<0.05$). The increase in score 1 in Group 4 and 5 was statistically significant compared to other groups ($p<0.05$).

Mononuclear Leukocyte Infiltration Scores (MNLS)

Group 1 showed a significant increase in score 2 ($p<0.05$). Group 2 and Group 3 had a significant increase in score 1 when compared to Group 1 ($p<0.05$). There was no statistically significant difference between Group 2 and Group 3 ($p>0.05$). Group 4 and Group 5 showed a significant increase in score 1 compared to Group 1 ($p<0.05$). Groups 1, 2, 3 and 5 showed a significant increase in score 2 compared to Group 4 ($p<0.05$).

Neovascularization Scores (VS)

Groups 1, 2 and 4 did not show any statistically significant difference when compared to each other ($p>0.05$). When

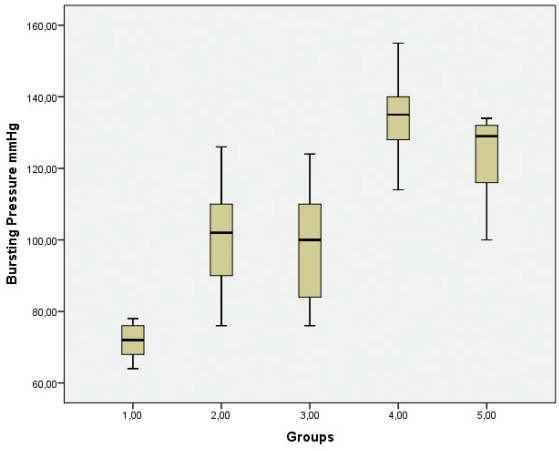

Figure 2. The mean burst pressure values of the groups

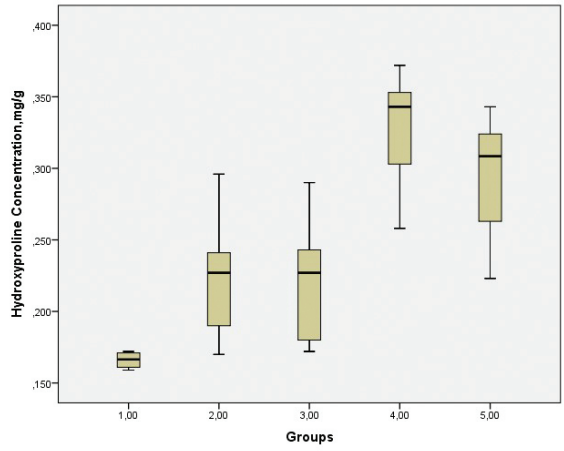

Figure 3. The mean tissue hydroxyproline levels of the groups

Table 1. Burst pressure values and tissue hydroxyproline values of all groups (mean ± standard deviation)

	BPV (mmHg)	HV (mg/g)
Group 1 (n=10)	71.6±4.6	0.166±0.004
Group 2 (n=10)	100.6±15.2	0.222±0.036
Group 3 (n=10)	97.6±15.3	0.218±0.038
Group 4 (n=10)	135.1±11.6	0.329±0.035
Group 5 (n=10)	123.8±10.7	0.295±0.039

BPV: Burst pressure values, HV: Hydroxyproline values

Table 2. Histopathological scores of the groups

	PNLS	MNLS	VS	CFS
Group 1	+++/++	++	++/+++/+	++/+
Group 2	+++/++	++/+	+/++/+++	++
Group 3	++/+++	+/++	++	++
Group 4	+++/++/+	+	++/+++/+	++
Group 5	++/+	+/++	+/++	++

PNLS: Polymorphonuclear leukocyte score, MNLS: Mononuclear leukocyte score, VS: Neovascularization score, CFS: Collagen fiber score

Groups 1, 2 and 4 were compared with Group 3, the increase in scores 1 and 3 were statistically significant ($p<0.05$). When Groups 1, 2 and 4 were compared with Group 5, the increase in score 3 was statistically significant ($p<0.05$). Group 5 showed a significant increase in scores 1 and 2 compared to Group 3 ($p<0.05$).

Collagen Fiber Scores (CFS)

Group 1 showed a statistically significant increase in scores 1 and 2 ($p<0.05$). Groups 2, 3, 4 and 5 had a significant increase in score 2 ($p<0.05$). When Group 1 was compared to Groups 2, 3, 4 and 5, the increase in score 1 was statistically significant ($p<0.05$). Groups 2, 3, 4 and 5 did not show a statistically significant difference when compared to each other ($p>0.05$). Table 2 shows the distribution and comparison of statistically significant scores according to groups.

