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Turkish Journal of
COLORECTAL DISEASE

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Address: Latilokum Sk. Alphan İşhanı No: 3 Kat: Mecidiyeköy Şişli, İstanbul, Turkey
Phone: +90 21356 01 75-76-77 Gsm: +90 53300 736 Fax: +90 21356 01 78
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Aims and Scope

Turkish Journal of Colorectal Disease is an open access, scientific and peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of the Turkish Society of Colon and Rectal Surgery.

The journal is published quarterly in March, June, September, and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high-quality, peer-reviewed publications of scientific and clinical importance that address current issues at both national and international levels.

Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions, and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic, and therapeutic studies relevant to managing small intestine, colon, rectum, anus, and pelvic floor diseases.

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

Turkish Journal of Colorectal Disease is currently indexed in **TÜBİTAK/ULAKBİM, British Library, ProQuest, CINAHL, IdealOnline, EBSCO, Embase, Gale/Cengage Learning, Index Copernicus, Turkish Citation Index, Hinari, GOALI, ARDI, OARE, AGORA J-GATE** and **TürkMedline**.

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

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.

Author(s) and the copyright owner(s) grant access to all users for the articles published in the Turkish Journal of Colorectal Disease as free of charge.

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Advertising fees are transferred to the Turkish Society of Colon and Rectal Surgery, which are used for publishing expenses of the journal.

This journal's advertising sales and editorial processes are separated to ensure editorial independence and reduce the effects of financial interests.

Current or potential sponsors and advertisers do not affect editorial decisions in the journal. Advertisers and sponsors have no control or influence over the results of a user's website searches.

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Statements or opinions stated in articles published in the journal do not reflect the views of the editors, editorial board and/or publisher; The editors, editorial board and publisher do not accept any responsibility or liability for such materials. All opinions published in the journal belong to the authors.

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Address: Latilokum Sok. Alphan İşhanı No: 3 Kat: 2, Şişli, İstanbul, Türkiye

Telephone: +90 (212) 356 01 75-76-77

Gsm: +90 (532) 300 72 36

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Authors should submit the following during the initial submission:

• Copyright Transfer and Author Contributions Form

• ICMJE Potential Conflict of Interest Disclosure Form which has to be filled in by each author.

Turkish Journal of Colorectal Disease is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of Turkish Society of Colon and Rectal Surgery. The journal is published quarterly in in March, June, September and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high quality, peer-reviewed publications of scientific and clinical importance address current issues at both national and international levels. Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic and therapeutic studies relevant to the management of small intestine, colon, rectum, anus and pelvic floor diseases.

Reviewed and accepted manuscripts are translated from Turkish to English by the Journal through a professional translation service. Before printing, the translations are submitted to the authors for approval or correction requests, to be returned within 7 days. The editorial board checks and approves the translation if any response is received from the corresponding author within this period.

All manuscripts submitted to the Turkish Journal of Colorectal Disease are screened for plagiarism using the 'iThenticate' software. This journal does not accept articles that indicate a similarity rate of more than 20%, according to iThenticate reports. 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.

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The evaluation and publication processes of the Turkish Journal of Colorectal Disease are shaped in acceptance with the guidelines of ICMJE (International Committee of Medical Journal Editors), COPE (Committee of Publication Ethics), EASE (European Association of Science Editors), and WAME (World Association of Medical Editors). Turkish Journal of Colorectal Disease also is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

As a peer-reviewed journal that is independent, impartial and in compliance with the principles of double-blinded peer review, after checking the compliance of the submitted manuscript with the writing rules and plagiarism control, all articles are reviewed by the editor-in-chief, section editor, at least two reviewers, and statistic editor. All evaluation process except Editor-in-Chief is done double-blinded. After all these processes are completed, the Editor-in-Chief decides whether to publish or reject the article. In the final stage, the plagiarism review is repeated once more

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 "Turkish Journal of Colorectal Disease". Articles previously published in any language will not be considered for publication in the journal. Authors cannot submit the manuscript for publication in another journal. All changes in the manuscript will be made after obtaining written permission of the author and the publisher. Full text of all articles can be downloaded at the web site of the journal www.turkishjcrd.com/archives.

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Disclosure Statement

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"Conflicts of Interest and Source of Funding:"

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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 the address, telephone, fax and e-mail address of the corresponding author.

Manuscript Submission Guidelines

All manuscripts should be submitted via the online submission system. Authors are encouraged to submit their manuscripts via the internet after logging on to the website www.manuscriptmanager.net/tjcd.

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The correspondent author's ORCID (Open Researcher and Contributor ID) number 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 delays in publication. Manuscripts should be prepared as a word document (*.doc) or rich text format (*.rtf). After logging on to the web www.manuscriptmanager.net/tjcd double click the "submit an article" icon. All corresponding authors should be provided with a password and a username after providing the information needed. After logging on to the article submission system with your own password and username, please read the system's directions carefully to provide all needed information not to delay the processing of the manuscript. Attach the manuscript, all figures, tables and additional documents. Please also attach the cover letter with the "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);

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.);

STARD checklist for reporting 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.);

STROBE statement, a checklist of items that should be included in reports of observational studies;

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 standard, 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 e-mail 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;

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

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 by any authors, should be clearly cited and referenced.

All clinical trials must be registered in a public trials registry acceptable to the International Committee of Medical Journals Editors (ICMJE). Authors of randomized controlled trials must adhere to the CONSORT guidelines, 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 keywords or short phrases. Do not use abbreviations as keywords.

Introduction: State the purpose and rationale for the study concisely 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.

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Instruction for Authors

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 essential observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion:

1. State the importance and significance of your findings but do not repeat the details given in the Results section.

2. Limit your opinions to those strictly indicated by the facts in your report.

3. Compare your finding with those of others.

No new data are to be presented in this section.

Acknowledgements: 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 acknowledgement 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 the 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.

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 of 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 a description of a new surgical technique and its application in 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).

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Acknowledgments.

Tables and figures: Including legends.

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, MPEG-PS, 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 info@galenos.com.tr. All videos must include 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

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

Editorial Comments

Article length: Not to exceed 1000 words.

Reference Number: Not to exceed 10 references.

The Editor exclusively solicits editorials. Editorials should express opinions and/or provide comments on papers published elsewhere in the same issue. A single author is preferred. No abstract is required, but please include a brief title. Editorial submissions are subject to review/request for revision, and editors retain the right to alter text style.

Peer review of study protocols:

TJCD will consider publishing without peer review protocols with formal ethical approval and funding from a recognized, open Access, supporting research-funding boy (such as those listed by the JULIET Project). Please provide proof that these criteria are met when uploading your protocol. Any protocols that do not meet both these criteria will be sent for open external peer review, with reviewer comments published online upon acceptance, as with research articles. Reviewers will be instructed to review for clarity and sufficient detail. The intention of peer review is not to alter the study design. Reviewers will be required to check that the study is scientifically credible and ethically sound in its scope and methods. There is sufficient detail to instil confidence that the study will be managed and analyzed correctly.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicized. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any variations from the protocol that occur during the conduct of the study)

The SPIRIT (Standart Protocol Items for Randomized Trials) statement has now been published. It is an evidence-based tool developed through a systematic review of a wide range of resources and consensus. It closely mirrors the CONSORT statement and also reflects essential ethical considerations.

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on reporting reviews evaluating randomized trials but can also be used as a basis for writing systematic reviews of other types of research, particularly evaluations of interventions.

General TJCD policies apply to manuscript formatting, editorial guidelines, licence forms and patient consent.

- Protocol papers should report planned or ongoing studies: Manuscripts that report work already carried out will not be deemed protocols. The dates of the study must be included in the manuscript and cover letter.

Protocol for studies that will require ethical approval, such as trials, is unlikely to be considered without receiving that approval.

- Title: This should include the specific study type, randomized controlled trial

- Abstract: This should be structured with the following sections—introduction; Methods and analysis; Ethics, and dissemination. Registration details should be included as a final section, if appropriate.

- Introduction: describe the rationale for the research and what evidence gay it may fill.- Methods and analysis:

- Ethics and dissemination: Ethical and safety considerations and any dissemination plan should be covered here

- Full references

- Authors contributions

- Funding Statement

- Competing Interests Statement

- Word Count: Not to exceed 4000 words.

Research Involving Human Participants and/or Animals

Statement of human rights: When reporting studies that involve human participants, authors should include a statement that the studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Suppose doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards. In that case, the authors must explain the reasons for their approach and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

The following statements should be included in the text before the References section: Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

For retrospective studies, please add the following sentence: "For this type of study, formal consent is not required."

Statement on the welfare of animals: The welfare of animals used for research must be respected. In experimental animal studies, the authors should indicate that the procedures followed were in accordance with animal rights as per the Guide for the Care and Use of Laboratory Animals, and they should obtain animal ethics committee approval. When reporting experiments on animals, authors should indicate whether the international, national, and/or institutional guidelines for the care and use of animals have been followed, and that the studies have been approved by a research ethics committee at the institution or practise at which the studies were conducted (where such a committee exists).

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Ethical approval: "All applicable international, national, and/or institutional guidelines for the care and use of animals were followed."

If applicable (where such a committee exists): "All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted."

If articles do not contain studies with human participants or animals by any of the authors, please select one of the following statements:

"This article does not contain any studies with human participants performed by any of the authors."

"This article does not contain any studies with animals performed by any of the authors."

"This article does not contain any studies with human participants or animals performed by any of the authors."

Informed Consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. Hence it is essential that all participants gave their informed consent in writing before inclusion in the study. They are identifying details (names, dates of birth, identity numbers and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scientific purposes and the participant (or parent or guardian if the participant is incapable) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should assure that alterations do not distort scientific meaning.

The following statement should be included: Informed Consent: "Informed consent was obtained from all individual participants included in the study."

If identifying information about participants is available in the article, the following statement should be included:

"Additional informed consent was obtained from all individual participants for whom identifying information is included in this article."

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All correspondences can be done to the following postal address or to the following e-mail address, where the journal editorial resides:

Turkish Society of Colon and Rectal Surgery

Address: Latilokum Sok. Alphan İşhanı No:3 Kat:2 Mecidiyeköy-Şişli-İstanbul/Turkey

Phone: +90 (212) 356 01 75-76-77

Gsm: +90 (532) 300 72 36

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Online Manuscript: www.manuscriptmanager.net/tjcd

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REVIEW

Investigating Post-Discharge Experiences in Ileostomy: Systematic Review and Meta-analysis

Evin Korkmaz, Fatma Eti Aslan

Bahçeşehir University Faculty of Health Sciences, Department of Nurse, İstanbul, Turkey

ABSTRACT

In case of diseases such as cancers of the gastrointestinal system, traumas, and inflammatory bowel diseases, there is a need for an opening, called a stoma, that changes the excretory pathway for patients. Stoma, a word of Greek origin, means "mouthing, opening, mouth". The type of stoma that causes the greatest metabolic changes is called an ileostomy. These changes may negatively affect the recipient's adjustment to ileostomy and coping with this new circumstance. This systematic review and meta-analysis aimed to investigate post-discharge experiences of individuals who have undergone ileostomy. Cross-sectional, cohort, and qualitative studies, which were published between January 2010-September 2020, were assessed. Suitable studies were identified from Medline, CINAHL, PsycINFO, Ovid, and PubMed databases on 21.09.2020. Results from a total of 20 studies (11 cross-sectional, 5 cohort, and 4 qualitative) were combined. Analysis of the combined reports showed: 29% had wound complication; 26% had wound dehiscence; 29% had skin complications; 7% had stomal complications; 11% had an anastomosis; 7% had ileus; and 10% had infection. It was concluded that individuals with ileostomy had problems with their social environment and healthcare team, as well as with communication, role change, adjustment, and psychological and ileostomy-related complications. It was concluded that individuals with ileostomy had problems with their social environment and healthcare team as well as on communication, role change, adjustment, and psychological and ileostomy-related complications.

Keywords: Ileostomy, patient expectations, post-discharge experiences, ileostomy complications

Introduction

In case of gastrointestinal system diseases, such as cancers, traumas, and inflammatory bowel diseases, there is may be a need for an opening, known as a stoma (from the Greek for mouth, opening), that changes the excretory pathway for patients.[1,2] In a report entitled "Estimated global cancer incidence, mortality, and prevalence", published by the International Agency for Research on Cancer, colorectal cancer is the third most common type of cancer in men and the second most common type of cancer in women globally. More than half (55%) of colorectal cancer cases are reported from developed countries. Considering that an intestinal stoma is opened in most of these cases, cancer and stoma have gained importance as the co-existence of two conditions because of the effects on patients lifestyle.[2,3] In the gastrointestinal system, colostomy is defined as the opening of the colon to the abdominal wall and ileostomy is defined as a similar opening of the small intestine.[4] Stoma volume and metabolic changes in the body differ, depending on the type of stoma (ileostomy or colostomy). The ileostomy type of stoma is reported to cause more metabolic changes than the colostomy.[4] An average of 500-800 mL of drainage per day is observed in ileostomy. Dehydration due to this drainage can cause metabolic changes, such as drainage-related skin complications and electrolyte losses associated with digestive enzymes.[4]

An ileostomy is the procedure of temporarily or permanently mouthing the lumen of the ileum to the abdominal wall through a surgical opening.[5] The purpose of an ileostomy is to drain the stool from the body through the ileum instead of the normal way through the anus. The stoma procedure, which causes a change in the digestive tract, may cause problems for the individual.[5] It was found that if precautions were not taken against these problems, it would cause complications for the individual, inability to manage personal health, and an increase in the rate of hospital admissions. It is known that

Address for Correspondence: Evin Korkmaz, MD,
Bahçeşehir University Faculty of Health Sciences, Department of Nurse, İstanbul, Turkey
E-mail: ewinkrkmz@hotmail.com **ORCID ID:** orcid.org/0000-0003-0965-1443
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among individuals with stoma, individuals with ileostomy have more problems related to malnutrition and stoma management.[6] It has been reported that among individuals with stoma, 71% have experienced ileostomy complications and that 43% have experienced colostomy complications.[7] When stomal complication rates are analyzed, peristomal skin irritation was seen in 15-85% of cases, peristomal hernia in 1-37%, stomal prolapse in 2-25%, stoma stenosis in 2-10%, and stoma retraction in 1-11%.[7] The main problems individuals with stoma experience include involuntary gas discharge, odor, leakage, skin problems, lack of personal care, body image deterioration, asthenia, weakness, loneliness, decreased self-respect, rejection by the family, social isolation, sexual problems, and deterioration in work and social relations.[2,6,8] These problems can negatively affect the individual's adjustment to the stoma and the ability to cope with the stoma. Despite these adversities and the fact that the stoma has a negative effect on the quality of life, it can prolong their life and help them return to a healthy life.[3,6] In our experience these problems occur during the post-discharge period due to lack of symptom management. The role of healthcare professionals in ileostomy stoma care is of the utmost importance, both during the period of hospitalization and after they are discharged. Problems that individuals with stoma experience can be reduced or eliminated with suitable care, training and counseling services. Therefore, these types of support should be provided in a holistic fashion to encompass physical, social, and psychological aspects.

There is no comprehensive literature review reflecting the experiences of individuals with ileostomy. This systematic review and meta-analysis aims to investigate post-discharge experiences of individuals who have undergone ileostomy.

Research Questions

What are the experiences of patients with ileostomy regarding stoma and metabolism-related problems that develop in the post-discharge period, complications related to ileostomy wounds and systems, and re-admission to a health institution?

Method

This study was conducted as a systematic review and meta-analysis. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) criteria were used in preparing and reporting the study.[9]

Eligibility Criteria

The selection of studies suitable for this systematic review and meta-analysis was determined according to patient/problem/population; exposure; outcomes; study design; Table 1. Cross-sectional, cohort, and qualitative studies that were published in English, between January 2010 and September 2020, were included. Intervention studies, reviews, and case studies were excluded.

Query Strategy

To find suitable studies, the databases investigated were Medline, CINAHL, PsycINFO, Ovid, and PubMed, which were accessed on 21.09.2020 The queries were conducted using the keywords "ileostomy OR colostomy OR stoma" AND "patient expectations OR post-discharge experiences" AND "ileostomy complications OR complications OR ostomy complication". In addition, reference lists of included studies were checked.

Selection of Studies

Based on the inclusion criteria, two researchers reviewed titles and abstracts and selected full texts independently. Any inconsistencies in the selection process of included articles were resolved through discussion. Reference lists of suitable articles were reviewed.

Evaluation of the Methodological Quality of Studies

Critical appraisal checklists developed by the Joanna Briggs Institute (JBI) for analytical cross-sectional, cohort, and qualitative studies were used for quality assessment of articles.[10] JBI's critical appraisal checklist developed for

Table 1. PEOS

Question components	Definition/description	Keywords	Alternative query terms
Patient/problem participants (P: Patient/problem/population)	Individuals with ileostomy	Ileostomy	Colostomy Stomy Ostomy
Exposure (E: exposure)	Ileostomy	Ileostomy care	
Outcomes (O: Outcomes)	Post-discharge experiences Post-discharge problems	Patient expectations Post-discharge experiences	Ileostomy complications complications ostomy complication
Study design (S: Study design)	Cross-sectional, cohort and qualitative studies		

analytical cross-sectional studies consists of eight items, the checklist for cohort studies has eleven items, and the checklist for qualitative studies has ten items. Questions on these checklists are answered with "yes, no, unclear, and not/applicable" options.[11] The evaluation results for each included study are given in Table 2 as "quality score". The quality assessment process was conducted independently by two researchers, and questions that were answered differently were resolved through discussion and combined into a single text.

Data Retrieval (Extraction/Withdrawal)

Research data were obtained with the data extraction tool developed by the researchers. Using this tool, data on the author and publication year of studies, study design, type of ileostomy, sample size, age range, and experiences of individuals with ileostomy were obtained. This process was conducted independently by two researchers and compared and combined to a single text. In cases where there were different data, the relevant article was checked again and the correct data were taken.

Statistical Analysis

In this systematic review, the data obtained from quantitative studies (16 studies) were combined by conducting a pooled estimates meta-analysis. The meta-analysis of the study was conducted using Comprehensive Meta-Analysis Version 3-Free Trial (https://www.meta-analysis.com/pages/demo.php). The heterogeneity between studies was assessed by the Cochrane Q and Higgins I^2 tests, and an I^2 value greater than 50% was considered to indicate a statistically significant heterogeneity. In cases where the I^2 value was equal to or greater than 50%, random effect results were taken whereas fix effect results were taken in cases where it was smaller than 50%. 95% confidence interval (CI) and estimated ratios were calculated for each outcome variable.[11] Data from qualitative studies are presented in narrative form.

Results

Query Results

The initial search identified 7667. These articles were first examined independently by two researchers, in terms of their title and abstract. After the review, the full text of the remaining 40 articles was analyzed. Of these forty articles, the following were excluded: 13 articles for being traditional reviews; three articles for having data collected before 2000; one article for including ileostomy complications in low-birth-weight infants; and three studies for analyzing ileostomy and colostomy rates combined, so that it was not clear which findings specifically related to ileostomy. The remaining 20 articles were included in this study (Figure 1).

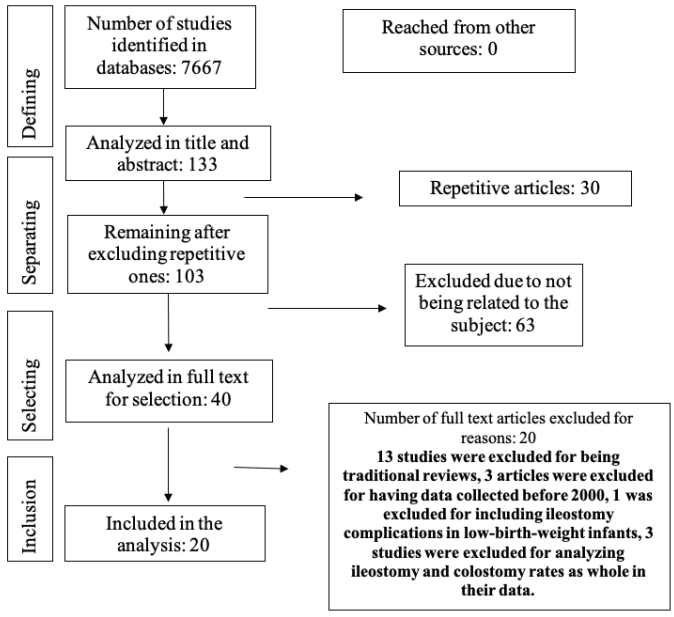

Figure 1. PRISMA flow diagram
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Characteristics of Studies and Participants

Of the studies included in the systematic review and meta-analysis, two were prospective and nine were retrospective cross-sectional studies, while five were cohort and four were phenomenological qualitative studies. The sample size in these studies ranged from 10 to 22,034. The data reported in the studies included in the analysis were collected after 2000 and published between 2012 and 2020 (Table 2).

Quality Assessment Results

Among studies included in this systematic review and meta-analysis, it was found that 5-7 items in the 8-item quality assessment tool for 11 cross-sectional studies, 8-10 items in the 11-item quality assessment tool for five cohort studies, and 8-9 items in the 10-item quality assessment tool for the four qualitative studies had "Yes" as an answer (Table 2).

Meta-analysis Results

In studies included in this systematic review and meta-analysis, problems related to the wound in the ileostomy were defined in three different ways (Figure 2). Wound complications were reported in two of these studies.[12,13] Based on the combined results of these studies, it was found that an estimated 29% of individuals with ileostomy developed a wound complication (95% CI: 0.007-0.958; z=-0.444; p=0.657; I^2=99%) (Figure 2a). Two of the studies reported dehiscence at the wound site.[12,14] The estimate obtained from the combined results of these studies was that 26% of individuals with ileostomy had wound dehiscence (95% CI: 0.065-0.165; z=-8.016; p<0.001; I^2=96%) (Figure 2b). According to the meta-analysis results based on the

findings of seven studies, it was found that an estimated 29% of individuals with ileostomy developed skin complications

Table 2. Quality assessment scores

Author's name, year of study	Type of study	Quality score
Thorpe et al.[28] (2014)	Phenomenological qualitative study	Yes: 8/10 No: 2/10
Mohil et al.[11] (2012)	Prospective cross-sectional study	Yes: 7/8 No: 1/8
Liu et al.[12] (2020)	Retrospective cross-sectional study	Yes: 7/8 No: 1/8
Fish et al.[24] (2017)	Retrospective cross-sectional study	Yes: 6/8 No: 2/8
Chan et al.[21] (2019)	Retrospective cross-sectional study	Yes: 7/8 No: 1/8
Taneja et al.[15] (2017)	Cohort study	Yes: 8/11 No: 3/11
Tyler et al.[22] (2014)	Cohort study	Yes: 10/11 No: 1/11
Hayden et al.[27] (2013)	Retrospective cross-sectional study	Yes: 6/8 No: 2/8
Sarkut et al.[14] (2015)	Retrospective cross-sectional study	Yes: 7/8 No: 1/8
Spiers et al.[29] (2016)	Phenomenological qualitative study	Yes: 8/10 No: 2/10
Li et al.[20] (2017)	Retrospective cross-sectional study	Yes: 6/8 No: 2/8
Justiniano et al.[26] (2018)	Cohort study	Yes: 8/11 No: 3/11
Kandagatla et al.[25] (2018)	Retrospective cross-sectional study	Yes: 6/8 No: 2/8
Lindholm et al.[16] (2013)	Retrospective cross-sectional study	Yes: 7/8 No: 1/8
Koc et al.[17] (2017)	Retrospective cross-sectional study	Yes: 6/8 No: 2/8
Morris and Leach[30] (2017)	Phenomenological qualitative study	Yes: 8/10 No: 2/10
Carlsson et al.[18] (2016)	Prospective cross-sectional study	Yes: 5/8 No: 3/8
Taneja et al.[19] (2019)	Cohort study	Yes: 8/11 No: 3/11
Seo et al.[23] (2018)	Cohort study	Yes: 9/11 No: 2/11
Smith et al.[31] (2017)	Phenomenological qualitative study	Yes: 9/10 No: 1/10

in the wound area (95% CI: 0.123-0.524; z=-1.776; p=0.076; I^2=96%) (Figure 2c).[12,14-19]

The meta-analysis revealed that systemic complications observed in individuals with ileostomy developed in four different systems (Figure 3). Complications related to the respiratory system were found in three of these studies.[12,13,20] Based on the combined results of these studies, it was concluded that an estimated 8% had respiratory system complications (95% Cl: 0.004-0.636; z=-1.594; p=0.111; I^2=99%) (Figure 3a). Complications related to the renal system were reported in six of these studies[12,13,20-23] and again an estimated 8% developed complications in the renal system (95% Cl: 0.062-0.125; z=-11.840; p<0.001; I^2=96%) (Figure 3b). Complications related to the abdominal system were reported in two of these studies[13,20] so that an estimated 4% of abdominal complications were found (95% Cl: 0.007-0.257; z=-3.034; p=0.002; I^2=98%) (Figure 3c). Complications related to the gastrointestinal system were reported in three studies, and according to the combined results, this complication rate was estimated to be 9% (95% Cl: 0.062-0.148; z=-9.119; p<0.001; I^2=92%) (Figure 3d).[13,23,24]

Four different problems from seven studies related to stoma were reported in individuals with ileostomy (Figure 4).[12-14,17,21-23] Stomal complications were found with an estimated rate of 7% (95% Cl: 0.024-0.191; z=-4.492; p<0.001; I^2=99%) (Figure 4a). Anastomosis due to ileostomy

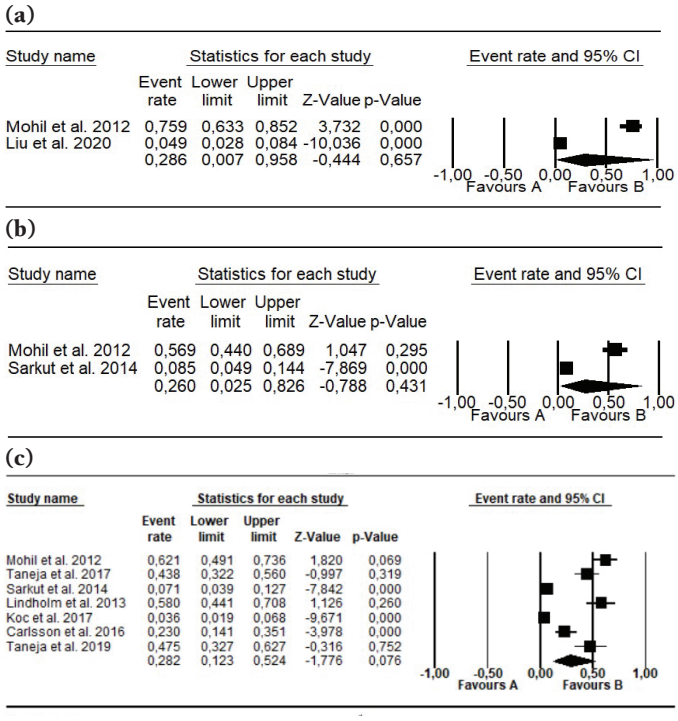

Figure 2. Complications related to ileostomy wound. (a) Wound complication, (b) wound dehiscence, (c) skin complication
CI: Confidence interval

were reported in two studies[12,23] with an estimated prevalence of 11% (95% Cl: 0.013-0.561; z=-1.749; p=0.080; I^2=91%) (Figure 4b). Two studies reported ileus, and according to the combined results, the rate of ileus was estimated to be 7% (95% Cl: 0.009-0.372; z=-2.458; p=0.014; I^2=97%) (Figure 4c).[12,23] Infection due to ileostomy was reported in four studies.[12,20,23,25] The rate of reported infection was 10% (95% Cl: 0.065-0.165; z=-8.019; p<0.001; I^2=96%) (Figure 4d).

In terms of hospital useage, the rate of hospitalization[19] in one study while hospital readmission rates were reported in seven.[13,19-22,24,26] An estimated 93% of individuals with ileostomy re-attended the hospital (95% Cl: 0.792-0.976; z=4.185; p<0.001; I^2=0.00) (Figure 5a) and 26% were re-hospitalized (95% Cl: 0.172-0.377; z=-3.815; p<0.001; I^2=99%) (Figure 5b).

Four different metabolic problems related to ileostomy exit were reported in studies (Figure 6). Sepsis was reported

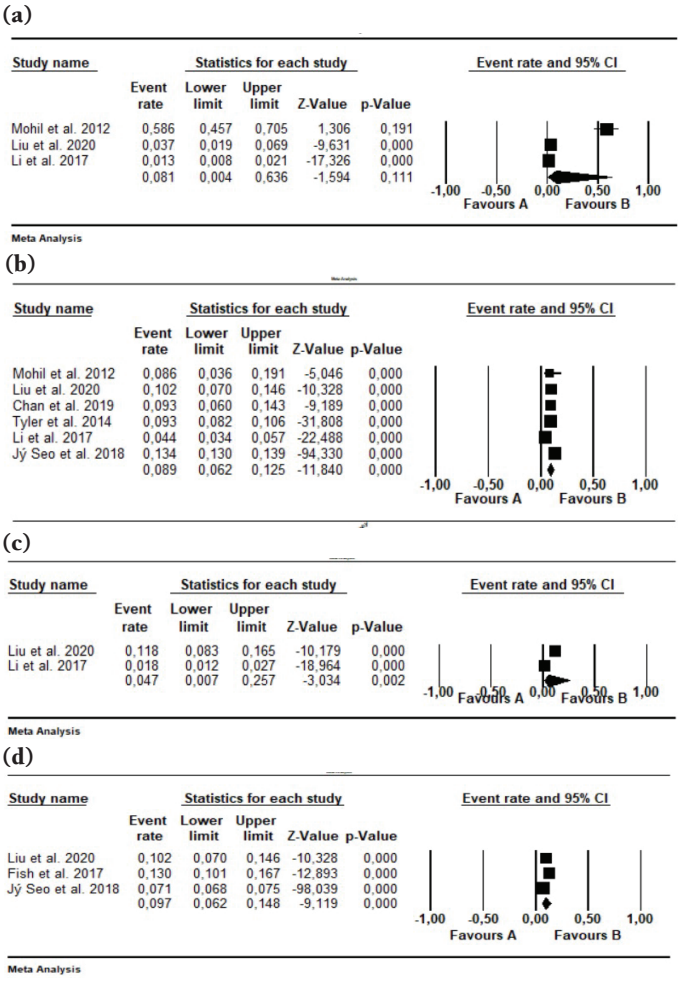

Figure 3. Complications for systems. (a) Complications related to the respiratory system, (b) Complications related to the urinary/renal system, (c) Abdominal complications, (d) Complications related to the gastrointestinal system
CI: Confidence interval

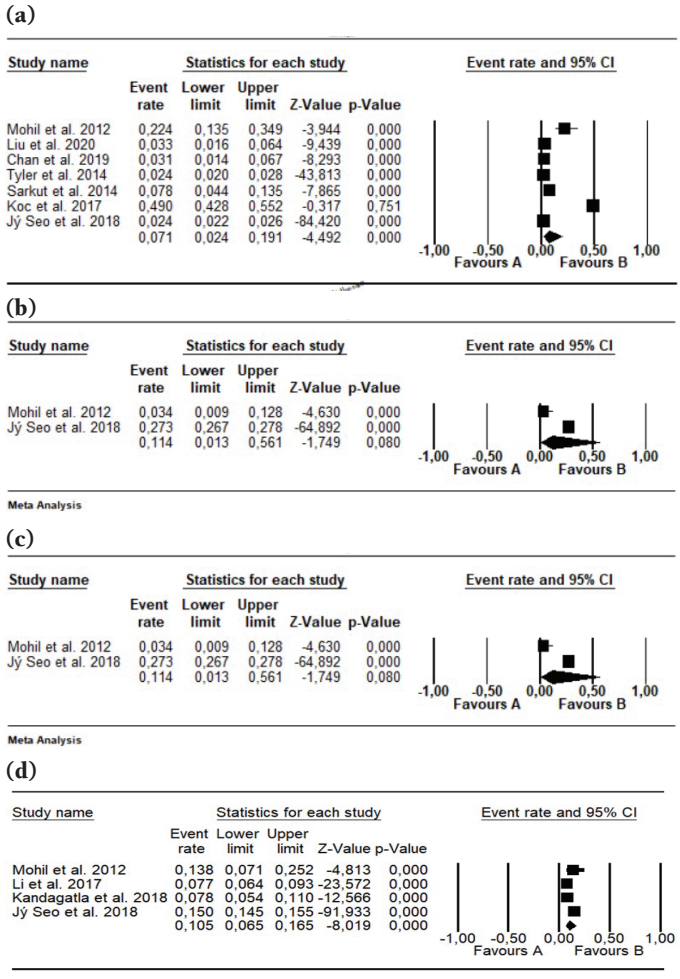

Figure 4. Reported problems due to stoma. (a) Stomal complications, (b) Anastomosis, (c) ileus, (d) infection

in three[20,22,23] and the estimated sepsis rate was 2% (95% Cl: 0.014-0.044; z=-12.183; p<0.001; I^2=98%) (Figure 6a). Three studies reporting fluid-electrolyte imbalance[20,22,27] with an estimated rate of 4% (95% Cl: 0.011-0.151; z=-4.410; p<0.001; I^2=97%) (Figure 6b). Dehydration was reported in six studies.[12,13,20,23,25,26] According to the combined results, the estimated dehydration rate was 9% (95% Cl: 0.074-0.132; z=-13.436; p<0.001; I^2=89%) (Figure 6c). One study reported weight loss[15] which reported a rate of weight loss in the patients of 43% (95% Cl: 0.311-0.560; z=-1.047; p=0.295; I^2=0.00%) (Figure 6d).

Results from Qualitative Studies

The experiences of individuals with ileostomy were reported in four qualitative studies included in this systematic review.[28-31] The results of these studies were combined under six themes: Individuals' communication with their environment; role change; communication with the multidisciplinary healthcare team; problems caused by complications due to ileostomy; adjustment to ileostomy; and psychological effects on the individual. In two studies,

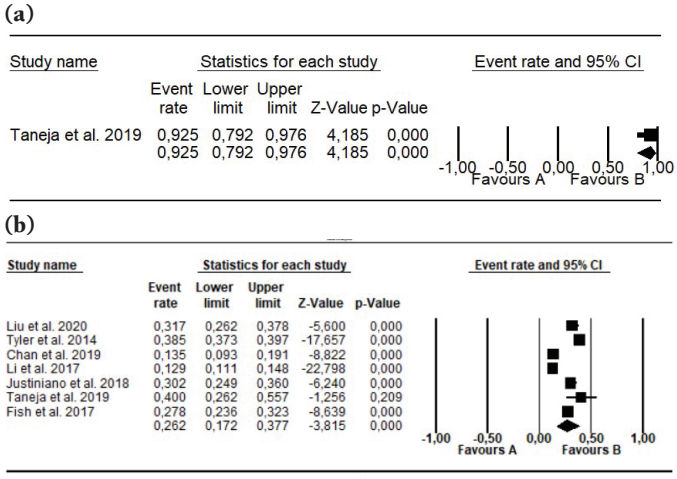

Figure 5. Re-admission to the healthcare facility due to stoma. (a) Re-admission to the hospital, (b) re-hospitalization

it was reported that patients had positive and negative experiences of communication with their environment after ileostomy.[30,31] In one study, it was reported that ileostomy created confusion in some individuals' self-perception and that this caused changes in interpersonal roles.[31] In three studies reporting the communication experiences of the individual who had undergone ileostomy with a multidisciplinary healthcare team, patients reported both positive and negative experiences about the healthcare team.[28-30] It was reported that individuals who shared positive experiences was affected by the fact that they could reach the healthcare team more easily, that they had healthcare professionals trained on stoma and that they trusted the healthcare team.[28-30] Three studies reported experiences of individuals who experienced complications related to ileostomy.[28-30] It was concluded that some of the individuals with ileostomy went to the hospital again due to complications, that they experienced pain, that their daily activities were affected, and that they had difficulty in adjusting to the stoma.[28-30] In two studies, it was reported that some individuals adjusted to ileostomy and that others could not.[29,30] In two studies reporting the psychological effects of ileostomy, it was concluded that the presence of complications and communication had psychological effects on the process of accepting and adjusting to ileostomy.[30,31]

Discussion

This study was conducted as a systematic review and meta-analysis in order to investigate post-discharge experiences of individuals with ileostomy. The combined results of 16 quantitative and four qualitative studies were analyzed. We hope that the results obtained may contribute to the improvement of post-discharge follow-up and care of individuals with ileostomy.

