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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, 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.

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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.

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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

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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.

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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.

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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).

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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.

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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. 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"

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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.

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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).

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

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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.

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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.

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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

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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.

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RESEARCH ARTICLE

Comparison of Surgical and Oncological Outcomes Between Sporadic and Familial Adenomatous Polyposis-Associated Abdominal Desmoid Tumors: A Single Center Retrospective Study

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ABSTRACT

Aim: Desmoid tumors (DT) originate in musculoaponeurotic tissues. However, there is scarce data regarding DT-related clinical and oncological outcomes. This study presents the oncological outcomes of patients who underwent surgery for abdominal DT in our clinic over a 10-year period and compares the outcomes between sporadic and familial adenomatous polyposis (FAP)-associated DTs.

Method: The records of patients who underwent surgery for DT between January 2011 and 2021 were retrospectively analyzed.

Results: The study included 18 patients, of which 15 were female, and with a median age of 43 (range: 21-59) years. Of the 18 cases, four developed DT following surgery for FAP coli syndrome. The mean age was lower in patients with FAP-associated DTs than in those with non-FAP-associated tumors (28 vs. 46.5 years, p=0.574). After a follow-up period of 68.1 months (95% confidence interval: 12,799-123,519), four patients developed recurrence, and the recurrence rate was higher (50% vs. 14.28%, p=0.130). Additionally, the time to recurrence was shorter in patients with FAP-associated DTs than in those without FAP (31.3 vs. 120.9 months, p=0.028). The tumor board decided that adjuvant tyrosine kinase inhibitor therapy would be administered to four patients and adjuvant 50.4 Gy radiotherapy to three patients.

Conclusion: DT are more common in women. As recurrence is more common and the time from index surgery to recurrence is shorter in patients with FAP-associated DTs, more intensive follow-up protocols would be necessary in this group.

Keywords: Desmoid, familial adenomatous polyposis, surgery

Introduction

Desmoid tumor (DT), known also as desmoid-type fibromatosis, is a monoclonal, non-metastatic, locally aggressive, sometimes multifocal, and fibroblastic proliferative disease that originates from connective tissues.[1] The incidence of DT is very low, with only 2-4 new cases per million each year. Approximately 85-90% of DT cases are sporadic and harbor mutations in the β-catenin-encoding *CTNNB1* gene, while the remaining 10-15% of cases are associated with familial adenomatous polyposis (FAP) and harbor germline APC mutations.[2,3]

The biology of DT that can point to a standard therapeutic approach is poorly understood. Several treatment options are available for DTs, including antiestrogen therapy, non-steroidal anti-inflammatory drugs, radiotherapy, chemotherapy, and surgical resection. Due to its local aggressiveness and non-metastatic nature, complete macroscopic surgery has been the standard approach for many years. However, many questions remain unanswered regarding early diagnosis, the role of surgery (indication, role, timing, and scope), and the place of conservative therapy. Despite radical local treatment, local recurrence or regional spread in many patients has led to difficulties in the management of patients with DT.[3-5]

There are several differences between sporadic and FAP-associated DTs in terms of the demographic characteristics, clinical behaviors, and mutational statuses.[6,7] Sporadic DTs

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can occur in any part of the body but are often located in the abdominal wall and limbs, whereas FAP-associated DTs are more commonly located intra-abdominally.[4,8]

There are limited studies in the literature comparing the clinical characteristics and management of sporadic and FAP-related DTs, and the question of how the emerging characteristics of this rare tumor affect its clinical management has not yet been fully addressed.[6,7] The present study compares the clinical characteristics of sporadic and FAP-associated DTs as well as their surgical outcomes.

Materials and Methods

The Çukurova University Local Ethics Committee's approval was gained for the study (approval number: 114/31, date: 10.09.2021), which included patients who underwent surgical therapy for DT between January 2011 and 2021. The patients' medical records were reviewed retrospectively for the collection of clinical data. In our institution, all patients diagnosed with DTs were treated following the clinical management guidelines for FAP,[9] in which an intraoperative diagnosis or clinical diagnosis during follow-up with computed tomography (CT) or magnetic resonance imaging (MRI) is considered sufficient. For patients with sporadic DTs, the histopathological confirmation of the diagnosis was mandatory, especially for differential diagnoses such as malignant mesenchymal tumors.

The patients were divided into the following two groups: group 1 included patients with sporadic DTs, and group 2 featured those with FAP-associated DTs. The two groups' demographic and clinical characteristics, presenting symptoms, medical history, applied surgical therapy, tumor size, surgical margin positivity, need for reoperation, need for chemotherapy/radiotherapy during the follow-up, presence of recurrence, time to recurrence, and size of recurrence masses were compared.

The extent of surgical resection aimed to obtain a negative surgical margin. Adjuvant treatments were decided by considering tumor-related and patient-based factors in the multidisciplinary tumor council, accompanied by the guidelines shown in Figure 1.[2,3] Patients with DT were routinely followed up in the clinic with a CT or MRI every 4-6 months for the first 2 years of treatment and then every 12 months until the disease was documented as sustained and stable.

Statistical Analysis

A statistical analysis of the study data was carried out with IBM SPSS Statistics (version 23.0. Armonk, NY: IBM Corp.). Descriptive statistics were presented as the mean, standard deviation, median, frequency, ratio, and minimum/maximum. A Shapiro-Wilk test was used to assess the normality of the continuous variables; a Mann-Whitney U test was used to compare non-normally distributed data; and Pearson's chi-square, Fisher-Freeman-Halton, and Fisher's exact tests were used for the comparison of categorical variables. A Kaplan-Meier analysis and log-rank test were used for the survival analyses. The level of statistical significance was set at 0.05 for all tests.

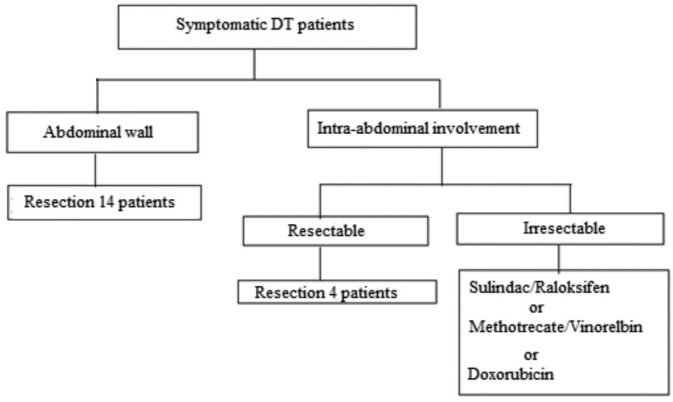

Figure 1. Treatment algorithm
DT: Desmoid tumors

Results

Of the 18 patients included in the study, four developed FAP-associated DTs. There was a female predominance in both groups (78.6% vs. 100% p=0.574), and comorbidities were more common in group 1 (57.1% vs. 0%, p=0.43). The demographic and clinical characteristics are presented in Table 1.

The development of tumors in the location of previous surgical incisions was common in both groups (50% vs. 75%, p=0.375), and the tumor size was similar in the two groups (6.6 cm vs. 11.5 cm, p=0.192). Surgical treatment was applied to one patient in group 2 due to recurrence, and local excision with intestinal resection was performed in this patient. Local excision was performed in two patients with recurrence in group 2. The conducted surgical procedures are presented in Table 2.

Oncologic follow-up data are presented in Table 3. Although the difference was statistically insignificant, recurrence was more frequent in group 2 patients (14.3% vs. 50%, p=0.13) (Figure 2). The time to recurrence was shorter in group 2 than in group 1 (31.3 vs. 120.9 months, p=0.028) (Table 3). In line with the tumor board's decision, adjuvant tyrosine kinase inhibitor therapy was applied to four patients after the first surgery, and adjuvant 50.4 Gy radiotherapy was applied to three patients after the second surgery.