Discussion

It has been shown that CaD not only has inhibitor activity on VEGF production, but also improves microvascular hemodynamics and shows anti-leakage effects by reducing plasma endothelin-1 levels in experimental diabetic retinopathy.[21,23] Despite its antioxidant and anti-inflammatory effects, studies investigating the effects of CaD on wound healing are limited. Eventually, no studies have investigated the therapeutic efficacy of CaD on colon anastomosis healing. It has been previously reported that CaD inhibits platelet aggregation and prevents thrombus formation.[19,20,24,25,28,29] Both platelet aggregation and thrombus formation are essential for surgical hemostasis during primary hemostasis after the initial injury.[36] In order to avoid any hemostatic problem in our study, we started CaD administration at post-operative 12th hour. BPV has been used as a direct measure of the strength of CA.[33] On the other hand, hydroxyproline is a part of collagen that was demonstrated to be positively correlated with the amount of collagen and healing of CA.[9] Regardless of the administration method, both BPV and HV levels were significantly increased in the experimental groups that were treated with CaD ($p<0.05$). This increase was much more evident when CaD dose was 100/kg per day ($p<0.05$). PNL is known as a potential source of collagenase in the wound healing site and is directly related to collagen catabolism.[4] High collagenase activity plays an important role in anastomotic healing, causing low anastomotic strength early after the formation of an anastomosis because of collagen lysis.[35] In our study, as there was decreased PNLS count and increased CFS accompanied by an increase in both BPV and HV in Groups 4 and 5 compared to Group 1, intraperitoneal administration of 100/mg/kg CaD per day was shown to have positive effect on CA healing. This result might be related to the expected consequences of antioxidant, neuroprotective, anti-inflammatory and capillary effects of CaD. Neovascularization, which promotes collagen synthesis, enhances anastomotic strength.[9] The decrease in VS levels at the given dose seems to be a disadvantage. However, a significant increase in BPV and HV, and their positive effects on CA healing may be associated with suppression of overexpression by CaD on angiogenesis.[22] CaD was reported to exert aforementioned effect through VEGF and endothelin one.[21,23] CaD showed no anti-angiogenic effect when used as gavage at a dose of 100 mg/kg per day; this result may be related to excretion of 50% of the administrated drug via fecal material without any biotransformation. Further studies with higher doses of CaD application are needed to clarify the effects of gavage. In this study, when Group 1 and Group 2 were compared, no significant difference was observed in terms of BPV, HV and CFS ($p>0.05$). We also found the same findings when Group 4 and Group 5 were compared. These findings may be caused by a single daily dose of medication. Previous *in vivo* and *in vitro* studies have shown that repetitive CaD administrations within a day increase both antioxidant effect and lymphatic circulation.[18,27,30] Administration of CaD at a dose of 50 mg/kg/day was found to have no effect in PNLS. However, administration of CaD at a dose of 100 mg/kg/day reduced PNLS ($p<0.05$). This decrease was more prominent in Group 5 than in the other groups ($p<0.05$). The decrease in MNLS was more prominent in the experimental groups than in the control group. The decrease in MNLS was more prominent in Group 4 ($p<0.05$). Finally, with CaD administration at a dose of 100 mg/kg/day, both acute and chronic histopathological parameters of inflammation levels decreased significantly ($p<0.05$). In addition to the above, VS decreased when CaD was administered at a dose of 100 mg/kg/day ($p<0.05$). Moreover, CaD administration increased CFS in experimental groups ($p<0.05$). The aforementioned effects of CaD (reducing

capillary hyperpermeability and fragility by regulating capillary membrane resistance, enhancing plasticity and flexibility of thrombocytes, decreasing blood viscosity and increasing of blood fluidity, augmentation of lymphatic drainage and stimulation of lymph circulation, reducing protein-rich edema by increasing normal proteolysis, etc.) are known to be associated with macrophages and lymphatic transport.[16,18,23,30,36] The decrease in serum protein levels (especially albumin) is critical for the healing of CA. A limitation of our study is the lack of biochemical parameters of blood such as albumin, and further studies are needed in this section.

Conclusion

To summarize, we found that CaD not only reduces pathological inflammation parameters, but also strengthens CA mechanically and biochemically. Although the decrease in neovascularization appears to have negative outcomes on CA, we know that CaD inhibits over-expression in angiogenesis. Finally, these effects of CaD seemed to depend on the administration doses rather than the administration methods. Further researches are needed to clarify this topic.

Ethics

Ethics Committee Approval: Ethical protocol of the current research was approved by Ethics Committee of İstanbul University, İstanbul, Turkey. Institutional Review Board (IRB) (number: 2006/ 30826).

Informed Consent: Not applicable.

Authorship Contributions

Surgical and Medical Practices: S.D., S.D., Ö.S., G.B.D., H.U., Concept: S.D., S.D., Ö.S., G.B.D., H.U., T.İ., Design: S.D., S.D., Ö.S., G.B.D., H.U., T.İ., Data Collection or Processing: S.D., S.D., Ö.S., G.B.D., H.U., T.İ., Analysis or Interpretation: S.D., E.H., A.O., S.D., Ö.S., G.B.D., H.U., E.A., S.Ç., A.T., Z.S., İ.T., T.İ., Literature Search: S.D., E.H., A.O., S.D., E.A., S.Ç., A.T., Z.S., İ.T., T.İ., Writing: S.D., E.H., A.O., S.D., E.A., S.C., A.T., Z.S., İ.T., T.İ.

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CASE REPORT

Type 4 Congenital Pouch Colon without Fistula with Anal Agenesis and Lower Vaginal Agenesis in a Female Fetus: A Rare Autopsy Case Report

Dişi Fetüste Anal Agenezi ve Alt Vajinal Agenezi ile Fistülü Olmayan Tip 4 Konjenital Poş Kolon: Nadir Bir Otopsi Olgu Sunumu

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ABSTRACT

Congenital pouch colon is a rare anorectal malformation of unknown embryogenesis in which all or part of the large intestine is replaced by a pouch-like dilatation that usually communicates with the urogenital tract via a fistula. This condition is more common among males in North Indian population and is associated with various anomalies such as uterovaginal malformations. It has been classified into five types that are showing a shift over the years towards less severe types such as type 4. We report a case of type 4 congenital pouch colon with anal agenesis without fistula and lower vaginal agenesis in a 29-week-old female fetus diagnosed during autopsy. The absence of a fistula and association with vaginal agenesis in a female fetus, which gets overlooked even in live births, makes it a unique case. Early prenatal diagnosis and awareness about this condition are essential for appropriate management and favorable surgical outcome.

Keywords: Congenital pouch colon, anorectal malformation, anal agenesis, vaginal agenesis

ÖZ

Konjenital poş kolon, kalın bağırsağın tamamının veya bir kısmının, genellikle bir fistül yoluyla ürogenital sistem ile bağlantı kuran, kese benzeri bir dilatasyon ile yer değiştiği bilinmeyen bir embriyogenezisin nadir bir anorektal bozukluğudur. Bu durum Kuzey Hint popülasyonundaki erkekler arasında daha yaygındır ve uterovajinal malformasyonlar gibi çeşitli anomalilerle ilişkilidir. Yıllar içinde tip 4 gibi daha az ciddi tiplere doğru kayma gösteren beş tipe ayrılmıştır. Otopsi sırasında tanı alan 29 haftalık dişi fetüste fistülsüz anal agenezi ve alt vajinal agenezi ile görülen konjenital poş kolon olgusunu sunmayı amaçladık. Fistülün olmaması ve canlı doğumlarda bile göz ardı edilen vajinal agenezis ilişkisi olgumuzu değerli bir hale getirmektedir. Doğum öncesi erken tanı ve bu durum hakkında farkındalık uygun tedavi ve avantajlı cerrahi sonlanım için gereklidir.