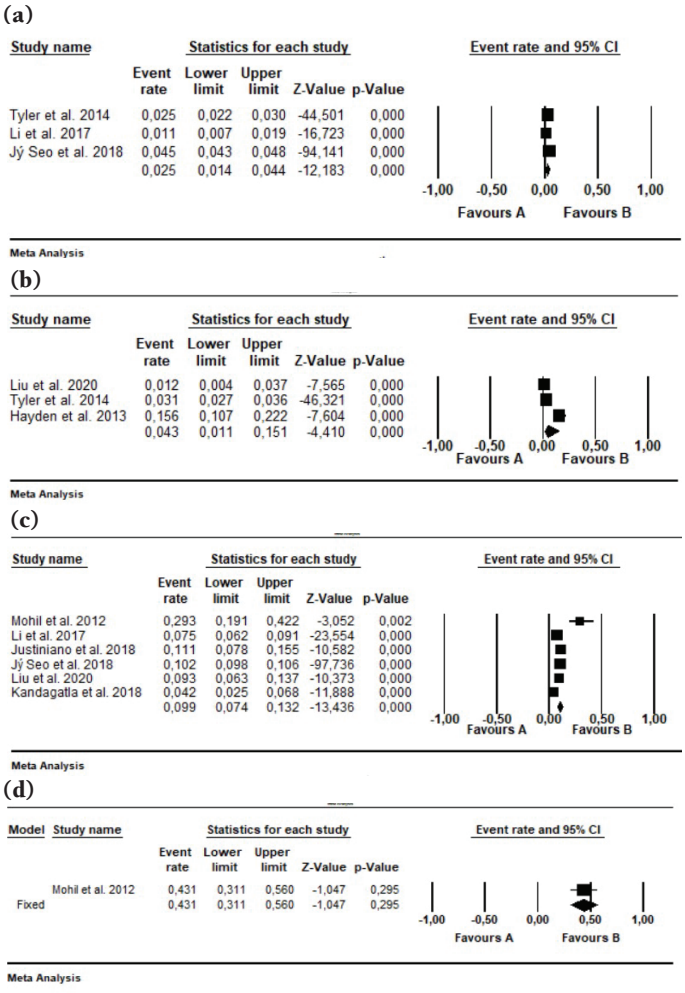

Figure 6. Metabolic problems with ileostomy. (a) Sepsis, (b) Liquid electrolyte disturbance, (c) dehydration, (d) weight loss

In this study, post-ileostomy experiences of individuals who had undergone ileostomy were reported. In the literature, in a review study conducted by Rajaretnam and Lieske[5] in 2020, it was observed that similar results were reported in 20% of individuals with ileostomy after stoma opening.

In this systematic review and meta-analysis, it was found that an estimated 29% of individuals with ileostomy developed wound complication, that 26% had wound dehiscence, and that 29% developed skin complications in the wound area. In the systematic review by Malik et al.[32], it was reported that 14% of individuals with ileostomy had skin complications and Ambe et al.[33] reported that 25-34% of individuals with stoma had skin complications and that this was the highest in individuals with ileostomy.[22] Mehboob et al.[34] reported that 19.4% of individuals had skin complications and that 13% had wound complications. Based on these results, it can be said that wound dehiscence and skin complications in the wound area are common, especially in individuals with ileostomy. These complications are thought to develop as a result of fecal leakage onto the skin.

In our study, it was found that stomal complications (7%), anastomosis (11%), ileus (7%), and infection (10%) developed in some patients with ileostomy. Other studies conducted on this subject have reported a rate of ileus in individuals with ileostomy of 11-18% and 3.8%[32,33] which is consistent with the findings presented here. Stoma separation (5.9%)[32] and stoma-related complications (0.7-5.9%)[32] have also been previously reported, again in line with the current findings. Mehboob et al.[34] reported that stomal complications developed due to reasons such as retraction (4.7%), high flow fistula (3.5%), parastomal hernia (2.3%), stomal necrosis (2.3%), bleeding (1.1%) and stomal occlusion (11.9%). We anticipate that training and informing individuals with ileostomy on stoma care will reduce these rates.

In the present study most individuals with ileostomy (93%) re-attended the hospital and that a significant portion (26%) were rehospitalized. Ambe et al.[33] reported that the rate of hospital readmission (16.9%) was lower. This difference may be explained by differences in sample populations.

In our study, serious systemic problems, such as sepsis (2%), fluid-electrolyte imbalance (4%), dehydration (9%), and weight loss (43%) occurred in some individuals with ileostomy. In another systematic review it was reported that 20% of individuals with ileostomy had dehydration and that 43% of hospital readmissions were due to dehydration.[33] As reported in the literature and in our study, dehydration experienced in individuals with ileostomy is thought to be associated with consequent fluid-electrolyte imbalance and weight loss.

This study identified problems related to communication with their social environment and healthcare team were reported by individuals with ileostomy together with difficulties related to role change, adjustment, psychological problems and ileostomy complications. Ambe et al.[33] also reported that ileostomy significantly changed an individuals' life, creating physical, psychological and social effects in their life. Allison et al.[35], on the other hand, reported that nurses providing care for individuals with ileostomy did not have the right approach due to lack of training on the subject and that this situation had a negative effect on the care and adjustment process of these individuals. In line with the results of our study and the literature, we think that the positive experiences of individuals with ileostomy can be improved and adjustment to ileostomy can be achieved through an effective informing and training process. This approach can allow early detection and possible prevention of complications that may arise and thus reduce re-admissions and hospitalization rates. We believe that the individual's adjustment to ileostomy and effective communication with the healthcare team will yield positive physical, psychological, and social results.

Conclusion

In this systematic review and meta-analysis, more than a quarter of patients individuals with ileostomy had wound complication, wound dehiscence, and/or skin complications, while a smaller but appreciable proportion had stomal complications, anastomosis, ileus, and infection. It was also found in this study that some individuals with ileostomy experienced serious systemic problems, including sepsis, fluid-electrolyte imbalance, dehydration, and weight loss, and that an estimated 93% of them re-attended hospital because of their ileostomy while 26% were rehospitalized. Furthermore, patients receiving an ileostomy also reported problems with their social environment and healthcare team, as well as with communication, role change, adjustment, and psychological and ileostomy-related complications.

Based on these results, we suggest that many of these reported problems may be addressed through stoma training and counselling services provided by trained and experienced healthcare professionals, which should be continuous and easily accessible in order to increase adjustment to stoma in individuals with ileostomy and to early detect problems that may arise. We recommend that health institutions use technological facilities to organize training sessions for individuals with ileostomy and that these must be easily accessible. Solutions should be developed for problems that individuals with ileostomy experience and the efficacy of these solutions should be supported with further prospective, large and well-designed studies.

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

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

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INVITED REVIEW

Pelvic Exenteration in Rectal Cancer

Selman Sökmen, Berke Manoğlu, Tayfun Bişgin

Dokuz Eylül University Faculty of Medicine, Department of General Surgery, Colorectal and Pelvic Surgery Unit, İzmir, Turkey

ABSTRACT

Primary rectal cancer can recur loco-regionally in the pelvic compartment despite multidisciplinary treatment being given and oncological principles of total mesorectal excision being instituted. Recurrent disease in the tumor bed exhibits special characteristics in terms of pelvic location, tumoral extent, and extra-pelvic metastatic status. The effective treatment of this heterogeneous tumor family depends on adequate staging, skillset for doing multi-organ resection, logical usage of adjuvant chemoradiotherapy, and crucial decision-making by the tumor board. For many years, the surgical community was reluctant to perform these radical, aggressive exenterative surgical interventions due to high morbity/mortality and technical difficulties. However, in solid tumor surgery, because of the proven independent and robust prognostic association between complete tumor resection and overall survival, the number of centers doing radical pelvic exenteration in properly selected patients has gradually increased in the last 10 years. With the aid of modern technology, advances in pelvic oncologic surgery and anesthesiology, and optimum patient care, the morbity and mortality rate has decreased and overall survival has increased. Advanced age, uncontrollable co-morbidities, refractory to medical treatment, multi-organ resection, septic complications, and a lack of surgical experience are powerful prognosticators. Research into this complex surgical field in terms of colorectal cancer is still ongoing.

Keywords: Rectum cancer, pelvic exenteration, oncologic outcomes

Introduction

Oncological outcomes with curative surgery for rectal cancer have improved considerably in recent years. These positive oncological results are a result of both developments in surgical technique for total mesorectal excision and the clinical application of neoadjuvant treatments.[1-5] However, local recurrence (4-11%) remains a challenging problem.[6-12] Locally recurrent rectal cancer (LRRC) is traditionally considered to be an "unrecoverable condition" and a 3-year survival rate is reported to be less than 4% in untreated patients.[13-16] When palliative chemotherapy (CT) and/or radiotherapy (RT) is applied, this survival rate can reach 8.5%. Infiltrative and/or destructive tumors can frequently destroy intrapelvic organs and structures, leading to malignant fistulas, severe pain, intestinal obstruction, incontinence and rapid collapse of the patient. Even palliative supportive treatments may render them inapplicable due to tumor-related toxic effects. Although palliative treatments are beneficial in the first stage, even in the best conditions, long-term benefit cannot be expected and they should be reserved for end-stage disease. Radical exenterative surgery is a potentially curative treatment modality for pelvic oncologic colorectal surgery. Today, potentially curative (R0 resection) pelvic exenteration (PE) is performed in specialized centers with low morbidity and mortality rates in properly selected patients. Five-year overall survival is reported to be 40-50%.[1-16] In light of the mounting evidence and with the development of pelvic surgery, yesterday's concerns (high morbidity and mortality rates) are reduced, the number of trained centers that can apply the surgical technique has increased, oncological patient outcomes have improved, and the quality of life of patients has reached reasonable levels within six months. In order to understand PE, it is necessary to first understand radical pelvic oncology and causes of local recurrence.

Address for Correspondence: Selman Sökmen MD,
Dokuz Eylül University Faculty of Medicine, Department of General Surgery, Colorectal and Pelvic Surgery Unit, İzmir, Turkey
E-mail: selmansokmen@gmail.com **ORCID ID:** orcid.org/0000-0001-8235-7246
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Radical Pelvic Surgery

The pelvis is a three-dimensional, compartmental and complex anatomical space.[17-20] Gastrointestinal, gynecological, vascular, neurological and urological systems are all in close proximity. These systems are supported by a wide variety of bones, muscles and ligaments. There is a dense lymphatic, vascular and neurologic network that is intertwined between these units and that tumor cells can also use to spread.[17-20] Knowing the relationships between these different embryological developmental compartments is essential for successful surgery. The surgery of pelvic organs and structures, known as a "no go" area for many years, has been divided into sub-branches. Although the sub-branches describe their specific specialty, none can provide a holistic overview of the whole of pelvic surgery.[21-23] In standard surgical training, however, it is not possible to train for the pelvis and retroperitoneum. Moreover, there are not enough experienced trainers specialized in these subjects and three-dimensional pelvic anatomical dissection experience cannot be taught while tumors are, of course, three dimensional entities. The curious surgeon can learn as much as he/she can see and understand during surgeries simply by looking at cloned or poorly copied drawings in books. In both of these cases, the "burglar" tumor that has reached the vital-risk organs of the retroperitoneum and pelvis, which is generally withdrawn, cannot be "chased home" by the surgeon, and tumor cells that have traveled with intercompartmental transgression cannot be completely excised (resection resulting in R1-R2 margins!). The lack of experience of cadaver surgery makes the situation even more difficult. Thus, without an accurate anatomical road map, the surgical team will make mistakes, which will result in complications and/or oncological failure. Retrospective follow-up traces of many unwanted complications and local recurrences lead to technically limited and insufficient surgery.[24-26] *The authors draw attention to the importance of adding retroperitoneal and pelvic surgery training to the standard surgical training for effective radical resection of LRRC.*

Local Recurrence Problem

Local recurrence in solid organ cancers is a serious and under-emphasized problem. This also applies to rectal cancer. There are few publications about the question of why it can recur despite *potentially curative radical resection* in primary or recurrent rectal cancer.[27-30] It is surprising that research has focused on primary carcinogenesis, but that despite the application of all oncological principles, no study has investigated recurrent tumorigenesis. The clinical recurrence of specific tumor cells in the primary surgical site (tumor bed) or at the adjacent-surrounding tissue border is called local recurrence (LR) - although this could actually be considered a cellular persistence. LR often refers to the incomplete removal of cancer cells in the periphery of the initial/index cancer. The location and extent of these LRs, whether they are together with lymph nodes or not, extend beyond the compartment (anatomical borders are tumor suppressors), and how many organs they involve, are the subjects that the oncological colorectal surgeon most wants to know. If the surgical team has not developed an expanded multi-organ resection technique, cells from the tumor that have escaped the compartment, or made anatomical border violations will lead to tumor recurrence and dissemination, and then recurrences in the early period and/or metastatic disease will be inevitable because of a loss of tumor control.

Recurrent tumor cells are cells that are genetically unstable, grow rapidly, have a short *sojourn time* in the tissue, and show cellular de-differentiation.[28] They have increased metastatic ability. According to the "spectrum model", proposed by Samuel Helman in 1994, 65% of recurrent tumor cells are present for a long time, and if they are recognized early, the final result will be positively affected. Ten percent are systemic from the start and cannot be controlled by scanning. Twenty five percent do not have clinical metastatic potential and do not benefit from follow-up and systemic therapy.[28-30]

When we categorize the biological basis of pelvic recurrence, the following factors emerge:[30,31]

A) Intrapelvic and perineal tumor cell implants;

B) Tumor cell implants in anastomosis;

C) Ovarian tumor metastases;

D) Distal and radial (lateral) positive margins;

E) Lymph node metastasis in residual mesorectum;

F) Lateral pelvic lymph node metastasis;

G) and presence of tumor cells in the lymphatic leakage flowing into the area as a result of surgical trauma.

Complicating Risk Factors

Prognostic and predictive risk factors include large tumors, irradiated bowel, disrupted/unionized anatomical planes, technical difficulties due to tumor compartment disruption, fibrosclerotic ceramicized tissues, complex anatomy, inflexible and non-retractable deep and narrow pelvis, short and schinesic rectal stump, chronic abdominopelvic inflammation or persistent low-grade infection, "medically high-risk patient" who will not have a second chance, previously incomplete (inadequate) surgical attempts, inexperienced surgical team, long-term (more than 15 sessions) CT, poor performance, presence of malnutrition/cachexia/sarcopenia/frailty, and the presence of poorly managed multiple co-morbidities in the patient.[32-34] When we delve further into these critical issues, it emerges that the important factors are the anatomically anterior angulation of the pelvis, non-retractable bone margins, very narrow male pelvis structure (android), the close course of valuable

vascular, neural and urological structures, their complex relationships and the rich vascular anatomy of the sacrum. Physiopathological factors include the difficulty of reaching the tumor, which is the main target, as a result of the small intestine ridges turning/bending to attach to the pelvic entrance or being fixed by embedding, the ureters to take an ectopic position in the postoperative pelvis, and the union of the the previous intestinal anastomosis or rectal/vaginal stump to the surrounding organs/structures and surfaces without serosa. *En bloc multicompartmental "outline" radical resection* should be performed in order to fully resect this tumor burden and the multiple organs that it has involved, by carefully studying the intrapelvic position and extent of the tumor with a very comprehensive preoperative radiological evaluation.[28-34] Naturally, this oncological technical sensitivity brings with it reconstructive difficulties: difficulties in providing anatomical "fresh" living tissue and the complete lack of available artificial organs. In principle, pelvic cancer surgery has reached a stage that requires complex cancer surgery due to the often advanced disease, instead of a blind surgical technique that goes directly into the tumor from top to bottom.[1-8] *The patient does not need the so-called standard surgeries (because it is not enough!). The patient needs an extended radical surgery suitable for the extraordinary needs of his/her disease, that is an attempt at PE.*[1-7]

Oncological Significance of Pelvic Intracompartmental and Supracompartmental Resection

Visceral morphogenetic units and endopelvic parietal compartments are shown in Figure 1. Radical pelvic surgery is a compartment surgery. Most recurrent rectal tumors involve more than one compartment and often require en-bloc resection of multiple organs in the multiple compartments.[30-36] When we say radically compartmentalized surgery, we must understand that a morphogenetic unit or a segment of it is resected. Pelvic examples of this are TME for rectal cancer and total mesometrial resection for cervical cancer.[30-36] When we say ultra-radical (Extended) compartmentalized surgery, two or three morphogenetic units are resected en bloc. According to this oncological principle, exenterative surgery is performed by multi-mesovisceral excision and dissection along the rectum, genital tract, bladder, hind intestine, and Müllerian and urogenital morphogenetic sections. The resection of the visceral morphogenetic sections can be extended laterally to include the *lateral endopelvic parietal compartments (LEER)*[37], endopelvic fascia and pelvic floor muscles. These definitions have been developed using the concept of the embryological compartment. It is well known that the compartment containing the tumor, whether it is rectal or gynecological, can hide residual tumor cells thus allowing local spread of cancer. In there, tumor cells spread by "following the embryological developmental steps of the tumor as if in a hereditary memory fraternity" (Höckel[37]) and by benefiting from trauma and inflammation. Detection of unusual spread to different pelvic lymph nodes is also due to inadequate resection of the tumor in the presence of advanced tumor progression of these pelvic visceroparietal compartments. *Therefore, in locally advanced or locally very advanced primary and recurrent rectal cancers or other pelvic cancers, the oncological colorectal surgeon should always predict and plan the surgery accordingly, taking account of radial progressive tumor permeation (involvement of the extra-radial margin) that threatens the functional anatomy.*

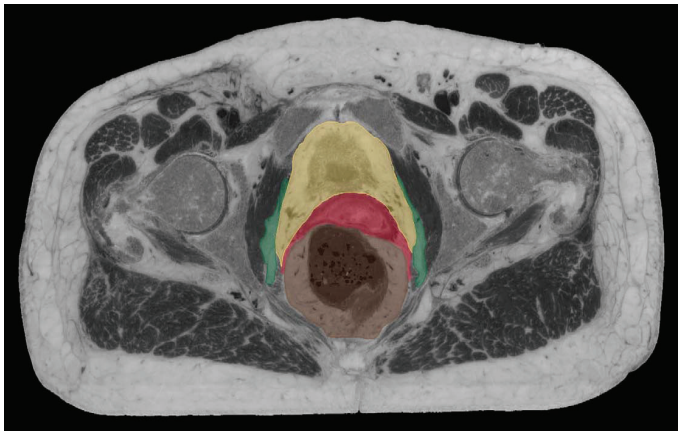

Figure 1. Visceral morphogenetic units (MGU) and endopelvic parietal compartments
Yellow: Urogenital MGU. Red: Mullerian MGU. Brown: rectal MGU, Green: Paravisceral endopelvic compartments

Local Recurrence Classification

Many different centers have proposed classification systems for LRRC according to the anatomical location of the recurrence in the pelvis.[4-12] Most of these classifications bring together important technical points in exenterative surgery. Classification first identifies the anatomical connection between the tumor and the adjacent organ, then expresses the relationship of the tumor with neurovascular and bone structures in the periphery of the pelvis. These factors determine the technical difficulty of performing R0 resection and the complexity of the surgery. These classifications also determine the functional outcomes for the patient and the required reconstructions (urinary, vascular, orthopedic and plastic repair of the perineal defect). Posterior and lateral compartment resections, which were associated with poor oncologic outcomes in the past, could now be performed with better results in prominent experienced centers. Posterior recurrences can infiltrate the presacral fascia, sacrum and its nerve roots, and require radical sacrectomy for oncologic clearance. Lateral compartment recurrences

appear as isolated iliac nodal recurrences or as infiltrative tumor recurrences, that start from the center and attack neurovascular structures in the pelvic side-wall. Anteriorly located recurrences may even erode the urological organs, leading to malignant fistulas and encavitation. Especially after abdominoperineal resection (APR), it can lead to devastating catastrophic fistulizations for the patient from the closed perineal space, tumor shedding with tumor necrosis, and deep pelvic sepsis (Figure 2). Since different types of recurrences require different exenterations, there is no universally accepted terminology yet. In general, upper pelvic recurrences that are centrally located, involve at most two organs, are fixed to a single point and do not show lateral wall infiltration are more suitable for complete resection. On the other hand, recurrences that are fixed in many areas, obliterate the natural spaces, infiltrate the side-walls, or have vascular/neural invasion have a poor prognosis. *In summary, it determines the pelvic tumor burden and location. However, no classification truly reflects the possible diversity of exenteration processes because the magnitude of the surgical procedure for each patient is different.*

Terms to Describe PE

At our center we use the "Magrina Classification" for total PE (TPE).[38,39] TPE is an en-bloc resection of the internal reproductive organs, bladder, and rectosigmoid. In superiorly located tumoral lesions, adequate tumor resection can be performed by resecting the viscera above or at the level of the levator muscles (supralevatoric TPE). In this procedure, the levator muscle, anus and urogenital diagram are preserved. In very low-lying malignant lesions, we perform "Infralevatoric" TPE, in which the levator muscles, urogenital diagram, anus and perineal soft tissues are carefully resected. Additional tissues (small intestine, vein, bone) are resected in "Extended" TPE procedure.

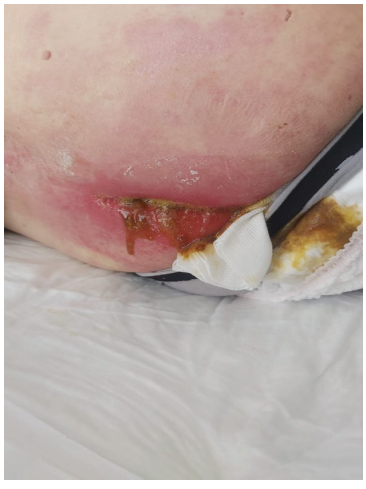

Figure 2. Malignant entero-vesico-perineal fistulization caused by recurrent disease after abdominoperineal resection

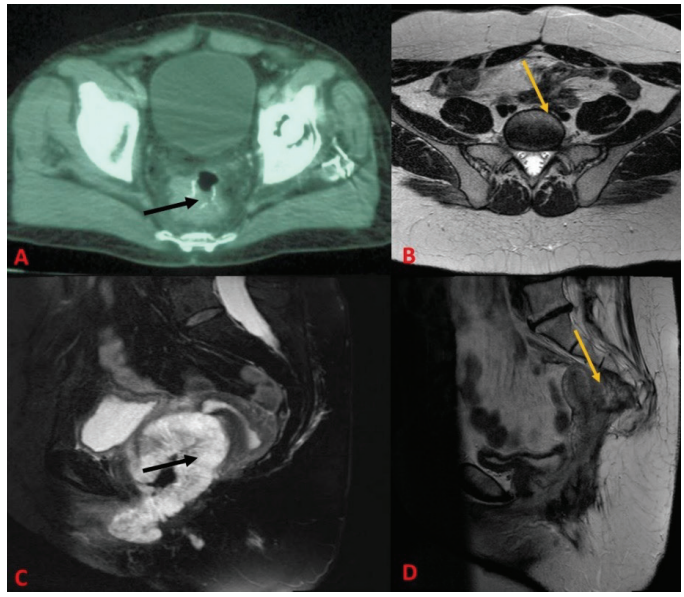

Figure 3. (A) Peri-anastomotic recurrence, (B) Recurrence around the iliac vessels and ureter, (C) Large vaginal recurrence (D) Recurrent mass invading the distal sacrum and uterus

Apart from the definition of LEER[37] and ElSiE[40], we also make use of the classification used by the team of Georgiou et al.[36,41]. In other words, TPE can be expanded to the posterior compartment, with the addition of the coccyx, presacral fascia, partial or total sacrectomy, or to the lateral compartment by expanding to include the external and/or internal iliac vessels. Wide resection can be performed by including the lateral pelvic lymph nodes, sciatic nerve, S1-S2 nerve roots, priformis, and obturator internus muscle[42-46].

The Management of the Patient with Recurrent Rectal Cancer

PE in all its forms are applied at a rate of 70-80% for pelvic cancer other than colorectal cancer (most commonly cervical cancer). It can be performed in approximately 20% of cases of recurrent rectosigmoid cancer and patient management can be examined in three stages. These are: stage 1, diagnosis, evaluation and preoperative staging of the disease (studies of diameter, location, extent and metastatic burden of the disease); stage 2, preoperative chemoradiotherapy (CRT) in suitable candidates; and stage 3, surgical approach to local pelvic recurrence (Table 1-3).

Stage 1

Overall Assessment and Staging[36,41,42,46]

The surgical point to be reached is a complete resection with a negative margin, if technically possible. Patients who are too physically or psychologically debilitated to undergo curative radical resection, or patients with ASA IV-V are not suitable candidates. We can only recommend combined treatments for candidates whose motivation, realistic expectations and

Table 1. Stage 1 in the management of LRRC

General assessment and risk identification
Healthy, good performance (ASA I-III)
Nutritional prognostic index
Glasgow prognostic index
Charlston co-morbidity index
Initial staging: exclusion of contraindications
Prove local disease (Bx > tissue evidence)
Determine resectability (advanced radiological examination)
- Clinical rectal and vaginal touch
- Systemic and abdominal examination
- Imaging
Conventional CT (spiral CT when necessary)
MRI
ERUS
PET-CT

LRRC: Locally recurrent rectal cancer, ASA: American Society of Anaesthesiologists, CT: Chemotherapy, MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography

Table 2. Stage 2 in the management of LRRC

Preoperative treatment
If the patient has not received RT before > CT-RT should be given
If limited RT has been given before > modified regimen is given
If the patient has previously received a full dose of RT > no additional RT is given, CT can probably be given
Restaging is required to exclude distant metastases in the interval period.

LRRC: Locally recurrent rectal cancer, CT: Chemotherapy, RT: Radiotherapy

emotional status are suitable and who receive family support. Patients should have an open mind to understand short- and long-term risks and functional limitations. Despite all efforts, they should display a compatible mental structure that accepts the possibility of postoperative complications or disease recurrence. Table 1 lists the imaging methods we use to understand the location, extent and extrapelvic extension of the local disease. In addition to these, a full body examination, rectal and bimanual recto-vaginal palpation are required. In addition to the evaluation of extraluminal recurrence, of course, intraluminal recurrence should be investigated by using colonoscopy. Since pelvic recurrence is often extraluminal, magnetic resonance imaging [magnetic resonance imaging (MRI); Figure 3A-D] provides the most important information to reveal the relationship of the main tumor mass with vessels, bones, nerves, muscles and soft tissue at in terms of adhesion, abutment, invasion and infiltration. Positron emission tomography/computed tomography (PET/CT; Figure 4), on the other hand, provides an understanding of the extrapelvic disease at different levels (pluri-metastatic disease) together with conventional CT. The task of distinguishing between benign fibrosis and recurrent rectal cancer remains a challenging one. The distinction between post-RT inflammation and recurrent disease can be attempted by multiple biopsies. Endo-anal ultrasonography (USG) and/or transvaginal USG guided biopsies may be helpful. A comprehensive radiological discussion is beyond the scope of this section.

Multidisciplinary Tumor Board for Colorectal and Pelvic Malignancy

Patient selection and treatment planning should be performed by a multidisciplinary team, dedicated to colorectal and pelvic surgical oncology. Over the years, it has been shown that multidisciplinary meetings, consisting of special units that include different disciplines and offer different oncological views, improve patient outcomes. The role of these councils is to make the correct patient selection. It is always the duty of this council to reduce the number of non-curative (R2) resections and "open-close" laparotomies, thus protecting the patient from unnecessary morbidity and preventing the implementation of palliative treatments from being delayed. Interdisciplinary communication is maintained in the perioperative period, and the problems that may arise should be tackled. In the busy working environment, patients who have been reviewed and discussed in the council are not left unattended at critical decision stages and responsibility is shared. The council determines the selection and succession of the right treatment method with the most up-to-date information.

To Determine Resectability

Resectability varies depending on the anatomical structures in which the recurrent tumor mass is attached/fixed to the intrapelvic location. What is resectable in LRRC varies widely between surgeons and centers, and the technical skill process is still evolving. Due to anatomical and technical limitations, many units have reported absolute and relative contraindications for curative surgery. With the development of lateral neurovascular surgical techniques and composite bone resection techniques in the last decade, more radical "high and wide" (Sagar[3]) pelvic resections can be performed. In our center, TPE is applied if possible R0 resection is foreseen in selected patients who are medically fit, whose co-morbidities are under control, who understand the treatment process, are willing, and

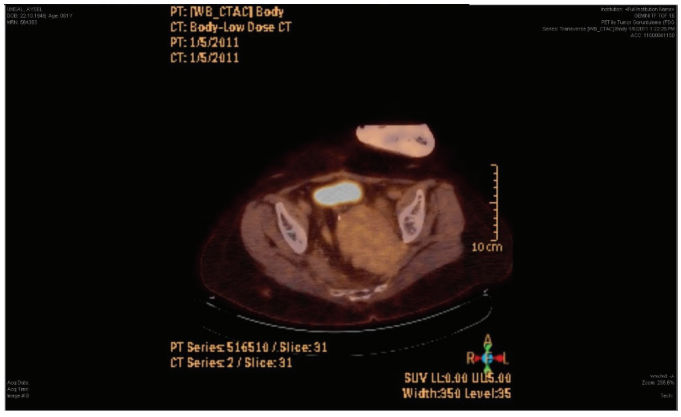

Figure 4. PET/CT shows left lateral wall invasion of LRRC
PET/CT: Positron emission tomography/computed tomography, LRRC: Locally recurrent rectal cancer

have sufficient performance. Bias-withdrawal towards pelvic sidewall involvement, which is traditionally considered a contraindication, is due to potential catastrophic bleeding and neurological damage. Since 2009 this has been used in certain centers (Mayo, MSCCC, St. Mark's, Sydney and Tokyo) with successful results (R0: 21-53%, final 69%). A small number of specialized centers have accumulated en-bloc resection experience in tumors that go beyond the iliac vessels and surround the sciatic nerve.[40,47] Radical resection of the sciatic notch includes en-bloc resection of the internal iliac vein, pyriformis and obturator internus muscles, along with the sacrospinous ligament, and the ischial spine. This may or may not be accompanied by sacrectomy. Partial or complete sciatic nerve resection can be performed with R0 rates comparable to central recurrences (65%).[47-53] In a recent study involving 64 patients with sciatic nerve resection, 96% of patients were able to walk with ankle-foot orthoses and an assisted mobility device despite complete nerve excision. Physical quality of life returned to preoperative levels after 12 months. When we look at the results of these leading centers, it can be seen that sciatic nerve involvement does not prevent the patient from being a candidate for curative surgery.[52,53] In LRRC in which recurrence extends directly to the posterior compartment, composite sacrectomy is performed to achieve R0 resection. Lower (partial) sacral amputation can be performed without major morbidity. However, the hope of curative surgery is controversial when there is high sacrum involvement above the S2/3 junction. Often this situation is considered inoperable in many centers. Again, in the last ten years, it has been proven in centers that have accumulated experience that high sacrectomy is possible and safe.[54-58] Based on PelvEx data from exenteration units with international cooperation, en-bloc sacrectomy can be performed with an R0 resection, similar to partial sacrectomy.[51-58] However, high sacrectomy is naturally associated with higher blood loss, more complications, and neurological loss. According to these latest data, high sacrectomy is not an absolute contraindication for curative surgery. However, additional morbidity should always be considered and included in the consent. A complete R0 resection with microscopic negative margins is the strongest predictor of survival, as has been shown on numerous occasions in specific studies. It has been reported that many factors affect the possibility of radical resection. Factors assocaited invariably with low success rates include: advanced age; male gender; advanced stage of the primary tumor; high carcinoembryonic antigen concentration; previous APR; extensive pelvic sidewall involvement; sciatic nerve involvement; high sacral involvement; and presence of bilateral hydronephrosis. We have stated that there are classifications for tumor location and extent that guide the patient selection and help guide the surgical technique. *However, at the end of the day, all these classifications cannot fully predict resectability in the preoperative period, not least because new findings detected intraoperatively can change earlier decisions.* Another important issue is the contraindications for surgical resection. It is evident that many issues that were accepted as absolute contraindications previously are now seen as indications for surgery, for example in some studies carried out in recent years such as those from Sydney and St Mark's teams. Therefore, we would like the reader to make an in-depth effort about this complex cancer surgery.

Contraindications Include:

1) Unresectable metastatic-extrapelvic disease or metastatic disease that does not respond to preoperative CT;

2) Sacral root involvement (a relative contraindication);

3) Pelvic sidewall involvement;

4) S1-S2 neural involvement (a relative contraindication as this was performed in Dokuz Eylül University Faculty of Medicine;

5) Patient with high surgical risk (ASA IV-V);

6) The patient who does not have the ability to "recognize and be responsible" for the outcomes that the treatment process may result in. The patient should be able to think clearly and be in control of and responsible for their own actions - "compos mentis").

Stage 2

Preoperative Multimodal Treatment

Curative radical surgery is the mainstay of treatment in locally recurrent cancer. However, on the basis of past surgeries, radical resection is not always possible due to the opportunistic and invasive nature of the tumor throughout the compartments. In order to improve oncological

outcomes, RT and CT should be used whenever possible (Table 2).

Metastatic Disease

When LRRC is diagnosed, 36-41% of patients have synchronous distant metastases.[51] In patients with unresectable metastatic deposits, local recurrence resection with curative intent is no longer possible. However, if patients with resectable visceral metastases are motivated and good candidates for exhaustive surgery, radical pelvic surgery and metastasectomy are performed. Although each patient is decided on a patient-disease basis, synchronous metastasectomy is generally avoided because radical resection of pelvic recurrence is associated with increased morbidity rates, involves prolonged surgery time and requires a durable team. Of course, naive patients will receive primary RT in the presence of recurrent disease. However, the more common situation is that the role of re-irradiation is controversial in patients who have received high-dose pelvic RT previously.[52,53] There are centers that do not prefer re-irradiation due to increased radiation toxicity concerns and the relative radioresistance of the recurrent tumor. In some centers and also in Dokuz Eylül University Faculty of Medicine, RT can be applied again using hyperfractionated regimens. More studies and evidence are needed concerning this subject.