Table 1. Patient demographics

	Sporadic DT, (n=14)	FAP-associated DT, (n=4)	Total, (n=18)	
	n (%)	n (%)	n (%)	
Gender				
Male	3 (21.4)	0 (0)	3 (16.7)	0.310
Female	11 (78.6)	4 (100)	15 (83.3)	
Age	46.5 (26-59)	28 (21-33)	43 (21-59)	0.574
Comorbidities				
No	6 (42.9)	4 (100)	10 (55.6)	0.043
Yes	8 (57.1)	0 (0)	8 (444)	
Previous surgery				
No	4 (28.6)	0 (0)	4 (22.2)	0.225
Yes	10 (71.4)	4 (100)	14 (77.8)	
Symptoms				
Palpable mass	6 (42.9)	2 (50)	8 (44.4)	0.800
Abdominal pain	8 (57.1)	2 (50)	10 (55.6)	
Localization				
Intra-abdominal	1 (7.1)	0	1 (5.6)	
Anterior abdominal wall	13 (92.9)	1 (25)	14 (77.8)	0.002
Intra-abdominal + anterior abdominal wall	0	3 (75)	3 (16.7)	

DT: Desmoid tumors, FAP: Familial adenomatous polyposis

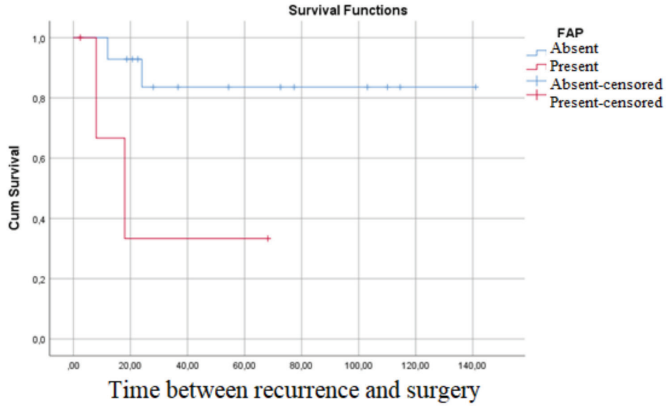

Figure 2. Kaplan-Meier curves for local recurrence rates in group 1 and group 2

FAP: Familial adenomatous polyposis

Discussion

By comparing sporadic and FAP-associated DTs, the present study has revealed that FAP-associated DTs recurred faster and more often. There is evidence that FAP-associated DTs represent a challenging disease. Compared with sporadic tumors, FAP-associated DTs have been reported to originate more often from more critical anatomical regions, have a higher risk of complications, and have a higher chance of being intra-abdominal.[3] In this study, DTs in FAP patients also tended to be located in a complicated intra-abdominal region. Contrary to previous findings, there was no size difference between the sporadic tumors and FAP-associated tumors.[6]

A study of the literature comparing the characteristics of sporadic and FAP-associated desmoid-type fibromatoses revealed FAP in 70 (16%) out of 447 DT patients,[10] which is a lower rate than reported in the present study (22%).[6,7] Some patients who present with sporadic desmoid-type fibromatoses may have undiagnosed FAP, and these patients may benefit from screening colonoscopy.

The female predominance reported in DTs in earlier studies[7,11] is supported by the present study, and although this is associated with DT expressing estrogen receptors, and thus being exposed to the proliferative effect of estrogen, the exact mechanism is unknown. While some studies failed to establish a significant age difference between DT development in FAP and non-FAP settings,[10] other have

Table 2. Surgical outcomes

		Sporadic DT, (n=14) n (%)	FAP-associated DT, (n=4) n (%)	Total, (n=18)	
Location of desmoid tumor previous surgical incision					
No		7 (50)	1 (25)	8 (44.4)	0.375
Yes		7 (50)	3 (75)	10 (55.6)	
Surgery					
Debulking + right oophorectomy		0 (0)	1 (25)	1 (5.6)	
Local excision		13 (92.5)	2 (50)	14 (77.8)	0.158
Local excision + segmental small bowel resection		1 (7.5)	1 (25)	2 (11.1)	
Surgical margin positivity					
No		12 (85.7)	3 (75)	15 (83.3)	0.612
Yes		2 (14.3)	1 (25)	3 (16.7)	
Size		6.5 (3-23)	11.5 (4-23)	7 (3-23)	0.192
Secondary surgery					
No		10 (71.4)	3 (75)	13 (72.2)	0.888
Yes		4 (28.6)	1 (25)	5 (27.8)	
Reason for secondary surgery	Metachronous recurrence	2 (50)	1 (100)	3 (60)	N/A
	Positive surgical margins	2 (50)		2 (40)	
Secondary surgical procedure	Local excision	2 (50)	0	2 (40)	291
	Local excision + intestinal resection	0	1 (100)	1 (20)	
	Re-excision for positive surgical margin	2 (50)	0	2 (40)	

DT: Desmoid tumors, FAP: Familial adenomatous polyposis, N/A: Not applicable

Table 3. Oncological follow-up data

	Sporadic DT, (n=14) n (%)	FAP-associated DT (n=4) n (%)	Total, (n=18) n (%)	
Chemotherapy				
No	11 (78.6)	2 (50)	13 (72.2)	0.261
Yes	3 (21.4)	2 (50)	5 (27.8)	
Radiotherapy				
No	12 (85.7)	3 (75)	15 (83.3)	0.612
Yes	2 (14.3)	1 (25)	3 (16.7)	
Recurrence				
No	12 (85.7)	2 (50)	14 (77.8)	0.130
Yes	2 (14.3)	2 (50)	4 (22.2)	
Size of recurrence mass	9 (3-15)	7.25 (4.5-10)	7.25 (3-15)	N/A
Time to recurrence in groups (months)	120,904±13.09 95% CI (95,247-146,561)	31,386±15.196 95% CI (1,602-61,171)	**0.028**	

DT: Desmoid tumors, FAP: Familial adenomatous polyposis, N/A: Not applicable

reported DT development at an earlier mean age in FAP patients than in those without FAP.[6,7] In the present study, the age distribution was similar in patients with FAP-associated and non-FAP-associated DTs, which the authors believe makes it unreliable for individual patients as a distinguishing factor for the identification of FAP.

The most important predisposing factor for the development of DTs in FAP patients is previous surgical trauma. Previous studies have reported that prophylactic colectomy-related surgical trauma increases the risk of tumor formation in FAP patients.[12] Clark et al.[13] reported that 82% of patients with FAP-associated DTs in their study had previous predisposing surgery. It has further been shown that sporadic DTs occur in 3% of the first laparotomy but are responsible for up to 30% in subsequent laparotomy procedures.[14] Since patients with FAP are up to 100% more likely to develop colorectal cancer, prophylactic surgery is unavoidable for these patients. In their study, Church et al.[15] compared the incidence of DT at follow-ups between FAP patients undergoing ileal pouch-anal anastomosis (IPAA) and those treated with total abdominal colectomy-ileorectal anastomosis and reported a higher DT incidence in patients who underwent IPAA. This may be attributed to the increased surgical trauma associated with pelvic dissection.[15] This study also provided evidence that previous surgical trauma increases the development of DT, which supports earlier studies. All FAP patients in this study had undergone proctocolectomy and IPAA, which supports this finding.

The reported rate of recurrence is 23-31%, and the 5-year recurrence-free survival is 69% in sporadic desmoid fibromatoses, while the recurrence rate in FAP-associated tumors has been reported to be at the same level as in their sporadic counterparts. A positive resection margin, young age, large tumor size, and tumor location in the extremities have been shown to predict recurrence.[7,16-19] In their 35-year series, Koskenvuo et al.[6] reported a recurrence rate of 26% when FAP patients were included, a 5-year recurrence-free survival of 50% in the FAP group, and 74% in the sporadic group. In the study, the median time to recurrence was 29 months in the sporadic group and 26 months in the FAP group.[6] This rate is supported by the literature, where studies reported as short a time as 14-22 months.[20-22] In the present series, the recurrence rate was 22% when all patients were included, which is relatively lower compared with the literature. In this respect, the authors believe that close follow-up protocols for DTs would be appropriate, especially in cases of FAP treated with a total proctocolectomy.