Anahtar Kelimeler: Konjenital poş kolon, anorektal malformasyon, anal agenezi, vajinal agenezi

Introduction

Congenital pouch colon is a rare form of anorectal malformation of uncertain embryogenesis, in which all or part of the large intestine is replaced by a pouch-like dilatation that is usually connected with the urogenital tract via a fistula. The absence of fistula is considered a rare variant of anorectal malformation. It was first described by Spriggs in 1912 in a London museum specimen. This condition is frequently reported in males from northern parts of India and neighboring countries.[1] The incidence of vaginal agenesis with anorectal malformation is difficult to estimate as it is often overlooked in the majority of the cases due to lack of awareness. Herein, we present a case of pouch colon with a unique association with anal agenesis without fistula and lower vaginal agenesis in a female fetus diagnosed on autopsy.

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Case Report

A 24-year-old woman (gravida=2, abortion=1) with a history of seven months of amenorrhea presented with complaints of decreased movements with fetal ascites. Her previous pregnancy was a triplet pregnancy in which she underwent medical termination of pregnancy at two and a half months amenorrhea one year ago. She had regular antenatal check-ups at a local hospital. There was no significant medical history. Ultrasonography done at 28th week revealed a single live intrauterine fetus of 27 weeks and 4 days period of gestation with severe fetal ascites and low-lying placenta. Thus, she was referred to our hospital for further management. After draining the ascitic fluid under ultrasound guidance, she delivered a dead fetus of 29-week-old weighing 1.998 kg by vaginal delivery with episiotomy. The fetus was received for autopsy. The external examination revealed unidentifiable external genitalia and imperforate anus along with grossly distended abdomen containing a large amount of straw-colored fluid and low set ears. On internal examination, upon tracing the gastrointestinal tract, the large intestine was noted to terminate in a blind pouch measuring 4x3x2.5 cms, which was dilated at the distal end and contained fecal material. The section from the pouch showed large intestinal lining with mild congestion in the wall. No anus was identified grossly and it was microscopically suggestive of pouch colon with anal agenesis. There was a thin band connecting uterus to the pouch. However, there was no fistula or lumen communication. Uterus with bilateral fallopian tubes and ovaries was identified establishing the gender of the baby as female. The lower end of the uterus and uterine cavity were dilated and contained a clear fluid with few whitish specks. Vagina was ending blindly, suggestive of lower vaginal agenesis (Figure 1). The rest of the organs were both macroscopically and microscopically normal. With the above findings, a final diagnosis of type 4 congenital pouch colon without fistula with anal agenesis and lower vaginal agenesis was made.

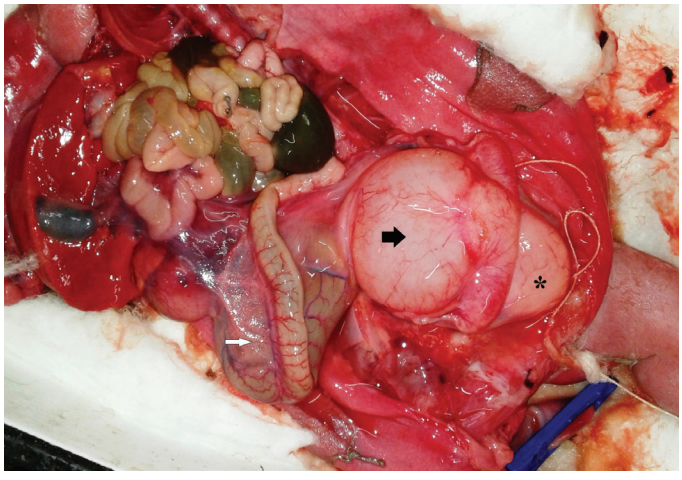

Figure 1. Internal examination revealed large intestine ending in a blind pouch (white arrow), distended uterus with cervix (black arrow) and bladder in front (marked by*)

Discussion

Anorectal malformations are a complex group of congenital anomalies that present with a wide spectrum of defects, most commonly urogenital defects. The incidence of anorectal malformation ranges from 1 per 1500 and 1 per 5000 live births.[2] Congenital pouch colon is an unusual anorectal malformation with pouch-like dilatation of a shortened colon. In India, it was first reported by Singh and Pathak in 1972 and described as "short colon".[1] Cases have been reported mainly from North India with a significant male preponderance, with a male/female gender ratio ranging from 2.25:1 to 7:1.[3] In contrast, the present case is a female fetus from a similar geographical region. As in our case, most cases present in the early neonatal period within the first seven days of birth. Very rarely, they present late when the fistula is large as in a female child with colocloacal fistula.[1] The embryogenesis of congenital pouch colon is still unknown. Various theories proposed by authors include chronic obstruction, obliteration of the inferior mesenteric artery early in fetal life, primary disorder of the proximal end of the hindgut or postsplenic gut, faulty rotation and fixation of the colon, vascular insult at the time of the partitioning of the cloaca by the urorectal septum, and the combined effect of defective development of the splanchnic layer of the caudal fold and failure of rotation of the gut. As in the present case, the factors attributable to the predominance of cases in north Indian belt are nutritional deficiency, especially iodine deficiency, pesticide use in fields, vegetarian diet and low socioeconomic status. These factors may affect the inutero development of hindgut and differentiation into urinary and intestinal tracts.[1] The widely accepted classification of congenital pouch colon is by Narasimha et al.[4] which is based on the length of the normal colon present proximal to the dilated pouch. Although type 1 and 2 have previously been common, recent trend shows a shift towards less severe type 4, as in this case. Apart from the four types described by Narasimha et al.[4] Saxena and Mathur[5] have described a rare type, type 5, which is a double pouch colon with short normal interpositioned colon segment (Table 1). The pouch usually communicates distally with the genitourinary system via a fistula, which was absent in this case. Anorectal malformations without fistula represent approximately 5% of all anorectal malformations and are usually associated with Down's syndrome and lower incidence of urologic defects.[6] Pandey et al.[7] described four cases of congenital pouch colon without fistula; 75% of them were of type 2 and