Stage 3

Surgical Technique and Intraoperative Radiotherapy[6-10]

TPE is a complex set of surgical interventions consisting of heterogeneous surgical procedures. The extent of resection and reconstruction is determined by the anatomical location of the recurrence and the degree of local invasion. While there can never be a uniform, well-defined TPE suitable for every tumor burden/distribution, in general, all types of surgery can be considered in three basic phases:

1. Investigation of the abdomino-pelvic region for metastatic disease;

2. Dissection and resection phase in which the tumor is constantly removed together with the organs it has seized;

3. Reconstruction phase.

Teamwork should be performed with at least two exenteration-trained colorectal surgeons in patient preparation. Furthermore, the patient should be seen by onco-orthopedic, onco-plastic and vascular surgeons. Surgery should be scheduled as the first patient and no other difficult case should be put on the list. The patient is placed in the modified Lloyd-Davis position, supported by gel pads. The lumbar curve is supported by tilting the pelvis forward-upward from the operating table. Positioning legs, Thompson abdominal wall retraction system and fume extractor aspirator equipment are essential. The right or left arm is closed according to the surgeon's preference. Three illuminated pelvic retractors should be available. A ureteric stent can be placed in selected patients.[59] Adequate erythrocyte suspension (ES) and fresh frozen plasma (FFP) should be provided. If any, the stoma site should be covered with occlusive pad and drape. Planned stoma locations must be marked. If potentially required, the myocutaneous flap donor site (vertical, oblique and transverse rectus abdominus muscles [RAM]) should be carefully marked.[60] If vascular reconstruction is considered, the lower extremity is covered up to the knee to obtain an autologous vein graft. In all other cases, the leg is painted up to the root and covered. Exploration is started with a midline laparotomy, all adhesions are removed and the small intestine is confined to the upper abdomen in the Trendelenburg position. The presence of paraaortic, paracaval, or peritoneal metastatic LAP/deposit is investigated (Figure 5). Presence of metastatic disease (radiologically occult in the preoperative period) and/or cytopositive peritoneal tumor with evidence of frozen section will eliminate the chance of curative intervention, and the team should be aware that TPE will transform into a palliative intervention. However, resectable oligo-metastatic, hepatic and/or peritoneal involvement does not change the chance of curative TPE. The small intestine coil, which is fixed to the pelvic inlet, especially adheres to the tumor, is divided on both sides with a stapler and left on the specimen (Figure 6). The ureters are dissected and suspended at the beginning of the surgery. In the next stage, the ureters are divided from the distal part approaching the tumor, the tip is sent for frozen section examination and it is proven to be tumor-free. Then, a thin oxygen catheter is placed and the urine output is collected. If intestinal continuity is planned, the left colon is mobilized and divided proximal to the recurrent tumor, confined to the upper abdomen for the neorectum. Knowing the fixed pelvic anatomical landmarks, the surgeon creates and maintains pelvic "situational awareness" (Nelson H.) for themselves throughout the surgery. The iliac vascular compartment elements are suspended. Without ligating and dividing the internal iliac artery, the external iliac artery does not relax (floating), and the internal and external iliac veins cannot be reached. The internal iliac artery is ligated after giving the superior gluteal artery if the gluteal flap is to be used for perineal defect reconstruction. The anterior branch of the internal iliac artery is followed. Pararectal and paravesical spaces are revealed. The ureter is followed in the Okabayashi space, and each organ anterior to the ureter is easily dissected. At this point, the surgical team should remember the "Catch-22 phenomenon": this concept

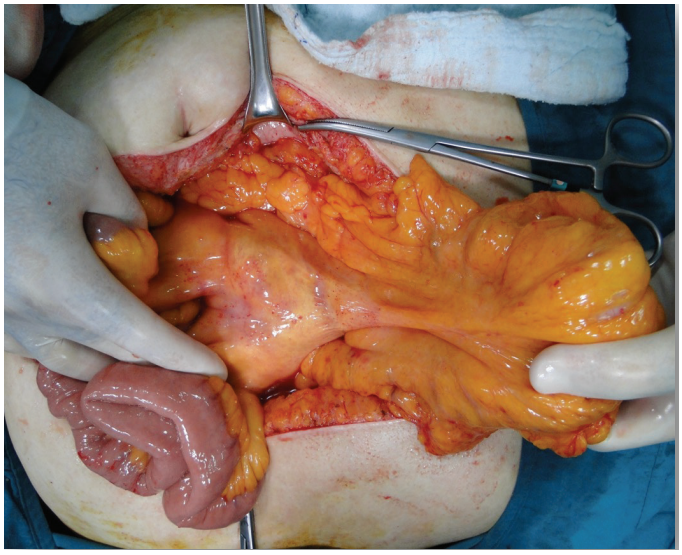

Figure 5. Clustered mesenteric metastatic lymph nodes

should be paid attention to in order not to pass the "point of no return" and not harm the patient. A Catch 22 is a situation in which you cannot do a second thing until you have done a first thing, but you cannot do the first thing until the second thing has been performed - a Catch 22. This concept can be very difficult for the surgeon because of anatomical limitations in complex, multi-visceral, multi-compartmental, intrapelvic resections, encountering huge tumors, fibrosclerotic brazed plans, and party time of bacteria (opening the organ cavity). After these stages are completed, the course of the intervention is divided into complex technical pathways, including central recurrence, posterior recurrence, anterior-dominant recurrence or vascular-sacral-neurovascular resection originating from lateral dominant recurrence (Figure 7A-D).[2-12] In other words, the location of the recurrence naturally guides the surgical techniques to be performed, for example, sacrectomy, pubic bone resection,[61] lateral extended pelvic wall resection, and lateral iliac vessel or nerve resection. At this point, the authors recommend that the reader examine the relevant specific sources in depth.[2-14,52,53]

Reconstruction

The reconstruction elements will also vary, depending on how much dissection and which structures are to be resected in order to achieve a complete oncological clearance. If a portion of the vessel is removed from the iliac vein, vascular repair is performed with a veil, or if a complete vessel resection is performed, vessel reconstruction is performed with an interposition graft.[62] Vascular reconstruction should be done immediately. Distal ureterectomy or partial cystectomy often requires uretero-neocystomy with the Boari flap technique.[2-11] Total cystectomy, on the other hand, often requires ileal or urinary reconstruction with

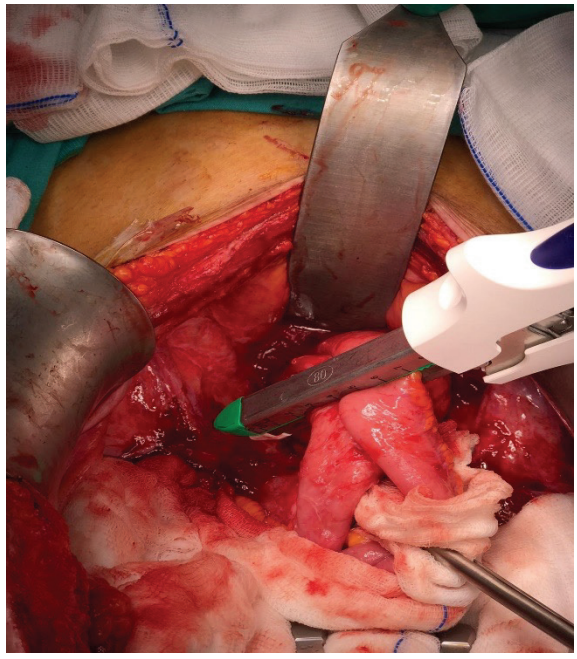

Figure 6. Small intestinal loop fixed to LRRC and obscuring the pelvic inlet, recurrent mass is left on by following the oncological principle of an block resection
LRRC: Locally recurrent rectal cancer

colonic conduit, especially if the patient has a short life expectancy.[63] We perform uretero-enteric anastomoses over a thin feeding catheter. If we have performed abdomino-sacral resection, we complete the urinary reconstruction in the supine position. Small bowel anastomosis is performed after ileal conduit. Urostomy and colostomy are matured. If the abdominal wall is not depleted of stomata, we perform perineal defect closure with a type of RAM flap or, if it is depleted, with a gluteus maximus flap, in the prone position (flip-flap).[64,65]

Intraoperative Radiotherapy

After the recurrent tumor mass is resected, frozen section samples are sent from the suspected surgical margins. At this point, if the center is able, the patient is transferred to the intraoperative radiotherapy (IORT) unit and treated for selective margin involvement (R1), as the tumor is almost invariably locally extensive beyond physical and radiological examination. On the other hand, the major limitation of pelvic external RT is that the dose required to achieve local tumor control exceeds the tolerance of the surrounding healthy tissue. The most promising approach to overcome this limitation is IORT. Although the oncological benefit obtained in various studies has been reported to tend towards the positive, the dearth of effective prospective randomized studies and the high-cost infrastructure setup have affected the widespread use of IORT. Moreover, IORT carries risks of complications; the most common are peripheral neuropathy, ureteral stenosis, and osteonecrosis.[6-12]

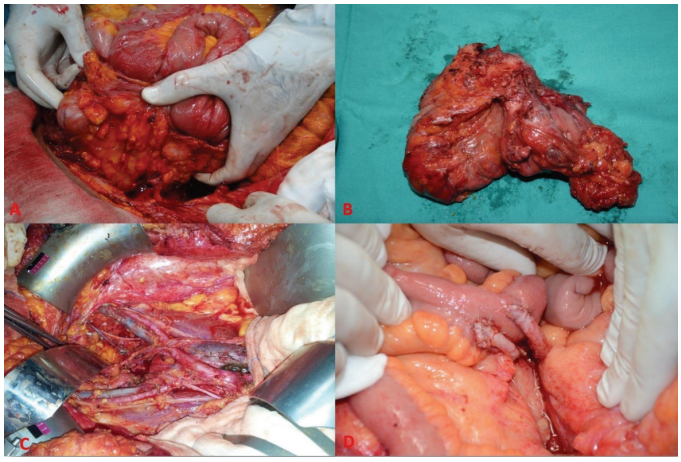

Figure 7. (A) Giant tumoral mass, (B) TPE resection material, (C) Intrapelvic multiorgan resection (D) Ureteric reimplantation to ileal conduit
TPE: Total pelvic exenteration

Palliative TPE: to Whom and When?

We would like to highlight three important points:

1. Surgeons learn to operate over time. This is even more valid when considering difficult and complex surgeries;

2. We physicians make decisions based on the best available evidence, knowledge and experience, and patients experience the results;

3. It has been shown repeatedly that there is a primary T4 advanced or recurrent colorectal cancer type that does not metastasize but remains locally invasive for a long time, which, despite its expansile and infiltrative growth, surprisingly cannot metastasize.

However, tumor necrosis as a result of CRT, causes serious symptoms which seriously impair patient quality of life, including severe pain, tumor fragmentation, malignant fistulas, urine-stool coming from the vagina, tumor shedding with foul-smelling discharge, and loss of soft tissue that is digested with intestinal contents and infected. In the evaluation of the patient, there is no obvious distant organ metastasis or it has a low volume and responds to CT. Although palliative TPE is a major, complicated and risky intervention in such candidate patients, it has been increasingly recommended by experienced centers in recent years, since it is an intervention that controls symptoms, improves quality of life, and ensures the continuation of systemic CT.[66-68] Although it is very controversial, palliative TPE can be applied if these issues are handled very carefully and the patient is selected and comprehensive consent is obtained. *However, it should not be forgotten that the oncological gain of palliative surgery cannot be measured, and the expectations of the patient's relatives will almost always exceed what the surgical team can give*. A major complicated operation should never be offered as a salvage or curative

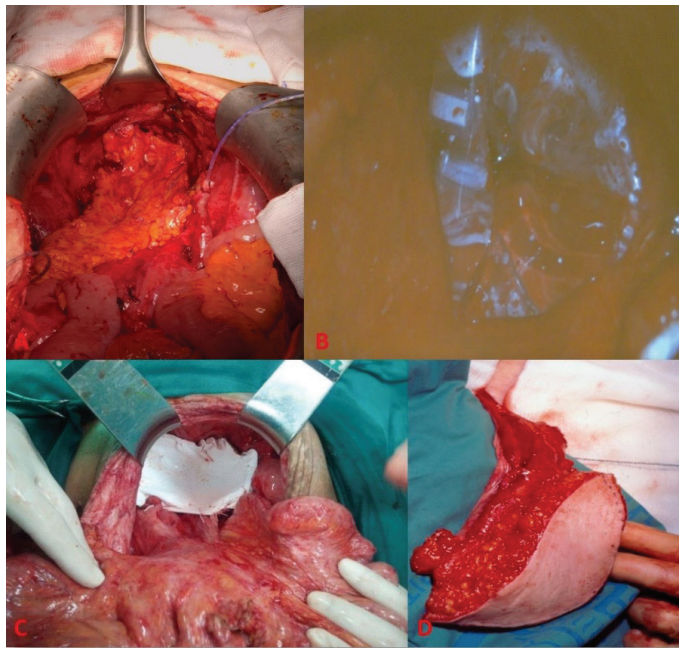

Figure 8. (A) Omental J-flap with pelvic partition (hammock), (B) Hammock with breast prosthesis, (C) Hammock with synthetic biomaterial (D) Rectus abdominus flap

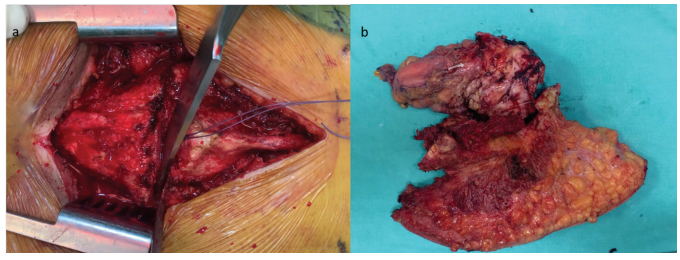

Figure 9. In a patient with irradiated LRRC for the second time invading the sacrum bone, (a) the sacrum is divided by an osteotome between the sacral 3 and 4 foramen, (b) the distal sacrum 4-5 and the coccyx are resected en-block together with the bladder and recurrent rectal mass.
LRRC: Locally recurrent rectal cancer

method to an exhausted, debilitated, cachectic, sarcopenic and terminally ill patient. Palliative support care should be given to patients with medical problems and low performance who cannot tolerate the risks of surgery, while the effort of the surgical team and hospital resources should be used in a way that does not harm the patient.[66-68]

Morbidity-Mortality and Oncological Outcomes[6-12]

One third of the patients who have undergone an exenterative intervention live for 5 years. Recurrence is observed in one third (re-resection is performed if possible in selected patients) and a third die from disseminated metastatic disease. In a study conducted by the PelvEx colloborative group including 1,184 patients, the rate of major postoperative complications was reported to be 32%, the mean hospital stay was 15 days, and the surgical re-exploration rate was 10%. Complications are mainly

related to four areas: cardiopulmonary; infectious (pelvic sepsis); intestinal obstruction; and fistula development. The most common systemic complications are SIRS/sepsis, disseminated intravascular coaggulation, pulmonary embolism and acute respiratory distress syndrome. Re-operation of these complications has a high mortality. All efforts should therefore be made to prevent them during exenteration. The R0 resection rate was reported to be 55% in the PelvEx study and 58% in the current analysis by Platt et al.[57]. We must repeat: the most important predictor for survival is R0 resection. In a recent study involving 210 patients, it was shown that even the millimetric width of the margin positivity negatively affected local recurrence and survival rates.[51] Recurrent disease develops in 55% of patients after salvage surgery for LRRC. Of these 14-21% are isolated local recurrences. Rescue surgery can be attempted a second time in appropriate patients,[69] but often patients fail systemically and die from distant metastasis.[51] In very experienced centers, the mortality rate is 0.6-4% (the rate reported in the past was 7-22%).[52,53]

Combined Application of TPE, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Cytoreductive surgery (SRC) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) are curative treatments for selected patients with peritoneal carcinomatosis. PE is a treatment option for locally advanced pelvic cancers. Due to the high-risk of complications arising from each oncological procedure, most researchers do not recommend applying SRC + HIPEC together with TPE. However, TPE + SRC + HIPEC, which has been tried in selected patients in highly experienced centers, is an ultra-radical intervention, and it is known that there are centers that attempt this marathon.[70,71] The presence of pelvic peritoneal/multiorgan involvement in a suitable-indicated patient for SRC and HIPEC should not be considered as a definitive contraindication if an R0 resection is targeted.[71] Of course, there is a need to evaluate the oncological benefit and increased morbidity-mortality rates with a longer follow-up and to investigate how the quality of life is affected.[71]

The Experience of the Medical Faculty of Dokuz Eylül University

As the Dokuz Eylül University Faculty of Medicine Colorectal Team, we would like to describe our total PE experience. We performed TPE in 29 patients with clear indications for various pathologies, 17 (58.6%) had rectal cancer, 6 (20.7%) had cervical cancer and 6 (20.7%) had other different diagnoses. Of the 17 rectal cancer patients in whom we performed TPE, 5 (29.4%) had locally advanced rectal cancer and the remaining 12 (70.6%) had recurrent rectal cancer. Of these patients, 14 (82.35%) received neoadjuvant chemo-RT, and 5 (29.4%) underwent TPE after receiving RT for the second time after recurrence. Again, 5 (29.4%) of these 17 patients had peritoneal carcinomatosis, and we performed a pelvic exenterative procedure. Eleven (64.7%) of our patients were male and 6 were female. The mean age was 49.7 years (22-76 years). The mean ± standard deviation operative time was 521.7±250.6 minutes. Sacrum resection (Figure 9A, B) was performed in 4 of 17 patients, 4 of them underwent sacrum 4-5 resection (partial) and 1 patient underwent total sacrectomy. Postoperative perineal reconstruction was achieved with primary closure in 11 (64.7%), gluteal rotation flap in 4 (23.5%), vertical rectus abdominus myocutaneous flap in one (5.9%), and a prosthetic patch in one (5.9%). Morbidity/mortality developed in 10 (58.8%) patients in the postoperative period; Clavien-Dindo (C/D) grade I-II morbidity in 1 (5.9%) patient, C/D grade III-IV morbidity in 8 (47.1%) patients, and perioperative mortality in 1 (5.9%) patient. In the postoperative period, 8 (47.1%) developed infection. Local recurrence in 3 (17.6%) of our patients who underwent TPE for rectal cancer, extensive intra-abdominal disease in 4 (23.5%), and distant

Table 3. Stage 3 in the management of LRRC

Surgical resection
Abdominopelvic introspection
Rule out severe-metastatic disease (preop. undetected)
Identify anatomical fixed points (promontory, sacrum, iliac bifurcation, bladder)
Surgical margins: Plural? Nearest border?
What about adjacent structures: iliac vascular structures, ureter, obturator nerve, sciatic notch, sacrum, bladder, and vagina?
Disection, mobilization, resection, stoma or anastomosis
Extended radical resection when needed (interdisciplinary teamwork)
Exenteration (anterior, posterior, total)
Extended TPE (for example, sacrectomy and/or lateral sidewall resection)
Frozen section sampling from borders
IORT if needed/possible
Reconstruction[72-75]
Vascular repair
Ileal conduit
Omental J-flap (Figure 8A) or if the omentum has been depleted, right colon pelvic hammock, breast prosthesis (Figure 8B), or hammock (pelvic partition) with synthetic biomaterial (Figure 8C)
A type of rectus abdominus flap (Figure 8D)
Gluteal muscle flap if the anterior abdominal wall is depleted by stomata

LRRC: Locally recurrent rectal cancer

metastasis in 1 (5.9%) patient developed. The mean follow-up period of our patients was 12.4 months (27 days-34.5 months). One- and two-year overall survival times were 53.2% and 21.5%, respectively.

Horizon

The treatment of LRRC has changed radically in the last two decades. With a multidisciplinary approach, each patient management strategy is discussed and extended radical resection becomes the standard treatment. The surgical philosophy of PE can be summarized as follows:

- It is the most radical surgical option against pelvic cancer. Basically, all pelvic organs are removed.

- The goal of exenterative surgery is always tumor resection with negative surgical margins.

- Applying PE in limited forms may protect the organs that are not involved, but the cost is an increased risk of recurrence.

- The more advanced the primary rectal cancer is, the more likely it is to fail central therapy.

- The patient and his/her relatives should be informed about all the risks, losses and gains of this complex and intensive surgery.

- The patient should confirm that he/she understands and accepts all possible consequences.

- An equally curative form of treatment for intrapelvic destructive recurrent disease is not yet available.

- TPE can provide a significant recovery rate in patients with LRRC.

- In patients with limited response rates and limited duration of action and in whom CT resistance develops, PE should be considered in every case in order to clear the recurrent malignancy.

- TPE and extended TPE are very stressful operations for both the patient and the surgeon. Both need to be very resilient and selfless.

- A stereotypical, template-like and smooth exenterative surgical technique is not possible.

- Unanswered issues include whether to perform concomitant PE-metastasectomy, repeat pelvic RT, high rates of systemic failure despite adjuvant CT, and whether better functional outcomes can be achieved.

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

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RESEARCH ARTICLE

The Clinical Course of Acute Appendicitis During Pregnancy: Comparison of Reproductive Age Patients and Pregnant Patients

Osman Bozbıyık, Can Uç, Tayfun Yoldaş, Cemil Çalışkan, Erhan Akgün, Mustafa Ali Korkut

Ege University Faculty of Medicine, Department of Surgery, İzmir, Turkey

ABSTRACT

Aim: The differential diagnosis of acute abdominal pain in women of reproductive age is challenging. Acute appendicitis is the most common cause of acute abdomen during pregnancy. This study aimed to compare pregnant women with nonpregnant women of reproductive age in terms of diagnostic approach, clinical management, and surgical outcomes in acute appendicitis and to identify any differences occurring in pregnant patients.

Method: Female patients aged between 18-45 years, who underwent appendectomy between January 2015 and December 2018 were included in this retrospective study. Pregnant and non-pregnant patients were compared in terms of clinical presentation, management, and outcomes.

Results: A total of 277 patients (28 pregnant and 249 non-pregnant) were included. In terms of diagnostic imaging, ultrasound was used in all pregnant patients, and 57.1% also underwent magnetic resonance imaging. In the non-pregnant group, computed tomography (CT) was used in 87.9%. There was a higher negative appendectomy rate in the pregnant group (21.4 vs 8.8%; p=0.038). Laparoscopic surgery was performed significantly more often in the non-pregnant group (21.4 vs 59.8%; p=0.001). Duration of diagnosis and length of stay was longer in the pregnant group. Both groups had similar rates of complicated appendicitis (7.1 vs 10.8%; p=0.416) and overall postoperative complications (14.2 vs 8.8%; p=0.316).

Conclusion: The use of CT in the diagnosis of acute appendicitis was common in women of reproductive age. In pregnant women, negative appendectomy rates were higher. Clinical management and surgical outcomes were similar in pregnant women and non-pregnant women of reproductive age.

Keywords: Acute appendicitis, pregnancy, surgical outcomes

Introduction

Acute appendicitis is the leading abdominal surgical emergency in the world.[1] The diagnosis can usually be made with clinical and laboratory findings.[2] However, a diagnosis may be challenging in women of reproductive age due to possible additional intra-abdominal pathologies.[3,4] In women of reproductive age, diagnosis based on history, clinical findings, and laboratory results are often difficult. Reliable clinical features may be absent in up to 70% of patients with suspected appendicitis.[5] Over the past decades, computed tomography (CT) has been increasingly used for the assessment of patients with possible appendicitis. CT can reduce both unnecessary surgery and delay of surgery.[6] Today, especially in adult female patients, diagnostic difficulties are largely eliminated with routine use of CT.[7,8]

Another subgroup that creates diagnostic difficulties for the clinician is pregnant patients. During pregnancy, acute appendicitis is the most common non-obstetric pathology that requires surgical intervention.[9] The diagnosis is more challenging due to anatomical and physiological changes during pregnancy.[10] It is known that both delayed cases and unnecessary operations increase maternal and fetal morbidity.[11] Therefore, it is important to make an accurate diagnosis in pregnant women. Traditional teaching states that there is an increased risk of complications in pregnant patients with acute appendicitis.[12,13] Recent studies indicate

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Address for Correspondence: Osman Bozbıyık MD,
Ege University Faculty of Medicine, Department of Surgery, İzmir, Turkey
E-mail: bozbiyiko@gmail.com **ORCID ID:** orcid.org/0000-0002-1827-2720
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similar clinical presentation and outcomes in pregnant patients with acute appendicitis[14,15].

This study aimed to compare pregnant patients with non-pregnant, reproductive age patients to reveal whether the clinical course of appendicitis is affected by pregnancy.

Materials and Methods

This was a retrospective analysis of a tertiary referral university hospital database. The study protocol was approved by the Ege University Faculty of Medicine Local Ethics Committee (approval number: 20-4.1T/35). This study was conducted in accordance with the ethical standards of Helsinki Declaration. All female patients aged between 18-45 years, who underwent appendectomy for acute appendicitis between January 2015 and December 2018 were included in the study. Patients, all of whom were of reproductive age, were divided into two groups; pregnant and non-pregnant. The two groups were compared in terms of preoperative, operative, and postoperative clinical results.

Emergency department medical records, radiological data, surgical operation reports, follow-up records, and pathology reports of the patients were evaluated retrospectively. Included parameters were: fever; leukocyte count; C-reactive protein (CRP) level; imaging method used which included ultrasound [USG], CT, and/or magnetic resonance imaging (MRI); preoperative hospital interval; pregnancy gestation week; operation type (open/laparoscopic); perforation; duration of hospitalization complications; re-attendance at hospital within 30 days; fetal loss or preterm birth; and histopathological results. Hospital admission time was defined as the time from onset of abdominal pain to admission to the hospital. Preoperative hospital interval was defined as the time from hospital admission to surgery. Before surgery, all pregnant patients were evaluated by a gynecologist and obstetrician for confirmation of fetal well-being and gestational age. Fetal USG was performed on all pregnant patients before they were discharged from the hospital, and postoperative fetal well-being was checked. Complications were classified according to Clavien-Dindo classification. Negative appendectomy was defined as no signs of acute or chronic inflammation, no tumor or infection on histopathological examination.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Continuous variables are presented as mean ± standard deviation and data were compared using an unpaired t-test. Categorical variables are expressed as numbers and percentages and analyzed for comparisons using a chi-square test. For all hypothesis tests, $p \leq 0.050$ was considered statistically significant.

Results

A total of 277 patients, 28 (10.1%) in the pregnant group and 249 (89.9%) in the non-pregnant group, were included in the study. The mean age was 29.2±7.4 years. Table 1 summarizes the information about the demographics, clinical data, laboratory data, and imaging differences between the groups.

At time of diagnosis, 5 (18%) women in the pregnant group were in the first trimester, 18 (64%) were in the second trimester and 5 (18%) were in the third trimester. There were no significant difference between the groups in terms of hospital admission time (p=0.185), total leukocyte count (p=0.343), lymphocyte count (p=0.310), or body temperature (p=0.748). CRP values were higher in non-pregnant patients (p=0.005). When the physical examination

Table 1. Comparison of pregnant women and non-pregnant women of reproductive age

	Pregnant group (n=28)	Non-pregnant group (n=249)	p
Age (year)	28.3±5.7	29.3±7.6	0.390
Body temperature (^{0}C)	36.6±0.4	36.8±2.2	0.748
Leukocyte (10^3/μL)	14.6±4.0	13.9±4.0	0.343
Neutrophil (%)	80.2%	77.2%	0.237
C-reactive protein (mg/dL)	2.1±4.0	4.7±6.9	**0.005**
Hospital admission time (days)	1.6±0.9	2.1±1.8	0.185
Pre-op hospital interval (hours)	14.0±8.4	7.2±4.3	0,001
Diagnostic US	28 (100%)	173 (69.4%)	-
Diagnostic CT	0	219 (87.9%)	-
Diagnostic MRI	16 (57.1%)	0	-
Laparoscopic surgery	6 (21.4%)	149 (59.8%)	**<0.001**
Complicated appendicitis	2 (7.1%)	27 (10.8%)	0.416
Thirty-day readmission	3 (11%)	17 (7%)	0.328
Negative appendectomy	6 (21.4%)	22 (8.8%)	**0.038**
Overall complication	4 (14.2%)	22(8.8%)	0.316
Length of hospital stay (days)	2.9	2.0	**0.001**

US: Ultrasonography, CT: Computed tomography, MRI: Magnetic resonance imaging, normal C-reactive protein value: <0.5 mg/dL

findings were evaluated, in the pregnant appendicitis group isolated abdominal tenderness was found in 15 (53.5%) patients and tenderness and rebound in 13 (46.4%) patients. In the control group, isolated tenderness was found in 96 (38.5%), tenderness and rebound in 136 (54.6%), and tenderness and defence in 17 (6.8%) patients.

In terms of cross-sectional imaging methods, no diagnostic CT was used in the pregnant group, while diagnostic MRI was used in 16 (57.1%) pregnant patients. In the control group, the main imaging method was CT and was used in 219 patients (87.9%). Comparison of CT and MRI findings with histopathological results can be seen in Table 2, 3. When histopathalogical results were evaluated, the negative appendectomy rate was significantly higher in the pregnant group compared to the control group (21.4% vs 8.8%, respectively; p=0.038).

Laparoscopic surgery was performed at a significantly higher rate in the non-pregnant group compared to the pregnant group (59.8% vs 21.4%, respectively; p=0.001). Complicated appendicitis (perforation or abscess) rates were similar (7.1 and 8.8%). There were no significant differences between the pregnant and non-pregnant groups in terms of complications (p=0.316) and thirty-day readmission rates (p=0.328) (Table 4). Length of stay was longer in pregnant patients (p=0.001). Preterm labor occurred only in one pregnant patient at the 29th week of pregnancy. No fetal losses occurred in association with acute appendicitis.

Table 2. CT and histopathological findings of non-pregnant women of reproductive age

CT findings	Histopathological findings	n
Consistent with acute appendicitis (n=200)	Acute appendicitis	182
	Appendix vermiformis	14
	Other appendiceal pathologies	5
Suspicious for acute appendicitis (n=12)	Acute appendicitis	5
	Appendix vermiformis	6
	Other appendiceal pathologies	1
Normal appendix (n=2)	Acute appendicitis	2
	Appendix vermiformis	0
	Other appendiceal pathologies	0
Non diagnostic (n=1)	Acute appendicitis	1
	Appendix vermiformis	0
	Other appendiceal pathologies	0
CT was not taken (n=34)	Acute appendicitis	32
	Appendix vermiformis	2
	Other appendiceal pathologies	0

CT: Computed tomography

Table 3. MRI and histopathological findings of pregnant women

MRI findings	Histopathological findings	n
Consistent with acute appendicitis (n=9)	Acute appendicitis	6
	Appendix vermiformis	3
Suspicious for acute appendicitis (n=2)	Acute appendicitis	1
	Appendix vermiformis	1
Normal appendix (n=1)	Acute appendicitis	0
	Appendix vermiformis	1
Non diagnostic (n=4)	Acute appendicitis	3
	Appendix vermiformis	1
MRI was not taken (n=12)	Acute appendicitis	12
	Appendix vermiformis	0

MRI: Magnetic resonance imaging

Table 4. Clavien-Dindo classification grades of complications

Clavien-Dindo grade	Pregnant group (n=28)	Non-pregnant group (n=249)	p
I	4	19	
II	0	1	
III	0	2	
IV	0	0	
V	0	0	
Overall complication	4 (14.2%)	22 (8.8%)	0.316

Discussion

The diagnosis of acute abdominal pain has distinctive difficulties in women of reproductive age. Gynecological pathologies may have clinical findings similar to acute appendicitis. Therefore, a diagnostic approach to acute abdominal pain is a challenging process, especially in women of reproductive age. According to accepted knowledge, pregnant women are thought to be less likely to have a classical clinic course of appendicitis than non-pregnant women[10,13]. Recently, increased use of cross-sectional diagnostic imaging modalities and improvement in minimally invasive surgical techniques have called this belief into question. In this study, the selection of the imaging method used was the foremost difference between groups. CT was used for diagnostic purposes in 87.9% of non-pregnant patients, and the negative appendectomy rate was found to be 8.8% in these patients. In comparison, the rate of negative appendectomy was higher in pregnant women in which USG was used as the primary imaging modality,

with a rate of 21.4%. Negative appendectomy rates have decreased in recent decades, which is likely attributable to the increased use of CT[16]. Today, CT has become the preferred method in the imaging of suspected appendicitis in adults[7]. Women are more than twice as likely as men to have a nontherapeutic appendectomy for suspected acute appendicitis. Liberal use of CT scan dramatically decreases the negative appendectomy rate, especially in adult female patients[17].

The recommendation of the American College of Radiology is that ultrasonography should be the first-line imaging method in diagnosis. However, the use of MRI has increased in pregnant women due to technical difficulties in localizing the appendix and compressing the appendix sufficiently. It is important to make an accurate diagnosis before surgery to eliminate unnecessary surgeries and potentially negative fetal effects[11]. In this study, USG was used in all pregnant women, and half of the pregnant women also underwent MRI. Despite this, the negative appendectomy rate was high in the pregnant group. Although this rate was compatible with many previous studies, it was significantly higher than the control group where CT was routinely used[6,15,18]. Since late diagnosis in pregnant women may increase fetal morbidity, the decision for surgical intervention is made easier. Therefore, higher negative appendectomy rates are expected in pregnant women[14].

A delay in diagnosis of acute appendicitis has been associated with higher complications and fetal mortality rate[19]. Therefore, accurate and fast diagnosis is crucial during pregnancy[15]. In this study, the hospital interval was longer in the pregnant group. Although it remained within acceptable limits, the difference between the means of "time from admission to the operation" was about seven hours[20]. In previous studies, there were conflicting results in terms of hospitalization time and hospital intervals in pregnant patients[14,15,21]. A few factors may cause long hospital waiting time in pregnant patients. Firstly, all pregnant patients were evaluated by the gynecologist in the preoperative period. Another factor was the delay between USG and any subsequent MRI in those who are not diagnosed with initial USG. Both these procedures may cause long preoperative waiting time in pregnant patients.

Pregnancy is characterized by low-grade systemic inflammation and therefore the use of leukocytosis to aid the diagnosis of acute appendicitis is of less utility[22]. Leukocyte counts increase from the first to the third trimester and the increase is mainly due to neutrophilia[23]. In the present study, at the time of presentation, many parameters, including leukocyte count, lymphocyte count and body temperature were similar, whereas CRP values were higher in the non-pregnant group. Inflammatory markers such as CRP and complete blood cell count (CBC) parameters play an essential role in the diagnosis of acute appendicitis[24]. We found that CBC parameters were similar between groups and these parameters had a diagnostic value. The difference in CRP levels between the groups could be explained by the low rate of negative appendectomy in non-pregnant patients.

In this study, the use of laparoscopic surgery was rare in pregnant patients. Laparoscopy may be thought to be contraindicated in pregnancy. However, it has been shown repeatedly that the maternal and fetal results following laparoscopy during pregnancy are acceptable. In general, laparoscopy is the first choice for pregnant women in the first and second trimesters, while open surgery is preferred in the third trimester due to the size of the uterus and technical difficulties[9,25,26]. In our study, all laparoscopic procedures were performed in the second trimester. The surgeon's experience, gestational condition, the patient's structure, and the patient's desire are factors that influence the surgeon's decision to perform laparoscopic or open surgery[26].

In this cohort, perioperative and postopertive outcomes were similar between groups. There was no difference between groups in terms of perforated or complicated appendicitis. It is well known that complicated appendicitis increase maternal and fetal morbidity[13]. The complicated appendicitis rate was similar in our study. Probably as a result of this, no difference in morbidity was detected between groups. Pregnancy alone does not significantly increase the risk of major surgical morbidity[21,27]. Length of stay was longer in pregnant patients. A reason for having a longer length of stay in the pregnant group could be a result of higher open surgery rates, as well as postoperative obstetric assessment.

Study Limitations

The present study has certain limitations. This was a single-institution experience with retrospective nature and small size. Our study comprised only those who had undergone surgery with suspicion of acute appendicitis. Despite these limitations, an evaluation was made on objective criteria by using the data of a well-documented electronic database.

Conclusion

In pregnant women with acute appendicitis the most obvious difference is limited use of cross-sectional imaging methods and pregnant women have higher negative appendectomy rates than non-pregnant women. Nevertheless, there is no difference between pregnant and non-pregnant women in terms of clinical course and postoperative outcomes of acute appendicitis.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ege University Faculty of Medicine Local Ethics Committee (approval number: 20-4.1T/35).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: O.B., C.U., Design: O.B., T.Y., C.Ç., Supervision: M.A.K., E.A., C.Ç., Data Collection or Processing: C.U., O.B., Analysis or Interpretation: O.B., T.Y., E.A., M.A.K., Literature Search: C.U., T.Y., C.Ç., Writing: O.B., C.U., Critical Review: C.C.

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RESEARCH ARTICLE

The Prognostic Value of Preoperative Serum Levels of CEA and CA 19-9 in Patients with Colorectal Cancer

Didem Can Trabulus[1], Nüvit Duraker[2], Zeynep Civelek Çaynak[3]

[1]University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, Okmeydanı Training and Research Hospital, Clinic of Surgery, İstanbul, Turkey
[3]Bayındır Levent Hospital, Clinic of Surgery, İstanbul, Turkey

ABSTRACT

Aim: Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most frequently used tumor markers in clinical evaluation of colorectal cancer patients. In this study, we investigated the prognostic significance of CEA and CA 19-9 in colorectal cancer patients without distant metastasis.

Method: We assessed colorectal cancer patients with measured preoperative serum CEA and CA 19-9 levels between 1993 and 2004. Peripheral venous blood samples were taken before surgery. Tumor marker analyses were accomplished with a two-site immuno-radiometric assay. Patients' demographic, clinico-pathological and treatment data were retrieved from the patients files.

Results: A total of 548 patients were included. Mean age was 59.6±12.3 years and 52.5% were male. Serum CEA and CA 19-9 levels were positive (above the cut-off values) in 190 (34.6%) and 97 (17.7%), respectively. In the univariate analyses, CEA and CA 19-9 positive patients showed poorer cancer-specific survival rates than marker negative patients (log-rank x^2=16.935, p<0.001 and log-rank x^2=12.431, p<0.001, respectively). In multivariate Cox analyses, CEA (p=0.003) and CA 19-9 (p=0.001) had independent prognostic significance. When CEA and CA 19-9 were included together in the Cox analysis, CEA (relative risk=1.39, 95% confidence interval (CI)=1.03-1.88, p=0.030) and CA 19-9 (relative risk=1.64, 95% CI=1.15-2.33, p=0.006) maintained their independent prognostic significances.

Conclusion: Preoperative serum CEA and CA 19-9 have prognostic importance independent of clinico-pathological factors in colorectal cancer patients without distant metastasis. These tumor markers can be used in the planning of adjuvant therapy of colorectal cancer patients.

Keywords: CEA, CA 19-9, colorectal carcinoma, survival

Introduction

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are the most frequently used tumor markers in clinical evaluation of colorectal cancer patients. Since both markers have low sensitivity in diagnosis of colorectal cancer, they are not used as diagnostic toll.[1] Although the predominant opinions regarding the prognostic significances of preoperative levels of these markers support that they are beneficial tolls, there are also studies stating that both CEA[2-7] and CA 19-9[6-9] do not have prognostic significance. In some experimental studies, it has been suggested that CEA[10,11] and CA 19-9[12] function as intercellular adhesion molecules and thus they may lead to metastasis. In some clinical reviews[1,13,14] both CEA and CA 19-9 are indicated as intercellular adhesion molecules. It is also stated that CEA induces the release of suppressor lymphokines from healthy human lymphocytes *in vitro*, which may cause immunosuppression in cancer patients.[15] Thus, high preoperative serum levels of CEA and CA 19-9 may be indicators of poor prognosis.

In this study, we investigated the relationship between preoperative serum levels of CEA and CA 19-9 and clinico-pathological features and outcomes, and thus the prognostic significance of CEA and CA 19-9 in colorectal cancer patients without distant metastasis.