Various treatment options are available for the induction of tumor remission or the management of symptoms. Surgical resection, radiotherapy, and pharmacological therapies have all been used, although there is no treatment yet that currently considers optimum.[23] The present series included patients who underwent surgical treatment. Due to the decision of the tumor board, adjuvant tyrosine kinase inhibitor therapy was administered to four patients and adjuvant 50.4 Gy radiotherapy to three patients, suggesting that a multidisciplinary approach should be adopted in the management of DT.

Study Limitations

The limitations of the present study include its retrospective nature and the limited patient population. The small sample size has created a concern that false positive results may occur in statistical analyzes. That said, considering the rarity of this tumor group, the authors believe that this study makes valid contributions to the literature.

Conclusion

Recurrence is more common and the time from index surgery to recurrence is shorter in patients with FAP-associated DTs; therefore, more intensive follow-up protocols would be necessary in this group.

Ethics

Ethics Committee Approval: This study was approved by the Çukurova University Local Ethics Committee (approval number: 114/31, date: 10.09.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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RESEARCH ARTICLE

Comparison of Patients' Compliances, Tolerances, and Experiences of Different Colonoscopic Bowel Preparation Agents: A Prospective Observational Study

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ABSTRACT

Aim: Patients' compliance and tolerance in terms of bowel cleansing agents and quality of bowel cleansing are important for a successful colonoscopy procedure.

Method: This is a prospective observational study that was conducted to compare the compliances, tolerances, and experiences of patients in whom polyethylene glycol (PEG), macrogol, and sennoside + enema agents were used for bowel cleansing before colonoscopy. The sample was composed of a total of 159 patients who received PEG (n=53), macrogol (n=53), and sennoside + enema (n=53) in the endoscopy unit in a university hospital in the province of Adana between March 1, 2020, and July 15, 2020. The "Descriptive Characteristics Form", which was developed by the researchers, and the "Colonoscopy Patient Assessment Form" and "Colonoscopy Procedure Assessment Form," which interrogated compliance, tolerance, and bowel cleansing quality and the patients' experiences, were used for data collection.

Results: In this study, compliance (p=0.115), bowel cleansing qualities (p=0.827), and experiences (p>0.05) were found to be similar in the patients in the three groups. However, it was found that the patients in the sennoside + enema group developed intolerance including nausea (p=0.039), vomiting (p=0.045), and malaise and fatigue (p=0.042) to a greater extent and needed more help (p<0.001) compared with the patients in the macrogol and PEG groups. Half of the patients (47.3%) described the bowel preparation for colonoscopy as tiring and wearing.

Conclusion: Sufficient bowel cleansing was provided with all three bowel cleansing agents used before colonoscopy in this study. The patients tolerated the PEG solution better than the sennoside + enema and macrogol agents. Comprehensive prospective randomized studies with large sample sizes are needed to better evaluate the effect of bowel cleansing agents and to help patients have a more comfortable colonoscopy procedure.

Keywords: Bowel preparation; colon cleansing, colonoscopy, comparative, agents

Introduction

Colonoscopy is an endoscopic procedure that is considered the gold standard and is currently used extensively in the screening of colorectal cancers or the diagnosis of colorectal diseases.[1,2] Successful bowel cleansing and providing a tolerable bowel preparation are important to visualize and evaluate colonic mucosa at a good level during the procedure of colonoscopy.[2,3] If a colonoscopy is performed with inadequate bowel preparation, the presence of a remnant of residual stool may lead to missing polyps, inability to complete the procedure, negative impact on patients in the psychological, physiological, and economic aspects due to prolonged procedure, and even to the development of complications.[4,5-7]

The ideal bowel preparation should be safe, efficient in terms of bowel cleansing, adequate, and tolerable.[8,9] Polyethylene glycol (PEG) is a laxative that is not absorbed and not metabolized. It minimalizes fluid exchange in the colonic membrane due to its balanced electrolyte content and isoosmotic structure. Although the macrogol group

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has a similar content to PEG, the percentages of PEG and electrolytes are different. It has been reported that patients have difficulty in consuming the PEG and macrogol groups because of unfavorable taste and excess quantity and that this group caused dyspepsy.[1,10,11] The senna group includes glycosidase and sennoside, and they perform bowel cleansing by being activated by colonic bacteria.[1,12] However, controversial results indicate that sennoside is effective in bowel cleansing when used in combination with laxatives or when combined with the PEG solution.[1,13] The literature involves studies comparing the efficiencies of the agents used in bowel preparation before colonoscopy.[1,4,8,13-15] However, there is a limited number of studies in Turkey that compare the three different agents in terms of compliance and tolerance of patients, quality of bowel cleansing, and patients' experiences.[7,9,12,16-18]

Based on this deficit, this study was planned and conducted to specify colonoscopy preparation agents appropriate for each patient, to help patients have a convenient and comfortable colonoscopy procedure by benefiting from bowel preparation experiences, and to provide optimal cleansing quality. In this study, answers to the following questions were sought: "Was there a difference between the patients who received three different agents of bowel cleansing before colonoscopy in terms of compliance, tolerance, and quality of bowel cleansing?" and "What were the experiences of the patients who received three different agents of bowel cleansing before colonoscopy?"

Materials and Methods

Design and Study Population

This was a prospective observational study. The study population consisted of 196 patients who met the inclusion criteria in the endoscopy unit of a university hospital in Adana between 2018-2019. In the calculation of the study sample, a two-sided hypothesis was established using the free-to-use G*Power software. It was found that a total of 159 patients, including 53 patients in each group (PEG, macrogol, and sennoside + enema), should be included in the study with 80% power, 0.05 type 1 error, and moderate effect size (0.25). The study was conducted between March 1, 2020, and July 15, 2020.

Inclusion and Exclusion Criteria

Patients aged 18-70 years who were willing to communicate and cooperate, wished to participate in the study, gave informed consent, were undergoing outpatient treatment, did not have any morbidity that could affect the ability to decide (dementia, psychological disorders, etc.), did not have visual, auditory or sensory losses, drank at least 75% of the solution and experienced urgent and active lower intestinal tract bleeding, were included in the study. Patients who did not meet these criteria were excluded from the study.

Administration of Bowel Cleansing Agents

The agents specified by the American Gastrointestinal Endoscopy Association and preferred by physicians were used in the endoscopy unit for bowel preparation before colonoscopy. After written and verbal informed consent was obtained from eligible patients by the researchers, an appointment for colonoscopy was made by the medical secretary at different times (the first group: sennoside + enema; the second group: macrogol; the third group: PEG).

The agent used for the PEG group (GoLytely® Braintree Laboratories, Inc, Braintree, MA) was a ready-to-use solution dissolved in 4 liters of water. Patients were informed that they should finish the whole solution between the hours of 18:00-22:00 in the evening before the procedure and encouraged to consume as much fluid as they could until 24:00.

For the agent used for the macrogol group (Endolfalk® Dr. Falk Phar-ma Ltd., Freiburg, Germany), the patients were instructed to mix eight packets into 4 liters of water in the evening before the procedure, finish it between 18:00 and 22:00, and drink as much fluid as they could until 24:00.

For the agent used for the sennoside + enema group (X-M tablet®, Yenişehir, Turkey), the patients were told to drink the first bottle and then 2 liters of water at 17:00 in the evening before the procedure and to drink the second bottle at 19:00 and then 2 liters of water. The patients were informed that they should administer the first enema at 24:00 (BT® enema 210 mlt contains 7.5 mg sennoside A+B Calcium) and the second enema one hour before the procedure.