25% were type 1, making the present case considerably rare since it is a type 4 congenital pouch colon without fistula. Lower vaginal agenesis was an additional anomaly noted in this case. Anorectal malformations are usually associated with other anomalies such as uterovaginal malformations. Even though uterovaginal malformations are common, they are often underestimated due to lack of awareness. The incidence of vaginal agenesis with anorectal malformation is difficult to estimate as many cases go undiagnosed and present after anorectoplasty or after detection of amenorrhea. An extensive series of anorectal malformations with absent vagina by Levitt et al.[8] described an incidence of 8 out of 1007 female patients with imperforate anus. Vaginal reconstructive surgery during infancy will cause much less complications compared to surgeries after puberty. Therefore, thorough physical examination, appropriate imaging techniques and endoscopy are essential to diagnose this, as early diagnosis has a significant implication on treatment.[9] The diagnosis of congenital pouch colon is made mainly by a plain erect X-ray of the abdomen, which classically shows a large loop of bowel with single air-fluid level occupying more than half of the total width of the abdomen and displacing the small intestine to one side (usually right). Its treatment involves a diversion colostomy at birth with or without the excision of the pouch followed by a pull-through.[1] An association with vaginal agenesis requires an additional sigmoid colovaginoplasty or vaginal pull-through at the time of the anorectoplasty to restore a functional uterovaginal tract along with repair of anorectal malformation.[9] Despite regular antenatal checkups and ultrasound imaging, the pouch colon with vaginal agenesis went undetected until autopsy in this case. Congenital pouch colon is an unusual anorectal malformation of uncertain embryogenesis. The present case is a rare autopsy case of type 4 congenital pouch colon with associated anal agenesis without fistula and lower vaginal agenesis in a female fetus. Since the condition was not diagnosed in the antenatal period due to lack of awareness, this comparatively less severe type of congenital pouch colon, which could have had a favorable surgical outcome, was ultimately detected by a meticulous autopsy.

Table 1. Classification of congenital pouch colon by Saxena and Mathur[5]

Type of congenital pouch colon	Classification
Type 1	Normal colon is absent and the ileum opens into the pouch colon
Type 2	Ileum opens into a normal cecum which opens into the pouch colon
Type 3	Normal ascending colon and transverse colon opens into the pouch colon
Type 4	Normal colon with rectosigmoid pouch
Type 5	Double pouch colon with short normal interpositioned colon segment

Ethics

Informed Consent: Informed consent was taken from parent of the deceased fetus before autopsy was performed.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.S., S.K., R.B., K.A., Concept: S.S., S.K., R.B., K.A., Design: S.S., S.K., R.B., K.A., Data Collection or Processing: S.S., S.K., R.B., Analysis or Interpretation: S.S., S.K., R.B., K.A., Literature Search: S.S., S.K., R.B., Writing: S.S., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

Malignant Fibrous Histiocytoma: A Rare Cause of Rectal Mass

Malign Fibröz Histiyositom: Rektumda Kitlenin Nadir Bir Nedeni

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ABSTRACT

Malignant fibrous histiocytoma is a type of soft tissue sarcoma that originates from mesenchymal tissues and that mostly affects extremities. Abdominal malignant fibrous histiocytoma usually has a poor prognosis and is rarely seen in the rectum. A 52-year-old female patient presented with rectal bleeding, tenesmus and anemia. She was operated for an obstructive rectal mass and postoperative pathology was reported as malignant fibrous histiocytoma. Herein, we aimed to report a case of malignant fibrous histiocytoma, a rare cause of rectal mass, who was treated with abdominoperineal resection + end colostomy.

Keywords: Malignant fibrous histiocytoma, rectal mass, abdominoperineal resection

ÖZ

Malign fibröz histiyositom, sıklıkla uyluk, kalça ve ekstemitelerde görülen bir yumuşak doku sarkomu tipi olup, mezenkimal dokulardan kaynaklanır. Abdominal kaynaklı malign fibröz histiyositom genellikle kötü prognozlu olup, rektumda da çok nadiren gözlenir. Elli iki yaşında kadın hasta, rektal kanama, tenesmus ve anemi semptomları ile başvurdu. Obstruktif rektal kitle nedeniyle opere edilen hastanın postoperatif patolojisi malign fibröz histiositom olarak raporlandı. Biz burada abdominoperineal rezeksiyon + uç kolostomi ile tedavi ettiğimiz, nadir görülen rektal kitlenin bir sebebi olan malign fibröz histiositom olgusunu liteatür eşliğinde sunmayı planladık.

Anahtar Kelimeler: Malign fibröz histiyositom, rektal kitle, abdominoperineal rezeksiyon

Introduction

Malignant fibrous histiocytoma (MFH), also known as pleomorphic undifferentiated sarcoma, is a type of soft-tissue sarcoma originating from mesenchymal tissues. It is usually seen in the thighs, hips and extremities.[1] Rectal MFH is an extremely rare condition reported only as a few case reports. Surgical resection is the first choice in the treatment of rectal MFH.