Materials and Methods

Patients

The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey,

Address for Correspondence: Didem Can Trabulus MD,
University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Surgery, İstanbul, Turkey
E-mail: didemcan73@gmail.com **ORCID ID:** orcid.org/0000-0003-1687-715X
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İstanbul Training and Research Hospital (approval number: 2840, date: 21.05.2021). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

We retrospectively assessed adult colorectal cancer patients (age >18 years) who underwent curative (R0) resection between January 1993 and December 2004. We collected the serum CEA and CA 19-9 levels of patients measured preoperatively from patient files. Among patients with colorectal cancer, those who received neoadjuvant therapy, patients with synchronous colorectal cancer, and patients with familial adenomatous polyposis coli were excluded. Patient demographic, clinico-pathological (tumor site, tumor size, T-stage, nodal status, histologic grade) and treatment (surgery, adjuvant chemotherapy and radiotherapy) data were retrieved from the patient files.

Patients were categorized into those who had elective or emergency surgery. In histopathological evaluation of the tumors, histologic grade was categorized as low grade (well and moderately differentiated) and high grade (poorly differentiated, undifferentiated, mucinous and signet ring cell). We also recorded whether patients received adjuvant chemotherapy and/or adjuvant radiotherapy.

Patients who died due to postoperative complications were not included in survival analysis. Survival data were obtained from the patient files in the oncology department and from the phone calls with patients or patients' relatives. The endpoint of the study was patient death. Cancer-specific survival (CSS) time was identified as the time interval between surgery and death due to disease recurrence. In patients who developed a secondary malignancy, the date of the diagnosis of second malignancy was considered as the last follow-up date. In patients who died due to a cause other than cancer, the date of death was considered as the last follow-up date.

Tumor Marker Measurements

Peripheral venous blood samples were taken from the patients before surgery, centrifuged and serum samples were stored at -20 °C until analyzed. A commercial kit, IRMA-coat CEA kit (Byke Sangtec Diagnostica GmbH, Dietzenbach, Germany) was used for CEA analysis, which had a recommended cut-off value of 5 ng/mL. Two different kits were used for CA 19-9 measurements: the IRMA-mat CA 19-9 (Byke Sangtec Diagnostica GmbH. Dietzenbach, Germany) with a recommended cut-off value of 37 U/mL and the GI-MA IRMA (EURO/DPC Ltd., Glyn Rhonwy, United Kingdom) with a lower recommended cut-off value of 29 U/mL. All analyses were accomplished with a two-site immuno-radiometric assay.

Statistical Analysis

Chi-square test was used to assess the relationship between tumor marker positivity and clinico-pathological features. Student's t-test was used to compare the mean ages of the patient groups. The Kaplan-Meier method was used to calculate CSS, and the two-sided log-rank test was used for comparison of the survival curves. The relative importance of the prognostic features was investigated using the Cox proportional hazards model. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 620 patients with colorectal cancer whose data were retrieved, 42 (6.8%) who received neoadjuvant therapy, 16 (2.6%) with synchronous colorectal cancer, and 14 (2.3%) with familial adenomatous polyposis coli were excluded. Thus, a total of 548 patients were eligible for this study. In these 548 the mean age was 59.6±12.3 years (median: 61, range: 19-91) and 52.5% of patients were male. Of the patients, 329 (60%) patients were younger and 219 (40%) were older than 65 years.

Demographic, clinico-pathologic and treatment features of patients are summarized in Table 1. Most of the patients had negative preoperative CEA and CA 19-9 serum levels. Almost all patients underwent elective surgery rather than urgent surgery. We found that the number of patients with tumors located in the colon and rectum were the same. Almost two-thirds of patients had tumors >5 cm in diameter and more than three-quarters had tumor T stage T3-T4. However, the rate of nodal involvement was just below 40%. Most of the tumors were low grade. While most of the patients received adjuvant chemotherapy, fewer patients were irradiated. A 5-fluorouracyl based chemotherapy regimen was used in patients who received adjuvant chemotherapy.

Thirty-seven patients died due to postoperative complications and were not included in survival analysis. Of the patients, 13 developed a secondary malignancy and 73 patients died from a cause other than cancer.

Relationship between Clinico-Pathological Features and CEA and CA 19-9 Positivity

Among the 548 patients, preoperative serum CEA of 190 patients (34.6%) and CA 19-9 levels of 97 patients (17.7%) were positive (above the cut-off values). As seen in Table 2, there was no correlation between CEA or CA 19-9 positivity and gender and age. There was no correlation between CEA positivity and tumor location. Patients who

Table 1. Demographic, clinico-pathologic and treatment characteristics of patients

Variable	Category	n (%)
Age	All	548 (100)
Age group	<65	329 (60)
	≥65	219 (40)
Gender	Male	288 (52.5)
	Female	260 (47.5)
CEA	Positive	190 (34.6)
	Negative	358 (65.3)
Ca 19-9	Positive	97 (17.7)
	Negative	451 (82.2)
Surgery	Elective	525 (95.8)
	Urgent	23 (4.1)
Tumor site	Colon	273 (49.8)
	Rectum	275 (50.2)
Tumor size, cm	≤5	192 (35)
	>5	256 (65)
T-stage	T1-T2	123 (22.4)
	T3-T4	425 (77.5)
Nodal status	Negative	330 (60.2)
	Positive	218 (39.8)
Histologic grade	Low grade	464 (84.7)
	High grade	84 (15.3)
Adjuvant chemotherapy	Yes	388 (70.8)
Adjuvant radiotherapy	Yes	193 (35.2)

CEA: Carcinoembryonic antigen, Ca 19-9: Carbohydrate antigen 19-9

had positive CA 19-9 levels tended to have colon located tumors (p=0.052). The proportions of tumors larger than 5 cm were significantly higher in CEA and CA 19-9 positive patients than tumor-marker negative patients (p<0.001 and p=0.003, respectively). While CEA positive patients had significantly more T3 and T4 tumors than negative patients (p=0.001), the rate of T3-T4 tumors was slightly higher in the CA 19-9 positive group and the difference approached significance (p=0.051). The ratio of lymph node positive patients was significantly higher in CA 19-9 positive patients than negative patients (p=0.001), whereas in the CEA positive patients, the ratio of lymph node positive patients was slightly higher, but the difference was not significant (p=0.084). Patients who had positive CEA and CA 19-9 levels had significantly more high-grade tumors compared to patients who had negative markers (p=0.007 and p=0.018, respectively).

Cancer-Specific Survival in the Patient Groups

Two hundred and three patients died because of colorectal cancer. Mean follow-up period for the surviving patients was 137.3 months. CEA and CA 19-9 positive patients showed poorer CSS rates than marker negative patients (log-rank x^2=16.935, p<0.001 and log-rank x^2=12.431, p<0.001, respectively) (Figure 1, 2). In multivariate Cox analyses, CEA (p=0.003) (Table 3) and CA 19-9 (p=0.001) (Table 4) had independent prognostic significance. When both CEA and CA 19-9 were included in the Cox analysis, both CEA [relative risk=1.39, 95% confidence interval (CI)=1.03-1.88, p=0.030] and CA 19-9 (relative risk=1.64, 95% CI=1.15-2.33, p=0.006) maintained their independent prognostic significances.

Discussion

In this study the preoperative serum CEA and CA19-9 levels of non-metastatic colorectal cancer patients were measured and the prognostic significance of CEA and CA 19-9 positivity in colorectal cancer patients was investigated. We found that 190 (34.6%) patients were CEA positive and 97 (17.7%) patients were CA 19-9 positive. CEA and CA 19-9 positive patients showed poorer CSS rates than marker negative patients. CEA and CA 19-9 had independent prognostic significance.

In some studies, CSS rate has been reported as 25.0-42.3% in non-metastatic colorectal cancer patients.[6,16-19] CA 19-9 positive rates are reported to vary between 13.5-25.1% in some studies.[3,16,17] We found CA 19-9 positive rates compatible with the literature. These low positivity rates confirm that serum CEA and CA 19-9 have no significance in diagnosis of colorectal cancer.

In our study, there was no correlation between CEA positivity and tumor location but CA 19-9 positivity rate was higher in colon tumors compared with rectal tumors. Recent studies stated no correlation between tumor location and CEA[6,18,20-23] or CA 19-9[6,24] positivity. In addition, the number of patients who have tumors >5 cm was more in both the tumor marker positive groups than tumor-marker negative patients. Some studies[21,25,26] reported significantly larger tumor size in CEA positive patients, and only one study[25] found significantly larger tumor size in CA 19-9 patients. On the contrary, some studies found no correlation between tumor size and high CEA[21] or CA 19-9[24] levels.

Some studies have found significantly higher CEA[18,25] and CA 19-9[24] positivity in T3-T4 tumors. There is only one study that reported no correlation between the depth of wall invasion and CA 19-9 positivity.[25] We found that the rate of T3-T4 tumors invading the muscularis propria was

Table 2. The relation between clinicopathological features and serum CEA and CA 19-9

Feature	CEA (-)		CEA (+)		p	CA 19-9 (-)		CA 19-9 (+)		p
	n	%	n	%		n	%	n	%	
Gender	-				**0.456**	-				**0.373**
Female	174	48.6	86	45.3		210	46.6	50	51.5	
Male	184	51.4	104	54.7		241	53.4	47	48.5	
Age, years	-				**0.291**	-				**0.339**
Mean	60.1		58.8			59.5		60.2		
Median	61.0		61.0			61.0		62.0		
Range	19.0-91.0		22.0-85.0			19.0-91.0		22.0-83.0		
Age, years	-				**0.204**	-				**0.460**
<65	208	58.1	121	63.7		274	60.8	55	56.7	
≥65	150	41.9	69	36.3		177	39.4	42	43.3	
Tumor site	-				**0.767**	-				**0.052**
Colon	180	50.3	93	48.9		216	47.9	57	58.8	
Rectum	178	49.7	97	51.1		235	52.1	40	41.2	
Tumor size, cm	-				**<0.001**	-				**0.003**
≤5	150	41.9	42	22.1		171	37.9	21	21.6	
>5	208	58.1	148	77.9		280	62.1	76	78.4	
T-stage	-				**0.001**	-				**0.051**
T1-T2	96	26.8	27	14.2		109	24.2	14	14.4	
T3-T4	262	73.2	163	85.8		342	75.8	83	85.6	
Nodal status	-				**0.084**	-				**0.001**
Negative	225	62.8	105	55.3		286	63.4	44	45.4	
Positive	133	37.2	85	44.7		165	36.6	53	54.6	
Histologic grade	-				**0.007**	-				**0.018**
Low grade	314	87.7	150	78.9		390	86.5	74	76.3	
High grade	44	12.3	40	21.1		61	13.5	23	23.7	

CEA: Carcinoembryonic antigen, Ca 19-9: Carbohydrate antigen 19-9

significantly higher in patients in the CEA positive group and approached significance in those with CA 19-9 positivity compared to those patients in the marker negative groups.

Lymph node positivity was significantly higher in CEA[18,25] and CA 19-9[24,25] positive patients in some studies. In our series, the rate of lymph node positive patients was significantly higher in CA 19-9 positive patients compared with CA 19-9 negative patients and this rate was slightly higher in CEA positive patients, although not significant. We also found that the rate of high histologic grade tumors was significantly higher in CEA and CA 19-9 positive patients compared with marker negative patients. However, many studies found no significant correlation between histologic type and CEA[6,18,21,22,25] or CA 19-9[6,24,25] positivity.

In this study, univariate analysis showed significantly poorer CSS in CEA and CA 19-9 positive patients compared with marker negative patients. In multivariate Cox regression analysis, CEA and CA 19-9 both had prognostic significance, independent of clinico-pathological features, separately and together. Some studies have found no significant correlation between survival of colorectal cancer patients and CEA[5,7] or CA 19-9[6,8,9]. In other studies, although CEA[8,23,25-27] and CA 19-9[25,27] positive patients had significantly poorer survival than marker negative patients in the univariate analysis, in multivariate analysis no independent prognostic significance was found. On the other hand, various studies showed poorer survival in CEA positive patients[9,18,21,22,28] and some other studies showed poorer survival in CA 19-9

Table 3. Cox proportional hazards model analysis of the clinicopathological and treatment features, and CEA

Feature	Relative risk	95% CI	p
Gender			**0.376**
Female	1.00	-	
Male	0.88	0.66-1.16	
Age, years			**0.017**
<65	1.00	-	
≥65	1.45	1.06-1.96	
Tumor site			**0.048**
Colon	1.00	-	
Rectum	1.34	1.01-1.79	
Tumor size, cm			**0.342**
≤5	1.00	-	
>5	0.86	0.62-1.17	
T-stage			**0.002**
T1-T2	1.00	-	
T3-T4	2.06	1.31-3.26	
Nodal status			**<0.001**
Negative	1.00	-	
Positive	2.93	2.19-3.91	
Histologic grade			**0.085**
Low grade	1.00	-	
High grade	1.37	0.95-1.97	
CEA			**0.003**
Negative	1.00	-	
Positive	1.54	1.15-2.05	
Surgery			**0.522**
Elective	1.00	-	
Urgent	0.78	0.36-1.67	
Adjuvant chemotherapy			**0.603**
Yes	1.00	-	
No	1.11	0.75-1.64	

CI: Confidence interval, CEA: Carcinoembryonic antigen

positive patients[19,20,26] compared with marker negative ones, and independent prognostic significance of these markers was maintained in multivariate analysis.

Study Limitations

Our study has some limitations. Since it is a retrospective study there may be some missing data. Some survival data were not available because of the lack of hospital visits.

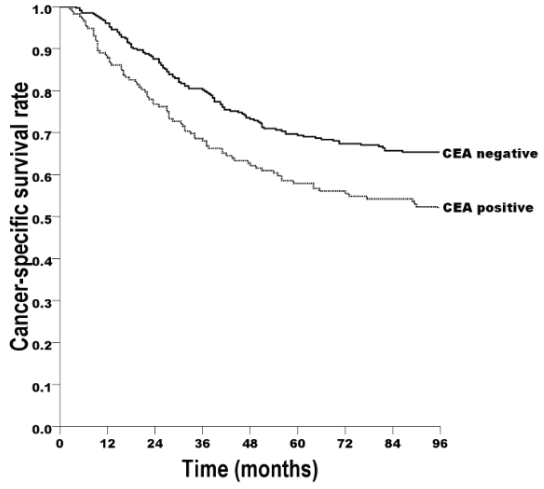

Figure 1. Cancer-specific survival rates of the CEA negative (336 patients) and positive (175 patients) colorectal cancer patients (log-rank x^2=16.935, p<0.001)

Number at risk									
Months	0	12	24	36	48	60	72	84	96
CEA negative	336	316	288	257	230	214	204	196	186
CEA positive	175	152	132	117	106	94	91	86	82
CEA: Carcinoembryonic antigen									

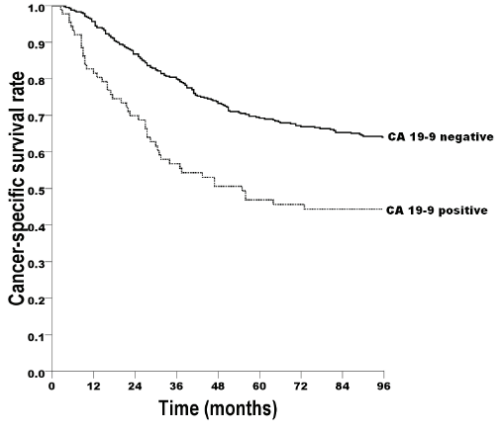

Figure 2. Cancer-specific survival rates of the CA 19-9 negative (421 patients) and positive (90 patients) colorectal cancer patients (log-rank x^2=12.431, p<0.001)

Number at risk									
Months	0	12	24	36	48	60	72	84	96
CA 19-9 negative	421	397	360	328	295	271	259	248	234
CA 19-9 positive	90	71	60	46	41	37	36	34	34
CA 19-9: Carbohydrate antigen 19-9									

Table 4. Cox proportional hazards model analysis of the clinicopathological and treatment features, and CA 19-9

Feature	Relative risk	95% CI	p
Gender			0.462
Female	1.00	-	
Male	0.90	0.68-1.19	
Age, years			0.039
<65	1.00	-	
≥65	1.37	1.01-1.86	
Tumor site			0.012
Colon	1.00	-	
Rectum	1.45	1.08-1.94	
Tumor size, cm			0.364
≤5	1.00	-	
>5	0.86	0.63-1.18	
T-stage			0.001
T1-T2	1.00	-	
T3-T4	2.23	1.41-3.52	
Nodal status			<0.001
Negative	1.00	-	
Positive	2.89	2.16-3.87	
Histologic grade			0.132
Low grade	1.00	-	
High grade	1.32	0.92-1.90	
CA 19-9			0.001
Negative	1.00	-	
Positive	1.82	1.29-2.55	
Surgery			0.617
Elective	1.00	-	
Urgent	0.82	0.38-1.76	
Adjuvant chemotherapy			0.372
Yes	1.00	-	
No	1.20	0.80-1.78	

CI: Confidence interval, Ca 19-9: Carbohydrate antigen 19-9

Conclusion

Preoperative serum CEA and CA 19-9 have prognostic importance, independent of clinico-pathological factors, in colorectal cancer patients with no distant metastasis and who did not receive neoadjuvant therapy. These tumor markers can be used to estimate prognosis and schedule adjuvant therapies for the colorectal cancer patients at high risk.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2840, date: 21.05.2021). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.C.T., N.D., Z.C.Ç., Concept: D.C.T., N.D., Design: D.C.T., N.D., Data Collection or Processing: D.C.T., N.D., Z.C.Ç., Analysis or Interpretation: D.C.T., N.D., Z.C.Ç., Literature Search: D.C.T., N.D., Z.C.Ç., Writing: D.C.T., N.D.

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RESEARCH ARTICLE

The Role of Basic Laboratory Parameters in Diagnosing Acute Appendicitis and Determining Disease Severity in the Elderly

Mustafa Yeni[1], Rıfat Peksöz[2]

[1]Erzurum Regional Training and Research Hospital, Clinic of General Surgery, Erzurum, Turkey
2Atatürk University Faculty of Medicine, Department of General Surgery, Erzurum, Turkey

ABSTRACT

Aim: Acute appendicitis (AA) is the most common cause of acute abdomen in elderly patients. The aim was to investigate the role of basic laboratory parameters in diagnosing AA and determining disease severity.

Method: Elderly patients aged over 65 years who underwent appendectomy were included. The patients were divided into groups according to the severity of AA: group 1 (negative appendectomy) and group 2 (AA). Group 2 was sub-divided into group 2a: uncomplicated appendicitis and group 2b: complicated appendicitis. Differences in basic laboratory parameters between the groups were evaluated statistically.

Results: One hundred and forty three elderly patients were examined. Sixty (41.95%) were male and the mean age of the whole cohort was 69.69±6.34 years (range: 65-104 years). Patient numbers in the groups were: group 1 (n=15) (10.5%); group 2a (n=79) (55.2%) and group 2b n=49 (34.3%). As the time of admission to the hospital increases, the severity of the disease increases (p<0.001). Group 2b had higher length of stay (p=0.007) and complication rates (p=0.042). When comparing group 1 with group 2, the most sensitive test (88%) was mean platelet volume, while the most specific test was bilirubin (85%). For distinguishing group 2a and group 2b, the most sensitive test (72%) was C-reactive protein (CRP) while the most specific test (82%) was platelet to lymphocyte ratio (PLR).

Conclusion: Preoperative laboratory parameters can be used as biomarkers to aid AA diagnosis in the elderly. Neutrophil to lymphocyte ration, PLR, red cell distribution width, CRP, and direct and total bilirubin levels may help identify complications in appendicitis.

Keywords: Geriatric patients, acute appendicitis, morbidity, laboratory parameters

Introduction

One of the most common causes of acute abdomen, acute appendicitis (AA), is caused by inflammation of the appendix. It is the most common condition that requires emergency surgery and has an incidence of about 7-10% throughout life.[1,2] While generally thought of as a condition affecting young people, the incidence of AA has been increasing in the elderly with increased life expectancy.[3] Abdominal pain constitutes the most common complaint for geriatric patients who present to the emergency department, with nearly 20% suffering from AA. In geriatric patients, emergency appendectomy is the third most common reason for abdominal surgery.[4,5]

The diagnosis of AA includes the use of anamnesis, physical examination, laboratory tests, and radiologic methods.[6] Classical appendicitis findings, such as right lower abdominal pain and tenderness, leukocytosis, and fever, are seen in only 26% of elderly patients.[2,7] Thus, it is difficult to diagnose AA in the elderly population. Geriatric patients undergo a number of physiological changes and in this patient group, clinical symptoms and signs are also weaker and atypical. Patients tend to present late to the emergency department, leading to delayed diagnosis and treatment. Elderly patients have a worse prognosis and higher complication rates compared to young patients.[2,3,8]

Moreover, elderly patients are likely to have more comorbid diseases, so that morbidity and mortality rates are also

Address for Correspondence: Rıfat Peksöz MD,
Atatürk University Faculty of Medicine, Department of General Surgery, Erzurum, Turkey
E-mail: rifat-peksoz@hotmail.com **ORCID ID:** orcid.org/0000-0003-4658-5254
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increased. Hence, early diagnosis and appropriate surgical intervention are vital for elderly patients.[8,9] Due to the greater unreliability of classical symptoms and findings, a hesitation in using advanced imaging methods for initial diagnosis, and the potential difficulty in accessing more informative imaging techniques particularly in rural regions, basic laboratory tests gain greater importance. These tests are simple, inexpensive, and easily accessible in almost all health institutions, providing information on biomarkers with an acceptable diagnostic value.[10] Although studies about this topic have increased recently, there is limited research on the diagnostic efficiency of laboratory parameters in geriatric AA.[1,9]

The aim of this study was to analyze elderly patients operated with the diagnosis of AA and to investigate the predictive value of basic preoperative laboratory parameters in diagnosing AA and determining disease severity.

Materials and Methods

Approval was obtained from the Ethics Committee of Erzurum Regional Training and Research Hospital (approval number: 2020/13-146). Between January 2015 and August 2020 a total of 3,856 adult patients aged over 18 years were operated for the diagnosis of AA. The clinical, demographic and laboratory data of patients aged over 65 years were extracted and retrospectively analyzed. Exclusion criteria were patients in whom blood parameters were affected by causes other than AA, including blood results not available, malignancy, multiple comorbid diseases and other surgical pathology.

Data items included patient sex, age, time from symptom onset to admission, comorbidities, preoperative blood results, preoperative images, type of anesthesia, type of surgery, length of hospital stay, complication status, and histopathological results for appendectomy materials which were obtained from the electronic hospital records. The patients were divided into two main groups (group 1 and group 2) based on the results of their appendix histopathology. Then group 2 was further divided into two subgroups (group 2a, b).

- **Group 1** (normal appendix, lymphoid hyperplasia, obliterative appendix) were evaluated as normal (negative appendectomy),
- **Group 2** (AA),
- **Group 2a** (phlegmonous appendicitis, catarrhal appendicitis, and suppurative appendicitis) were evaluated as non-complicated appendicitis.
- **Group 2b** (gangrenous appendicitis, perforated appendicitis, and plastron appendicitis) were evaluated as complicated appendicitis.

Statistical Analysis

Descriptive data were expressed as mean and standard deviation for the numerical variables and as number and percentages for the categorical variables. The distribution of the data was examined with histogram graphics. After examining the homogenity of the data, analysis was performed with One-Way ANOVA, Kruskal-Wallis tests. Tukey and Tamhane tests were used for post-hoc analysis. Chi-square test was used to compare two groups of categorical data. Receiver operating characteristic (ROC) curves were created to measure the ability of laboratory values to distinguish AA and complicated appendicitis status. The area under the curve (AUC) and cut-off value of each measurement were determined. Specificity, sensitivity and positive likely-hood ratio (LR+) cut-off values were calculated and evaluated together. A $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 23.0 (IBM Inc., Armonk, NY, USA).

Receiver Operating Characteristic Curve Analysis

ROC curves were created to examine the differentiation of laboratory parameters for pathology positivity. AUC and cut-off values of some parameters were determined and their sensitivity, specificity, and LR+ cut-off points were calculated. ROC analyses was carried out both for patients diagnosed with AA and those with normal appendix. Also, separate ROC analyses were performed for complicated and uncomplicated patients.

Results

Of the 160 elderly patients identified, 17 (10.65%) whose blood parameters were affected by causes other than AA were excluded: blood parameters not available (n=3); malignant pathology (n=3); patients with multiple comorbid diseases (n=5); and six with other surgical pathologies. Thus the final study included 143 (89.4%) of the patients aged over 65 years who had presented over a period of six years. Of the patients, 60 (41.95%) were male and 83 (58.05%) were female, with a mean age of 69.69±6.34 years (range: 65-104 years). More than two-thirds (69.9%) had a comorbid disease. The sample was divided into three groups. These were group 1 - negative appendectomy (n=15, 10.49%); group 2a - uncomplicated appendicitis (n=79, 55.24%); and group 2b - complicated appendicitis (n=49, 34.27%) (Table 1). There was no significant difference between the groups in terms of age, sex, or comorbid disease.

Time from the onset of abdominal pain to hospital admission was 1.67±1.04 days in group 1, 1.59±0.65 days in group 2a, and 3.33±1.28 days in group 2b, with a significant difference between the groups ($p<0.001$) (Table 1).

Table 1. Demographic and clinical features of the patients

Parameters	Group 1 (n=15)	Group 2a (n=79)	Group 2b (n=49)	p
Gender				0.110
- Male	8	27	25	-
- Female	7	52	24	-
Age (mean ± SD)	70.53±6.17	69.15±6.47	70.31±6.22	0.278
Comorbid disease				**0.518**
- Present	9	58	33	-
- Absent	6	21	16	-
Pre-hospital delay (day)	1.67±1.04	1.59±0.65	3.33±1.28	<0.001*
Length of stay (day)	3.13±2.56	3.34±2.01	6.59±5.93	0.007*
Postoperative complication				0.042
- Present	3	24	24	-
- Absent	12	55	25	-

*: Group 2b was significantly loner than other groups (group 1, group 2a) in post-hoc analysis. SD: Standard deviation

Table 2. The ROC analysis for group 1 and group 2

Parameters	Cut-off value	AUC (p)	Sensitivity (%)	Specificity (%)	LR+
CRP	1.23	0.668 (0.143)	77	57	1.81
WBC	8.97	0.722 (0.052)	85	57	1.98
Neutrophil	6.36	0.743 (0.033)	86	71	3.02
NLR	3.28	0.700 (0.080)	83	71	2.93
MPV	6.905	0.624 (0.277)	88	42	1.55
Total bilirubin	0.695	0.718 (0.057)	61	85	4.32
Direct bilirubin	0.235	0.716 (0.061)	65	85	4.58

AUC: Area under curve, CRP: C-reactive protein, WBC: White blood cell, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volüme, LR: Likelihood ratio, ROC: Receiver operating characteristic

Regarding advanced imaging methods, 77.6% of the patients were examined by ultrasonography (USG) and 69.9% by abdominal computed tomography (CT). CT was found to have a sensitivity of 77.7% and a specificity of 70%, while USG was found to have a sensitivity of 74.2% and a specificity of 18.2%.

The patients were evaluated for total bilirubin (TB), direct bilirubin (DB), C-reactive protein (CRP) and 11 hemogram subparameters. Only hemogram subparameters with a high diagnostic value were further analyzed. There were significant differences between the groups in terms of neutrophil, neutrophil to lymphocyte ratio (NLR), CRP, TB, and DB levels. White blood cell count (WBC), neutrophil count, NLR, mean platelet volume (MPV), TB, DB, and CRP levels were found to be markers with high diagnostic value for AA (Table 2, Figure 1).

NLR, Platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW), CRP, TB, and DB levels were found to be markers with high diagnostic value for differentiating between complicated and uncomplicated appendicitis (Table 3, Figure 2).

Of the patients, 2.8% were operated under spinal anesthesia and 97.2% under general anesthesia. One hundred and two of the operations (71.3%) were open (48.3% Mc Burney, 17.5% paramedian, 5.6% midline) and 42 (28.7%) were laparoscopic.

Mean length of hospital stay was 3.13±2.56 days in group 1, 3.34±2.01 days in group 2a, and 6.59±5.93 days in group 2b, with a significant difference between the groups ($p<0.05$) (Table 1). Postoperative complication rate was 35.7%. Complication rates in the groups were 20% in group 1, 30.4% in group 2a, and 48.9% in group 2b, with significant differences ($p<0.05$) (Table 1). No mortality was observed.

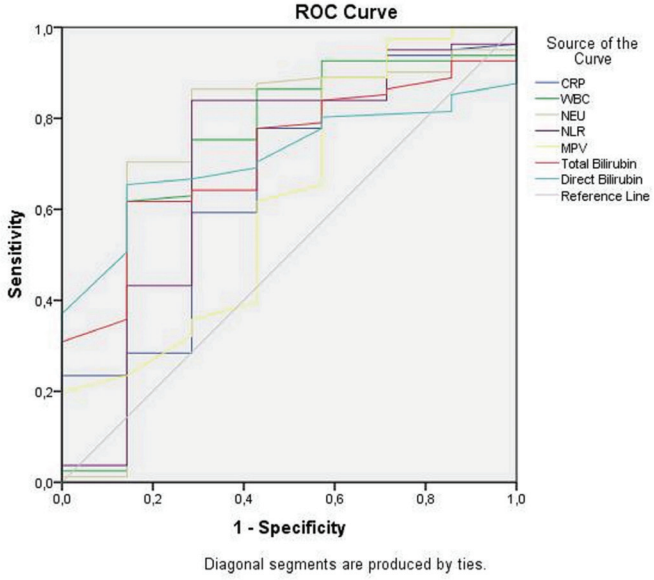

Figure 1. ROC analysis for normal appendix (group 1) and acute appendicitis (group 2)
ROC: Receiver operating characteristic, CRP: C-reactive protein, WBC: White blood cell count, NEU: Neutrophil, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume

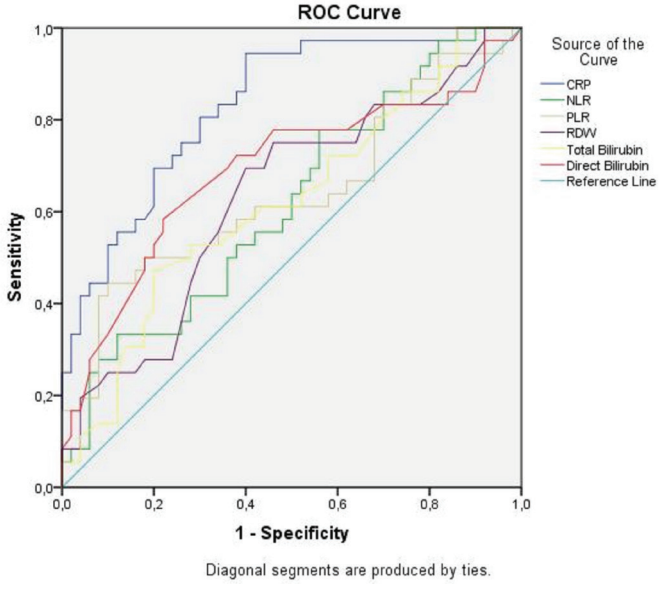

Figure 2. ROC analysis for uncomplicated and complicated appendicitis
ROC: Receiver operating characteristic, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width

Discussion

In elderly individuals, rebound sensitivity decreases due to atrophy of the abdominal muscles, along with increased pain threshold, due to conduction differences in the nervous system and certain changes in the detection and limitation of pain. Hence, the clinical picture tends to be atypical and less clear in the elderly.[11] The time from the onset of symptoms to hospital admission and surgery has also been reported to be higher in the elderly.[12,13] Delayed admission increases the risk of perforation of the appendix.

Perforation associated with AA is observed in 18-34% of the general population.[6] However, this rate increases up to 41-56.3% in geriatric patients.[2,3,9] Male sex, anorexia, fever ≥38 °C, and duration of pain before admission are risk factors for perforated appendicitis. The most important factor remains delayed admission to hospital.[3,6] Male patients are observed to be more reluctant for admission to hospital and therefore present later.[14] In the current study, the rate of complicated appendicitis was 34.27%, somewhat below the reported rates. Time to hospital admission remains the most important factor for perforation, with a mean of 3.3 days in the complicated appendicitis group. Gender played no role as a factor in the occurrence of complicated appendicitis.

Comorbid diseases tend to increase morbidity and mortality, although they have not been identified as a significant factor for perforation.[3] For elderly patients, the rate of comorbid disease is 43-60.7%.[3,6] The rate of comorbid disease in our sample was higher than the reports in the literature (69.9%), with no significant difference between the groups, suggesting that it was not a risk factor for complicated appendicitis.

There is single definitive clinical symptom, finding, laboratory test, or radiological method to diagnose AA. This proves even more complicated in geriatric patients.[15] Thus, studies have focused on easily accessible and cost-efficient markers with a high diagnostic value.[1,9] Surgeons have been interested in simple laboratory markers that can help diagnose AA and determine perforation status.[16]

Complete blood count (CBC) is an ideal marker for these properties.[10] WBC count is the most commonly used laboratory parameter for diagnosing AA.[16] One study reported that WBC had a cut-off value of 10.6, AUC: 0.66, a sensitivity of 71.2%, and a specificity of 68.2% for determining perforation in the elderly.[9] Here, WBC count

Table 3. The ROC analysis for group 2a and group 2b

Parameters	Cut-off value	AUC (p)	Sensitivity (%)	Specificity (%)	LR+
CRP	5.11	0.833 (<0.001)	72	76	3.00
NLR	5.10	0.617 (0.065)	72	44	1.28
PLR	190.62	0.641 (0.027)	50	82	2.77
RDW	13.15	0.634 (0.035)	69	60	1.73
Total bilirubin	0.87	0.621 (0.056)	52	72	1.88
Direct bilirubin	0.30	0.690 (0.003)	58	78	2.65

AUC: Area under curve, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width, LR: Likelihood ratio, ROC: Receiver operating characteristic

was found to be a marker with high sensitivity and low specificity for diagnosing AA (cut-off value: 8.97, AUC: 0.72, sensitivity 85%, specificity 57%). However, it was not found to be a biomarker with high diagnostic value for determining complicated appendicitis.

NLR has been used as a biomarker for morbidity, mortality, and survival in many disorders, including inflammatory and neoplastic diseases.[16-18] NLR has been demonstrated to be superior to other traditional infection markers, including WBC, neutrophil counts, and CRP, for determining AA severity.[9,19] Here, neutrophil count and NLR were determined to be biomarkers for diagnosing AA with similar diagnostic values, while only NLR was a significant biomarker for determining complicated appendicitis.

MPV is one of the routine CBC tests.[20] However, there are conflicting findings in the literature, some showing increased MPV in AA patients,[21] while others showing decreased MPV.[20,22] Similar to the literature, we obtained conflicting results on MPV. MPV was highest in the complicated appendicitis group. While MPV was expected to be the lowest in the negative appendectomy group, it was the lowest in the uncomplicated appendicitis group. Despite the conflicting findings, MPV was determined as a marker with the highest diagnostic value for appendicitis.

PLR is another inflammatory marker that can easily be obtained during simple hemogram tests. PLR levels can be used for diagnosing appendicitis.[23] Yıldırım et al.[24] found PLR to be a useful marker for differentiating between complicated and uncomplicated appendicitis. Our findings showed that PLR was an important marker for differentiating between complicated and uncomplicated appendicitis. Although it was found to have the lowest sensitivity, it had the highest specificity (cut-off value: 190.6, AUC: 0.64, sensitivity 50%, specificity 82%).

RDW is a subparameter that relates to the distribution of the volume of circulating erythrocytes.[22] RDW has been shown to increase significantly in complicated appendicitis, but its diagnostic values have not been specified.[25] Comparing those with appendicitis and those without, no significant difference has been found.[22,25] Similarly, in the current study, RDW was found to be a marker for differentiating between complicated and uncomplicated appendicitis with a high diagnostic value, but not a significant marker for diagnosing AA (cut-off value: 13.15, AUC: 0.63, sensitivity 69%, specificity 60%).

It is well known that bilirubin levels increase in AA.[26] Direct and TB levels increase in acute and complex appendicitis and are used as a diagnostic marker.[27] Despite few studies, research has shown hyperbilirubinemia to be a biomarker for predicting perforation in geriatric patients.[9] Here, both DB and TB levels were found to be important biomarkers for diagnosing AA and predicting complications. Also, they were the markers with the highest specificity for predicting AA status.