Instruments

The "Descriptive Characteristics Form," "Colonoscopy Patient Evaluation Form," and "Colonoscopy Procedure Assessment Form" were used for data collection. These were created by the researchers by reviewing the literature and obtaining expert opinions.[1,9,10,12,13] The standard Boston Bowel Preparation Scale (BBPS) was used to assess the quality of bowel cleansing in the "Colonoscopy Procedure Evaluation Form."

The Descriptive Characteristics Form: This form included nine questions related to age, sex, education status, body mass index (BMI), smoking status, mobility status, chronic disease status, drug use, and the reason for having a colonoscopy.

The Colonoscopy Patient Assessment Form: This form included ten questions related to the amount of preparation solution consumed, the amount of fluid consumed before

the procedure, status of compliance to diet, abdominal pain, nausea, vomiting, headache, status of intolerance to preparation solution, need for help for performing the bowel preparation, adequacy of the bowel preparation in terms of bowel cleansing, and experiences related to the colonoscopy procedure.

The Colonoscopy Procedure Assessment Form: This form included questions related to the duration of the procedure, BBPS, adequacy of bowel cleansing, and status of development of complications.

The BBPS was prepared by Lai et al.[19] to evaluate bowel cleansing and its reliability and validity were proven. It includes a scoring system ranging between 0-3 for each of three parts of the colon (right colon: cecum and ascending colon; transverse colon: hepatic and splenic flexure; left colon: descending colon, sigmoid colon, and rectum). The scores are as follows: excellent-adequate image, little amount of clear fluid, minimal aspiration, no need for washing (3); good-adequate image, excess amount of clear fluid, frequent aspiration (2); moderate-adequate image, mixture of liquid and semi-solid stool, can be aspirated or eliminated by washing (1); inadequate preparation-inadequate image, mixture of semi-solid and solid stool, cannot be eliminated by aspiration or washing "0". According to the BBPS, a score of 0 indicates inadequate cleanliness, and a score of 9 indicates perfect cleanliness. As the cleanliness score progresses from 0 to 9, it indicates that bowel cleanliness is approaching perfection.

Data Collection

A random list was created by the medical secretary, who assigned the patients into three groups in a 1:1:1 ratio using a computer-assisted simple random sampling method. The assignment of 53 patients from each group was made using the lottery method, and colonoscopy procedures were performed at different times (the first group: sennoside + enema; the second group: macrogol; the third group: PEG). The researchers provided standardized dietary education to the patients who wanted to participate in the study (they were informed that stewed fruit juice, vermicelli soup with small particles, and soup prepared with meat could be consumed 2 days before the procedure). It was stated that patients should not drink peach juice or apricot juice, they could consume pulpless apple and cherry juice, and they should not drink lentil soup. The education took place in the nurse's room in the endoscopy unit and lasted 10-15 minutes. At the end of the training, patients were given a standard education brochure prepared by the endoscopy unit.

On the day of the colonoscopy, the researchers filled in the "Descriptive Characteristics Form" and the "Colonoscopy Patient Assessment Form" to evaluate the states of compliance and tolerance. The BBPS scale in the "Colonoscopy Procedure Assessment Form" was completed by the researchers by questioning the physician who performed the colonoscopy procedure immediately after the procedure, and the development of complications was recorded. The patients were interviewed again 15-30 minutes after the procedure was completed for descriptions related to bowel cleansing. It took 30-40 minutes to fill out these forms, and no negative feedback was received from patients or physicians.

Ethical considerations

After approval was obtained from the Çukurova University Faculty of Medicine Clinical Research Ethics Committee (approval number: 64, date: 14.02.2020) and Academic Committee (25.02.2020), the study was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed by the researcher using a voluntary information form, and those who agreed to participate in the study gave written and verbal consent.

Statistical Analysis

In the assessment of the data, the categorical data were expressed as numbers and percentages, and the continuous data were expressed as mean, standard deviation, and minimum-maximum values. Compatibility of the variables with the normal distribution was examined using visual (histogram and probability graphs) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). In the comparison of the categorical variables, the chi-squared test was used. The Kruskal-Wallis test was used for more than two variables for the groups that were not compatible with the normal distribution. Fisher's exact test was used when the observed values were <5. In all tests, a p-value <0.05 was considered statistically significant.

Results

The descriptive characteristics of the patients included in the study are presented in Table 1. It was found that 54.7% of the patients (n=87) were female, 38.7% (n=67) were primary school graduates, 30.0% (n=48) were smokers, 43.3% (n=65) had comorbidities, 54% (n=81) used medications continuously, 71.0% (n=113) had a colonoscopy because of constipation, diarrhea, distension, or abdominal pain. The mean age was 50.08±12.4 years, and the mean BMI was 27.17±4.9.

A comparison of patients' compliance and tolerance between groups is presented in Table 2. In this study, a statistically significant difference was not found between the groups in terms of rates of complete consumption of the solution (p=0.397) and difficulty in complying with the

bowel preparation agent (p=0.115). However, the rates of complete consumption of the solution (n=46; 86%) were found to be higher, and rates of difficulty in complying with the bowel preparation agent (n=4; 8%) were found to be lower in the sennoside + enema group compared with the PEG and macrogol groups. When the patients' states of tolerance were compared in the study, the rates of vomiting (sennoside + enema group: 38; macrogol group: 26; PEG group: 16; p=0.045), nausea (sennoside + enema group: 74; macrogol group: 58; PEG group: 40; p=0.039), malaise and fatigue (sennoside + enema group: 64; macrogol group: 44; PEG group: 42; p=0.042) were found to be statistically significantly higher in the patients in the sennoside + enema group compared with the patients in the macrogol and PEG groups. In the patients in the sennoside + enema group, the rates of abdominal pain and distension (p=0.092), thirst, malaise and fatigue, and bleeding and irritation around the anus were found to be high, though the differences were not statistically significant (p>0.05).

A comparison of the efficacy of the three cleansing agents used for bowel preparation before colonoscopy is shown in Table 3. In the sennoside + enema, macrogol, and PEG groups, a statistically significant difference was not found in terms of favorable bowel cleansing quality (sennoside + enema group: 56; macrogol group: 50; PEG group: 48; p=0.827) and reaching the cecum and intubation of the terminal ileum (macrogol group: 94.0; sennoside + enema group: 88; PEG group: 90; p=0.576). In this study, the rate of patients in the sennoside + enema group who could not complete the colonoscopy procedure due to inadequate bowel preparation was lower than the patients in the PEG and macrogol groups but not significantly (sennoside + enema group: 18; macrogol group: 32; PEG group: 28; p=0.210).

Table 4 shows a comparison of patients' experience with three different cleansing agents used for bowel preparation before colonoscopy. There was no statistically significant difference among the patients in the sennoside + enema, macrogol, and PEG groups in terms of the agents being drinkable based on taste (p=0.458), thinking that they cleaned their bowels adequately (p=0.192), not being able to sleep due to frequent toilet visits (p=0.356), or their opinions about the colonoscopy procedure (p=0.090). The counts of need for help were found to be higher in the patients in

Table 1. Descriptive characteristics of the patients included in the study (n=159)