Case Report

A 52-year-old female patient presented with rectal bleeding, weight loss and tenesmus. She had a history of surgery for endometrial cancer 15 years ago with postoperative chemotherapy and radiotherapy. Her physical examination was unremarkable except for a huge bleeding mass palpated on the posterolateral sidewall of the rectum at a distance of two cm to anal verge. Laboratory tests revealed anemia (hemoglobin: 6.5 mg/dL). Carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 19-9 and other laboratory tests were unremarkable. Colonoscopy revealed a fragile, necrotic mass puffy from the mucosa in the distal rectum at the posterior wall, starting from the 2 cm distance to anal verge and extending up to 8 cm. Colonoscopic biopsy reported was as an undifferentiated malignant tumor. Abdominopelvic computed tomography

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scan yielded thickening of the posterior rectal wall (Figure 1). Positron emission tomography showed an increased fluorodeoxyglucose uptake in the 5.5x5x5.3 cm soft tissue lesion in the distal rectum standardized uptake value maximum: 2.7. Abdominoperineal resection with an end colostomy was performed. Intraoperatively, it was observed that the tumor was perforated from the posterior wall of the rectum. The patient was discharged on the 15th postoperative day due to surgical site infection in the postoperative follow-up. Pathological examination revealed 4.5x4x2 cm ulcerovegetant mass. Cross-sections showed invasion of the colonic mucosa, invading the bunch, and a tumoral tissue consisting of atypical mesenchymal cells with multiple eosinophilic cytoplasms with prominent nuclei (Figures 2 and 3). In addition, a large number of mitotic figures were observed in the tumor (20 mitoses in 10 large magnification areas). Immunohistochemical staining showed a positive reaction of tumor cells with CD68, Vimentin and focal smooth muscle actin (Figure 4). These findings, in ombination with the histomorphology and immunohistochemical staining evaluations, were consistent with MFH of the rectum. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Discussion

MFH, also known as pleomorphic undifferentiated sarcoma, originates from mesenchymal tissues and it was first reported by O'Brien and Stout in 1964.[1,2] Abdominal-derived MFH usually has a poor prognosis and is rarely seen in the rectum.[2,3] In their study, Kim et al.[3] reported that the main age of colorectal MFH was 62 years (range, 12-85) with only two pediatric cases. However, our patient was female and colorectal MFH was reported to have a male predominance according to the reported cases of 19 male patients.[3] MFH is a diagnosis of exclusion from carcinoma, gastrointestinal stromal tumor, sarcoma and malign melanoma by immunohistochemical studies.

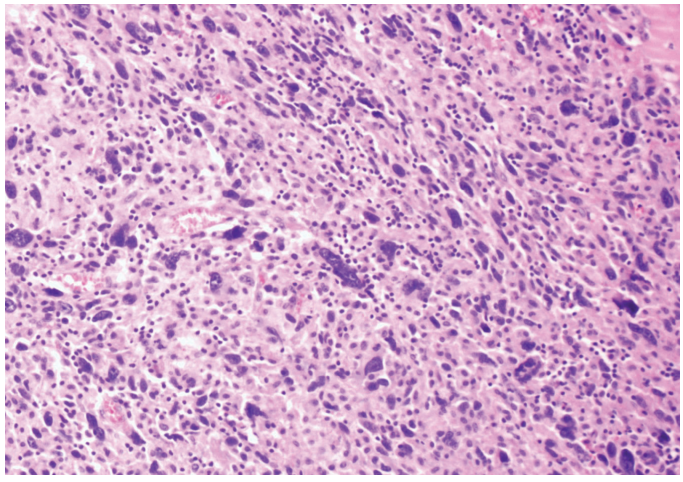

Figure 1. Tumor pleomorphic cells, hematoxylin and eosin, x200

Figure 2. Abdominopelvic computerized tomography scan showed the thickening of the posterior rectal wall

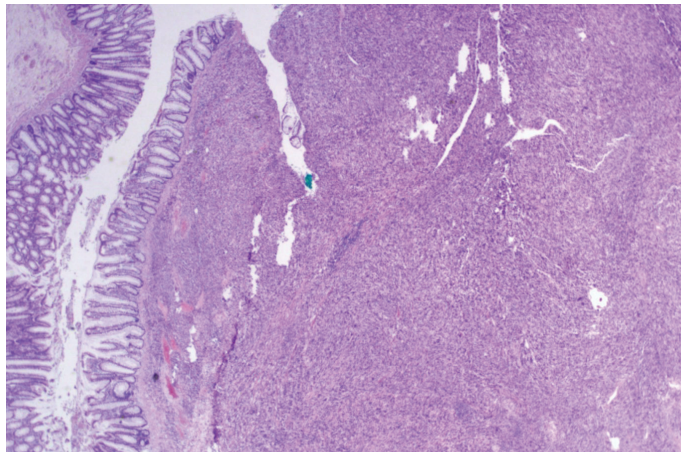

Figure 3. Tumor tissue in diffuse and bundles under the normal rectum mucosa, hematoxylin and eosin, x40

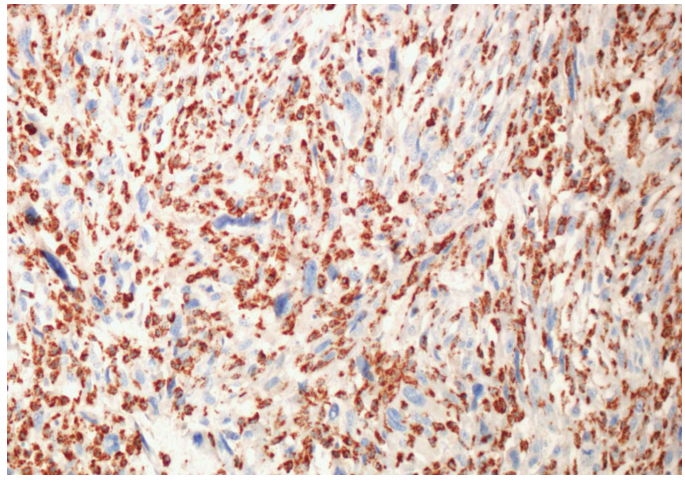

Figure 4. Immunohistochemical staining showed a positive reaction of tumor cells with CD68, diaminobenzidine x200