The most frequently used serological indicators for diagnosing AA are leukocyte counts and CRP levels. CRP is an acute-phase reactant that is synthesized in the liver in response to infection or inflammation[28]. Jung et al.[9] found CRP as a marker for determining perforation in geriatric patients with a high diagnostic value and a cut-off value of 2.09/mg/dL. Another study highlighted the high diagnostic value of CRP for determining perforation in elderly patients (AUC: 0.811 with a cut-off value of 10.19 mg/dL).[29] The most recent SIFIPAC/WSES/SICG/SIMEU guidelines recommend

the use of CRP and leukocyte levels together for diagnosing AA in the elderly.[30]

In determining perforation, CRP and TB are noted to be significant markers with high diagnostic value when used together.[31] In the present study, CRP was found to be an important marker for diagnosing AA and determining complication status. Again, similar to the findings in the literature, TB and CRP were found to increase in parallel to each other. To the best of our knowledge, this is the first study in the literature to demonstrate the diagnostic utility of MPV, PLR, and RDW for determining the severity of AA in the elderly. We suggest that these biomarkers may be useful as new diagnostic markers of AA for geriatric age patients.

USG and CT are some of the basic imaging modalities that are most commonly used for diagnosing AA and determining complications. CT has been reported to have a low sensitivity for detecting perforated appendicitis without abscess or phlegm.[32] In the current study, we found CT to have a sensitivity of 77.7% and a specificity of 70%, while USG had a sensitivity of 74.2% and a particularly low specificity of 18.2%.

Omari et al.[3] found a mean length of hospital stay of 4.2 days for uncomplicated appendicitis patients and 7.4 days for complicated appendicitis patients. In our patients, as expected, the longest length of stay was observed in the complicated appendicitis group, while the shortest length of stay was observed in the negative appendectomy group. With a descending order, length of hospital stay was 6.59, 3.34, and 3.13 days in our groups.

Prognosis for uncomplicated appendicitis is similar between young and elderly patients. However, in the case of perforation, morbidity and mortality increase dramatically in the elderly.[8,29] Elderly appendicitis patients have a postoperative complication rate of 21-60% and a mortality rate of 0.97-3%.[3,6,7] In our study, the rate of postoperative complications was 35.7%, with no mortality. The rate of complications was found to be higher in the perforated patient group. The low mortality and morbidity rates in our findings can be explained by the low number of perforated appendicitis cases.

Study Limitations

The major limitation of our study is that it was a retrospective study. Another limitation was a lack of analysis of symptoms and physical examination findings, which are crucial for diagnosing AA. Still, our research had certain strengths, including the high number of patients compared to most earlier studies, the analyses of many common biomarkers and obtaining new data, and providing more information by dividing the patients into three groups.

Conclusion

Elderly patients with abdominal pain present to hospitals later due to the lack of clinical clarity of their symptoms and signs. The high rates of comorbidities in the elderly also lead to more complicated appendicitis. This results in an increased rate of postoperative complications and longer hospital stay. The USG and CT modalities used for diagnosis have almost the same, or sometimes even lower sensitivity and specificity values compared to the laboratory parameters examined here. Preoperative WBC, neutrophil count, NLR, MPV, CRP, and direct and TB levels appear to have utility in the diagnosis of AA in elderly patients. Again, NLR, PLR, RDW, CRP, and direct and TB levels can be used to identify elderly patients with complications when AA has been diagnosed.

Ethics

Ethics Committee Approval: Ethics committee approval was received from the Erzurum Regional Training and Research Hospital Ethics Committee (approval number: 2020/13-146).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Y., R.P., Concept: M.Y., R.P., Design: M.Y., R.P., Data Collection or Processing: M.Y., R.P., Analysis or Interpretation: M.Y., R.P., Literature Search: M.Y., R.P., Writing: M.Y., R.P.

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

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RESEARCH ARTICLE

Comparison of Surgical Treatment with Crystallized Phenol Treatment in Recurrent Pilonidal Sinuses

Nizamettin Kutluer[1], Serhat Doğan[2], Bahadır Öndeş[2], Feyzi Kurt[3]

[1]Private Doğu Anadolu Hospital, Clinic of General Surgery, Elazığ, Turkey
[2]Malatya Turgut Özal University Faculty of Medicine, Department of General Surgery, Malatya, Turkey
[3]Adana Seyhan State Hospital, Clinic of General Surgery, Adana, Turkey

ABSTRACT

Aim: One of the most important complications of the treatment of pilonidal sinus disease (PSD) is recurrence. Despite all treatment modalities, there is still no method that promises zero recurrence rate. Additionally, there is no clear consensus about the treatment method in primary cases and uncertainty is even greater in the treatment of recurrent patients. The aim of this study was to compare the results of surgical treatment and crystallized phenol treatment in patients with recurrent PSD.

Method: This study included patients with recurrent PSD who underwent re-surgery or crystallized phenol application as secondary treatment in a general surgery clinic. Both methods were compared in terms of patients' gender, age, complaints and duration of complaints in the preoperative period and wound infection, length of hospital stay, recurrence and time to return to work in the postoperative period.

Results: Of the total of 38 patients 31 (81.6%) were male. The mean age was 25.9±4.51 years (range: 19-36 years). The site of recurrence site was at the incision line in 29 (76.3%) and lateral in 9 (23.7%). Twenty-one (53.3%) underwent surgery and 17 (44.7%) were treated with crystallized phenol application. The mean treatment-recovery time was 40.7±28.45 days in the phenol group, while it was 20.33±24.05 days in the surgery group. Recurrence was observed in 3 (17.6%) patients in the phenol group and 1 (4.76%) patient in the surgery group. There was a statistically significant difference in these two parameters.

Conclusion: While the surgical method was more effective in recurrent PSD, crystallized phenol is a less invasive method. It does not require hospitalization, can be applied under local anesthesia in outpatient settings, and can be repeated for a few sessions. Crystallized phenol is a preferred treatment method for recurrent PSD only in suitable cases.

Keywords: Recurrent pilonidal sinus, crystallized phenol, surgery

Introduction

Although pilonidal sinus disease (PSD) was described for the first time in 1833 by Mayo[1] as a sinus containing hair in the sacrococcygeal region in a female patient, it mostly affects young adult males.[1-3] The disease has remained controversial since it was first described. Many papers have reported on its etiology and treatment. However, there has been a loss of interest in the subject of etiology and no consensus has emerged for a definitive treatment. Almost all surgeons now agree that the disease is acquired[4] but despite the dozens of surgical treatment methods applied and their modified versions, non-surgical treatment of the disease has also remained on the agenda. In particular, the application of phenol has shown promise and found many advocates. Still, the ideal treatment has not been clarified, although almost two centuries have passed since its description.[5,6]

Recurrence is one of the most important complications of the treatment of this disease. Despite all treatment modalities, there is still no method that promises zero recurrence rate.[7] Additionally, there is no clear consensus about the treatment method in primary cases and uncertainty is even greater in the treatment of recurrent patients. There are opinions recommending re-surgery as well as authors suggesting conservative methods.[8]

The aim of this study was to compare the results of surgical treatment and crystallized phenol treatment in patients with recurrent PSD.

Address for Correspondence: Serhat Doğan MD,
Malatya Turgut Özal University Faculty of Medicine, Department of General Surgery, Malatya, Turkey
E-mail: drserhatdogan@gmail.com **ORCID ID:** orcid.org/0000-0002-3288-2963
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Materials and Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Adana City Training and Research Hospital Clinical Research Ethics Committee (approval number: 25.03.2020/53/776).

The data of the patients who were treated with a diagnosis of recurrent sacrococcygeal pilonidal sinus between January 2015 and January 2020 were obtained from computer records and patient registry and analyzed retrospectively. In order to ensure recurrence status, patients who had previously undergone surgical treatment for pilonidal sinus, had healed post-operative wounds and had a disease-free period of at least 3 months were included in the study.

Those with second recurrence, those with incomplete data and those presenting with abscess were excluded from the study. In addition, those who did not come to their routine follow-up visits and/or could not be reached were not included in the study.

In the treatment of recurrence, the decision to perform re-surgery or employ the conservative method was left to the surgeon's preference. The Karydakis[4] flap was performed on the patients as surgical treatment (Figure 1, 2). Written informed consent was obtained from all patients prior to surgery. Intestinal cleansing was performed by administering an enema 2 hours before surgery. Surgery was performed under spinal anesthesia and 1 g cefazolin sodium was administered intravenously as a prophylactic antibiotic 30 minutes before the induction of anesthesia. Vacuum drains were placed in all patients and removed when drainage fell below 20 mL post-operatively. Patients were checked every other day in the general surgery outpatient clinic after discharge. Sutures were removed on the tenth post-operative day in patients who did not develop any complications, and those with wound infection were called for daily follow-up visits and dressed until their infection regressed.

Crystallized Phenol Application

Before the procedure, the patients were advised to ensure their sacrococcygeal hair removal and hygiene. By creating a sterile environment in the outpatient settings, the sinus tract was cleaned from the sinus openings and curetted following local anesthesia. In patients with a small sinus cavity where the mosquito clamp (BH-109 Aesculap®, Aescuplap Werke AG, Tutlingen, Germany) cannot enter, the sinus opening was enlarged enough to allow the entry. The same procedure was applied separately for each sinus opening in patients with more than one sinus opening. While starting

Figure 1. Photograph of the patient's recurrence after sinus excision and primary closure

Figure 2. Photograph of the same patient after karydakis operation

the procedure, the surrounding skin tissue was protected with an antibiotic cream (Furacin® Eczacıbaşı İla. San. ve Tic. A.Ş., İstanbul, Turkey) against the caustic and irritant effects of undiluted, pure crystallized phenol. Debris and hairs in the sinus were completely removed. Crystallized phenol (BotaFarma İlaç Medikal Itriyat Kimya San. Tic. Ltd. Sti., Ankara, Turkey) was applied into the pilonidal sinus pouch with the same mosquito clamp. The irritant effect of crystallized phenol, which turned into liquid form at body temperature, was utilized. Approximately 3-5 grams of crystallized phenol was applied to each sinus opening[6,9]. The patients were advised to return to work rather than to rest. They were also advised to bathe whenever they wanted after a single dressing 24 hours later. The patients were followed-up and examined at three-week intervals. At the end of the 3-week follow-up, those with completely closed sinuses and no leakage were considered to be cured, while crystallized phenol session was repeated in the same way if the openings were not completely closed and leakage continued. Patients were stratified into those having crystallized phenol (group 1) or those undergoing surgery (group 2).

A visual analog scale (VAS) was used to evaluate the general health status of the patients, and the patients were asked to evaluate their general health on a vertical, unnumbered scale. Afterwards, their evaluations were graded with the help of a scale divided into 1/10 divisions of the same length as the scale: "0: no pain and 10: unbearable pain." This information was obtained from the "Satisfaction" section of the patient files and from outpatient records.

Both methods were compared in terms of patient gender, age, complaints and duration of complaints in the preoperative period and wound infection, length of hospital stay, recurrence and time to return to work in the post-operative period.

Recurrence time was accepted as the first time of admission to the hospital for similar reasons after the first surgery of the patients. Regarding treatment-recovery time, the time until the symptoms ended and the sinus openings were closed was calculated in the phenol group, while the time from the date of surgery to the time when the sutures were removed and the wound healed was calculated in the surgery group. The computer record of the last admission to the hospital for post-operative examination was used to calculate the follow-up period. The time between the procedure and last admission was calculated.

Complications included skin burn associated with phenol treatment, seroma and wound dehiscence associated with surgery, and abscess associated with either method. Recurrent patients were determined by the recurrence of their complaints after a disease-free period of at least 3 months.

Statistical Analysis

Statistical Package for Social Science for Windows, version 24.0, was used for statistical comparison (IBM Inc., Armonk, NY, USA). Percentage and frequency analysis were used for the variables of treatment method, gender, recurrence site, presence of complications, and presence of recurrence, and mean and standard deviation values were calculated for the variables of age, recurrence time, treatment-recovery time and follow-up period.

The Independent samples t-test was used to examine the differences in age, recurrence time, treatment-recovery time and follow-up period values of the patients in terms of treatment method applied. In addition, the chi-square independence analysis was applied to examine whether treatment methods were correlated with gender, recurrence site, presence of complications and presence of recurrence. The results were analyzed at the 99% ($p<0.01$) and 95% ($p<0.05$) confidence levels.

Results

A total of 38 patients were included in the study. In the whole cohort, the mean age was 25.9±4.51 years (range: 19-36 years) and 31 (81.6%) were male and 7 (18.4%) were female. The recurrence site was at the incision line in 29 (76.3%) patients and lateral in 9 (23.7%) patients. Twenty-one (53.3%) underwent surgery and were included in group 2 and 17 (44.7%) were treated with crystallized phenol and constituted group 1. There was no statistically significant difference between the two groups in terms of gender, age and recurrence site.

The mean age was 26.05±4.46 years in group 1 and 25.61±4.65 years in group 2. The mean recurrence time after the first surgery was 18.76±11.65 months in group 1 and 17.38±8.24 months in group 2. There was no statistically significant difference between the groups in terms of mean age and recurrence time after the first surgery. However, when the groups were evaluated in terms of treatment applied, the mean treatment-recovery time was 40.7±28.45 days in group 1, while it was 15.61±12.94 days in the surgery group. The mean treatment-recovery time was significantly shorter in the surgery group, which was statistically significant ($p<0.05$). Both groups had similar follow-up periods, and there was no statistically significant difference in terms of follow-up period (Table 1).

In group 1, 3 (17.7%) patients developed complications which were skin burn (n=2) (11.8%) and abscess (n=1) (5.9%). In group 2 4 (19.04%) patients developed complications, including abscess (n=2) (9.5%), seroma (n=2) (9.5%) and wound dehiscence (n=1) (4.76%). Recurrence occurred in 3 (17.6%) in group 1 and one (4.76%) patient in group 2, thus

significantly fewer patients undergoing surgical treatment experienced recurrence ($p<0.05$) (Table 1).

Discussion

There are many different methods employed in the treatment of PSD. Surgical excision of the sinus, primary closure, open healing and various flap techniques are the leading methods.[10] Some less invasive treatments have recently been used with crystallized phenol being foremost.[11] The main problem in surgical and less invasive methods is the frequent recurrence of this disease and aesthetic problems that may occur.[12] Although some characteristics of the patient, including gender, obesity, and disease complexity seem to have an effect in the development of recurrence, there are studies indicating that the main problem is due to the treatment applied.[13,14] In the current study, both groups showed similar characteristics. Therefore, there was no statistically significant difference between the two groups in terms of recurrence of the disease.

The main problem in the disease is recurrence and some aesthetic problems that occur after repeated surgical interventions during the treatment of these recurrences.[15] Although these surgical procedures have a high success rate in treating recurrent disease, some more non-invasive procedures are required. Methods such as laser hair removal and crystallized phenol are the leading procedures.[16]

Aygen et al.[8] reported the study with the longest follow-up period of 54.4 months with 36 recurrent pilonidal sinus cases previously undergoing surgical or conservative treatment. These authors concluded that crystallized phenol could be applied in recurrent cases, with a high success rate (91.7%). In our study, the success rate with crystallized phenol was significantly lower than in the surgery group and our success rate was lower compared to other published studies. These differences are probably due to the small sample sizes in this and the study of Aygen et al.[8] (Table 2).

There is a paucity of published evidence about how many sessions and how long crystallized phenol can be applied. In our clinic, a maximum of five sessions were applied at 21-day intervals. We believe that longer applications will considerably extend the treatment period. However, crystallized phenol may be preferred due to its advantages such as being a minimally invasive method, not requiring hospitalization, being applied with local anesthesia and more aesthetic wound healing.

Regarding complications, more minor and more tolerable problems for both the patient and surgeon may be encountered in the crystallized phenol method compared to surgical methods. Along with the side effects of local anesthesia, there are also complications specific to crystallized phenol application. These include mostly local side effects. Exfoliation occurs if the skin is not sufficiently protected during the application. In addition, infection and hematoma can be observed. The exfoliation rate was reported as 8.3% in the literature.[17] Infection and hematoma rates were reported as 8% and 4%, respectively.[18]

In our study, complications developed in three patients in the phenol group and four patients in the surgery group which was statistically similar. Problems such as abscess and wound dehiscence that develop in patients with PSD increase the rate of recurrence in later periods.[19] In our study, the complication rate in the surgery group was higher compared to the literature but this is due to seroma being included as a surgical complication, which was not consistently done in previous studies. Patients who were admitted to the outpatient clinic due to seroma and who underwent repeated aspiration were reasonably considered as experiencing a complication of surgery.

The follow-up period in both our study groups was just over 14 months, which was similar, but considerably shorter than that reported from some other studies. There are studies in the literature suggesting that the follow-up period should be 3 years.[20,21] Even considering only the results of our study, the patients were observed to develop recurrence within an average of 17-19 months after the first surgery. Therefore, our follow-up period is short, which constitutes the most important limitation of the study. It seems reasonable to assume that there would be changes in recurrence rates during longer follow-up periods.

It will not be surprising that the minimally invasive method will prevail when a surgical method and a minimally invasive method are evaluated in terms of VAS, and our study result supports this with VAS scores in group 1 being significantly lower than in the surgical group. Furthermore, studies have reported that phenol treatment improves the quality of life,[18] but we did not assess this aspect of treatment.

Conclusion

Different surgical flap techniques are still the most valid method in the treatment of recurrent PSD. However, the disease may recur after this. Therefore, crystallized phenol application may be one of the alternative treatment methods since crystallized phenol is cheap, can be applied in outpatient settings, is more aesthetically successful, can be applied multiple times and has advantages such as being a less invasive method. It can be applied safely in selected suitable patients and can be chosen as an alternative treatment to surgical methods. For example, crystallized phenol is unlikely to affect the patient in Figure 1. Therefore, crystallized phenol may be more effective when applied in

Table 1. Demographic data, treatment and follow-up periods of patients

		Group 1 (phenol) (n=17)	Group 2 (surgery) (n=21)	p
Age		26.05±4.46	25.61±4.65	0.77
Female/male		4/13	3/18	0.465
Recurrence time after the first surgery (months)		18.76±11.65	17.38±8.24	0.671
Procedure time (minute)		13.0±4.2	40.0±15.2	**0.018**
Total treatment time (days)		40.7±28.45	20.33±24.05	**0.022**
Length of hospital stay (days)		0.0	1.40±0.9	**<0.001**
VAS	VAS (12 hours)	1.8±1.4	4.2±1.1	**0.006**
	VAS (24 hours)	1.4±1.5	(3.4±2.4)	
	VAS (48 hours)	0.8±1.2	2.0±1.8	
Complication, n (%)		3 (17.7)	4 (19.04)	0.295
Follow-up period (months)		14.11±6.2	14.57±3.9	0.786
Recurrence, n (%)		3 (17.7)	1 (4.8)	**0.034**

VAS: Visual analog scale

Table 2. Studies in the literature on recurrent cases treated with crystalline phenol

	Age	Gender, (female/male)	Follow-up period (mean/month)	Complication	Single/multiple applications	Cure
Bayhan et al.[22]	25±4.7	5/21	12.1	4 wound infection	19/7	92.3%
Yüksel[23]	29.2±5.2	10/28	6	-	38/0	52.63%
Aygen et al.[8]	28.9	33/3	54.4	3 exfoliation		91.7%
Akici and Çilekar[24]	24.4±5.3	5/27	13.1	3 wound infection	22/10	90.7%
Kutluer et al.	26.05±4.46	4/13	14.1	2 exfoliation 1 abscess	10/7	82.4%

selected cases. However, based on the results of our study, surgical methods are superior in recurrent cases.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board of Adana City Training and Research Hospital Clinical Research Ethics Committee (approval number: 25.03.2020/53/776).

Informed Consent: The patients were informed of the procedures and consents were obtained prior to the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.K., S.D., F.K., B.Ö., Concept: N.K., S.D., F.K., B.Ö., Design: N.K., S.D., F.K., B.Ö., Data Collection or Processing: N.K., S.D., F.K., B.Ö., Analysis or Interpretation: N.K., S.D., F.K., B.Ö., Literature Search: N.K., S.D., F.K., B.Ö., Writing: N.K., S.D., F.K., B.Ö.

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RESEARCH ARTICLE

The One Hundred Most Cited Articles from Turkey about Pilonidal Disease: A Bibliometric Study

Alpaslan Şahin, Gürcan Şimşek

University of Health Sciences Turkey, Konya City Hospital, Clinic of Surgery, Konya, Turkey

ABSTRACT

Aim: To bibliometrically identify the top 100 most cited articles from Turkey concerning pilonidal disease (PD) and analyze their features.
Method: Databases searched in July 2021 included Web of Science (WoS) and Google Scholar to identify the most cited articles from studies about PD from Turkey. Each paper was evaluated in terms of publication year, number of authors, study group's institution, type and subject of the article, number of references, number of citations, and host journal.
Results: The mean number of citations of the first 100 articles was 37.5. The articles were published in 37 different journals. The leading journal was Diseases of the Colon and Rectum. There was no correlation between journal impact factors and citation counts. Ninety-three of the articles were clinical trials. There was no correlation between the article type and the number of citations. The most frequently discussed topic was flap repairs, with 51 articles. In the last decade there was an increase in the number of articles concerning the application of phenol. The most productive decade was 2010-2019, with 51 articles. While Gülhane Military Medical Academy had the highest number of articles and total citations, Harran University Faculty of Medicine had the most cited article and the highest number of citations per article. In addition, 38 of the top 100 most cited papers in the WoS database were sent from Turkey.
Conclusion: Turkey leads the world literature in articles on the PD. Diseases of the Colon and Rectum is the leading journal for Turkish PD studies. While flap repairs are the most discussed topic, the number of publications on the application of Phenol has increased in the last ten years.
Keywords: Pilonidal disease, bibliometrics, citations, flap repair, phenol application

Introduction

Citation is a reference to another article, and although it is not a stand-alone criterion, it gives a clue about the quality of an article, its contribution to science and the academic effectiveness of the author.[1,2] The impact factor, which indicates the quality of medical journals, is calculated according to the citation analysis of that journal.

Science Citation Index Expanded calculates impact factors according to the citation count of more than 10,000 journals in different fields. With the global development of biomedical publishing, the number of publications from Turkey has increased significantly. Articles from Turkey on hydatid cyst, pilonidal disease (PD), breast diseases and inguinal hernia are highly cited in the field of general surgery.[1]

Although there are similar studies in the literature, there is no bibliometric study on PD. The aim of this study was to identify the most cited articles about PD from Turkey.

Materials and Methods

Database Search

In July 2021, a search was conducted on the Web of Science to identify the most cited articles amongst studies from Turkey about PD. The keywords "PD" and "pilonidal sinus" were added to the search line. These keywords were searched for in titles, abstracts and keywords. Retrieved articles which were not about PD, or books/book sections and congress presentations were excluded from the study.

Ethical Approval

All data in this study were obtained from public access sources. Therefore, ethical approval was not required. No contact was made with the authors or their institutions to collect further data for the purposes of this study.

Address for Correspondence: Alpaslan Şahin MD,
University of Health Sciences Turkey, Konya City Hospital, Clinic of Surgery, Konya, Turkey
E-mail: alpaslan.sahin@sbu.edu.tr **ORCID ID:** orcid.org/0000-0001-5707-1203
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Evaluation of Data

In this study, the Declaration of Helsinki developed by the World Medical Association was adhered to for medical research involving human material and data. The 100 most cited articles were listed according to the number of citations and their full texts were retrieved. Each article was evaluated in terms of the publication year, the number of authors, the type of article (prospective study, retrospective study, systematic review, meta-analysis, case report-series, survey studies, laboratory studies), the subject of article (primary closure, flap repairs, epidemiology, phenol application, other), the institution of the study group, the number of references, the number of WoS citations, the number of Google Scholar (GSch) citations, the journal name, the journal area (surgery, dermatology, other), the journal impact factor, and the country of the journal.

Statistical Analysis

SPSS, version 22.0 was used for statistical analysis of the data (IBM Corp, Armonk, NY, USA). Qualitative variables are presented as frequency, and quantitative variables as mean and standard deviation (SD). The differences between the mean values were determined using the One-Way ANOVA test. A correlation coefficient (r) was calculated using the Spearman correlation test to determine the relationship of the recorded parameters with the citation numbers of the articles. A $p<0.05$ was considered statistically significant.

Results

Of the top 100 most cited articles about PD in WoS, 38 were from Turkey. The top 100 most cited articles sent from Turkey are presented in Table 1. The total number of citations of the first 100 articles was 3,753 (range: 12-119) in WoS and 7,316 (range: 17-250) in GSch. While the mean ± SD number of citations was 37.53±24.5 in WoS, it was 73.16±50.72 in GSch. The number of citations, the number of authors, and the number of references by publication year were evaluated in three consecutive decades (Table 2). The articles on the list were published after 1995. The most recent article was published in 2017. The most articles were published in 2010 (13 articles). The most productive 10 years were 2010-2019 (51 articles). As was expected, the number of citations increased as the publication year got older ($p<0.001$, Table 2).

Fifty one articles on flap repairs were published. Especially in the last two decades, articles on flap repairs were prominent. Of the 13 publications on phenol application, 11 were published between 2010-2019. In addition, primary repair (14 articles), epidemiology of PD (13 articles), and others (9 articles) were other categories examined in the articles (Table 3).

Forty nine of the articles were prospective studies and 44 were retrospective studies. The number of clinical trials was significantly higher compared to other types of studies ($p<0.001$). The study type had no significant effect on the number of citations (Table 4). The first 100 articles were published by 43 different institutions. The list included 64 articles from 26 university hospitals, 32 articles from 13 training and research hospitals, 3 articles from 3 state hospitals, and 1 article from 1 private hospital. There were 32 articles from Ankara, 13 from İstanbul, 5 from Mersin, 5 from Elazığ, and 45 from other provinces. The institution that published the highest number of articles and had the highest total number of citations in the list was Gülhane Military Medical Academy. Harran University Faculty of Medicine had the most cited article and the highest number of citations per article (Table 5). When the citation numbers of university hospitals and training and research hospitals were compared, no significant difference was found.

The articles were published in 37 journals. Diseases of the Colon and Rectum was the leading journal on the list, publishing 22 articles (Table 6). Fifty nine of the articles were published in journals in the United States, 11 in the United Kingdom, 5 in Japan, 4 in India, 3 in Germany, and 18 in other countries. Of the journals on the list, 78 were surgical journals and 22 were journals in other fields (general medicine, dermatology, plastic surgery, and pediatrics) (Table 7). The number of citations for articles in surgical journals was significantly higher than journals for other specialities ($p=0.04$). There was no significant relationship between journal impact factors and citation counts ($r=0.134$, $p=0.18$ for WoS citations). The mean values of impact factors of dermatology and surgical journals were higher than for other speciality journals (3.94±1.2 and 3.26±1.4, $p=0.002$, respectively). The number of authors ranged from 1 to 9, with a mean of 5.02±1.7. There was no significant relationship between the number of authors and the number of citations ($r=-0.049$, $p=0.63$ for WoS citations).

Discussion

Although high citation counts do not measure the quality of an article by itself, it indicates that the article is of scientific interest and is being discussed.[1] The average number of citations of the last articles of a journal is an important criterion in determining the impact factor.[3] It is expected that the citation numbers of publications in journals with high impact factor are high. However, in our study, there was no significant correlation between the journal impact factor and the number of citations.

Even the best scientific articles need years to reach high numbers of citations.[1] A published article starts to get citations after 1-2 years and approaches the maximum

Table 1. Top 100 pilonidal disease articles

	References	WoS citations	GSch citations
1	Akinci OF, Bozer M, Uzunköy A, Düzgün ŞA, Coşkun A. Incidence and aetiological factors in pilonidal sinus among Turkish soldiers. Eur J Surg 1999;165(4):339-342. doi:10.1080/110241599750006875	119	250
2	Ertan T, Koc M, Gocmen E, Aslar AK, Keskek M, Kilic M. Does technique alter quality of life after pilonidal sinus surgery?. Am J Surg 2005;190(3):388-392. doi:10.1016/j.amjsurg.2004.08.068	105	207
3	Akinci OF, Coskun A, Uzunköy A. Simple and effective surgical treatment of pilonidal sinus: asymmetric excision and primary closure using suction drain and subcuticular skin closure. Dis Colon Rectum 2000;43(5):701-707. doi:10.1007/BF02235591	104	210
4	Akca T, Colak T, Ustunsoy B, Kanik A, Aydin S. Randomized clinical trial comparing primary closure with the Limberg flap in the treatment of primary sacrococcygeal pilonidal disease. Br J Surg 2005;92(9):1081-1084. doi:10.1002/bjs.5074	97	198
5	Mentes BB, Leventoglu S, Cihan A, Tatlicioglu E, Akin M, Oguz M. Modified Limberg transposition flap for sacrococcygeal pilonidal sinus. Surg Today 2004;34(5):419-423. doi:10.1007/s00595-003-2725-x	96	195
6	Urhan MK, Kücükel F, Topgul K, Ozer I, Sari S. Rhomboid excision and Limberg flap for managing pilonidal sinus: results of 102 cases. Dis Colon Rectum 2002;45(5):656-659. doi:10.1007/s10350-004-6263-4	91	186
7	Bozkurt MK, Tezel E. Management of pilonidal sinus with the Limberg flap. Dis Colon Rectum 1998;41(6):775-777. doi:10.1007/BF02236268	83	157
8	Topgül K, Ozdemir E, Kiliç K, Gökbayir H, Ferahköşe Z. Long-term results of limberg flap procedure for treatment of pilonidal sinus: a report of 200 cases. Dis Colon Rectum 2003;46(11):1545-1548. doi:10.1007/s10350-004-6811-y	76	143
9	Cubukçu A, Gönüllü NN, Paksoy M, Alponat A, Kuru M, Ozbay O. The role of obesity on the recurrence of pilonidal sinus disease in patients, who were treated by excision and Limberg flap transposition. Int J Colorectal Dis 2000;15(3):173-175. doi:10.1007/s003840000212	75	152
10	Eryilmaz R, Sahin M, Alimoglu O, Dasiran F. Surgical treatment of sacrococcygeal pilonidal sinus with the Limberg transposition flap. Surgery 2003;134(5):745-749. doi:10.1016/s0039-6060(03)00163-6	75	154
11	Mentes O, Bagci M, Bilgin T, Ozgul O, Ozdemir M. Limberg flap procedure for pilonidal sinus disease: results of 353 patients. Langenbecks Arch Surg 2008;393(2):185-189. doi:10.1007/s00423-007-0227-9	73	146
12	Erdem E, Sungurtekin U, Neşşar M. Are postoperative drains necessary with the Limberg flap for treatment of pilonidal sinus?. Dis Colon Rectum 1998;41(11):1427-1431. doi:10.1007/BF02237061	71	115
13	Can MF, Sevinc MM, Hancerliogullari O, Yilmaz M, Yagci G. Multicenter prospective randomized trial comparing modified Limberg flap transposition and Karydakis flap reconstruction in patients with sacrococcygeal pilonidal disease. Am J Surg 2010;200(3):318-327. doi:10.1016/j.amjsurg.2009.08.042	69	147
14	Gencosmanoglu R, Inceoglu R. Modified lay-open (incision, curettage, partial lateral wall excision and marsupialization) versus total excision with primary closure in the treatment of chronic sacrococcygeal pilonidal sinus: a prospective, randomized clinical trial with a complete two-year follow-up. Int J Colorectal Dis 2005;20(5):415-422. doi:10.1007/s00384-004-0710-5	68	129
15	Cihan A, Ucan BH, Comert M, Cesur A, Cakmak GK, Tascilar O. Superiority of asymmetric modified Limberg flap for surgical treatment of pilonidal disease. Dis Colon Rectum 2006;49(2):244-249. doi:10.1007/s10350-005-0253-z	68	112
16	Ersoy E, Devay AO, Aktimur R, Doganay B, Ozdoğan M, Gündoğdu RH. Comparison of the short-term results after Limberg and Karydakis procedures for pilonidal disease: randomized prospective analysis of 100 patients. Colorectal Dis 2009;11(7):705-710. doi:10.1111/j.1463-1318.2008.01646.x	68	137
17	Cihan A, Mentes BB, Tatlicioglu E, Ozmen S, Leventoglu S, Ucan BH. Modified Limberg flap reconstruction compares favourably with primary repair for pilonidal sinus surgery. ANZ J Surg 2004;74(4):238-242. doi:10.1111/j.1445-2197.2004.02951.x	63	109
18	Dogru O, Camci C, Aygen E, Girgin M, Topuz O. Pilonidal sinus treated with crystallized phenol: an eight-year experience. Dis Colon Rectum 2004;47(11):1934-1938. doi:10.1007/s10350-004-0720-y	60	133
19	Harlak A, Mentes O, Kilic S, Coskun K, Duman K, Yilmaz F. Sacrococcygeal pilonidal disease: analysis of previously proposed risk factors. Clinics (Sao Paulo) 2010;65(2):125-131. doi:10.1590/S1807-59322010000200002	60	161

20	Aydede H, Erhan Y, Sakarya A, Kumkumoglu Y. Comparison of three methods in surgical treatment of pilonidal disease. ANZ J Surg 2001;71(6):362-364.	56	111
21	Karakayali F, Karagulle E, Karabulut Z, Oksuz E, Moray G, Haberal M. Unroofing and marsupialization vs. rhomboid excision and Limberg flap in pilonidal disease: a prospective, randomized, clinical trial. Dis Colon Rectum 2009;52(3):496-502. doi:10.1007/DCR.0b013e31819a3ec0	53	92
22	Dilek ON, Bekereciodlu M. Role of simple V-Y advancement flap in the treatment of complicated pilonidal sinus. Eur J Surg 1998;164(12):961-964. doi:10.1080/11024159875000514 7	52	84
23	Akin M, Leventoglu S, Mentes BB, et al. Comparison of the classic Limberg flap and modified Limberg flap in the treatment of pilonidal sinus disease: a retrospective analysis of 416 patients. Surg Today 2010;40(8):757-762. doi:10.1007/s00595-008-4098-7	51	78
24	Gurer A, Gomceli I, Ozdogan M, Ozlem N, Sozen S, Aydin R. Is routine cavity drainage necessary in Karydakis flap operation? A prospective, randomized trial. Dis Colon Rectum 2005;48(9):1797-1799. doi:10.1007/s10350-005-0108-7	50	92
25	Ates M, Dirican A, Sarac M, Aslan A, Colak C. Short and long-term results of the Karydakis flap versus the Limberg flap for treating pilonidal sinus disease: a prospective randomized study. Am J Surg 2011;202(5):568-573. doi:10.1016/j.amjsurg.2010.10.021	49	96
26	Daphan C, Tekelioglu MH, Sayilgan C. Limberg flap repair for pilonidal sinus disease. Dis Colon Rectum 2004;47(2):233-237. doi:10.1007/s10350-003-0037-2	48	108
27	Mentes O, Bagci M, Bilgin T, Coskun I, Ozgul O, Ozdemir M. Management of pilonidal sinus disease with oblique excision and primary closure: results of 493 patients. Dis Colon Rectum 2006;49(1):104-108. doi:10.1007/s10350-005-0226-2	47	95
28	Oram Y, Kahraman F, Karincaoğlu Y, Koyuncu E. Evaluation of 60 patients with pilonidal sinus treated with laser epilation after surgery. Dermatol Surg 2010;36(1):88-91. doi:10.1111/j.1524-4725.2009.01387.x	46	79
29	Neşşar G, Kayaalp C, Seven C. Elliptical rotation flap for pilonidal sinus. Am J Surg 2004;187(2):300-303. doi:10.1016/j.amjsurg.2003.11.012	45	85
30	Arda IS, Güney LH, Sevmiş S, Hiçsönmez A. High body mass index as a possible risk factor for pilonidal sinus disease in adolescents. World J Surg 2005;29(4):469-471. doi:10.1007/s00268-004-7533-y	45	93
31	Akin M, Gokbayir H, Kilic K, Topgul K, Ozdemir E, Ferahkose Z. Rhomboid excision and Limberg flap for managing pilonidal sinus: long-term results in 411 patients. Colorectal Dis 2008;10(9):945-948. doi:10.1111/j.1463-1318.2008.01563.x	45	109
32	Bali İ, Aziret M, Sözen S, et al. Effectiveness of Limberg and Karydakis flap in recurrent pilonidal sinus disease. Clinics (Sao Paulo) 2015;70(5):350-355. doi:10.6061/clinics/2015(05)08	44	101
33	Kayaalp C, Aydin C. Review of phenol treatment in sacrococcygeal pilonidal disease. Tech Coloproctol 2009;13(3):189-193. doi:10.1007/s10151-009-0519-x	44	93
34	Nursal TZ, Ezer A, Calişkan K, Törer N, Belli S, Moray G. Prospective randomized controlled trial comparing V-Y advancement flap with primary suture methods in pilonidal disease. Am J Surg 2010;199(2):170-177. doi:10.1016/j.amjsurg.2008.12.030	41	84
35	Unalp HR, Derici H, Kamer E, Nazli O, Onal MA. Lower recurrence rate for Limberg vs. V-Y flap for pilonidal sinus. Dis Colon Rectum 2007;50(9):1436-1444. doi:10.1007/s10350-007-0276-8	40	69
36	Onder A, Girgin S, Kapan M, et al. Pilonidal sinus disease: risk factors for postoperative complications and recurrence. Int Surg 2012;97(3):224-229. doi:10.9738/CC86.1	39	87
37	Arslan K, Said Kokcam S, Koksal H, Turan E, Atay A, Dogru O. Which flap method should be preferred for the treatment of pilonidal sinus? A prospective randomized study. Tech Coloproctol 2014;18(1):29-37. doi:10.1007/s10151-013-0982-2	39	69
38	Guner A, Boz A, Ozkan OF, Ileli O, Kece C, Reis E. Limberg flap versus Bascom cleft lift techniques for sacrococcygeal pilonidal sinus: prospective, randomized trial. World J Surg 2013;37(9):2074-2080. doi:10.1007/s00268-013-2111-9	38	68
39	Can MF, Sevinc MM, Yilmaz M. Comparison of Karydakis flap reconstruction versus primary midline closure in sacrococcygeal pilonidal disease: results of 200 military service members. Surg Today 2009;39(7):580-586. doi:10.1007/s00595-008-3926-0	37	79
40	Berkem H, Topaloglu S, Ozel H, et al. V-Y advancement flap closures for complicated pilonidal sinus disease. Int J Colorectal Dis 2005;20(4):343-348. doi:10.1007/s00384-004-0699-9	36	68