Descriptive characteristics		Groups				
		Sennoside + enema, (n=53)	Macrogol, (n=53)	PEG, (n=53)	Total, (n=159)	p
Gender, n (%)	Female	23 (44.0)	32 (60.0)	32 (60.0)	87 (54.7)	0.179
	Male	30 (56.0)	21 (40.0)	21 (40.0)	72 (45.3)	
Year (mean ± SD)		46.6±12.8	51.3±13.0	52.3±10.8	50.0±12.4	0.051
BMI (kg/m^2), mean ± SD		25.6±4.9	27.7±4.7	28.1±4.9	27.1±4.9	**0.026**
Education status, n (%)	Illiterate	5 (10.0)	3 (6.0)	3 (6.0)	11 (7.3)	0.927
	Primary school	23 (40.0)	23 (40.0)	21 (36.0)	67 (38.7)	
	Secondary school	4 (8.0)	4 (8.0)	3 (6.0)	11 (7.3)	
	High-school	12 (24.0)	9 (18.0)	11 (22.0)	32 (21.3)	
	University and above	9 (18.0)	14 (28.0)	15 (30.0)	38 (25.3)	
Status of smoking, n (%)		18 (34.0)	13 (24.0)	17 (32.0)	48 (30.0)	0.513
Mobility, n (%)	Mobile	48 (90.0)	53 (100.0)	48 (90.0)	149 (93.3)	0.069
	Limited movement	5 (10.0)	0 (0.0)	5 (10.0)	10 (6.7)	
Comorbidities, n (%), (cardiac disease, diabetes, hypertension, COPD**)		16 (16.0)	25 (50.0)	24 (48.0)	65 (43.3)	0.138
Current medication, n (%), (anti-diabetic, anti-hypertensive, anti-coagulant)		24 (48.0)	28(56.0)	29 (58.0)	81 (54.0)	0.569
Indication for colonoscopy, n (%)						
Constipation, diarrhea, distention, abdominal pain		36 (68.0)	35 (66.0)	42 (79.2)	113 (71.0)	0.576
Polyp, bleeding, malignancy screening		17 (32.0)	18 (34.0)	11 (20.8)	46 (29.0)	

PEG: Polyethylene glycol, SD: Standart deviation, *BMI: Body mass index, **COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of the efficacy of three different cleansing agents used for bowel preparation before colonoscopy

States of compliance and tolerance	Groups				p (post-hoc)
	Sennoside + enema[a], (n=53)	Macrogol[b], (n=53)	PEG[c], (n=53)	Total, (n=159)	
	n (%)	n (%)	n (%)	n (%)	
Compliances					
Drinking the solution					
Three-quarters of the solution	7 (14.0)	14 (26.4)	17 (32.2)	38 (23.9)	0.397
Complete solution	46 (86.0)	39 (73.6)	36 (67.9)	121 (76.1)	
Difficulty in complying with the preparation agents	4 (8.0)	12 (22.0)	6 (12.0)	22 (14.0)	0.115
Tolerance states					
Presence of vomiting	19 (38.0)	13 (26.0)	8 (16.0)	40 (26.7)	**0.045**[a,b]; 0.034
Presence of headache	17 (34.0)	22 (42.0)	18 (36.0)	56 (37.3)	0.682
Presence of nausea	39 (74.0)	31 (58.0)	21 (40.0)	90 (57.3)	**0.041**[a-c]; 0.040
Presence of abdominal pain	34 (68.0)	22 (44.0)	25 (50.0)	81 (54.0)	0.092
Presence of abdominal flatulance	28 (52.0)	26 (50.0)	16 (30.0)	70 (44.1)	0.231
Presence of thirst	20 (40.0)	11(22.0)	18 (40.0)	49 (32.6)	0.268
Malaise and fatigue	34 (64.0)	23 (44.0)	22 (42.0)	79 (50.0)	**0.042**[a-c]; 0.039
Bleeding and irritation around the anus	23 (44.0)	13 (24.0)	14 (26.0)	50 (31.4)	0.098

[a-c]: Bonferroni test was used in post-hoc analysis, PEG: Polyethylene glycol

Table 3. Comparison of the efficacy of three different cleansing agents used for bowel preparation before colonoscopy (n=159)

	Groups				p
	Sennoside + enema, (n= 53)	Macrogol, (n=53)	PEG, (n=53)	Total, (n=159)	
	n (%)	n (%)	n (%)	n (%)	
Bowel cleansing quality level according to BBPS					
Excellent	2 (4.0)	1 (2.0)	2 (4.0)	5 (3.3)	0.827
Good	31 (58.0)	27 (50.0)	26 (48.0)	84 (52.0)	
Moderate	18 (34.0)	24 (46.0)	22 (42.0)	64 (40.7)	
Inadequate	2 (4.0)	1 (2.0)	3 (6.0)	6 (4.0)	
Reaching the cecum region	47 (88.0)	50 (94.0)	48 (90.0)	145 (90.7)	0.576
Reaching the terminal region	44 (82.0)	47 (88.0)	45 (84.0)	136 (84.7)	0.698
Failure to complete the procedure					
Inadequate bowel preparation	9 (18.0)	17 (32.0)	15 (28.0)	41 (26.0)	0.210
Pain in the patient	40 (74.0)	34 (64.0)	38 (72.0)	112 (70.0)	
Excessive loops (fold)	2 (4.0)	-	-	2 (1.3)	
Obstructive lesion	2 (4.0)	2 (4.0)	-	4 (2.7)	

PEG: Polyethylene glycol, BBPS: Boston Bowel Preparation Scale

Table 4. Comparison of patients' experiences with three different cleansing agents used for bowel preparation before in colonoscopy preparation (n=159)

Experience		Groups				p
		Sennoside + enema, (n=53)	Macrogol, (n=53)	PEG, (n=53)	Total, (n=159)	
		n (%)	n (%)	n (%)	n (%)	
Drinkable taste of the solution		31 (58.0)	36 (68.0)	42 (80.0)	109 (68.6)	0.458
Thinking that adequate bowel cleansing is achieved		51 (96.0)	52 (98.0)	53 (100.0)	155 (98.0)	0.192
Need for help (family member, friend)		30 (56.0)	7 (14.0)	8 (16.0)	43 (28.7)	**<0.001**
Not being able to sleep due to frequent toilet visits		21 (40.0)	17 (32.0)	24 (46.0)	62 (39.3)	0.356
Opinions about the colonoscopy procedure	Difficult procedure	5 (10.0)	1 (2.0)	3 (6.0)	9 (6.0)	0.090
	Tiring and wearing process	25 (46.0)	26 (50.0)	26 (46.0)	71 (47.3)	
	Process that causes feeling of shame	7 (14.0)	3 (6.0)	12 (24.0)	22 (14.7)	
	Easy procedure	16 (30.0)	23 (42.0)	12 (24.0)	48 (32.0)	

PEG: Polyethylene glycol, BBPS: Boston Bowel Preparation Scale

the sennoside + enema group (sennoside + enema group: 56; macrogol group: 14; PEG group: 28.7; p<0.001) and the difference was statistically significant at a high level. It was found that 47.3% of all patients in this study described bowel cleansing for colonoscopy as tiring and wearing.

Discussion

In a successful colonoscopy procedure, compliance and tolerance of patients in terms of the agents used in bowel preparation are important.[8,20] In this study, a perspective is provided on the safety and efficacy of bowel cleansing agents used in colonoscopy preparation by assessing patients' compliance, tolerance, and experience.

It has been stated that 10-20% of the patients who have applied PEG, macrogol, sodium phosphate, and sennoside + enema agent for bowel cleansing have difficulty in complying with the diet and drinking the solution.[7,9,21-23] It has been reported that adequate bowel cleansing cannot be performed in at least 5-15% of the patients because of difficulty in drinking the preparation solution, which is 3-4 liters, or because of unfavorable taste.[1,24,25] In this study, it was found that 14% of all patients had difficulty in complying with bowel preparations, and the patients in three different groups were similar in terms of drinking the solution completely. In the sennoside + enema group, the rates of difficulty in complying with bowel preparation processes were found to be lower compared with the PEG and macrogol group, though the difference was not statistically significant. The patients' compliance with bowel cleansing was similar to the literature.[1,9,10,12,13] In this study, the social support levels of the patients and their previous knowledge and experience about colonoscopy procedures were not investigated. The fact that the patients in the sennoside + enema group had less difficulty compared with the other groups, although not significantly, may be explained by the fact that their knowledge and experience of colonoscopy procedures or social support levels may be slightly better.