Immunohistochemical tests are helpful to differentiate MFH. Carcinoma can be excluded with cytokeratin (CK) PanCK, CK7, CK20 negativity; gastrointestinal stromal tumor can be excluded with CD34 and CD117 negativity, and malign melanoma can be excluded with Melan-A, S100 and HMB45 negativity.[2,3] MFH cells often express CD68. However, CD68 may be interpreted as positive due to relatively high number of tumor-infiltrating histiocytes in MFH.[3] There are many predisposing factors such as genetic factors, chemical carcinogens, chronic inflammation and lymphedema for this rare tumor type.[2,3,4] History of radiotherapy and chemotherapy is also a risk factor, as in our case who was operated due to endometrial cancer.[2,3] Surgical resection with negative margins and a combination of adjuvant treatment modalities are the first choice for the treatment of localized rectal MFH. For the metastatic disease, standard treatment is chemotherapy although the outcome is poor.[4] In most reported cases, patients with rectal MFH were treated by abdominoperineal resection with an end colostomy. However, Kim et al.[3] reported a patient who refused abdominoperineal resection and had a combination of transanal excision with postoperative radiotherapy without local recurrence or distant metastasis for 15 months. However, the role of adjuvant chemotherapy in the treatment remains unclear and adjuvant radiotherapy is recommended for local control in patients with high-grade sarcoma. In addition to these current treatment modalities for MFH, Boxberg et al.[5] suggested immunotherapy including program death ligand (PD)-1 and its PD-ligand 1. In conclusion, because of the rarity of rectal MFH, larger case series may help for the better understanding of the treatment modalities without local recurrence for this disease.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.K., S.D.A., Concept: S.D.A., H.Ö., Design: S.D.A., C.A., Data Collection or Processing: H.Ö., D.S.K., Analysis or Interpretation: T.K., C.A., Literature Search: S.D.A., T.K., Writing: S.D.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT

A Rare Cause of Acute Appendicitis: Caecal Tuberculosis Mimicking Colon Cancer

Nadir Bir Akut Apandisit Sebebi: Kolon Kanserini Taklit Eden Çekum Tüberkülozu

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ABSTRACT

Tuberculosis (TB) is an infectious disease that can involve all organs and tissues. Although pulmonary TB is more common, extrapulmonary TB is an important clinical problem due to its nonspecific symptoms. Clinical presentation of abdominal TB includes abdominal pain, diarrhea, fever and weight loss, and it is difficult to make differential diagnosis with inflammatory bowel disease and gastrointestinal system malignancies. In this case report, we aimed to present a case of TB infection in the differential diagnosis of ileocecal region diseases in patients without a history of active or previous pulmonary TB mimicking colon tumor and presenting with acute appendicitis.

Keywords: Tuberculosis, colon, appendicitis, cancer

ÖZ

Tüberküloz (TB) tüm organ ve dokuları tutabilen bir enfeksiyon hastalığıdır. Daha çok pulmoner TB karşımıza çıkmakla birlikte, ekstrapulmoner tüberküloz nonspesifik semptomları nedeniyle önemli bir klinik sorundur. Abdominal TB'de klinik başvuru karın ağrısı, ishal, ateş, kilo kaybı şeklinde olup enflamatuvar barsak hastalığı ve gastrointestinal sistem maligniteleri ile ayırıcı tanı yapmak güçtür. Bizde bu olguda akut apandisit kliniği ile başvuran kolon tümörünü taklit eden aktif ya da geçirilmiş pulmoner tüberküloz öyküsü olmayan hastalarda ileoçekal bölge hastalıklarının ayırıcı tanısında tüberküloz enfeksiyonun da düşünülmesi gerektiğini sunmayı amaçladık.

Anahtar Kelimeler: Tüberküloz, kolon, apandisit, kanser

Introduction

Tuberculosis (TB) is an infectious disease that can involve all organs and tissues. Although pulmonary form is more commonly observed, extrapulmonary TB remains to be an important clinical issue. Although it is less prevalent in Western society, its incidence has increased in the last two decades. The incidence of TB is increasing due to immunosuppression-related TB cases caused by human immunodeficiency virus, immunosuppressive drugs following organ transplantation or chemotherapy of cancers that have become increasingly more prevalent lately. In developing countries, poor living conditions are seen as the main cause of TB infection.[1,2] Gastrointestinal system (GIS) TB occurs through infection of the abdominal organs and peritoneum by *Mycobacterium tuberculosis* spp. GIS is the sixth most commonly involved region in cases with extrapulmonary TB following genitourinary system, lymphatic system, skeletal system, meninges and miliary TB.[3] GIS TB may be either primary or secondary. The disease involves ileocecal region or jejunum in approximately 75% of cases with GIS TB.[4] Isolated colon involvement (other than ileocecal region) is extremely rare, accounting for 2-3% of all abdominal TB cases.[5] Abdominal TB presents with abdominal pain, diarrhea, fever and weight

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loss, making it difficult to differentiate from inflammatory bowel disease and GIS malignancies. Although it is valuable to show bacilli by biopsy in suspected cases with clinical and imaging findings, it is difficult to cultivate bacilli.[6,7] Here, we aimed to emphasize that TB should be considered in patients without history of active or previous pulmonary TB who present with clinical findings of acute appendicitis and mimics colon tumors.

Case Report

A 37-year-old woman presented to emergency department with abdominal pain. In her medical history, the patient reported pain in the right lower abdominal quadrant and nausea for 2-3 days. Physical examination revealed tenderness and defense in the right lower abdominal quadrant. Laboratory evaluations showed following results: hemoglobin:12.4 g/dL, hematocrit:37.6, white blood cell count:13400/µL, C-reactif protein:236 mg/dL. Biochemical values were within normal limits. In abdominal CT scan, the diameter of the appendix was reported to be 8 mm with contamination in the surrounding mesentery and enlarged lymph nodes. After consultation with anesthesiology clinic, surgery was initiated under general anesthesia with McBurney incision. Operative findings included diffuse inflammation in the peritoneum, and a mass was observed in the cecum. Appendix had a mucocele appearance. After planning right hemicolectomy, colectomy consent was obtained from the relatives of the patient. The incision was extended to the midline and the surgery was continued. Due to presence of diffuse lymph node involvement at pericecal area, right hemicolectomy plus side-to-side ileotranverse colostomy was performed. On the 6th after surgery, abdominal drain was removed, as there was no significant discharge. The patient was discharged uneventful. The histopathological examination of surgical specimens revealed necrotizing granulomatous inflammation and granulomatous lymphadenitis in 20 lymph nodes. The patient was referred to chest disease and TB outpatient clinic for further treatment of TB.