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42	Kepenekci I, Demirkan A, Celasin H, Gecim IE. Unroofing and curettage for the treatment of acute and chronic pilonidal disease. World J Surg 2010;34(1):153-157. doi:10.1007/s00268-009-0245-6	34	70
43	Ozgültekin R, Ersan Y, Ozcan M, et al. Therapy of pilonidal sinus with the Limberg transposition flap. Chirurg 1995;66(3):192-195.	33	30
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48	Ersoy OF, Karaca S, Kayaoglu HA, Ozkan N, Celik A, Ozum T. Comparison of different surgical options in the treatment of pilonidal disease: retrospective analysis of 175 patients. Kaohsiung J Med Sci 2007;23(2):67-70. doi:10.1016/S1607-551X(09)70377-8	31	69
49	Cubukçu A, Carkman S, Gönüllü NN, Alponat A, Kayabaşi B, Eyüboğlu E. Lack of evidence that obesity is a cause of pilonidal sinus disease. Eur J Surg 2001;167(4):297-298. doi:10.1080/110241501300091525	31	57
50	Aygen E, Arslan K, Dogru O, Basbug M, Camci C. Crystallized phenol in nonoperative treatment of previously operated, recurrent pilonidal disease. Dis Colon Rectum 2010;53(6):932-935. doi:10.1007/DCR.0b013e3181d8283b	30	55
51	Dag A, Colak T, Turkmenoglu O, Sozutek A, Gundogdu R. Phenol procedure for pilonidal sinus disease and risk factors for treatment failure. Surgery 2012;151(1):113-117. doi:10.1016/j.surg.2011.07.015	30	70
52	Isik A, Eryılmaz R, Okan I, et al. The use of fibrin glue without surgery in the treatment of pilonidal sinus disease. Int J Clin Exp Med 2014;7(4):1047-1051. Published 2014 Apr 15.	29	57
53	Sevinç B, Karahan Ö, Okuş A, Ay S, Aksoy N, Şimşek G. Randomized prospective comparison of midline and off-midline closure techniques in pilonidal sinus surgery. Surgery 2016;159(3):749-754. doi:10.1016/j.surg.2015.09.024	28	43
54	Kaya B, Eris C, Atalay S, et al. Modified Limberg transposition flap in the treatment of pilonidal sinus disease. Tech Coloproctol 2012;16(1):55-59. doi:10.1007/s10151-011-0799-9	27	60
55	Akinci OF, Kurt M, Terzi A, Atak I, Subasi IE, Akbilgic O. Natal cleft deeper in patients with pilonidal sinus: implications for choice of surgical procedure. Dis Colon Rectum 2009;52(5):1000-1002. doi:10.1007/DCR.0b013e31819f6189	27	66
56	Girgin M, Kanat BH, Ayten R, et al. Minimally invasive treatment of pilonidal disease: crystallized phenol and laser depilation. Int Surg 2012;97(4):288-292. doi:10.9738/CC130.1	27	51
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59	Uysal AC, Alagöz MS, Unlü RE, Sensöz O. Hair dresser's syndrome: a case report of an interdigital pilonidal sinus and review of the literature. Dermatol Surg 2003;29(3):288-290. doi:10.1046/j.1524-4725.2003.29063.x	24	49
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61	Gecim IE, Goktug UU, Celasin H. Endoscopic Pilonidal Sinus Treatment Combined With Crystalized Phenol Application May Prevent Recurrence. Dis Colon Rectum 2017;60(4):405-407. doi:10.1097/DCR.0000000000000778	23	33
62	Tezel E, Bostanci H, Anadol AZ, Kurukahvecioglu O. Cleft lift procedure for sacrococcygeal pilonidal disease. Dis Colon Rectum 2009;52(1):135-139. doi:10.1007/DCR.0b013e31819734f8	23	38

63	Karaca T, Yoldaş O, Bilgin BÇ, Ozer S, Yoldaş S, Karaca NG. Comparison of short-term results of modified Karydakis flap and modified Limberg flap for pilonidal sinus surgery. Int J Surg 2012;10(10):601-606. doi:10.1016/j.ijsu.2012.10.001	23	46
64	Sungur N, Koçer U, Uysal A, Arslan C, Cöloglu H, Ulusoy G. V-Y rotation advancement fasciocutaneous flap for excisional defects of pilonidal sinus. Plast Reconstr Surg 2006;117(7):2448-2454. doi:10.1097/01.prs.0000219170.74059.94	23	34
65	Afşarlar CE, Yılmaz E, Karaman A, et al. Treatment of adolescent pilonidal disease with a new modification to the Limberg flap: symmetrically rotated rhomboid excision and lateralization of the Limberg flap technique. J Pediatr Surg 2013;48(8):1744-1749. doi:10.1016/j.jpedsurg.2013.01.029	22	32
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68	Olmez A, Kayaalp C, Aydin C. Treatment of pilonidal disease by combination of pit excision and phenol application. Tech Coloproctol 2013;17(2):201-206. doi:10.1007/s10151-012-0903-9	21	47
69	Duman K, Gırgın M, Harlak A. Prevalence of sacrococcygeal pilonidal disease in Turkey. Asian J Surg 2017;40(6):434-437. doi:10.1016/j.asjsur.2016.04.001	21	47
70	Yildiz T, Ilce Z, Kücük A. Modified Limberg flap technique in the treatment of pilonidal sinus disease in teenagers. J Pediatr Surg 2014;49(11):1610-1613. doi:10.1016/j.jpedsurg.2014.06.011	20	33
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73	Krand O, Yalt T, Berber I, Kara VM, Tellioglu G. Management of pilonidal sinus disease with oblique excision and bilateral gluteus maximus fascia advancing flap: result of 278 patients. Dis Colon Rectum 2009;52(6):1172-1177. doi:10.1007/DCR.0b013e31819ef582	19	25
74	Acartürk TO, Parsak CK, Sakman G, Demircan O. Superior gluteal artery perforator flap in the reconstruction of pilonidal sinus. J Plast Reconstr Aesthet Surg 2010;63(1):133-139. doi:10.1016/j.bjps.2008.07.017	19	38
75	Colak T, Turkmenoglu O, Dag A, Akca T, Aydin S. A randomized clinical study evaluating the need for drainage after Limberg flap for pilonidal sinus. J Surg Res 2010;158(1):127-131. doi:10.1016/j.jss.2008.11.005	19	35
76	Topuz O, Sözen S, Tükenmez M, Topuz S, Vurdem UE. Crystallized phenol treatment of pilonidal disease improves quality of life. Indian J Surg 2014;76(1):81-84. doi:10.1007/s12262-012-0610-9	18	29
77	Demircan F, Akbulut S, Yavuz R, Agtas H, Karabulut K, Yagmur Y. The effect of laser epilation on recurrence and satisfaction in patients with sacrococcygeal pilonidal disease: a prospective randomized controlled trial. Int J Clin Exp Med 2015;8(2):2929-2933. Published 2015 Feb 15.	18	32
78	Kirkil C, Böyük A, Bülbüller N, Aygen E, Karabulut K, Coşkun S. The effects of drainage on the rates of early wound complications and recurrences after Limberg flap reconstruction in patients with pilonidal disease. Tech Coloproctol 2011;15(4):425-429. doi:10.1007/s10151-011-0782-5	18	41
79	Eryilmaz R, Okan I, Coskun A, Bas G, Sahin M. Surgical treatment of complicated pilonidal sinus with a fasciocutaneous V-Y advancement flap. Dis Colon Rectum 2009;52(12):2036-2040. doi:10.1007/DCR.0b013e3181beb537	18	41
80	Karaca AS, Ali R, Capar M, Karaca S. Comparison of Limberg flap and excision and primary closure of pilonidal sinus disease, in terms of quality of life and complications. J Korean Surg Soc 2013;85(5):236-239. doi:10.4174/jkss.2013.85.5.236	17	33
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86	Yildiz MK, Ozkan E, Odabaşı HM, et al. Karydakis flap procedure in patients with sacrococcygeal pilonidal sinus disease: experience of a single centre in Istanbul. Scientific World Journal 2013;2013:807027. Published 2013 May 14. doi:10.1155/2013/807027	16	44
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88	Bayhan Z, Zeren S, Duzgun SA, Ucar BI, Alparslan Yumun HN, Mestan M. Crystallized phenol application and modified Limberg flap procedure in treatment of pilonidal sinus disease: A comparative retrospective study. Asian J Surg 2016;39(3):172-177. doi:10.1016/j.asjsur.2015.12.007	15	32
89	Guner A, Ozkan OF, Kece C, Kesici S, Kucuktulu U. Modification of the Bascom cleft lift procedure for chronic pilonidal sinus: results in 141 patients. Colorectal Dis 2013;15(7):e402-e406. doi:10.1111/codi.12243	15	26
90	Kayaalp C, Olmez A, Aydin C, Piskin T. Tumescent local anesthesia for excision and flap procedures in treatment of pilonidal disease. Dis Colon Rectum 2009;52(10):1780-1783. doi:10.1007/DCR.0b013e3181b553bb	15	21
91	Yoldas T, Karaca C, Unalp O, et al. Recurrent pilonidal sinus: lay open or flap closure, does it differ?. Int Surg 2013;98(4):319-323. doi:10.9738/INTSURG-D-13-00081.1	15	33
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94	Balik O, Balik AA, Polat KY, et al. The importance of local subcutaneous fat thickness in pilonidal disease. Dis Colon Rectum 2006;49(11):1755-1757. doi:10.1007/s10350-006-0672-5	13	28
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100	Mentes O, Oysul A, Harlak A, Zeybek N, Kozak O, Tufan T. Ultrasonography accurately evaluates the dimension and shape of the pilonidal sinus. Clinics (Sao Paulo) 2009;64(3):189-192. doi:10.1590/s1807-59322009000300007	12	37

WoS: Web of Science, GSch: Google Scholar

number of citations in 10 years.[1] However, it may take 10-20 years for an article to be fully recognized and reach the maximum number of citations.[4] The lists in which the articles are ordered according to the number of citations are dynamic and their order may change over time.[2] Similarly, the articles that are not yet in the top 100 list may enter the list, or the order of some articles that are already in the list may change.[2] In addition, the citation and publication numbers

of the authors in the top 100 list may not fully reflect their overall productivity in these fields.[2] Van Noorden et al.[5] reported that 43.8% of all scientific publications were never cited, and 1.84% of all scientific publications remained in the 100-999 citation range.

Some publications that are expected to receive high citations may receive very low citations. For example, Salk[6] titled "Considerations in the preparation and use of poliomyelitis virus vaccine" published in the Journal of the American Medical Association (JAMA) in 1955 has surprisingly received only 127 citations in GSch to date. Again, Sabin's et al.[7] landmark article "Live Oral Poliovirus Vaccine" has received only 236 citations since it was published in JAMA in 1960 on GSch. The 1944 article by Avery et al.[8] heralding the era of molecular biology, could only reach 620 citations in Garfield's[9] 100 citation classics published in 1987, whereas today the number of citations in GSch was 4978. Garfield[9] cited the article by Watson and Crick[10] describing the double helix of DNA, which was almost the most debated article in the history of Science and received less than 1,300 citations in 1987, as an example of under-cited articles. However, the number of citations for this article has reached 15,858 in GSch today.

In our study, the most cited articles on PD were reviewed in order to evaluate the contribution of our country to the World literature. Thirty eight of the 100 most cited articles on this subject in the world were from Turkey. Turkey is far ahead of other countries in these publications, and this finding suggets that our country dominates the world literature. In addition, Mayir et al.[1] reported that 15.4% of the most cited articles in the field of general surgery in Turkey were related to PD.

Table 2. Average number of citations, author number and number of references for the most cited 100 Turkish articles about pilonidal disease by decade of publication

Data	1990-1999	2000-2009	2010-2019	p-values
Article counts	6	43	51	<0.001
WoS citations	77±32.02	45.5±25.6	26.2±12.9	<0.001
GSch citations	141±81.4	90.2±51.8	50.8±29.4	<0.001
Author numbers	3.7±1.97	4.8±1.6	5.3±1.7	0.045
Reference numbers	17.5±7	22.3±11.5	22.5±8.4	0.49

WoS: Web of Science, GSch: Google Scholar

Table 3. Distribution of article topics by decade

Topics	1990-1999	2000-2009	2010-2019	Total
Primary closure	1	8	5	14
Flap repairs	4	24	23	51
Epidemiology	1	6	6	13
Phenol application	-	2	11	13
Other topics	-	3	6	9

Table 4. Average number of citations by type of article

Type of study	Number of articles	WoS citations	GSch citations
Prospective clinical trial	49	41.08±25.3	79±52
Retrospective clinical study	44	35.7±24.6	70.6±51.8
Review, systematic review, and meta-analysis	2	30.5±19.1	63.5±41.7
Case reports or case series	2	18.5±7.8	35±19.8
Letter or comment to the editor	2	25±11.3	46.5±10.6
Survey study	1	21	47
p-values	<0.001	0.62	0.74

WoS: Web of Science, GSch: Google Scholar

Table 5. Institutions of the most cited authors and data on citations

Institution	Total number of citations	Total number of articles	WoS citations	GSch citations	Highest citation count for an article
Gülhane Military Medical Academy	712	7	45.6±23.5	101.7±50.4	161
Gazi University Faculty of Medicine	474	5	49.6±28.1	94.8±62	195
Harran University Faculty of Medicine	460	2	111.5±10.6	230±28.3	250
Ankara Numune Training and Research Hospital	434	6	37.7±33.7	67.4±29	207
Mersin University Faculty of Medicine	368	5	35.6±34.8	73.6±71.5	198
Bezmialem Vakıf University Faculty of Medicine	351	5	31.2±25.6	70.2±53.8	154
Başkent University Faculty of Medicine	269	3	46.3±6.1	89.7±4.9	93
Fırat University Faculty of Medicine	259	4	30.5±20.2	64.8±46	133
İnönü University Faculty of Medicine	258	4	33±16.1	64.5±36.4	96
University of Health Sciences Turkey, Konya Training and Research Hospital	235	4	33±5	58.8±12.3	69

WoS: Web of Science, GSch: Google Scholar

Table 6. Leading journals in the "Top 100 List" in pilonidal disease publications

Name of journal	Number of articles
Diseases of the Colon and Rectum	22
Techniques coloproctology	5
Colorectal disease	5
World Journal of Surgery	5
American Journal of Surgery	5
Surgery today	5
Surgery	4
International surgery	4
International Journal of Colorectal Disease	3
The European Journal of Surgery	3
Dermatologic surgery	3
Clinics	3

Table 7. Distribution of variables by journal fields

Journal field (n)	Impact factor	WoS citations	GSch citations
Surgery (78)	3.26±1.4	41.56±25.6	80.5±52.6
General medicine (12)	1.7±0.94	24.9±14.5	53.8±41.1
Dermatology (5)	3.94±1.2	22.4±14	42±23.2
Plastic surgery (4)	2.53±1.53	19.5±3.4	33.5±5.3
Pediatrics (1)	1.97	23	48
p-values	0.002	0.04	0.09

WoS: Web of Science, GSch: Google Scholar

Søndenaa et al.[11] published the most cited article from all global PD articles, with 237 citations in WoS and 523 citations in GSch. Akıncı et al. published the most cited article from Turkey and received 119 citations in WoS and 250 citations in GSch (Table 1). The article by Akıncı et al. was ranked seventh among the most cited PD articles in the world.

In our study, only three articles passed the 100 citation threshold in the WoS database, while another 23 articles were cited more than 50 times. In the GSch database, 23 articles passed the 100 citation threshold, and another 30 articles received more than 50 citations. While the average number of citations in WoS was 37.5, the average number of citations in GSch was 73.2. In our study, the number of articles increased significantly in the 2000-2009 period, and the most productive decade was 2010-2019.

In the bibliometric study conducted by Manuel Văzquez et al.[12] in 2019, the median number of citations of the first 100 articles citing general surgery published in five journals with the highest impact factor was 490. In our list, the median number of citations was 30 in WoS and 56 in GSch.

These 100 Turkish articles about PD were published by 43 institutions. Of the 10 most productive institutions, 8 were university hospitals while 45 articles were from Ankara (n=32) and İstanbul (n=13). Bas et al.[13] reported the apparent superiority of university hospitals in their bibliometric analysis on liver transplantation. In addition, 90% of the 271 articles in Onat's[14] bibliometric analysis investigating Turkey's contribution to medical publications were shown to be published by university hospitals. In our study, training hospitals were successfully included in the list together with university hospitals. We think that this

may be due to the fact that the treatment of PD can be easily applied in all surgical units. In our list, 64 articles were published from 26 university hospitals and 32 articles from 13 training and research hospitals. Ankara Numune Training and Research Hospital ranked second in the list according to the number of articles (Table 5). PD is a chronic inflammatory condition that is more common in young adult males.[15] This is probably reflected in the finding that Gülhane Military Medical Academy, where the majority of its patients were young male soldiers, ranked first in the list with seven publications (Table 5).

The articles on the list were published in 37 different journals. In previous citation analyses, this figure varied between 10 and 46.[2,16-20] Paladugu et al.[21] reported that the first 100 articles in general surgery were published in only 10 surgical journals. In our study, 78 of the articles were published in surgical journals and the number of citations from surgical journals was significantly higher (Table 7). The Diseases of the Colon and Rectum was found to be the best and leading journal in this study with 22 articles (Table 6). Of the publications on the list, 59 were published in United States journals.

Systematic review, meta-analysis and randomized controlled studies are considered the most valuable publications. In our study, there were 93 clinical studies, 49 of which were prospective and 44 were retrospective, in the top 100 list. Prospective studies had higher citation counts than other studies, but there was no significant difference. There was no significant correlation between the type of study and the number of citations (Table 4). In our study, the number of studies on flap repair was high. In addition, the number of studies about phenol application increased in the last few years (Table 3).

Study Limitations

There are some limitations of our study. Search for titles, abstracts and keywords was performed by typing "PD" and "pilonidal sinus" in the WoS database search line. However, articles on PD outside the search criteria might be overlooked. New articles that could not reach a sufficient number of citations were left out of the top 100 lists. This situation creates a limitation for new and current articles.[22] In addition, book chapters and congress presentations were excluded from the study.

Conclusion

Turkey is far ahead of other countries in articles on PD and dominates the world literature. Diseases of the Colon and Rectum is the leading journal for the most cited Turkish research about PD. While flap repairs are the most discussed topic, the number of publications on the application of phenol has increased in the last ten years.

Ethics

Ethics Committee Approval: All data in this study were obtained from public access sources. Therefore, ethical approval was not required. No contact was made with the authors or their institutions to collect further data for the purposes of this study.

Informed Consent: Informed consent were not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

Isolated Small Bowel Perforations: Etiology and Management

Ayberk Dursun[1], Gülşen Yücel Oğuzdoğan[2], Kenan Teker[3], Korhan Tuncer[3]

[1]Erciş Şehit Rıdvan Çevik State Hospital, Clinic of General Surgery, Van, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Radiology, İstanbul, Turkey
[3]University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital, Clinic of General Surgery, İzmir, Turkey

ABSTRACT

Aim: Small bowel perforations (SBP), which are among the rare causes of an acute abdomen, constitute a potentially fatal emergency. Non-traumatic isolated SBPs are encountered very infrequently. The aim of this study was to highlight the importance of correct diagnosis and early treatment with the help of computerized tomography (CT) findings and to contribute to the literature in light of the rarity of the condition.

Method: Patients who were followed-up for non-traumatic SBP without additional organ injuries between 01.01.2015 and 01.03.2020 were included. Data including demographic and clinical characteristics, anamneses, mortality and morbidity, and type of surgery. Direct and indirect CT findings of the patients were evaluated. The study was retrospective.

Results: A total of 59 patients, of whom 30 were male (50.8%), were included. Mean age was 62.4 years and 52.5% of the patients were older than 65 years. All patients underwent surgery and resection was preferred most frequently (83.1%). Mean duration of hospital stay was 11 days. Duration of hospital stay was significantly longer when major complications developed ($p<0.05$). The only significant relationship in subgroup analyses was identified between ileostomy and the occurrence of major complications ($p<0.05$). The most common causes of perforation were adhesions and metastatic tumor implants (16.9%). The most common cause of the metastases was lung cancer. CT showed intra-abdominal free fluid in 96.6% and free air in 61% of the patients. The rate of free air detection was higher with a history of malignancy ($p<0.05$).

Conclusion: Early diagnosis and treatment is critical in reducing SBP-related mortality and morbidity. When SBP is suspected in the presence of a clinical picture of an acute abdomen, CT is an important guide. SBP should be considered in the differential diagnosis in patients with lung cancer who manifest a clinical picture of an acute abdomen.

Keywords: Emergency surgery, general surgery, radiology, small bowel, small bowel perforation

Introduction

Small bowel perforations (SBP), which are among the rare causes of acute abdomen, constitute a potentially fatal emergency that can result in fecal peritonitis.[1] Non-traumatic isolated SBP that are not accompanied by additional organ injuries or the perforation of another hollow organ are encountered very infrequently. Adhesions and inflammatory bowel disease (IBD) are the most common causes of non-traumatic bowel perforations in developed countries, while infectious causes are more common in developing countries. SBP causes a clinical picture of an acute abdomen. In patients with small bowel or colon perforations, a definitive diagnosis regarding the cause of the perforation is not required prior to operation.[2] In suspected SBP, methods such as ultrasonography should not be the primary imaging method and the importance of computerized tomography (CT) is elevated in the diagnosis.[3] In the treatment of SBP, surgery takes precedence. However, the specific management of the treatment depends on the underlying cause of the perforation.[2] Early identification of SBP would reduce the resulting time to surgical treatment. It may contribute to the initiation of appropriate diagnostic and treatment methods.[4] The investigation of the etiological causes of isolated SBP in

Address for Correspondence: Ayberk Dursun MD,
Erciş Şehit Rıdvan Çevik State Hospital, Clinic of General Surgery, Van, Turkey
E-mail: dursunayberk845@gmail.com **ORCID ID:** orcid.org/0000-0001-9187-0463
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our clinic showed tumor implants to be associated with a much higher rate when compared with other studies. The aim of this study was to highlight the importance of the correct diagnosis and treatment of non-traumatic isolated SBP, to evaluate CT findings and to contribute to the literature given the relative rareness and thus paucity of evidence about management of SBP.

Materials and Methods

Patient Data

This study included patients operated for SBP occurring due to non-traumatic causes that are not accompanied by additional organ injuries, in a single general surgery clinic between 01.01.2015 and 01.03.2020. Data collected included patient demographics, anamneses, history of chronic disease, duration of postoperative hospital stay, 30-day perioperative mortality and morbidity data, type of surgery performed, perforated small bowel segment, daily patient observations and details of patients' follow-up. The complications that developed were categorized based on the Clavian-Dindo Classification (CDC). CDC 3 and 4 complications were evaluated as major complications. Patients younger than 18 years of age and patients with incomplete data were not included in the study.

Computerized Tomography Data

The CT images that were evaluated were obtained with or without contrast on the HITACHI Supria 64/128 device. Iodized contrast agent diluted with water as oral contrast and non-ionized iodinated contrast material was used as intravenous (IV) contrast. The most common protocol used in our center include mono-phasic portal venous phase injection of 80-120 mL (1.7-2 mL/kg) non-ionized iodinated IV contrast agent followed by 20 mL of saline solution, at 3-5 mL/s using an automated injector from the diaphragmic dome to the proximal femoral diaphysis (mA: 180, scan time: 0.75, kV: 120, FOV: 500 mm, colimation: 0.625x64). The axial slice was thin (1 mm) for all pre- and post-contrast acquisitions, but further thick-slice 5 mm axial and other 3-5 mm coronal and sagittal planes (multiplanar reformations and maximum intensity projection) were obtained. Direct CT findings included, independent of perforation site, the presence of extraluminal gas or extraluminal oral contrast, and bowel wall discontinuity from which contrast, air or luminal contents had spilled. Bowel discontinuity does not invariably cause pneumoperitoneum and may result into a localised phlegmon or an abscess. Indirect signs include segmental bowel wall thickening, abnormal wall enhancement, localized fat stranding and/or free fluid, phlegmon or an abscess, or small bowel distention. Approval for this study was obtained from the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/06-37).

Statistical Analysis

Statistical analyses were performed using SPSS software, version 25.0 (IBM Inc., Armonk, NY, USA). Normality of variables was investigated using analytical methods. Continuous variables with a normal distribution are presented as mean and standard deviation values. Variables with a non-normal distribution are presented as median (Q1-Q3) values. Normally distributed variables were compared using the t-test if continuous and using the Pearson's chi-square of Fisher's exact chi-square tests if categorical while non-normally distributed variables were compared using the Mann-Whitney U test. Independent factors were determined and multivariate logistic regression analysis was conducted. A value of $p<0.05$ was considered statistically significant.

Results

This study included 59 patients, of whom 30 (%) were male. Mean age was 62.4 years and 52.5% of the patients were older than 65 years of age (Table 1). All patients who were followed up for isolated SBP had undergone surgery during the specified date range and non-surgical follow-up was not preferred. The most commonly preferred surgical method was resection + anastomosis (49 patients, 83.1%). This was followed, in descending order, by ileostomy (10.2%) and primary repair (6.7%). The evaluation of the patients' anamneses revealed a history of malignancy in 24 patients (40.7%). The segment in which perforations occurred the most frequently was ileum (45 patients, 76.3%).

Median duration of hospital stay was 11 days. This duration was eight days in patients without major complications and was significantly shorter ($p<0.05$) than the 25 days in those with major complications. Four patients (6.8%) died and all of these patients were older than 65 years of age. The perforation had occurred due to an adhesion in all of these four patients (100%).

When the data of the 10 patients with major complications (CDC 3 and 4) were inspected, factors such as age, gender, history of malignancy, underlying etiological cause and segment of the small bowel with the perforation were not found to significantly influence complication rates ($p>0.05$). The development of major complications was only associated with the performance of ileostomy ($p<0.05$). Again, when all of these factors were evaluated, there was no factor that had a significant effect on the 30-day peri-operative mortality ($p>0.05$).

When the etiological factors were investigated, the most common cause of perforations were adhesions (20.3%), and interestingly, this was followed by tumor implants (16.9%) (Table 2). Among the 10 patients in whom

Table 1. Analysis of the general data of the patients

	All patients (n=59)	No major complications (n=49)	Major complications present (n=10)	p
Age, mean ± SD	62.4±15.6	62.5±16.7	62.4±9.4	0.993
Groups by age, n (%)				**0.494**
Younger than 65	28 (47.5)	22 (44.9)	6 (60)	-
65 and older	31 (52.5)	27 (55.1)	4 (40)	-
Gender, n (%)				**0.731**
Male	30 (50.8)	24 (49)	6 (60)	-
Female	29 (49.2)	25 (51)	4 (40)	-
Presence of malignancy, n (%)	24 (40.7)	18 (36.7)	6 (60)	0.289
Presence of chemotherapy, n (%)	14 (23.7)	12 (24.5)	2 (20)	1.000
Presence of leukocytosis, n (%)	35 (59.3)	27 (55.1)	8 (80)	0.177

SD: Standard deviation

perforations occurred due to tumor implants, the most common primary was lung cancer, in seven patients (70%). While eight of these 10 patients had received a diagnosis of cancer prior to surgery, two patients were diagnosed after perforation. Perforations occurred due to primary small bowel malignancies in two patients (3.4%) and both of these patients received a diagnosis of lymphoma of the small intestine postoperatively.

When the etiological factors were analyzed individually, the complication rate was highest in ischemic perforations, with a rate of 50%. Major complications occurred in two of the four ischemic perforations while this rate was 44.4% in perforations secondary to herniations.

Computerized Tomography Data

All patients included in the study had undergone an abdominal CT preoperatively. The most commonly used method was non-contrast CT in 29 patients (42.9%), followed by IV contrast only CT (23.7%) and oral + IV contrast CT (23.7%) in 14 patients each. Meanwhile, two patients were given only oral contrast. Intra-abdominal free fluid was observed in 96.6% and free air was observed in 61% of all patients (Table 3). In the analysis of the subgroups, the rate of intra-abdominal free air was 83.3% in patients with a history of malignancy, which was significantly higher when compared with those without history of malignancy ($p<0.05$) (Table 3). On CT, the presence of phlegmon or abscess elevated the rate of major complications, although this was not significant ($p>0.05$).

When the CT images of the patients who received chemotherapy were examined, the rate of free air detection was 85.7%, which was significantly higher when compared with those who did not receive chemotherapy (53.3%) (Table 4). The increase in small bowel diameter was greater in patients who did not receive chemotherapy (82.2%) than in patients who did (42.9%) (Table 4). Again, the findings showed free air on CT in 80% of the patients with perforations related to a tumor implant. The rate of free air detection was higher when compared with perforations that were not related to an implant (57.1%), but this was not significant (Table 4). Interestingly, in perforations secondary to a tumor

Table 2. Etiological factors and mortality/morbidity rates

	Total patients (n=59)	Major complication (n=10)	Mortality (n=4)
Etiology, n (%)			
Adhesion	12 (20.3%)	2	4 (100%)
Tumor implant	10 (16.9%)	0	0
Herniation	9 (15.3%)	4	0
IBD	6 (10.2%)	0	0
Foreign body	4 (6.8%)	0	0
Other	4 (6.8%)	2	0
Ischemia	4 (6.8%)	2	0
Tuberculosis	2 (3.4%)	0	0
Idiopathic	2 (3.4%)	0	0
Lymphoma	2 (3.4%)	0	0
Diverticulitis	2 (3.4%)	0	0
Phytobezoar	2 (3.4%)	0	0

IBD: Inflammatory bowel disease

Table 3. Analysis of the computerized tomography data of the subgroups stratified by complication, presence of malignancy and age

	Total patients (n=59)	No complications (n=49)	Complications present (n=10)	p	No history of malignancy (n=35)	History of malignancy present (n=24)	p	Younger than 65 years (n=28)	Older than 65 years (n=31)	p
Intra-abominal free air, (n, %)	36 (61)	28 (57.1)	8 (80)	0.288	16 (45.7)	20 (83.3)	**0.004***	18 (64.3)	18 (58.1)	0.625
Intra-abdominal free fluid, (n, %)	57 (96.6)	49 (100)	8 (80)	**0.026***	33 (94.3)	24 (100)	0.509	28 (100)	29 (93.5)	0.493
Bowel wall thickening, (n, %)	51 (86.4)	43 (87.8)	8 (80)	0.613	29 (82.9)	22 (91.7)	0.453	26 (92.9)	25 (80.6)	0.259
Loss of wall integrity, (n, %)	18 (30.5)	16 (32.7)	2 (20)	0.708	12 (34.3)	6 (25)	0.447	8 (28.6)	10 (32.3)	0.759
Abnormal wall enhancement, (n, %)	12 (20.3)	10 (20.4)	2 (20)	1.000	12 (34.3)	0	**0.001***	4 (14.3)	8 (25.8)	0.272
Infiltration of adjacent fat planes, (n, %)	55 (93.2)	47 (95.9)	8 (80)	0.130	33 (94.3)	22 (91.7)	1.000	26 (92.9)	29 (93.5)	1.000
Phlegmon and abscess, (n, %)	16 (27.1)	12 (24.5)	4 (40)	0.436	8 (22.9)	8 (33.3)	0.374	8 (28.6)	8 (25.8)	0.811
Increase in small bowel diameter, (n, %)	43 (72.9)	37 (75.5)	6 (60)	0.436	29 (82.9)	14 (58.3)	**0.037***	20 (71.4)	23 (74.2)	0.811
Small bowel diameter (mm), median (Q1-Q3)	37 (34-40)	37 (34-40)	54 (32-73)	0.104	38 (33-40)	37 (34-42)	0.696	38.5 (35-42)	34 (32-40)	**0.018***

Fischer's exact test was used. n: Number of patients, mm: Millimeter, p: p-value, Complication: Major complications (CDC 3 and 4)

Table 4. Analysis of CT data of patients with a history of chemotherapy and perforations resulting from a tumor implant

	No chemotherapy (n=45)	Received chemotherapy (n=14)	p	No tumor implant (n=49)	Tumor implant present (n=10)	p
Intra-abdominal free air, (n, %)	24 (53,3)	12 (85,7)	0,030*	28 (57,1)	8 (80)	0.288
Intra-abdominal free fluid, (n, %)	43 (95,6)	14 (100)	1,000	47 (95,9)	10 (100)	1.000
Bowel wall thickening, (n, %)	39 (86,7)	12 (85,7)	1,000	43 (87,8)	8 (80)	0.613
Loss of wall integrity, (n, %)	16 (35,6)	2 (14,3)	0,189	14 (28,6)	4 (40)	0.475
Abnormal wall enhancement, (n, %)	12 (26,7)	0	0,052	12 (24,5)	0	0.105
Infiltration of adjacent fat planes, (n, %)	43 (95,6)	12 (85,7)	0,236	47 (95,9)	8 (80)	0.130
Phlegmon or abscess, (n, %)	10 (22,2)	6 (42,9)	0,172	16 (32,7)	0	**0.049***
Increase in small bowel diameter, (n, %)	37 (82,2)	6 (42,9)	0,013*	37 (75,5)	6 (60)	0.436
Major complication, (n, %)	8 (17,8)	2 (14,3)	1,000	10 (20,4)	0	0.186
Mortality, (n, %)	4 (8,9)	0	0,564	4 (8,2)	0	1.000

Fischer's exact test was used. n: Number of patients, mm: Millimeters, p: p-value, CT: Computerized tomography

implant, the rate of intra-abdominal abscess/phlegmon was significantly lower and major complications also occurred at lower rates, however this was not significant (Table 4). Similarly to patients who received chemotherapy, abnormal wall enhancement was less evident in perforations related to a tumor implant.

Discussion

SBPs are among the rare causes of a clinical picture of an acute abdomen and the etiology may be wide-ranging.[5] Traumatic perforations of the small bowel are more frequent than non-traumatic perforations.[6] Although there is an increasing amount of published data regarding SBP, there remains a paucity of data about non-traumatic perforations localized in the small bowel that are not accompanied by other organ injuries. Early detection and quick surgical treatment are essential to reduce morbidity and mortality.[7] In contrast with gastroduodenal perforation, extraluminal gas is either found at low amounts or not found at all in SBPs.[8] This complicates the diagnosis and prolongs the treatment time. In patients with a clinical picture of an acute abdomen, typically an abdominal CT is requested first as a diagnostic imaging method and this is clinically useful in the diagnosis of SBP.[5] Our study did not include traumatic SBPs and only patients with non-traumatic perforations were enrolled, which resulted in a limited number of patients in our study. In line with the literature, a full abdominal CT was performed in patients with the clinical picture of an acute abdomen in our clinic in consideration of SBP and other differential diagnoses.

Previous publications have reported the associated mortality rates to be as high as 40%.[9] Although mortality rates are gradually decreasing due to the broader opportunities for a quick diagnosis and early treatment with the advances in imaging methods, the improvements in the surgical technique, appropriate antimicrobial treatment and perioperative intensive care support, they remain high. The mortality rate was 19.1% in a study conducted in Singapore.[10] In our patient series, the mortality rate was 6.8%, which is at an acceptable level when compared to the literature. When clinical characteristics of the patients were examined, there were no factors with a significant influence on 30-day peri-operative mortality. This was attributed to the low number of total patients and mortality cases in our patient series.