Bowel cleansing can lead to disturbances such as flatulence, nausea, vomiting, pain, and diaper rash in the anal region due to frequent defecation and insomnia.[1,6,7,10] Some studies have reported that prolonged abdominal distension and the development of paralytic ileus affected the recovery process negatively.[5,27] In this study, the rates of vomiting, nausea, malaise, and fatigue were found to be higher in the patients in the sennoside + enema group compared with the macrogol and PEG groups. Studies in the literature have reported that nausea, vomiting, and abdominal pain develop at a higher rate in patients in whom the sennoside bowel cleansing agent is applied, in line with this study.[14,27] In contrast to this study, other studies reported that there was no difference between patients' compliance and tolerances.[12,28] Further randomized controlled studies with larger sample sizes are needed to evaluate patients' tolerance states.

It was found that the bowel cleansing quality and the rates of detecting polyps and reaching the cecum were similar in patients who were administered PEG, sennoside, macrogol, picoprep (sodium picosulfate/magnesium citrate combination), and sodium phosphate agents.[12,15,21,27,29] In the study conducted by Kaplan,[11] however, it was reported that bowel cleansing quality and patients' tolerances were better in the PEG solution compared with the sennoside without enema agent. In this study, the good level bowel cleansing rates in the sennoside + enema group were found

to be higher than in the PEG and macrogol groups, though the difference was not significant. The percentage of patients whose colonoscopy procedures could not be completed due to inadequate bowel cleansing was found to be low. It is thought that the three agents met the ideal criterion for qualified colonoscopy assessment in bowel cleansing; none of them was superior to the other, and all yielded results that were compatible with the literature.

Studies have reported that endoscopic interventions mostly caused anxiety and concern in patients (discomfort, pain, or feeling embarrassed in the pre-procedural preparation period or during the procedure), but patients were very satisfied with the healthcare team's professional behavior and pleasant attitude.[30-32] Çakır et al.[9] and Yakut et al.[32] reported that almost half of the patients using the sennoside + enema agent for bowel preparation before a colonoscopy described the procedure as tiring and reported that they would not repeat it if the procedure failed. In this study, the patients in the sennoside + enema group might have needed more help because it was difficult for them to perform the enemas themselves while experiencing nausea, vomiting, malaise, and fatigue. Although Çakır et al.[9] and Yakut et al.[32] did not investigate the need for assistance in patients who used sennoside + enema for bowel preparation before a colonoscopy in their study, their description of bowel preparation as a tiring experience supports the authors' findings. In this study, almost half of the patients in the three groups described the procedure as troublesome and wearing, and they were unable to sleep due to going to the toilet frequently. In accordance with the literature, this result shows that although the bowel cleansing quality of the agents used in bowel preparation before a colonoscopy is adequate, patients get tired, they need help, and tolerance, compliance, and comfort level are still important issues. In this context, the bowel preparation process for colonoscopy and the agents that are used should be studied further to increase tolerance, compliance, and comfort in patients.

Study Limitations

The results cannot be generalized because the limitations of this study were that it was single-center, the sample was small, and it was not a randomized controlled study.

Conclusion

In this study, compliance with bowel preparation, bowel cleansing qualities, and experiences with bowel preparation were found to be similar in the patients who were administered sennoside + enema, macrogol, and PEG solutions. However, it was found that the patients in the sennoside + enema group developed intolerance involving nausea, vomiting, malaise, and fatigue with a higher frequency, and they needed help in applying the cleansing agent to a greater extent compared with the patients in the macrogol and PEG groups. It was found that almost half of the patients in the three groups described the colonoscopy procedure as tiring and wearing. In conclusion, this study demonstrated that adequate bowel cleansing for colonoscopy could be achieved in three different groups using different bowel cleansing agents. The PEG solution was tolerated better by patients compared with the sennoside + enema and macrogol solutions. Further prospective randomized studies with large sample sizes are needed to better evaluate bowel cleansing agents and to help patients have a more comfortable experience in bowel cleansing.

Ethics

Ethics Committee Approval: After approval was obtained from the Çukurova University Faculty of Medicine Clinical Research Ethics Committee (approval number: 64, date: 14.02.2020) and Academic Committee (25.02.2020), the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Patients were informed by the researcher using a voluntary information form, and those who agreed to participate in the study gave written and verbal consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

The Long-Term Effectiveness of Sacral Neuromodulation in Treating Low Anterior Resection Syndrome: A Single Center Experience

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ABSTRACT

Aim: Sacral neuromodulation (SNM) has emerged as an effective treatment option for patients with fecal incontinence (FI). The efficacy of SNM in the treatment of low anterior resection syndrome (LARS) following rectal cancer surgery is encouraging. The aim of this study is to review the long-term outcomes of patients treated with SNM for LARS.

Method: A review of a prospectively maintained database of consecutive SNM procedures for LARS between June 2017 and June 2020 was conducted. Bowel habits diaries, the Cleveland Clinic Florida-Fecal Incontinence Score (CCF-FIS), the Fecal Incontinence Quality of Life (FIQoL) scale, and the LARS score were evaluated at baseline, 3 months, and 24 months after definitive SNM implantation.

Results: The study included 14 patients; 11 were males, and the mean age was 59.2 (±10.2). Thirteen patients underwent permanent implantation of the SNM device. The mean score of FI episodes was reduced from 16 to 4 ($p<0.001$), and the mean CCF-FIS dropped from 15.2 to 6.5 ($p<0.001$). All patients showed a substantial increase in their FIQoL scale ($p<0.001$). Additionally, there was a significant amelioration in the LARS score (36.7 to 17.3, $p<0.001$) and all symptoms of LARS except incontinence of liquid stool ($p=0.97$).

Conclusion: SNM improves bowel dysfunction and QoL in patients with LARS following rectal cancer surgery and maintains its effectiveness over time.

Keywords: Sacral neuromodulation, low anterior resection syndrome, rectal cancer

Introduction

During the past decades, there have been remarkable improvements in the treatment of rectal cancer with the widespread adoption of total mesorectal excision and neoadjuvant chemoradiotherapy (CRT) regimens, which have reduced the rate of local recurrence and the requirement for permanent ostomy. However, the quality of life (QoL), including functional outcomes, is still a problem.[1] Following rectal cancer surgery, many patients experience increased stool frequency, urgency, clustering, and incontinence for flatus and/or feces. The combination of these symptoms is considered low anterior resection syndrome (LARS).[2] It is reported that 25-80% of patients develop LARS after sphincter-preservation rectal surgery, which is associated with poor QoL.[3-5] Conservative treatments, which are primarily empirical and symptom-focused, such as medical treatment, dietary counseling, pelvic floor rehabilitation, and biofeedback, are still primary treatment options for LARS. However, they have not yielded the expected therapeutic success.[6,7]

Sacral neuromodulation (SNM) has emerged as an effective treatment option in patients with fecal incontinence (FI) who have failed conservative management.[8,9] There is significant data on the effects of SNM on LARS.[10] The majority of them are case reports or small case series with low numbers. In addition, three meta-analyses reported favorable outcomes on this topic. However, the data has certain drawbacks, such

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as a small patient population and heterogeneity in outcome evaluation scores, and extensive multicentric studies are yet to be published.[11-13]

This study aimed to review over the long term an institutional series of patients treated with SNM for LARS with the utilization of globally accepted evaluation scores, such as the LARS score, and to analyze the factors associated with the therapy's success.

Materials and Methods

The entire process of this study followed the ethical standards of the Declaration of Helsinki and its later amendments. The Dokuz Eylül University Non-Interventional Research Ethics Committee approved the study (approval number: 2022/28-25, date: 31.08.2022). All patients provided written informed consent for the surgery and participation in the study.

A review of a prospectively maintained database of consecutive SNM procedures for LARS at Dokuz Eylül University Hospital between June 2017 and June 2020 was conducted. The indications for SNM for LARS treatment were as follows: previous LAR for rectal cancer, ongoing FI for more than 6 months after the reversal of a diverting ileostomy, failed conservative measures with diet and lifestyle modifications, medications, and/or biofeedback therapy, and no evidence of local and/or distant recurrence of the disease. Patients with a follow-up period of less than 2 years after SNM, younger than 18 years of age, and undergoing SNM for indications other than LARS were not included. Additionally, patients who had intersphincteric LAR for rectal cancer were excluded from the study.