Discussion

GIS TB, caused by *Mycobacterium tuberculosis*, can be seen in any localization throughout GIS. Although GIS TB is rarely seen in Western countries, it remains an important cause of morbidity and mortality in developing countries. While extrapulmonary TB accounts for 15-20% of all TB cases, abdominal TB accounts for 2-3% of cases with extrapulmonary TB.[5,8] The patients suffer from non-specific complaints, while majority of patients present with abdominal pain. Diarrhea, fever, loss of appetite and weight loss can also be seen. It may also lead to partial or complete obstruction by lesions that cause restriction of the intestinal lumen. It is difficult to suspect GIS TB in the absence of active or previous pulmonary disease. In our case, the presenting complaint was abdominal pain. On physical examination, a palpable mass can be detected in the right lower abdominal quadrant in 25-50% of patients. In our case, there was tenderness and defense in the right lower abdominal quadrant on physical examination. GIS is the sixth most common involved region in cases with extrapulmonary TB. It commonly involves ileocecal region, followed by ascending colon, jejunum, appendix, duodenum, stomach, esophagus, sigmoid colon and rectum. Multiple foci of intestinal TB may occur, but isolated colon involvement is extremely rare. The findings of imaging studies are non-specific in GIS involvement. Stricture or apple core sign in barium enema may be suggestive for abdominal TB. In CT scan, omental thickening, ascites, abdominal lymph node involvement and thickened intestinal wall may be seen. However, these findings alone are not diagnostic and disease-specific. Colonoscopy is a valuable tool in the diagnosis of TB in the ileocecal region or colon. Ulceration, nodular appearance, mass appearance in cecum and ileocecal valve deformation can be detected in colonoscopy.[9,10] The disease can be diagnosed by colonoscopy and biopsy.[11] In our case, no imaging study other than CT scan could be performed due to acute presentation. No finding suggestive of TB was detected in CT scan. The differential diagnoses include inflammatory bowel disease, colon cancer, diverticulitis, appendicitis and other causes of infectious colitis. The medical management includes anti-TB agents. In intestinal TB, surgical treatment should be considered in case of complications. Intestinal obstruction, GIS fistula, perforation and GIS bleeding are the most common complications. In our case, diffuse inflammation and mass appearance in the cecal region were observed during surgery. It was seen that appendix had mucocele appearance. Due to presence of diffuse lymph node involvement in the pericecal area, right hemicolectomy plus side-to-side ileotranverse colostomy was performed. In conclusion, TB should be kept in mind in patients without history of active or previous pulmonary TB who presented with non-specific GIS symptoms, who had inflammation and mass lesion during surgery and who had enlarged lymph nodes in cecum in preoperative CT scan. We think that TB should be suspected in case of granulomatous inflammation in biopsy samples obtained from GIS organs in our country with high TB incidence.

Ethics

Informed Consent: Patient consent was obtained.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.P., Concept: M.P., D.A.Ç., Design: T.G., Y.Y., Data Collection or Processing: M.P., T.G. Analysis or Interpretation: D.A.Ç., Y.Y., Literature Search: D.A.Ç., T.G., Writing: M.P.

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CASE REPORT

Synchronous Appendiceal Neoplasia of Ascending Colon Cancers: Three Case Reports And Review of the Literature

Senkron Primer Apendiks ve Asendan Kolon Tümörü: Üç Olgu Sunumu ve Literatür Derlemesi

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ABSTRACT

Colorectal carcinomas are the most common malignancies of the gastrointestinal tract. The incidence of synchronous primary appendicular neoplasms associated with colorectal cancer has been reported as 0.3-4.1%, but most of the studies are case reports and the actual incidence still remains unclear. Appendix embryologically originates from the large intestine, so the actual incidence of synchronous appendix tumors may increase. In this study, we aimed to report three patients who underwent right hemicolectomy for ascending colon adenocarcinoma and who had synchronous primary appendicular neoplasia determined histopathologically.

Keywords: Synchronous tumor, appendix, ascending colon

ÖZ

Kolorektal kanserler, gastrointestinal sistemin en sık görülen maligniteleri olup, kolorektal kansere eşlik eden senkron apendiks tümörleri ile ilgili literatürde yetersiz sayıdaki çalışmanın çoğunluğu olgu sunumu şeklinde olması nedeniyle senkron apendiks tümörlerinin sıklığı net olmamakla birlikte %0,3-4 olarak bildirilmiştir. Apendiksin embriyolojik olarak kolondan köken alması göz önünde bulundurularak kolorektal tümör varlığında senkron appendiks tümör insidansının daha yüksek olabileceği değerlendirilerek; çalışmamızda insidental olarak senkron primer apendiks tümörü ve sağ kolon adenokarsinomu tespit ettiğimiz 3 olguyu sunmayı amaçladık.

Anahtar Kelimeler: Senkron tümör, appendiks, asendan kolon

Introduction

The most common malignancies of the gastrointestinal tract are colorectal tumors. It has been reported that synchronous colorectal neoplasms are 3-5% and metachronous colorectal neoplasms are 2-3%.[1]

Neoplastic lesions of the appendix are rare, and approximately 25% of patients with appendix tumors are reported to be synchronous or metachronous colon tumors.[2] The appendix is originated embryologically from large intestine and has a similar mucosal pattern to the colon and rectum, therefore, any neoplastic alteration of colon and rectum will affect appendix.[3,4] Appendiceal tumors are usually detected incidentally in patients who were operated for acute appendicitis and preoperative diagnosis is rare.[3] We present three cases of appendix tumors, which we detected incidentally in the right hemicolectomy specimens of ascending colon tumor cases.

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Case Reports

Case 1

A 73-year-old female patient was diagnosed as adenocarcinoma of cecum by colonoscopy performed for anemia etiology. In terms of regional and distant organ metastasis, whole body radiological examination was performed and it revealed no additional pathology except for wall thickening of cecum. Right hemicolectomy was performed. Histopathological examination of the specimen revealed a moderately differentiated subserosal adenocarcinoma of cecum of 3x2.5x0.7 cm and a synchronous 0.3 cm neuroendocrine tumor (NET) of appendix (Figure 1a). Tumor was considered as T3N1aM0 (stage 3b-AJCC 2017) due to one metastasis from 30 removed lymph nodes. Postoperative adjuvant chemotherapy was performed and 37th month follow-up continues without any complications or recurrence.