When the underlying etiological causes were investigated, the most common causes were adhesions, IBD and infectious diseases. Perforations secondary to tumor implants are encountered rarely and have previously mostly been published as case reports.[11,12] The most common cause was also adhesion in our study and this was followed by perforations related to malignant metastatic implants. Particularly, bowel metastasis from lung cancer was reported to be associated with a high incidence, varying between 2-14% in autopsy studies, in contrast with that previously known.[11] SBPs related to metastatic non-small cell lung cancer occur in patients in advanced stages and very rarely. Aggressive surgery may provide effective palliation but the overall prognosis of the disease is poor.[11] In our patient group, small bowel metastases related to tumors occurred at a rate of 16.9%, which is high when compared with the literature. In total, perforations secondary to tumor implants were detected in 10 of our patients; seven of these (70%) were metastases from lung cancer.

In contrast, lymphomas of the small intestine are rare and comprise approximately 1% of malignant gastrointestinal tumors. Non-Hodgkin lymphoma is encountered the most commonly. Cases of lymphoma of the small intestine have been reported in the literature, but emphasis on emergency surgery is extremely uncommon.[13] Our results included two patients with perforations caused by intestinal cancer and the primary was small bowel lymphoma of the non-Hodgkin subtype in both cases. By means of a quick diagnosis, perioperative mortality did not occur in either patient.

In SBP, which is an aggressive disease, the most vital factors in reducing mortality and morbidity are an early diagnosis and a quick surgical treatment.[7] We believe that the fact that all patients with the picture of an acute abdomen were able to immediately undergo a CT (a separate tomography device is dedicated for the use of emergency services) made an early diagnosis and treatment possible, culminating in the low mortality rate. Lung radiographs typically do not show pneumoperitoneum. Tan et al.[10] detected free air in the lung radiographs of only 23.4% of the patients in their patient group. Therefore, they reported adopting CT scans in the evaluation of patients presenting to their institution with an acute abdomen and performing CT scans in 68.1% of their patients.[10]

In the case of SBP, CT findings are usually non-specific but when present, they may be helpful for the radiologist in identifying a specific cause for the perforation.[5] When compared with plain abdominal X-rays, CT is more sensitive in identifying small amounts of free air.[13] Direct CT findings of bowel perforations are: Free gas in the abdominal cavity; visible transmural lesion of bowel wall; and extraluminal leakage of orally administered contrast material.[14,15] Notably, in some clinics, oral contrast material is not used for these indications[13] and thus this CT indication would not be present. Meanwhile, indirect CT findings of bowel perforations include misty mesentery, free fluid in the abdominal cavity, bowel wall thickening and extraluminal fecal matter.[15] While free air is not usually found in SBPs, free fluid represents an important finding of intestinal damage when associated with the suspicion of perforation.[16]

Our results determined intra-abdominal free air in 61% of the patients and bowel wall thickening in 86.7% of the patients. Meanwhile, intra-abdominal free fluid was present in 96.6%, which is extremely high. Loss of bowel wall integrity was reported in only 30.5% of the patients. Increases in small bowel diameter were found at significantly higher rates in the group that did not receive chemotherapy and did not have a history of malignancy (Table 4). As a reason for this, it was considered that a decision on emergency surgery could be made earlier, since bowel perforations have a more eventful course and manifest symptoms more quickly in groups that have a history of malignancy and that received chemotherapy. Thus, ileus and bowel dilation, which are later findings, may have occurred less frequently due to early surgery.

When the CT findings were examined, free air on CT was found at a higher rate in perforations related to tumor implants compared with other perforations (80% vs 57%) but this was not found to be significant. Interestingly, the rate of intra-abdominal abscess/phlegmon in perforations related to implants was significantly lower. In the same way, major complications also occurred at lower rates, although this was not significant. Similarly to patients who received chemotherapy, abnormal wall enhancement was present at a lower rate in perforations related to tumor implants. This might be because intra-abdominal air is encountered more frequently in perforations related to implants and a perforation is suspected at earlier stages.

For treatment, a small bowel resection was performed on most of the patients, and creating a stoma was found to be associated with poorer clinical outcomes.[10] In our practice, resection + anastomosis (83.1%) was also the most commonly preferred method. In line with the literature, performing an ileostomy was found to be significantly associated with the occurrence of major complications. This was probably because ileostomy was preferred in patients with more aggressive findings, who were not appropriate for anastomosis (presence of extensive intra-abdominal abscess, a condition of fecal peritonitis and presence of other gross pathologies).

Study Limitations

The limitations of our study include its retrospective design, the limited number of patients due to the exclusion of patients with traumatic SBPs and SBPs accompanied by additional organ injuries.

Conclusion

In conclusion, early diagnosis and treatment play a vital role in reducing the mortality and morbidity associated with SBP. Thus, CT might serve as the biggest guide for the surgeon in patients with a clinical picture of an acute abdomen that are suspected of having SBPs. SBP should be considered in the differential diagnosis in the case of patients with lung cancer who manifest a clinical picture of an acute abdomen.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/06-37).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: A.D., Ke.T., Ko.T., Concept: A.D., G.Y.O., Design: A.D., G.Y.O., Ko.T., Data Collection or Processing: A.D., Ko.T., Analysis or Interpretation: A.D., G.Y.O., Ke.T., Ko.T., Literature Search: A.D., G.Y.O., Writing: A.D., G.Y.O., Ke.T., Ko.T.

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RESEARCH ARTICLE

The Importance of Platelet Count and Mean Platelet Volume, Platelet Distribution Width, and Monocytes Count in the Differentiation of Colorectal Cancer and Colon Polyps

Doğukan Durak[1], Ertuğrul Gazi Alkurt[1], Hüseyin Köseoğlu[2], Veysel Barış Turhan[1]

[1]Hitit University Çorum Erol Olçok Training and Research Hospital, Clinic of General Surgery, Çorum, Turkey
2Hitit University Çorum Erol Olçok Training and Research Hospital, Clinic of Gastroenterology, Çorum, Turkey

ABSTRACT

Aim: Mean platelet volume (MPV) is a marker of platelet activity that has been found to be lower in people with colon cancer than in healthy people. In order to forecast the probability of colon cancer development in colon polyps, we looked at the predictive values of MPV, platelet distribution width (PDW), platelet count/MPV (Plt/MPV) and monocyte (Mo) count.

Method: This was a retrospective study. The study comprised colonoscopy procedures performed at a single hospital between 02.01.2019 and 05.05.2021. Colon polyps detected during colonoscopy in 425 patients were included. Colon polyps that underwent polypectomy were separated into two groups based on histopathological analysis into benign and malignant. Standard complete blood count parameters were assessed in both groups and Plt/MPV, Plt/PDW, neutrophil/lymphocyte ratio (NLR), and Mo/lymphocyte ratio (MLR) values were calculated.

Results: The total number of polyps removed was 754. Haemoglobin and red cell distribution width values were statistically lower in the adenocarcinoma group ($p<0.001$ for both). When the values of NLR, MLR, Plt/PDW, and Plt/MPV were compared, the Plt/PDW and MLR were significantly higher in the adenocarcinoma group ($p=0.036$ and $p=0.004$, respectively).

Conclusion: The Mo count and MLR and Plt/PDW ratios were useful for detecting malignancies that may arise from colon polyps in this retrospective cohort. Polyps detected in patients with a high Mo count or MLR or Plt/PDW ratio measured before the procedure may be associated with a higher risk of cancer but these results should be confirmed in larger prospective studies.

Keywords: Colorectal polyps, monocytes count, platelet count/platelet distribution width

Introduction

Colorectal cancers (CRC) are the most prevalent cancers of the gastrointestinal tract and the fourth most common cancer in developed countries.[1] CRC are usually at an advanced stage by the time they manifests symptoms. The mortality rate from CRC has fallen by more than 20% as a result of the rapid development of early detection techniques and efficient treatment.[2] Despite this, only 40% of people with CRC are detected at an early stage.[3]

Most CRC develop from normal-looking mucosa to adenoma, dysplasia, and carcinoma. Most CRC develop against a background of a pre-existing polyp (adenoma).[4] The majority of colon polyps, however, do not progress to cancer. High-grade, dysplastic, villous adenomas are more prone to develop into cancer. Early detection is critical in CRC, as it is in other malignancies. After the age of 50, a routine colonoscopy is suggested to detect colorectal malignancies early. Recent evidence suggests that patients with no abnormalities at previous colonoscopy have a significantly lower risk of CRC.[5] Screening colonoscopy was linked to a 67% reduction in CRC incidence and a 65% reduction in death in a cohort trial of average-risk patients.[6]

The tumor structure and the patient's inflammatory response have a complicated relationship.[7] Platelet count and mean

Address for Correspondence: Doğukan Durak MD,
Hitit Univesity Çorum Erol Olçok Training and Research Hospital, Clinic of General Surgery, Çorum, Turkey
E-mail: dogukandurak404@hotmail.com **ORCID ID:** orcid.org/0000-0003-0693-5715
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platelet volume (Plt and MPV) are inversely connected, resulting in a relatively constant total platelet mass.[8] Studies have revealed that thrombotic activity develops in more than 76% of cancer patients. Platelets are non-nucleated cells produced from megakaryocytes in the bone marrow, play a key role in blood clotting but are also linked to inflammation and thrombosis.[9] Tumor cells are associated with various cytokines that stimulate platelet production, such as platelet-derived growth factor, vascular endothelial growth factor and other growth factors.[10] The enhanced destruction of large platelets in an inflammatory milieu can cause a decrease in MPV, possibly because larger platelets are more sensitive to stimulation, and thus larger platelets are more likely to be selectively cleaved in this situation. MPV is a marker of platelet activity that has been found to be lower in people with colon cancer than in healthy people.[11] Platelet distribution width (PDW), like MPV, is a simple platelet index that measures platelet activity and is measured during a routine complete blood count (CBC).[12] MPV and PDW show similar increases in platelet activation.[13]

Blood monocytes (Mo) from patients with CRC at different stages have been shown to be activated by various immunomodulators, inducing specific cytolytic activity against tumor cells, and the Mo could also recognize and lyse tumorigenic cells, but did not affect non-tumorigenic cells. Even after repeated doses of radiotherapy and chemotherapy, the tumoricidal activity of Mo has been reported in blood Mo from patients.[14] Moreover, a six-fold increase in Mo count has been reported in metastasizing colorectal tumours compared to the normal intestine.[15] Therefore, the Mo count may be expected to increase in colorectal tumours.

The aim of this study was to investigate the use of parameters measured by or derivable from CBC in order to forecast the probability of colon cancer development in colon polyps. The predictive values of MPV, PDW, Plt/MPV ratio and Mo count was retrospectively investigated in patients undergoing polypectomy.

Materials and Methods

The study comprised data from patients undergoing colonoscopy procedures performed at Hitit University Çorum Erol Olçok Training and Research Hospital performed by the General Surgery Department, Gastroenterology Surgery Sub-Division Member and in the Gastroenterology Clinic between 02.01.2019 and 05.05.2021 were included. The patients included in the study were those older than 18 years of age and those who had polyps on colonoscopy. Patients who underwent polypectomy during colonoscopy were included in the study. The data were scanned retrospectively using the Hospital Information Management System, with the approval of the hospital's chief physician and the approval of the ethics committee. Patients under the age of 18, those with diseases that may affect blood values, such as cirrhosis or chronic kidney failure, and patients with ulcerovegetative mass lesions during colonoscopy were not included in the study. Ethics committee approval was received from Hitit University Faculty of Medicine, Non-Interventional Research Ethics Committee in 2021 (approval number: 2021-78).

Colonoscopy procedures were performed by specialist doctors. One of two different procedures was performed in patients who underwent polypectomy. In all cases, an Olympus Medical Systems variable stiffness colonoscope (Olympus, Tokyo, Japan) was used. The distal tip of this instrument was 12.2 mm in diameter, while the insertion tube was 12.0 mm in diameter (working length, 133 cm; diameter of the accessory canal, 3.2 mm). The appendix orifice and ileocecal valve were identified during a complete colonoscopy. Polyps were removed if they were discovered during any colonoscopy. The location of each polyp was documented. A snare was put on the polyp for hot snare polypectomy, and the current was administered while the snare was closed. For an endoscopic mucosal resection procedure, 1 to 3 mL of epinephrine diluted 1:10,000 in saline was injected submucosally into each polyp. A detailed visual assessment of the region was performed by the same endoscopist after each polypectomy to establish whether polyp eradication was complete. The adequacy of resection was assessed visually in a standard manner. The presence of residual tumor was determined according to the experience and discretion of the endoscopist.

Patient demographic information, such as age and gender, was recorded. All the colon polyps detected during colonoscopy procedures were grouped according to size, location, polyp type, and histopathological features. Parameters from the CBC performed in all patients prior to the colonoscopy procedure were collected, including white blood cell count (WBC), Mo count, lymphocyte count (Ly), Plt, neutrophil count (Ne), MPV, PDW, red cell distribution width (RDW) and haemoglobin (Hb) values. Additionally, Plt/MPV, Plt/platelet distribution volume ratio (Plt/PDW), Ne to lymphocyte count ratio (NLR), Mo count to lymphocyte count ratio (MLR) values were calculated from the blood samples taken.

Polypectomy was undertaken on colon polyps that were discovered during the colonoscopy process. Excised colon polyps were separated into two groups based on histopathological report: benign and malignant. The CBC parameters derived from pre-colonoscopy blood samples were compared between the benign and malignant polyp groups.

Statistical Analysis

SPSS for Windows, version 22.0, was used for statistical comparison of data (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to assess if the parameters followed a normal distribution. Mean ± standard deviation was used to represent normally-distributed continuous variables. A receiver operating characteristic (ROC) curve analysis was used to measure diagnostic capabilities, and ROC curves and Youden index were created to examine the trade-off between sensitivity and specificity. A p-value of <0.05 was assumed to define statistical significance. The statistical power and power analysis were calculated with the open-source software G*Power version 3.1.9.2. A priori sample size was calculated as 35 patients in each group for a power of 0.80, the alpha error probability of 0.05, and the effect size of 0.80 according to the primary outcome measure.

Results

The study comprised 425 participants who had colorectal polyps removed during colonoscopy. Of the patients included in the study, 277 (65.2%) were male and 148 (34.8%) were female. Forty-two (9.9%) of these patients had adenocarcinoma as their final pathology result. According to the diagnosis of adenocarcinoma or other polyps, the patients were separated into two groups. There were 383 (90.1%) patients in the benign group and 42 (9.9%) patients in the adenocarcinoma group. The total number of polyps removed was 754 (Table 1). Of the polyps, 30 (4%) were removed from the cecum, 103 (13.7%) from the ascending colon, 135 (17.9%) from the transverse colon, 131 (17.4%) from the descending colon, 177 (23.5%) were from the sigmoid colon and 178 (23.6%) from the rectum. There was no difference between the two groups in terms of polyp excision location (p=0.146). Percentages according to polyp subtypes are given in Table 1.

There was no statistical difference between the groups in terms of age and gender (p=0.898 and p=0.089, respectively). Patients with multiple polyps were more likely to develop adenocarcinoma than those with single polyps. The mean largest diameter of polyps in the adenocarcinoma group were significantly larger than those in the other polyp group (Table 1). When CBC data were examined, it was found that lymphocyte counts were significantly lower in adenocarcinoma (p=0.013). Moreover, Hb and RDW values were also significantly lower in the adenocarcinoma group (p<0.001 for both). When the values for NLR, MLR, Plt/PDW, and Plt/MPV were compared, it was found that the Plt/PDW and MLR were significantly elevated in the adenocarcinoma group compared to the other polyp group (p=0.036 and p=0.004, respectively) (Table 2).

ROC curve analysis was used to calculate the diagnostic utility of the found values (Table 3). According to the ROC curve and the Youden index [1-(1-sensitivity) + (1-specifity)], Mo was shown to be the most valuable laboratory value in predicting the diagnosis of adenocarcinoma with a sensitivity of 86% and a specificity of 83% (Table 3). In this retrospective cohort the probability of polyps being malignant was 2.42 times higher in patients with a pre-colonoscopy Mo count >0.85.

Discussion

The results of this single-center retrospective analysis suggest that a number of commonly available absolute and derived CBC values may aid in the early detection of CRC. These parameters include the absolute Mo count, which had the best combination of sensitivity and specificity for predicting adenocarcinoma in polyps in this cohort, but consideration should also be given to the MLR, Hb value and Plt/PDW ratio parameters.

Colon polyps are the most common cause of CRC. Colon polyps may cause symptoms, depending on the size or amount of bleeding. The intensity of systemic inflammation should be considered while classifying circulating small and large platelets.[16] Cancer is a systemic inflammatory condition in which many pro-inflammatory cytokines are secreted. High-grade inflammation is negatively correlated with MPV. When an adenoma develops into a carcinoma, the malignant cells invade the mucosal layer, causing a systemic inflammatory response. MPV is also linked to disease activity/severity and is an indication of inflammatory disorders.[17] In patients with CRC, low MPV readings are expected.

It has been reported that the MPV is significantly lower in CRC patients.[11] The MPV values of patients in whom colon polyps were benign or contained adenocarcinoma did not differ significantly in our research. We suspect that the reason for this difference from the study of Wu et al.[11] that CRC patients were selected in the earlier study, while in our study, patients were selected for having polyps excised, only some of which were later found to be adenocarcinoma. Therefore, we believe that our findings can be explained because the activity of the inflammatory process is reduced in malignancies that are followed by polyps.

The mechanism that results in the association between Plt/MPV ratio and the formation or advancement of malignant tumors is unknown. Nonetheless, there are more studies about MPV and Plt independently than there are about the Plt/MPV ratio. Cho et al.[18] reported that the Plt/MPV ratio was more useful than MPV alone in discriminating

Table 1. Demographic and clinical characteristics of all patients and those with adenocarcinoma or other type of polyp

		All polyps (n=754)	Other polyps (n=709)	Adenocarcinoma (n=45)	p
Gender	Male	516 (68.4%)	486 (68.5%)	30 (66.7%)	0.792
	Female	238 (31.6%)	223 (31.5%)	15 (33.3%)	
Age	Min-max (median) Mean ± SD (median)	20-89 (65)	64.33±11.63 (65)	67.62±12.31 (68)	0.069
Location	Cecum	30 (4%)	29 (4.1%)	1 (2.2%)	0.146
	Ascending	103 (13.7%)	98 (13.8%)	5 (11.1%)	
	Transverse colon	135 (17.9%)	133 (18.8%)	2 (4.4%)	
	Descending	131 (17.4%)	120 (16.9%)	11 (24.4%)	
	Sigmoid	177 (23.5%)	163 (23.0%)	14 (31.1%)	
	Rectum	178 (23.6%)	166 (23.4%)	12 (26.7%)	
Polyp size	Mean ± SD	4.47±3.40	4.31±3.11	7.05±5.96	**<0.001***
	Min-max (median)	1-27 (3)	1-27 (3)	3-25 (5) high red	
Polyp types	Inflammatory	65 (8.6%)			
	Hyperplastic	158 (21%)			
	Adenoma	486 (64.5%)			
	Adenocarcinoma	45 (6%)			
	Serrated	7 (1.3%)			
Adenoma polyp subtypes (474)	Tubular	394 (83.2%)			
	Tubulovillous	54 (11.4%)			
	Villous	19 (4.1%)			
Dysplasia (14.7% | 111)	Low grade	73 (65.8%)			
	Moderate	2 (1.8%)			
	High grade	36 (4.8%)			
Differentiation for adenocarcinomas (12)	Well differentiated	7 (58.3%)			
	Moderately differentiated	4 (33.3%)			
	Poorly differentiated	1 (8.3%)			

Statistically significant values are bold*. SD: Standard deviation

between cancer and healthy individuals in a study carried out in patients with hepatocellular carcinoma. Wu et al.[11] stated that the Plt/MPV ratio showed superior diagnostic performance compared to MPV, NLR, or PLR alone to distinguish CRC from benign colorectal polyps. The Plt/MPV ratio was slightly higher in colon adenocarcinoma polyps in our study, but this was not significant. We believe that this may be due to the low number of adenocarcinomatous polyps.

PDW, another platelet index, is a measure of variation in platelet size. The relationship between PDW and cancer is unclear.[19] The variation of MPV and PDW in different cancer types is inconsistent. PDW was found to be higher in gastric and lung cancers, but lower in thyroid and breast cancers.[19] Although PDW values were lower in patients with polyps with colon cancer in our study, again the difference was not significant. Nonetheless, the Plt/PDW ratio was found to be higher in adenocarcinomas. Thus, we believe that evaluating PDW in conjunction with Plt, rather than separately, will yield more diagnostic utility.

A high MLR may be a sign of high tumor burden, as both a high Mo count and low lymphocyte count reflect suppressed immune activity.[20] MLR levels were shown to be elevated in cancers of the right colon and rectum in the MIMIC trial.[21] MLR values were higher from patients with polyps with adenocarcinoma in our analysis, which is in agreement with the findings of the MIMIC trial.

Table 2. Examination of all patients and comparison between patients with and without adenocarcinoma

		All patients (n=425)	Benign (n=383)	Adenocarcinoma (n=42)	Statistical significance
Gender	Male	277 (65.2%)	250 (65.3%)	27 (64.3%)	0.898
	Female	148 (34.8%)	133 (34.7%)	15 (35.7%)	
Age	(Years)	65 (20-89)	64 (20-89)	69.5 (43-86)	0.089
Polyp count		1 (1-12)	1 (1-12)	2 (1-10)	**<0.001**
Solitary/multiple	Solitary	259 (60.9%)	253 (66.1%)	6 (14.3%)	**<0.001**
	Multiple	166 (39.1%)	130 (33.9%)	36 (85.7%)	
WBC	Unit	7.62±2.64 (7.21)	7.63±2.66 (7.18)	7.55±2.48 (7.25)	0.911
Ne	Unit	4.72±2.30 (4.23)	4.71±2.31 (4.19)	4.86±2.31 (4.45)	0.651
Ly	Unit	2.07±0.78 (2.02)	2.10±0.79 (2.04)	1.79±0.53 (1.70)	**0.013**
Hb	Unit	13.10±2.21 (13.4)	13.24±2.16 (13.4)	11.85±2.34 (11.25)	**<0.001**
Plt	Unit	250.14±87.88 (238)	248.86±88.09 (237)	261.81±86.12 (251.5)	0.294
MPV	Unit	10.40±1.06 (10.4)	10.41±1.07 (10.4)	10.21±1.00 (10.2)	0.127
Mo	Unit	0.78±0.30 (0.58)	0.72±0.30 (0.57)	0.87±0.27 (0.64)	**<0.001**
PDW	Unit	12.39±2.23 (12.1)	12.47±2.20 (12.1)	11.64±2.38 (11.7)	**0.019**
PMR		25.24±17.99 (23.3)	25.14±18.68 (23.07)	26.13±9.89 (23.91)	0.173
PLT/PDW		21.23±9.60 (19.78)	20.95±9.44 (19.57)	23.78±10.73 (22.04)	**0.036**
NLR		2.68±2.15 (2.08)	2.64±2.13 (2.07)	3.12±2.35 (2.34)	0.124
MLR		0.33±0.21 (0.28)	0.33±0.21 (0.27)	0.41±0.23 (0.33)	**0.004**
Polyp type	Benign	383 (90.1%)			
	Adenocarcinoma	42 (9.9%)			

Statistically significant values are bold*. Ly: Lymphocyte count, Hb: Heamoglobin value, Plt: Platelet count, MPV: Mean platelet volume, Mo: Monocyte count, PDW: Platelet distribution width, Plt/MPW: Plateletcount to mean platelet volume ratio, Plt/PDW: Platelet count to platelet distribution width ratio, NLR: Neutrophil count to lymphocyte count ratio, MLR: Monocyte count to lymphocyte count ratio

Table 3. Complete blood count parameter diagnostic utility for adenocarcinoma including values for cut-off, sensitivity, specificity, area under the curve, odds ratios and Youden index (J)

	Diagnostic values				
	Cut-off	Sensitivity	Specifity	AUC (SE)	J
Ly	1.62	50.0%	73.4%	0.487 (0.047)	0.234
Hb	12.60	64.2%	64.3%	0.512 (0.052)	0.285
Plt	240.50	47.8%	47.6%	0.524 (0.045)	-0.046
MPW	10.35	51.4%	52.4%	0.491 (0.050)	0.038
Mo	0.85	86.0%	83.0%	0.556 (0.047)	0.69
PDW	11.95	54.9%	52.9%	0.520 (0.049)	0.078
Plt/MPW	23.70	46.2%	45.2%	0.517 (0.046)	-0.086
Plt/PDW	20.62	44.4%	42.9%	0.599 (0.044)	-0.127
NLR	2.23	42.8%	42.9%	0.580 (0.052)	-0.143
MLR	0.29	43.1%	42.9%	0.559 (0.052)	-0.14
Solitary/multiple	-	85.7%	66.1%		

Ly: Lymphocyte count, Hb: Heamoglobin value, Plt: Platelet count, MPV: Mean platelet volume, Mo: Monocyte count, PDW: Platelet distribution width, Plt/MPW: Plateletcount to mean platelet volume ratio, Plt/PDW platelet count to platelet distribution width ratio, NLR, neutrophil count to lymphocyte count ratio, MLR: Monocyte count to lymphocyte count ratio

Study Limitations

The fact that our study was single-centred can be considered as a limitation. It also had a retrospective design that could not completely resolve the confounding factors and will produce a certain degree of bias. The results may have been influenced by the large number of polyps analyzed and the low frequency of adenocarcinoma polyps. We therefore suggest that our results should be validated by larger, prospective, multicenter studies.

Conclusion

We believe that the absolute Mo count and the MLR and Plt/PDW ratios have diagnostic utility in detecting malignancies that may arise from colon polyps. We further suggest that polyps detected in patients with a high Mo count or elevated MLR or Plt/PDW ratios have a higher risk of cancer. Our results should be validated by larger prospective studies but in the meantime we propose a more thorough colonoscopic examination and screening in these patients.

Ethics

Ethics Committee Approval: Ethics committee approval was received from Hitit University Faculty of Medicine, Non-Interventional Research Ethics Committee in 2021 (approval number: 2021-78).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.D., H.K., Concept: D.D., Design: D.D., Data Collection or Processing: D.D., E.G.A., H.K., Analysis or Interpretation: V.B.T., Literature Search: D.D., V.B.T., Writing: D.D., E.G.A., H.K., V.B.T.

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

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CASE REPORT

A Rare Cause of Intestinal Pseudo-obstruction: Colonic Amyloidosis

İsmet Çelik[1], Aydın Aktaş[2], Burcu Kemal Okatan[3]

[1]University of Health Sciences Turkey, Kanuni Training and Research Hospital, Clinic of Surgery, Trabzon, Turkey
[2]University of Health Sciences Turkey, Kanuni Training and Research Hospital, Clinic of Gastrointestinal Surgery, Trabzon, Turkey
[3]University of Health Sciences Turkey, Kanuni Training and Research Hospital, Clinic of Pathology, Trabzon, Turkey

ABSTRACT

Intestinal amyloidosis is a rare entity. A 78-year-old male patient presented to the emergency department with complaints of abdominal pain, nausea, vomiting and inability to pass gas/stool for five days. The patient had a history of weight loss and had attended hospital on multiple occasions for ileus. Ileus in the bowel and mass in the sigmoid colon were detected on computed tomography. Anterior resection and end colostomy were performed. Pathological examination revealed amyloid involvement in the sigmoid colon. Intestinal amyloidosis should be considered in patients with long-term and recurrent symptoms. Surgical treatment should be performed in complicated patients.

Keywords: Amyloidosis, acute abdomen, ileus, surgery

Introduction

Intestinal pseudo-obstruction is an urgent clinical condition. Intestinal pseudo-obstruction may be accompanied by abdominal pain, nausea, vomiting, inability to pass stool, and abdominal distension. Amyloidosis, which is a systemic disease characterized by the accumulation of amyloid protein in the tissues/organs is a rare cause of intestinal pseudo-obstruction.[1,2] Amyloidosis alters intestinal function by involvement of the myenteric plexus and vascular structures in the gastrointestinal system and may lead to pseudo-obstruction.[3] Conservative approaches are usually preferred in its treatment. However, in some cases, it may cause acute abdomen that requires emergency surgery.[4-6]

Herein, we present a patient in whom emergency surgery was performed due to localized amyloidosis affecting the sigmoid colon.

Case Report

A 78-year-old man presented to the emergency department with complaints of diffuse abdominal pain, nausea, vomiting, and inability to pass gas and stool for five days. There was no history of systemic disease or surgery in his history. However, the patient had a history of weight loss and had attended the hospital on multiple occasions for ileus attacks in the last one year. Physical examination revealed diffuse tenderness, abdominal distension, and a reduction of bowel sounds. There was no stool on rectal examination. Biochemical analysis revealed anemia (9.4 g/dL), leukopenia (2300/µL) and hypoalbuminemia (2.5 g/dL). Preoperative endoscopy was not performed. On abdominal computed tomography (CT) imaging there was dilatation and edema in the small intestine, and segmental wall thickness in the large bowel (Figure 1a). The patient was taken to emergency surgery with the pre-diagnosis of acute abdomen. On exploration, there was the accumulation of about 500 cc serous-like fluid in the abdominal cavity, a gangrenous obstructed mass in the 10 cm segment of the sigmoid colon, and dilatation (up to 8 cm) in the colon segments proximal of the mass (Figure 1b). An anterior resection and end colostomy was performed. Amyloid deposition was detected in the vascular and neural structures on histopathological examination of the colon specimen (Figure 2). However, subgroup typing could not be done for technical reasons. Systemic scanning was performed

Address for Correspondence: Aydın Aktaş MD,
University of Health Sciences Turkey, Kanuni Training and Research Hospital, Clinic of Gastrointestinal Surgery, Trabzon, Turkey
E-mail: aydinaktas2004@gmail.com **ORCID ID:** orcid.org/0000-0003-3407-0210
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in the patient, and a multiple myeloma was detected in his bone marrow. Chemotherapy (cyclophosphamide and dexamethasone) was started. Our patient was in the postoperative 3rd year his general condition was good.

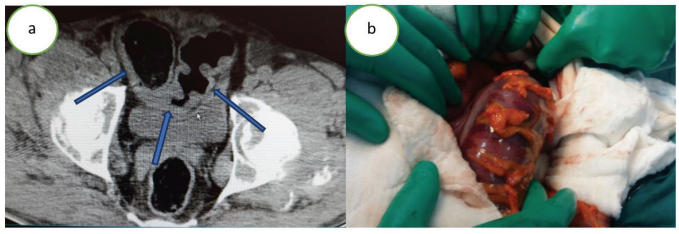

Figure 1. (a) Segmental wall thickness at the sigmoid colon on computed tomography; (b) Intra-operative view of the colon

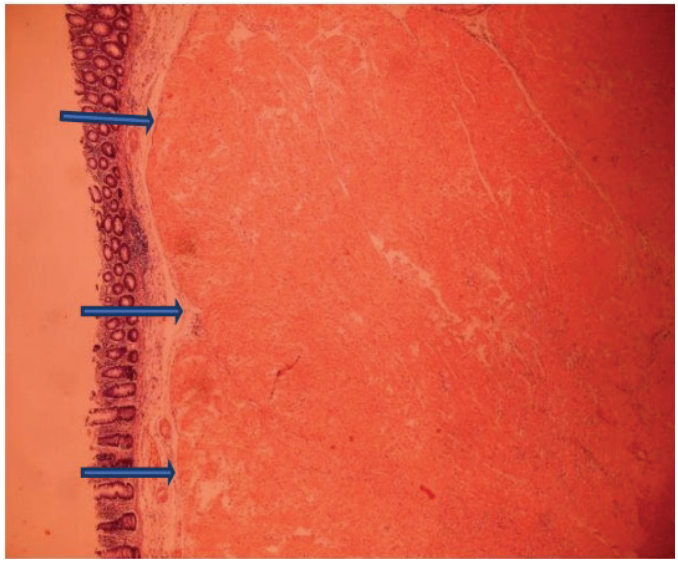

Figure 2. Accumulation of amyloid protein in the colon tissue staining orange (congo red; x4 magnification)

Discussion

Intestinal pseudo-obstruction is divided into three types according to the clinical course: Chronic intestinal pseudo-obstruction; Ogilvie's syndrome; and toxic megacolon.[7] When symptoms last longer than six months, the disease is defined as chronic intestinal pseudo-obstruction.[8] Intestinal pseudo-obstruction is divided into primary and secondary, according to etiology. Amyloidosis is one of the common reasons for secondary intestinal pseudo-obstruction.[9] It usually involves the large intestine but the small intestine may be involved.[7] There are two main subtypes of amyloidosis: Amyloidosis A (AA) and monoclonal immunoglobulin light chains amyloidosis (AL). While 15% of AL patients have multiple myeloma, AA patients are associated with chronic inflammatory, infectious, and neoplastic diseases.[10] In terms of intestinal maifestation, AL amyloidosis usually presents with constipation, mechanical obstruction, or chronic intestinal pseudo-obstruction, while AA amyloidosis presents with diarrhea and malabsorption.[11] In addition, when amyloid protein involvement of vascular structures of the intestine occur, it may be cause hemorrhage and hematoma.[12] Gastrointestinal involvement is mostly seen in the AA type.[10] The patient in the present case had findings of ileus, and he had applied to the emergency department with similar complaints many times in the course of the previous year. However, hemorrhage was not observed in this patient.

Gastrointestinal amyloidosis usually includes non-specific symptoms, and thus its diagnosis can be difficult.[12] Imaging methods and endoscopy can be useful. Plain X-rays may reveal paralytic ileus and "double halo" appearance may be present on CT.[13] Preoperative endoscopy was not performed in the present case, since the mass in the sigmoid colon was considered the primary neoplasm of the colon. There was mass in the sigmoid colon, and dilatation at proximal colon and small intestine on CT.

The aim of treatment of amyloidosis is to reduce the formation of amyloidogenic proteins that cause dysfunction in the organ/tissues. For this, the first-line recommended treatment is combination chemotherapy regimens that include high-dose chemotherapy, such as melphalan and dexamethasone, and hematopoietic stem cell transplantation. Prokinetic agents, parenteral nutrition and anti-diarrheal agents as supportive measures can be beneficial.[14] Complications due to amyloidotic involvement of the colon are very rare. Colectomy may be required in some cases.[4-6] Here, we report a case in which anterior resection and end-colostomy was performed with a preliminary diagnosis of acute abdomen, secondary to a primary neoplasm of the sigmoid colon. For this reason, chemotherapy was given in the postoperative period.

Conclusion

It should be kept in mind that colonic obstruction due to amyloidosis may develop in the colon and these patients may require emergency surgery. Therefore, secondary causes should be considered and further investigations should be performed in the patients with signs of pseudo-obstruction in the colon.

Ethics

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.Ç., A.A., B.K.O., Concept: İ.Ç., A.A., B.K.O., Design: İ.Ç., A.A., B.K.O., Data Collection or Processing: İ.Ç., A.A., B.K.O., Analysis or Interpretation:

İ.Ç., A.A., B.K.O., Literature Search: İ.Ç., A.A., B.K.O., Writing: İ.Ç., A.A., B.K.O.

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CASE REPORT

A Rare Cause of Recurrent Intestinal Obstruction: Abdominal Cocoon

Kasım Çağlayan[1], Tamer Sağıroğlu[1], Nurten Türkel Küçükmetin[2], Sibel Özkan Gürdal[1], Hadi Sasani[3]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Surgery, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Gastroenterology, Tekirdağ, Turkey
[3]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Turkey

ABSTRACT

Abdominal cocoon (AC) is a rare disease in which the small intestine is completely or partially surrounded by a thick fibrous membrane. A 56-year-old male patient was admitted to the hospital with complaints of abdominal pain, nausea and vomiting. It was observed that the small intestine segments from the Treitz ligament to the cecum were surrounded by a thick, fibrous peritoneum in the patient who was operated due to intestinal obstruction. The peritoneal sac was excised. Adhesions between the small intestine loops were separated and the small intestines were completely freed. The patient, whose complaints regressed in the postoperative period, was discharged on the seventh day. AC is a rare disease that causes intestinal obstruction. Preoperative diagnosis is based on a high index of suspicion along with imaging modalities because of clinically nonspecific findings.
Keywords: Abdominal cocoon, intestinal obstruction, diagnosis, treatment.

Introduction

Encapsulating peritoneal sclerosis (EPS) is a chronic inflammatory disease in which the small intestine is surrounded by a dense, fibro-collagenous membrane. This disease is divided into primary (idiopathic) and secondary EPS, caused by an underlying etiological factor.[1] Abdominal cocoon (AC), also known as idiopathic EPS and first described by Foo et al. in 1978, in which the small intestine is surrounded by a fibrous membrane. The disease has also been called idiopathic sclerosing peritonitis, primary sclerosing peritonitis, and sclerosing encapsulating peritonitis.[2] Clinical findings vary according to the severity of the disease, its duration, and the immunological status of the person.[1] There are usually signs and symptoms of acute or subacute intestinal obstruction. The etiology and pathogenesis are not exactly known. Preoperative diagnosis is difficult due to the lack of specific findings and is usually made by laparotomy and biopsy.[2,3]

In this article, the preoperative findings of a case with AC operated for intestinal obstruction, are presented and discussed in the light of literature.