Baseline Assessment

Patients were evaluated at baseline using bowel habits diaries, the Cleveland Clinic Florida-Fecal Incontinence Score (CCF-FIS),[14] the Fecal Incontinence Quality of Life (FIQoL) scale,[15] and the LARS score.[2] A regularly recorded bowel habits diary for a minimum of 1 month was used for baseline FI frequency and severity. FI was described as the involuntary loss of solid or liquid stool for at least 1 month in a patient who had normal control previously.[16] In addition, all patients were evaluated with anal manometry, flexible sigmoidoscopy, and, if necessary, a transanal ultrasound.

Sacral neuromodulation procedure: The SNM procedure was performed as a two-stage process: (1) the tined lead testing phase and (2) the permanent implantation phase, as previously described by Matzel et al.[17,18]. Both stages were performed in the operating room under intravenous sedation with local anesthesia by two specialist colorectal surgeons (TB, AEC). Preoperative antibiotic prophylaxis was administered routinely.

Tined Lead Testing Phase

The patients were placed in the prone position with the head, chest, and hips well supported in an effort to minimize lumbar lordosis. The feet and toes were lifted off the table to allow validation of the toe and foot response upon stimulation. The patient's buttocks were taped away so the cheeks were exposed to observe the anus during electrostimulation.

After the sacral skin was sterilized with an antiseptic solution, the procedure was initiated with an X-ray AP view of the sacrum, assuming the patient was in the optimal position. The sacral foramina's medial edges were the X-ray landmarks. A vertical line on each side of the sacral foramen and a line connecting the lower edges of the sacroiliac joint were used as markings. All were marked on the skin, producing an "H" figure. The intersection points of this "H" defined the upper medial portion of the S3 foramen, which is the optimal entry point for the tined lead. The S3 foramen was located using these radiological landmarks, and a needle was then inserted through this foramen. After identifying the S3 nerve root and eliciting the appropriate response (the flexion of the big toe and bellowing of the anal opening), the curved tined lead with four electrodes (Medtronic, Minneapolis, MN, USA) was positioned at the S3 foramen. The electrode was then tunneled to a subcutaneous pocket in the buttock, followed by the percutaneous extension wire to be used for external stimulation during the test period.

During a test period of at least 2 weeks, a bowel habits diary and the CCF-FIS were used to evaluate the efficacy of the treatment. The test period was considered successful if there was a >50% improvement in the continence score or a >50% decrease in the number of FI episodes. If the test period was successful, a permanent device was implanted.

Permanent Implantation of the Sacral Neuromodulation Device

Following a successful test period, the external pulse generator was removed, and the intern pulse generator (IPG) (or permanent pulse generator) was connected and placed in the subcutaneous pocket previously created.

Follow-Up

One week after the definitive SNM implantation, a first consultation was planned to examine the surgical wound and evaluate the efficacy of the therapy. Program settings were modified as necessary. Two weeks after implantation, a similar clinical appointment was arranged. Follow-ups were conducted in the first year at the 3rd, 6th, and 12th months, and annually thereafter. The bowel habits diary, the CCF-FIS, the FIQoL scale, and the LARS score were used to monitor the treatment's efficacy. Treatment success was defined as at least a 50% decrease in FI episodes, at least a 50% improvement in the FI scores compared to the baseline,

and a reduction to minor or no LARS [the LARS score was categorized as no LARS (0-20), minor LARS (21-29), and major LARS (30-42)].[2]

Statistical Analysis

Statistical analysis was performed by a biostatistician (HE) using SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA). Data were described using mean, standard deviation, median, and minimum-maximum. The association between the categorical variables and the success of the SNM treatment was determined with Fisher's exact test. The association between the continuous variables and the success of the SNM treatment was tested by the Mann-Whitney U test. Associations were performed using the Friedman test for analytic comparisons (pre-SNM; post-SNM 3rd-month, post-SNM 24th-month scores, such as Fl episodes, the CCF-FI, the FIQOL scale, and the LARS score). P-values <0.050 were defined as statistically significant.

Results

Study Population

Fourteen patients were included in the study; 11 (78.6%) were male, and the mean age was 59.2 (±10.2). Twelve patients (85.7%) had at least one comorbid condition. Thirteen (92.9%) patients received neoadjuvant CRT. A coloanal anastomosis was performed in eight (57.8%) patients. The median distance from the anal verge to the anastomosis was 2.3 cm (ranging from 0 to 6 cm). A diverting loop ileostomy was conducted in all patients. The median interval to the diverting ileostomy closure was 10 months (range: 5-21). The median interval after a diverting ileostomy closure to the SNM test period was 23 months (range: 6-95). The median follow-up time was 35 months (range: 2458). Table 1 provides a detailed summary of all patient characteristics.

Sacral Neuromodulation

The SNM testing period included 14 patients with LARS. However, one patient showed no improvement in symptoms and did not progress to the phase of permanent implantation. As a result, 13 (92.8%) patients underwent permanent SNM implantation. The median duration of the test phase was 14 days (range: 9-59). One patient's test period was extended to 59 days unintentionally due to the coronavirus disease-2019 pandemic.

During the postoperative period, one patient underwent explantation of the tined lead and IPG due to an infection at the surgical site, followed by successful reimplantation 3 months later. During the follow-up period, the authors explanted the SNM device from two patients: one who developed lumbar stenosis 50 months after implantation and needed an magnetic resonance imaging (MRI) for diagnosis, and another who developed local recurrence 32 months after implantation and underwent abdominoperineal resection. Finally, one patient required SNM replacement 62 months after implantation due to a depleted battery. Figure 1 shows the follow-up charts of the patients' SNM test and permanent implantation phases.

Sacral Neuromodulation Outcome

During the follow-up period at baseline, 3 months, and 24 months after permanent implantation, the mean number of FI episodes were 16, 4, and 4; respectively (p<0.001), the mean CCF-FIS was 15.2, 6.6, and 6.5; respectively (p<0.001), the mean FIQoL score was 45.4, 86, and 86; respectively (p<0.001), and the mean LARS score was 36.7, 16.2, and 17.3; respectively (p<0.001). There was a significant decrease in FI episodes, the CCF-FIS, and the LARS score, and a significant improvement in the FIQoL score (Figure 2).

Before SNM, all patients had major LARS (scores ranging from, 31-41). At the follow-up, 24 months after implantation, four of the 13 patients had minor LARS (scores ranging from, 25-27), and nine of the 13 patients had no LARS (scores ranging from, 5-19). An analysis of the LARS score components revealed a consistent pattern of score reduction, except for liquid stool incontinence. For LARS question 1 (LARS 1: incontinence for flatus), the mean score decreased significantly from 4.73 to 0.36 (p<0.001); for LARS question 3 (LARS 3: frequency of bowel movements), the mean score decreased significantly from 4 to 2.9 (p=0.001); for LARS question 4 (LARS 4: clustering of stools), the mean score decreased significantly from 9.9 to 5.1 (p=0.001); and for LARS

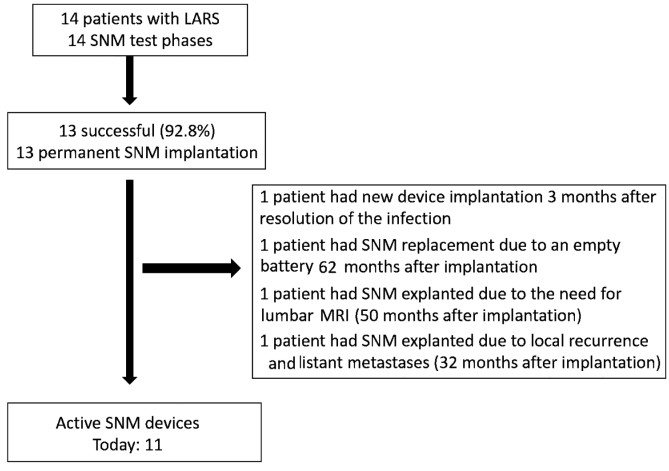


Figure 1. Flowchart of the sacral neuromodulation process and follow-up

LARS: Low anterior resection syndrome score, SNM: Sacral neuromodulation, MRI: Magnetic resonance imaging