Case 2

A 58-year-old male patient was admitted to our clinic with complaints of abdominal pain, change in defecation habits and weight loss (20 kg/3 months). Colonoscopy showed an ulcerovegetant mass at hepatic flexure and biopsy was reported as adenocarcinoma. Right hemicolectomy was performed. Histopathological evaluation of the right hemicolectomy specimen revealed 8x2.5 cm, moderately differentiated subserosal adenocarcinoma with a mucinous component located at hepatic flexure. In addition, a 0.4 cm NET of appendix invading the superficial muscle layer was reported (Figure 1b). Metastatic involvement was one out of 46 removed lymph nodes. The patient was considered as T3N1aMO (stage 3b-AJCC 2017). Postoperative adjuvant chemotherapy was performed and 34th month follow-up continues without any complications or recurrence.

Case 3

An 80-year-old female patient was admitted to our clinic with complaints of weakness, colic-type abdominal pain and weight loss (5 kg/2 months). Colonoscopy showed an ulcerovegetant mass that narrowed the lumen of the ascending colon. Abdominal CT revealed wall thickening of cecum without any metastasis. Right hemicolectomy was performed and histopathological examination of the right hemicolectomy specimen revealed 5.5x5 cm moderately differentiated serosal adenocarcinoma of cecum and a low-grade mucinous neoplasia of appendix (Figure 1c). There was no metastasis in 27 removed lymph nodes. The patient was considered as T4aN0M0 (Stage 2b-AJCC 2017). Twelfth month follow-up without adjuvant chemotherapy continues without any complications or recurrence.

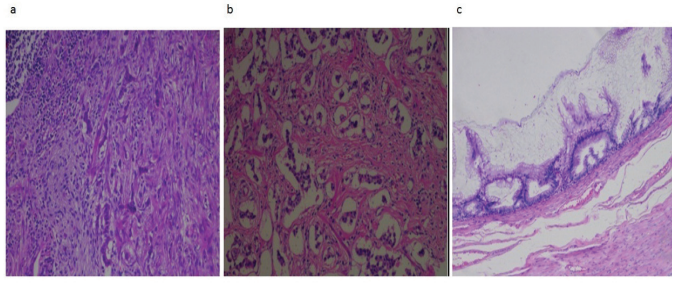

Figure 1. Histopathology of primary appendix neoplasia. a, b) Appendix vermiformis; small conglomerations and lined like trabecular modality of neoplastic cells without mitosis and atypia, (neuroendocrine tumor grade 1), haematoxylin and eosin x200, c) appendix vermiformis neoplasia (low grade appendiceal mucinous neoplasm); partly composed of villous structures with low grade atypia and floored by epithelial cells consisting of apical mucin, haematoxylin and eosin x100

Discussion

Tumors of the appendix are very rare. Preoperative diagnosis is difficult and most of them are diagnosed incidentally after histopathologic examination of appendectomy specimens of acute appendicitis cases. The incidence of appendiceal tumors was reported as 1%, but actual incidence was accepted up to 5% because of missed histopathologic examination of appendectomy specimens.[4] There are studies reporting that appendix tumors are more common in colorectal tumor patients,[2,5] because the appendix originates embryologically from the colon and has a similar mucosal structure like colon and rectum.[6,7] Tumors of the appendix are NET, mucoceles and adenocarcinomas. NETs, commonly referred to as carcinoid tumors, are the most common tumors of the appendix. They constitute 80% of all appendiceal masses and 0.5% of appendectomy materials.[8] NET mostly originates from appendix in gastrointestinal system at a rate of 40-50%.[9] The clinical importance of NET is being synchronous with other gastrointestinal malignancies at a rate of 55%.[10] Mucocele constitutes 0.2-0.5% of all appendiceal neoplasms.[11] Appendiceal adenocarcinoma accounts for 6% of appendiceal tumors and 0.2-0.5% of all gastrointestinal tumors.[12] The appendix tumors with these clinical features do not have any pathognomonic signs or symptoms, and it is difficult to diagnose them preoperatively. In our study, two cases were NET and one was mucinous neoplasia.

Recently, some studies have recommended incidental appendectomy during colorectal cancer operations because of the difficulties in the diagnosis of synchronous appendix tumors preoperatively. Khan and Moran[13] reported the incidence of synchronous appendiceal and colorectal cancer as 4.1% in 169 patients with colorectal cancer who had incidental appendectomy. In the same study, the authors reported that more appendix tumors

were diagnosed histopathologically for rectal cancers than right hemicolectomy surgeries[13] and it was considered that separate appendectomy specimens were examined more carefully than appendix in a right hemicolectomy specimen. Albright et al.[14] defined a lifetime appendectomy risk of 6-7%. They considered that additional appendectomies for colorectal malignancies were cost effective because additional appendectomy would not prolong operative time and future appendectomies would be more difficult because of previous abdominal operations. Lohsiriwat et al.[15] reported that the rate of synchronous primary appendix tumor was 0.3%, and the secondary appendix tumor/appendix metastasis was 1% in 293 cases who underwent incidental appendectomy. Some authors recommend incidental appendectomy in colorectal tumor surgery, defining that appendectomy does not cause an additional risk of infection in major bowel surgery, and some authors argue this association as coincidental because of they are being the most common gastrointestinal tumors. In our study, we detected only three appendix tumors in the last 5 years in patients who underwent right hemicolectomy due to colon tumors. We deliberated that prospective studies consisting of large case series are needed for the decision of incidental appendectomy in colorectal tumor surgery. Incidental appendectomies during colorectal malignancy surgeries will not affect wound infection rates and mortality or morbidity rates, so that incidental appendectomies can be added for all colorectal malignancy surgeries.

Ethics

Informed Consent: Written informed consent obtained from all cases.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.B., Concept: İ.Y., M.S., Design: İ.Y., Data Collection or Processing: M.T.B., A.S., Analysis or Interpretation: M.T.B., A.S., Literature Search: O.E., Writing: İ.Y., M.S.

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