Case Report

A 56-year-old male patient was admitted to the hospital with complaints of abdominal pain, nausea and vomiting. On physical examination, bowel sounds were normoactive, there was some abdominal tenderness but no defense or rebound was detected. He had no history of previous abdominal surgery or trauma. The patient did not have any comorbidity and did not use any medication. Standing, direct abdominal X-ray was evaluated as normal. On laboratory tests, leukocyte values were within normal limits. Abdominal ultrasonography showed free fluid between the intestinal loops in the lower abdominal quadrant. The patient's oral intake was discontinued. Intravenous (IV) fluid therapy was started and a nasogastric tube was inserted. After the partial regression of the patient's complaints, it was decided to continue medical treatment. In contrast enhanced (IV and oral) abdominal computed tomography (CT), the stomach was distended with the contrast agent, and the third and fourth parts of the duodenum were dilated. Minimal prominence in the jejunal structures and also fluid densities adjacent to the jejunal loops were observed. After the patient's complaints

Address for Correspondence: Kasım Çağlayan MD,
Tekirdağ Namık Kemal University Faculty of Medicine, Department of Surgery, Tekirdağ, Turkey
E-mail: kasimcaglayan@hotmail.com **ORCID ID:** orcid.org/0000-0001-8856-1969
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regressed, oral intake was started and the patient, who tolerated resumed oral intake, was discharged.

The patient presented with complaints of abdominal pain, nausea and vomiting one month later and was re-evaluated. Oral intake of the patient, whose leukocyte, urea and creatinine levels were found to be high, was discontinued. A nasogastric tube was inserted, IV fluid therapy and antibiotic therapy were started. Multiple air-fluid levels were observed at the small intestine level on the standing direct abdominal X-ray. Contrast-enhanced abdominal CT showed increased wall thickness at the stomach pyloric level and lesser curvature, and dilatation in the first, second and third parts of the duodenum. In the fourth part of the duodenum the aorto-mesenteric calibration was decreased, jejunal loops showed a tortuous course in the left upper quadrant of the abdomen, there was increased wall thickness in the jejunum and encapsulated fluid accumulation were observed (Figure 1). The patient underwent endoscopy under sedation anesthesia, which revealed that the gastric mucosa was edematous and the second and third segments of the duodenum were dilated. The jejunum was reached, but the lumen could not be opened in the proximal jejunum (Figure 2). Since the findings of intestinal obstruction did not regress, the decision was taken to proceed to surgery. The abdomen was entered with a midline incision. In the exploration, it was observed that a dense membrane surrounded the small intestines from the Treitz ligament to the cecum and the small intestines were intertwined, resembling an accordion (Figure 3, 4). Membranes were separated by blunt and sharp dissection and all small intestines were freed. The histopathology result reported

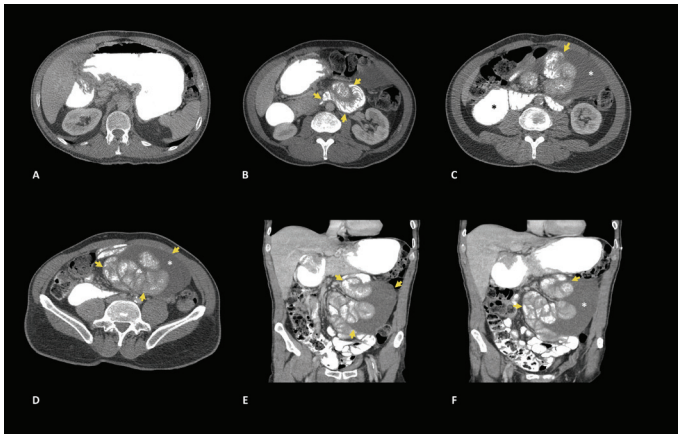

Figure 1. Axial (A-D) and coronal plane (E, F) contrast-enhanced abdominal computed tomography examination. Dilation in the second part of the duodenum (black asterisk, A-C), decrease in the calibration of the fourth part of the duodenum at the aortomesenteric level (C), starting from the duodenojejunal junction, encapsulated with the jejunal loops (yellow arrows) in accordion form and surrounded by the fluid density (white asterisk). Slight thickening of the jejunal loops and wall (B-F)

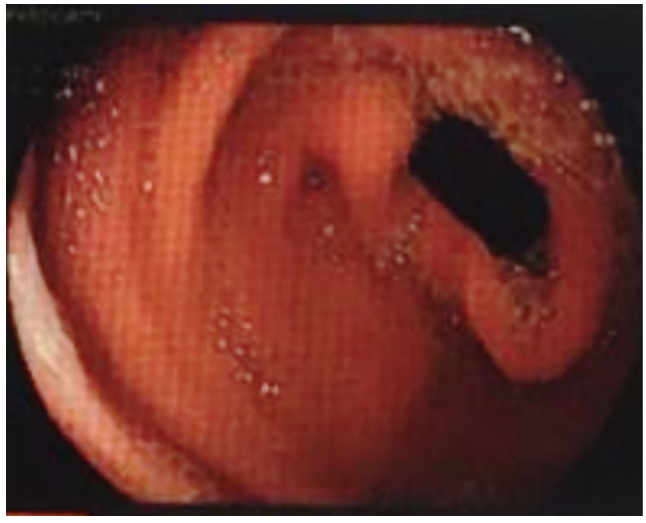

Figure 2. Jejunal segment stenosis was seen on endoscopy

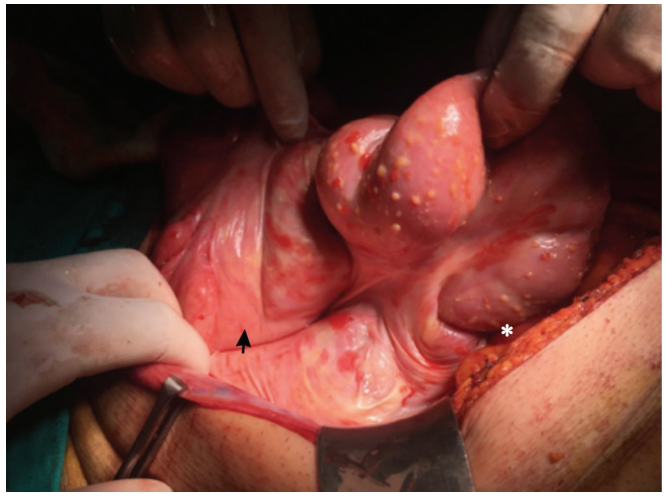

Figure 3. From the ligament of Treitz, there are thick dense membranes that completely surround the jejunal loops (arrow) and calcifications on the serosal surfaces (duodeno-jejunal junction: asterisk)

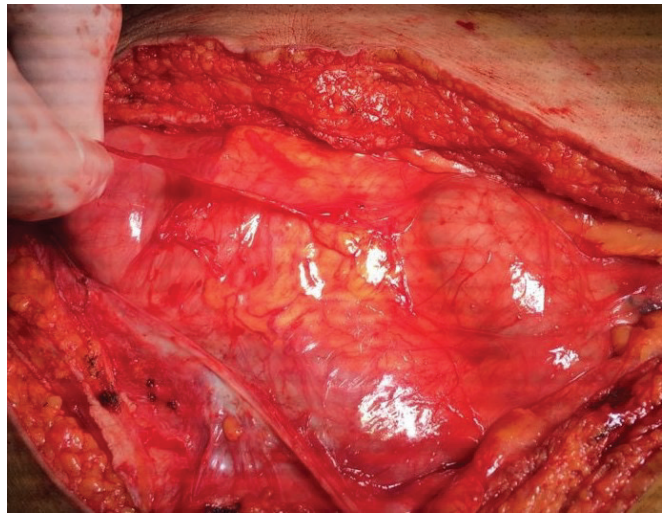

Figure 4. The dense membrane surrounding the small intestine is seen

tissue compatible with calcified, fibro-hyalinized cyst wall and capsule wall surrounding the small intestine.

The patient's complaints regressed in the postoperative follow-up, oral intake was started on the fifth postoperative day and the patient was discharged without any problem. At the time of writing the patient is in the sixth postoperative month and has no complaint. The patient was informed and informed consent was obtained.

Discussion

The etiology of AC is not known exactly. Although AC has classically been described in young adolescent women in tropical regions, it has also been reported in adult cases in temperate regions.[4] EPS is divided into primary and secondary according to its etiology and pathological features of the fibrocollagen membrane. Primary EPS, the idiopathic form, is known as AC, and although there is no underlying cause in this form, cytokines and fibroblasts have an effect on the formation of peritoneal fibrosis and neoangiogenesis. In secondary EPS, local or systemic factors initiate inflammatory processes in the peritoneum. Secondary EPS usually develops into chronic, asymptomatic peritonitis, such as endometriosis, retrograde menstruation, peritoneal dialysis, abdominal tuberculosis, abdominal trauma, and/or liver cirrhosis.[1,3,5]

Although there are clinical findings, such as recurrent abdominal pain, nausea, vomiting, loss of appetite, weight loss, malnutrition, acute or chronic intestinal obstruction attacks, and painless abdominal mass, some cases may be asymptomatic.[4] In the presented case, there were complaints of recurrent abdominal pain, nausea and vomiting for about a month.

On diagnostic imaging, air-fluid levels and enlarged bowel loops are seen on direct abdominal X-ray. Ultrasonography may show a three-layered bowel wall, dilated and adherent bowel loops to the posterior abdominal wall, loculated stomach acid and fibrous adhesions, and intertwined accordion-shaped bowel segments. However, CT may be more useful in early diagnosis and planning of optimal treatment. On CT, small bowel loops surrounded by thick membrane can be seen in the midline of the abdomen, helping to confirm a more precise diagnosis.[4] Findings such as peritoneal calcifications, peritoneal thickening, peritoneal clarification, loculated fluid collection, conglomerated bowel loops with fluid in the peritoneal cavity, small bowel loops surrounded by a thin membrane, thickening of the intestinal wall, and calcifications on the serosal surface of the intestine may be seen. It also provides information about complications and other causes of intestinal obstruction. In our case, diffuse air-fluid levels at the level of the small intestine were observed in the abdomen on direct X-ray. On contrast-enhanced CT, conglomerated small intestine segments in the left upper quadrant of the abdomen were detected.[4,6]

Preoperative diagnosis is challenging because the clinical findings are non-specific for diagnosis and thus a high index of clinical suspicion is required. Exclusion of other etiological factors that may cause obstruction in non-strangulated intestinal obstruction cases combined with clinical suspicion are important in preoperative diagnosis. Preoperative diagnosis helps for planning optimal treatment.[4] However, although all imaging methods, such as ultrasound or CT are used, the diagnosis is made incidentally during laparotomy in most cases.

Although it is often argued that surgical treatment is necessary, the treatment management of EPS is still a matter of debate. According to the literature, in cases with minimal symptoms, oral intake, resting the bowels, nasogastric decompression and parenteral nutrition can be done.[7] Many treatment options are recommended, such as surgical subtotal excision of the membrane, enterolysis, intubation of the small intestine, and medical treatment after exploratory laparotomy in cases with a high risk of bowel resection and perforation.[4] In order to avoid mortality and morbidity, such as postoperative anastomotic leakage and short bowel syndrome, it has been advised to free the intestines by separating the membranes with as little resection as possible in cases with normal intestinal viability.[4,8-10] In the current case, air-fluid levels were found in the small intestines on direct abdominal X-ray. No obvious pathology was detected in the abdominal ultrasound. In the CT of the abdomen with IV-oral contrast, dilated segments of the duodenum were detected and a tortuous appearance was evident in jejunal segments. Loculated fluid density was observed adjacent to the jejunal segment. The patient was taken to operation because his complaints did not regress despite medical treatment. During exploration, AC was considered and the small intestines were freed. No resection procedure was applied to the small intestines.

Conclusion

EPS is one of the rare causes of intestinal obstruction. Preoperative diagnosis is challenging due to the nonspecific clinical findings. Preoperative diagnosis is possible with the combination of high clinical suspicion and imaging findings. Based on the patient's history, peritoneal dialysis and peritoneal tuberculosis should be considered among the secondary causes. Cases without findings suggesting strangulation can be followed up with medical treatment. However, in cases where no diagnosis can be made or surgery is chosen based on clinical findings, we think

that enterolysis and membrane excision is sufficient while avoiding resection as far as is possible.and unless absolutely necessary.

Ethics

Informed Consent: The patient was informed and informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.S., K.Ç., N.T.K., Concept: K.Ç., T.S., S.Ö.G., Design: K.Ç., T.S., H.S., S.Ö.G., Data Collection or Processing: K.Ç., N.T.K., H.S., T.S., Analysis or Interpretation: K.Ç., H.S., N.T.K., Literature Search: K.Ç., N.T.K., S.Ö.G., Writing: K.Ç., T.S., N.T.K.

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

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CASE REPORT

A Rare Cause of Gastrointestinal Bleeding: Jejunal Angiodysplasia

Kasım Çağlayan[1], Tamer Sağıroğlu[1], Nurten Türkel Küçükmetin[2], Sibel Özkan Gürdal[1], Hadi Sasani[3]

[1]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Surgery, Tekirdağ, Turkey
[2]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Gastroenterology, Tekirdağ, Turkey
[3]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Radiology, Tekirdağ, Turkey

ABSTRACT

In this article, the diagnosis and treatment process of a case examined for gastrointestinal system (GIS) bleeding and found to have jejunal angiodysplasia (JA) is presented. A 65-year-old female was examined due to intermittent melena persisting for about one year. Laboratory findings were unremarkable, except for iron deficiency anemia. Upper GIS endoscopy, colonoscopy, computed tomography (CT) and CT angiography were normal. Capsule endoscopy revealed multiple lesions consistent with angiodysplasia in the proximal jejunum. Intra-operative enteroscopy revealed multiple JAs between 10 and 20 cm from the Ligament of Trietz. The patient underwent segmental resection and was discharged on the seventh postoperative day.

Keywords: Jejunal angiodysplasia, capsule endoscopy, intraoperative enteroscopy

Introduction

Although intestinal vascular malformations are rare, they should be kept in mind in the differential diagnosis of gastrointestinal system (GIS) bleeding and chronic anemia. Approximately 4% of all GIS bleeds originate from the small intestine.[1] Although angiodysplasia is a common pathology in the gastrointestinal tract, only 15% of the lesions are seen in the small intestine and 77% in the cecum or ascending colon. Angiodysplasia results from ectasia of submucosal vessels and although the mechanism of formation is not fully understood, it is thought to be caused by chronic venous obstruction.[2] Endoscopic examinations, such as gastroscopy, colonoscopy, enteroscopy, and intraoperative enteroscopy, multidetector computed tomography (CT), magnetic resonance angiography, and capsule endoscopy are the methods used for diagnosis.[1,2]

Case Report

A 65-year-old female was admitted with complaints of persistent weakness and palpitation for about one year. Iron deficiency anemia was detected in the blood tests performed elsewhere and iron replacement therapy was started. She was referred to our hospital for examination due resumption of complaints a few months after the medical treatment and a decrease in the routine follow-up hematocrit. On physical examination, the skin and conjunctiva were pale, S1 and S2 sounds were tachycardic (104/min/rhythmic). Melena was detected on rectal examination. Laboratory results were: hematocrit 24.1% (normal range: 35-47%); hemoglobin 7.41 g/dL (normal range: 12.5-16.0 g/dL); ferritin 15.89 ng/mL (normal range: 13-150 ng/mL); iron level: 16.0 µg/dL (normal range: 37-145 µg/dL); iron binding capacity: 435 µg/dL (normal range: 135-392 µg/dL). Iron deficiency due to GI bleeding was considered and etiological investigation was performed. No pathology was detected on gastroscopy and colonoscopy and combined intravenous and oral contrast-enhanced CT (portal phase) was evaluated as normal. Capsule endoscopy was performed with a Pillcam II capsule whose angiography was performed and no bleeding focus could be detected. The capsule passed to the duodenum at approximately 28 minutes and to the colon at the fourth hour. At about 67-69 minutes of capsule transit multiple

Address for Correspondence: Kasım Çağlayan MD,
Tekirdağ Namık Kemal University Faculty of Medicine, Department of Surgery, Tekirdağ, Turkey
E-mail: kasimcaglayan@hotmail.com **ORCID ID:** orcid.org/0000-0001-8856-1969
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lesions consistent with angiodysplasia were detected in the proximal jejunum (Figure 1). Other regions of the GIS were evaluated as normal. Despite medical treatment, the patient's blood values did not normalize and surgery was decided. Preoperatively, two erythrocyte suspensions were transfused. Laparotomy was performed under general anesthesia. On exploration, edema and dilatation were detected in the jejunal segment approximately 40 cm from the Ligament of Trietz, and enterotomy was performed just distal to the dilated segment and enteroscopy was performed intra-operatively. On enteroscopy, multiple angiodysplastic lesions were seen between 10 and 20 cm from the Ligament of Trietz (Figure 2). Segmental jejunal resection to include the lesions was performed and end-to-end anastomosis was used. The patient was discharged on the seventh postoperative day. At the six-month follow-up, hemoglobin (12.5 g/dL) and hematocrit (36.5%) values were within normal limits. Informed consent was obtained.

Discussion

Gastrointestinal angiodysplasia (GIAD) is an acquired vascular lesion, which typically presents as bright red, irregular, round, slightly raised lesions on visualization. Intestinal angiodysplasias are frequently seen in patients over 60 years of age and are usually localized to the cecum and ascending colon. GIAD was defined in 1974 as a single or multiple vascular superficial lesion that develops from the mucosa or submucosa of the gastrointestinal tract. Today, these lesions are generally referred to as arterio-venous malformation, telangiectasia, angiectasia, or vascular ectasia. This disease increases at similar rates in both genders and after the age of 60, usually in predisposing conditions, such as aortic stenosis, chronic renal failure and von Willebrand's disease, atherosclerosis, cirrhosis or pulmonary disease.[3,4] Although there are some hypotheses about the etiological mechanism, there is as yet no consensus. It has been suggested that the etiology is multifactorial and may involve mild chronic venous obstruction, chronic mucosal ischemia, and potential underlying causes such as comorbidities.

Figure 1. Capsule endoscopy shows multiple angiodysplastic lesions in the jejunal loops (arrows)

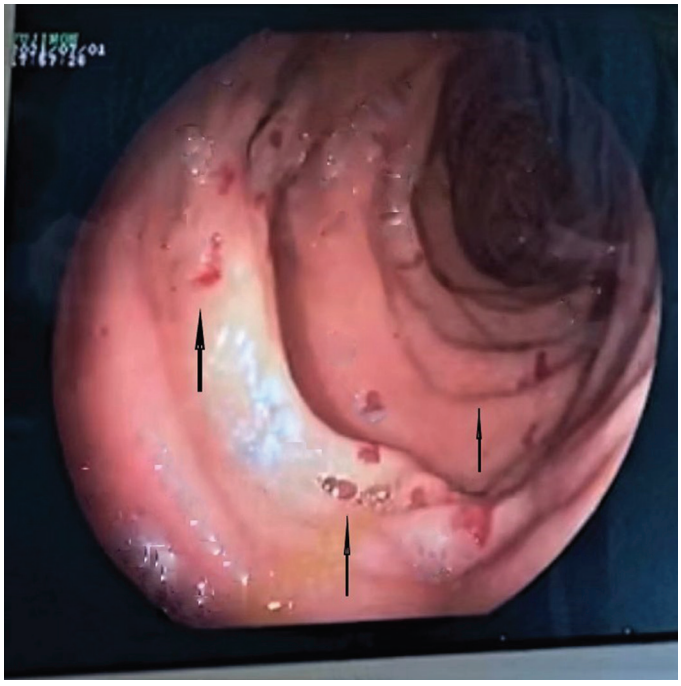

Figure 2. Multiple lesions are seen on intra-operative enteroscopy (arrows)

Since GIADs are mostly asymptomatic, the true prevalence is not known, and they are usually diagnosed in investigations due to unrelated symptoms. Symptomatic GIADs can cause life-threatening heavy bleeding from occult bleeding. Depending on the location of the lesions, the findings may present as hematochezia, melena, or hematemesis. Although the first bleeding stops spontaneously in approximately 90% of cases, there is a tendency to re-bleed. Factors leading to rebleeding include previous bleeding history, history of heart disease, valve abnormalities, arrhythmias, chronic kidney disease, anticoagulant use, cirrhosis, and the presence of multiple angiodysplasia.[5,6] In the current case, melena was detected as a sign of GIS bleeding. In the laboratory findings of the patient, iron deficiency anemia was detected due to

of the patient, iron deficiency anemia was detected due to chronic blood loss, but acute bleeding attacks that could threaten the patient's life were not observed.

Direct endoscopic imaging is the gold standard in the diagnosis of GIAD. On endoscopy, the lesions appear as thin-walled, dot-shaped, mucosal lesions, usually 5-10 mm in size, with a cherry red color and pale surrounding mucosa. Approximately 10-15% of GIADs are located in the small intestine. Small intestines are difficult to investigate due to their anatomically long and curved nature. However, it is possible to overcome this difficulty with a non-invasive method, such as capsule endoscopy. Although there is a high probability of false negatives in capsule endoscopy, there better accuracy with the combined use of capsule and balloon endoscopy. CT angiography, MRI, and radionucleotide scans are potential imaging options for location of acute hemorrhages.[6,7] In the present case, gastroscopy and colonoscopy were performed primarily for diagnosis and CT angiography was performed when the lesion could not be detected. However capsule endoscopy was performed as the diagnosis could not be made. On capsule endoscopy, multiple angiodysplastic lesions were detected in the jejunal proximal segments.

Although there is a tendency to rebleed from multiple lesions, the treatment options for GIADs are still controversial, as bleeding stops spontaneously in approximately 90% of cases. In clinical practice, an individual decision is made about the treatment approach according to the patient's condition. In the literature, hormones (estrogen and progesterone), somatostatin analogs and antiangiogenic drugs are included in the treatment as pharmacological agents.[8] In general, conservative treatments, such as correction of anemia can be performed in asymptomatic cases, but pharmacological treatments are not appropriate in cases that need transfusion.[6] GIAD treatment options, other than pharmacological agents, include endoscopic treatments (argon plasma coagulation, mechanical clip placement, multipolar electrocoagulation, laser photoablation, sclerotherapy, and band ligation), angiographic embolization, and surgical resection. Despite the rates of recurrent bleeding, endoscopic methods are effective in the initial treatment of GIADs.[5] Surgical interventions may be considered in cases where endoscopic or radiological hemostasis cannot be achieved.[6,9] Examination of the entire small intestine with intra-operative enteroscopy during surgery is an appropriate approach. In the current case, surgical treatment was chosen because the patient needed continuous blood transfusions and curative treatment was technically unfeasible with endoscopic or radiological methods. After multiple angiodysplastic foci were detected in the proximal jejunum by capsule endoscopy, resection margins were determined to include all angiodysplastic foci, aided by intra-operative enteroscopy, and a segment of approximately 30 cm was resected.

JA(s) constitutes a small proportion of the etiologies of GIS bleeds, and angiodysplasias should be considered in patients without pathology in the upper and lower endoscopic examinations. Capsule endoscopy is an important diagnostic method for location in cases without acute bleeding but may be combined with balloon endoscopy. Intra-operative enteroscopy has an important place in determining the exact location and extent of the lesions and determining the resection margins in cases undergoing surgical resection.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.S., K.Ç., N.T.K., Concept: K.Ç., T.S., S.Ö.G., Design: K.Ç., T.S., H.S., S.Ö.G., Data Collection or Processing: K.Ç., N.T.K., H.S., T.S., Analysis or Interpretation: K.Ç., H.S., N.T.K., Literature Search: K.Ç., N.T.K., S.Ö.G., Writing: K.Ç., T.S., N.T.K.

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CASE REPORT

A Rare Multiple Primary Cancer: A Case Report of Quadruple Primary Cancer

Zafer Şenol[1], Bülent Güleç[1], Taygun Gülşen[1], Neslihan Kaya Terzi[2]

[1]University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Medical Patology, İstanbul, Turkey

ABSTRACT

Multiple primary tumors, especially quadruple primary cancers, are extremely rare with a reported incidence of 0.007%. In this study, a very rare case of quadruple primary cancer found and treated in a 74-year-old male patient over a 15-year period is presented.
Keywords: Multiple primary cancer, quadruple primary cancer, cancer

Introduction

Multiple primary cancer is the detection of two or more cancer types that are histologically unrelated to each other in the same or different organs of a patient. From this definition it is clear that metastasis must be excluded. Multiple primary cancers account for 2-6.3% of all cancers. With the development of diagnostic techniques and prolongation of life expectancy, patients with multiple primary cancers are being reported more frequently and the vast majority of these are patients in whom two different types of cancer have been described. As the number of primary cancer types included in multiple primary cancers increases, the incidence decreases. The incidence of quadruple primary cancer is less than 0.1%.[1] In this study, a patient with multiple primary cancer with four different types of malignancy, namely laryngeal, lung, prostate and colon cancer, is presented.

Case Report

In this study, a 74-year-old male patient with four types of primary cancer is presented. There was no history of cancer in the mother, father and children. Laryngopharyngectomy and adjuvant radiotherapy were performed with the diagnosis of squamous cell carcinoma located in the hypopharynx. Due to palpation of hard lymphadenopathy in the left neck during radiotherapy, the treatment was interrupted and left neck dissection was performed. Since no malignancy was detected in the pathological examination of the neck dissection material, the adjuvant radiotherapy program was continued and completed.

The patient was admitted to the urology clinic of our hospital with the complaint of inability to urinate in 2018 and was diagnosed as having prostate cancer by biopsy after further examination and treatment. On April 10, 2018, transurethral resection of the prostate (TUR-P) was performed. He was diagnosed as having prostatic acinar adenocarcinoma in TUR-P material. In the immunophenotypic examination of the material, positive staining was observed in the tumoral glands for prostate specific antigen (PSA) and alpha-methylacyl-CoA racemase. No positive staining was observed for p63 protein and high molecular weight cytokeratin.

The patient was admitted to the chest diseases outpatient clinic of our hospital with the complaint of cough in October 2018, and a mass lesion suspicious for cancer was observed on thorax tomography in the upper lobe of the right lung (Figure 1).

A diagnosis of pulmonary adenocarcinoma was made on October 16, 2018 by transthoracic biopsy. With staging suggesting locoregional early stage lung adenocarcinoma, chemoradiotherapy treatment was started. Colonoscopic evaluation was performed after detecting a hypermetabolic

Address for Correspondence: Zafer Şenol, MD,
University of Health Sciences Turkey, Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of General Surgery, İstanbul, Turkey
E-mail: zafersenol@yahoo.com **ORCID ID:** orcid.org/0000-0002-6865-3716
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area in the sigmoid colon on positron-emission tomography computed tomography during follow-up imaging. The colonoscopy revealed a tumor suspicious lesion in the sigmoid colon and a diagnosis of colonic type adenocarcinoma was made from the biopsies taken. In the immunophenotypic examination of the colon biopsy material, focal positive staining with cytokeratin 20, positive staining with CDX2, negative staining with PSA, negative staining with thyroid transcription factor 1 and NAPSIN A, used a double marker for lung adenocarcinoma, were observed. The patient, who was evaluated to be in the early stage both clinically and radiologically, underwent sigmoid colon resection on October 4, 2019, and the diagnosis of colonic adenocarcinoma was confirmed in the resection material.

Hematoxylin eosin and immunohistochemistry stained light microscopy images of prostate, colon, pericolonic lymph node and lung tumoral tissues are shown in Figure 2.

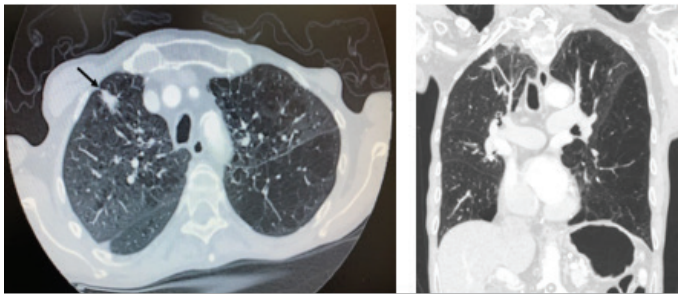

Figure 1. Mass detected in the upper lobe of the right lung on thorax CT
CT: Computed tomography

Discussion

More cases of multiple primary tumors have been identified due to advances in diagnostic techniques and prolongation of patient survival. However, among multiple primary cancers, quadruple cancers are still extremely rare with an incidence of 0.007%.[1]

Multiple primary cancer was first described by Billroth and von Winiwarter[2] in a case report. Diagnostic criteria for multiple primary cancer were defined by Warren and Gates[3] in 1932 and these criteria are still used today. Accordingly, each cancer should be histopathologically proven, cancer types should be histologically different, and the possibility of metastasis should be excluded. In the presented patient, four different primary cancer types, hypopharynx, prostate, lung and colon, were diagnosed histopathologically with typical immunophenotypic evidence.

According to the Warren and Gates[3] criteria, it is not always easy to distinguish multiple primary cancers from multicentric cancers. Therefore, Moertel et al.[4] created a new classification for multiple primary cancers. This classification is also widely used today. According to this classification, three groups are defined; Group 1 includes multiple primary cancers originating in organs with the same histology, while Group 2 includes multiple primary cancers originating from different tissues. Group 3, on the other hand, is the presence of primary cancer in different tissues or organs together with Group 1 in the presence of three or more primary cancers. Three subgroups are defined in Group 1, namely A, B and C. Group 1A includes primary cancer in the same tissues and organs, Group 1B includes primary cancer in the same tissue and different organs, and Group 1C includes primary cancer in bilateral organs. Our patient fits Group 3 in this classification.

Moertel et al.[5] classified multiple primary cancers into two groups as synchronous and metachronous according to the time between the occurrence of the malignancies included.

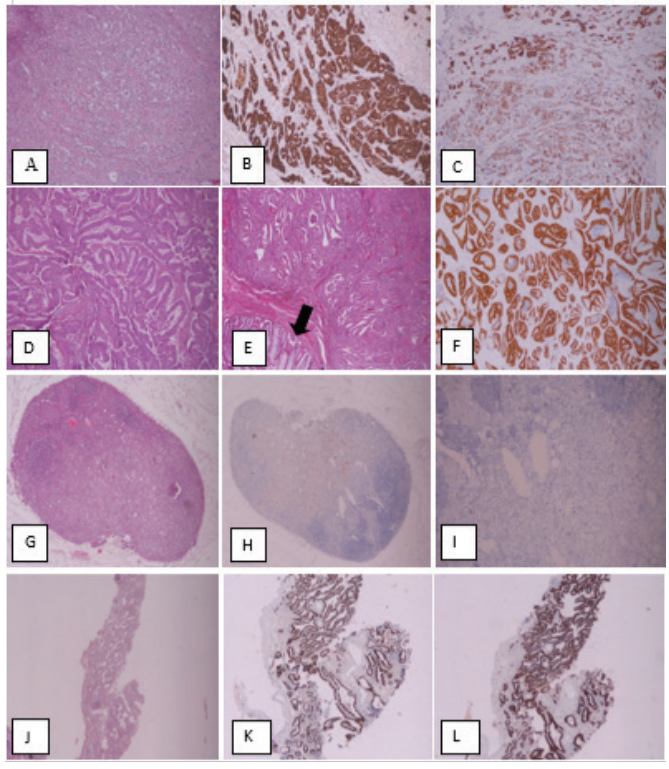

Figure 2. Microscopic examination of prostatic acinar adenocarcinoma (A-C), colon adenocarcinoma (D-F), metastatic pericolonic lymph node (G-I), and lung adenocarcinoma (J-L) Characteristic features of prostate adenocarcinoma (A), Tumor cells show cytoplasmic expression with immunohistochemical AMACR (B), Tumor cells show focal nuclear positivity with immunohistochemical p63 (C), Glandular pattern of colonic adenocarcinoma (D), Colon adenocarcinoma and non-tumor colonic mucosa (black arrow) (E), Tumor cells show cytoplasmic expression with immunohistochemical CDX2 (F), Pericolonic lymph node shows tumoral metastasis (G), Tumor cells show focal nuclear positivity with immunohistochemical p63 (H), Prostatic specific acid phosphatase (PSAP) staining shows positive for tumor cells (I), Lepidic pattern of lung adenocarcinoma (J), Tumor cells show nuclear expression with TTF-1 immunohistochemically (K), Tumor cells show cytoplasmic expression with immunohistochemical CK-7 (L)

Accordingly, if there is less than six months between the definitions/occurrence of primary cancers, these tumors are synchronous while primary tumors with a duration of more than six months are called metachronous. In the presented patient, tumors fit into the metachronous tumor class because of the duration of more than 6 months among the four tumors described. The mechanisms of occurrence of multiple primary cancers are not fully known. However, many hypotheses have been described, such as family history, immunological and genetic defects, prolonged exposure to carcinogens with similar characteristics, or receiving chemotherapy/radiotherapy for primary cancer. The presented patient has no known family history of cancer. However, he had a history of adjuvant radiotherapy due to the diagnosis of squamous cell carcinoma with location in the hypopharynx, which was the first cancer he was diagnosed as having. Post-radiotherapy-associated tumors are generally seen after 10 years, and they are known to be more likely to have sarcoma-type histology.[6] Again, among the chemotherapy-related secondary tumors, hematolymphoid neoplasms have been defined most frequently.[7] All of the tumors described in the presented patient were in the carcinoma group.

There is no established treatment rule in the treatment of multiple primary cancers. Optimal treatment should be determined by considering the type of cancer, the stage of the disease, the response to treatment, the expected life expectancy, and the general condition of the patient.

While retrospectively examining the extremely rare multiple primary cancers presented in this study, the importance of knowing the medical history of previous disease and their specific diagnostic evidence when evaluating patients with cancer was highlighted. Similarly, accurate and complete immunophenotypic studies in determining the histopathological types of tumors reveal the importance of distinguishing separate primary tumors from metastatic tumors. In some cases where the same histological type, for example squamous cell carcinoma, is shown in different locations, the differentiation of multiple primary and metastases may be more difficult, and in such cases the molecular characteristics of the tumors become increasingly important.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the presented study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.Ş., B.G., T.G., N.K.T., Design: Z.Ş., B.G., T.G., N.K.T., Data Collection or Processing: Z.Ş., B.G., T.G., N.K.T., Analysis or Interpretation: Z.Ş., B.G., T.G., N.K.T., Literature Search: Z.Ş., B.G., T.G., N.K.T., Writing: Z.Ş., B.G., T.G., N.K.T.

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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VIDEO ARTICLE

Wide Local Excision for Perianal Paget's Disease

Özgen Işık, Murat Şen, Burak Bakar, Tuncay Yılmazlar

Bursa Uludağ University Faculty of Medicine, Department of Surgery, Bursa, Turkey

ABSTRACT

Primary perianal Paget's disease (PPD) is extramammarian Paget's disease of the perianal skin without underlying cancer. In this video, we present a 53-year-old female with PPD who underwent wide local excision (WLE) with split thickness skin grafting (STSG). WLE is the procedure of choice in the treatment of primary PPD and the defect may successfully be reconstructed with STSG.
Keywords: Paget's disease, perianal, wide local excision

Introduction

This video (Video 1) presents the treatment of primary perianal Paget's disease (PPD). Primary PPD is extramammarian Paget's disease of the perianal skin without underlying cancer, such as anal canal or rectal carcinoma.[1,2]

The patient was a 53 year-old female with biopsy-proven primary PPD. All the diagnostic work up was performed in order to rule out underlying cancer and all results suggested there was none. The only abnormal laboratory test was an increased carcinoembriogenic antigen level of 10.6 ng/mL (laboratory range 0-5 ng/mL).

Mechanical bowel preparation was performed on the day before surgery. The patient underwent wide local excision (WLE) and split thickness skin graft (STSG) reconstruction in lithotomy position. A rubber rectal tube was placed for facilitating passing flatus and keeping the wound clean. The patient tolerated a fluid diet on postoperative day 1. She had pain at the perineum and the skin graft harvest site. The rectal tube and the wound dressings were removed on postoperative day 3 and she was discharged on postoperative day 4. The wound healed without complications and with acceptable cosmetic outcome.

WLE is the procedure of choice in the treatment of primary PPD. STSG is useful in reconstructing the perianal skin defect.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.I., M.Ş., B.B., Concept: Ö.I., T.Y., Design: Ö.I., T.Y., Data Collection or Processing: Ö.I., M.Ş., Analysis or Interpretation: Ö.I., B.B., T.Y., Literature Search: Ö.I., B.B., T.Y., Writing: Ö.I., M.Ş.

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Video 1.
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Address for Correspondence: Özgen Işık, MD,
Bursa Uludağ University Faculty of Medicine, Department of Surgery, Bursa, Turkey
E-mail: drozgen006@gmail.com **ORCID ID:** orcid.org/0000-0002-9541-5035
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