Table 1. Demographic and clinical characteristics of the patients

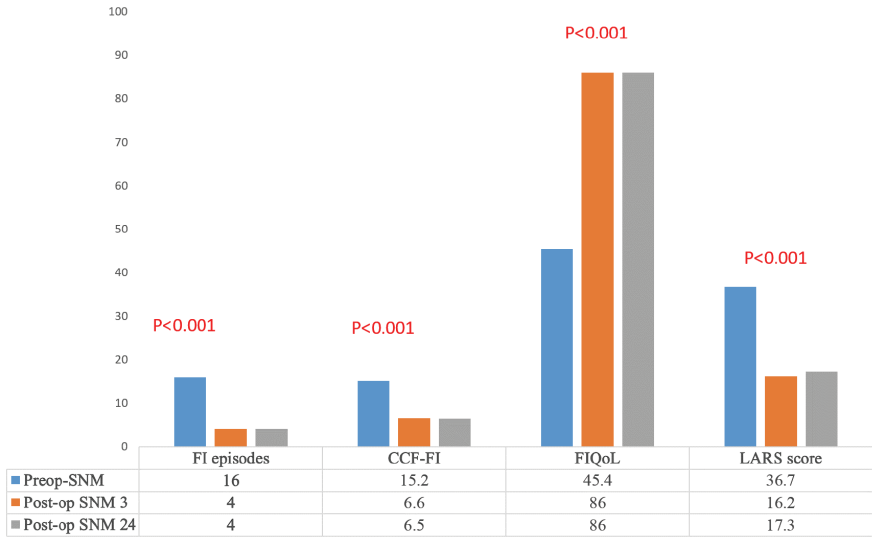
	(n=14)	Percentage (%)
Sex		
Male	11	78.6
Female	3	21.4
Age: mean (SD) (years)	59.2±10.2	
BMI: mean (SD)	24.8±3.5	
ASA		
I	7	50
II	7	50
Comorbidity	12	85.7
Diabetes	4	28.5
Arterial hypertension	6	42.8
Coronary heart disease	1	7.1
Others	1	7.1
Smoking	4	28.5
Clinical staging		
cT		
T2	1	7.1
T3	12	85.7
T4	1	7.1
cN		
N0	-	-
N+	14	100
Neoadjuvant chemoradiotherapy (+)	13	92.9
Surgical approach		
Open surgery	13	92.9
Laparoscopic surgery	1	7.1
Type of surgery		
PME	3	21.4
TME	11	78.6
Type of anastomosis		
Colorectal	6	42.9
Coloanal	8	57.1
Anastomotic technique		
End-to-end, stapled	14	100
Median anastomotic distance from the anal verge (range), cm	2.3 (0-6)	
Anastomotic leakage	1	7.1
Pathological staging		
pT		
T0	1	7.1
T1	1	7.1
T2	5	35.2
T3	7	50
pN		
N0	7	50
N+	7	50
Adjuvant chemoradiotherapy	12	85.7
Median interval until diverting ileostomy closure (range), months	10 (5-21)	
The median interval from a diverting ileostomy closure to the SNM test period (range), months	23 (6-95)	
Median duration test period (range), days	14 (9-59)	
Median follow-up duration (range), months	35 (24-58)	
Permanent SNM implantation rate	13	92.8

SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiologists classification, PME: Partial mesorectal excision, TME: Total mesorectal excision, SNM: Sacral neuromodulation

question 5 (LARS 5: urgency), the mean score decreased significantly from 13.7 to 7 (p=0.002). Only LARS question 2 (LARS 2: incontinence for liquid stool) had no significant improvements; the mean score decreased from 3 to 2.18 (p=0.97) (Figure 3).

Success of Sacral Neuromodulation Therapy

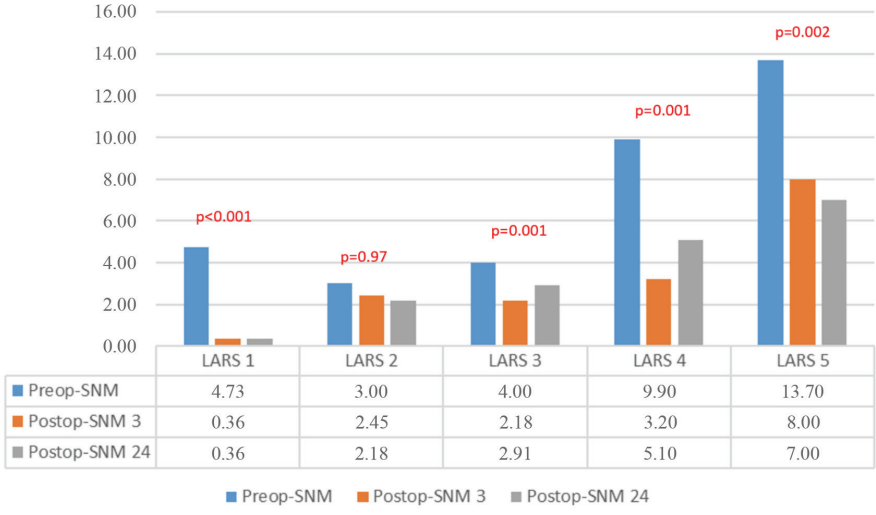
Of the 14 patients with LARS in the testing phase, 13 (92.8%) had a positive testing phase outcome. Age (p=0.210), gender (p=0.38), the American Society of Anesthesiology (ASA) score (p=0.051), body mass index (p=0.186), smoking (p=0.837), neoadjuvant CRT (p=0.588), the type of anastomosis (coloanal vs. colorectal) (p=0.707), the interval between the rectal cancer surgery and the diverting ileostomy closure (p=0.242), and the interval between the diverting ileostomy closure and the SNM test phase (p=0.139) were all thought to affect the success rate of therapy but were found to have no statistically significant impact.



	FI episodes	CCF-FI	FIQoL	LARS score
Preop-SNM	16	15.2	45.4	36.7
Post-op SNM 3	4	6.6	86	16.2
Post-op SNM 24	4	6.5	86	17.3

Figure 2. Fecal incontinence episodes, the CCF-FIS, the FIQoL scale, and LARS score before sacral neuromodulation (SNM) implantation and 3 and 24 months after SNM implantation

SNM: Sacral neuromodulation, FI: Fecal incontinence, CCF-FIS: Cleveland Clinic Florida-Fecal Incontinence Score, FIQoL: Fecal Incontinence Quality of Life, LARS: Low anterior resection syndrome score, p: Friedman test*



	LARS 1	LARS 2	LARS 3	LARS 4	LARS 5
Preop-SNM	4.73	3.00	4.00	9.90	13.70
Postop-SNM 3	0.36	2.45	2.18	3.20	8.00
Postop-SNM 24	0.36	2.18	2.91	5.10	7.00

Figure 3. LARS score components before SNM implantation and 3 and 24 months after SNM implantation

LARS 1: LARS question 1, reduced incontinence for flatus, LARS 2: LARS question 2, improvement of incontinence for liquid stool, LARS 3: LARS question 3, reduced clustering of stools, LARS 4: LARS question 4, reduced frequency of bowel movements, LARS 5: LARS question 5, reduced urgency, SNM: Sacral neuromodulation, p: Friedman test*

Discussion

This study showed that the long-term evaluation of the efficacy of SNM based on FI episodes, the CCF-FIS, the FIQoL scale, and the LARS score revealed that its effectiveness persisted significantly. During the median 35-month follow-up period, no SNM therapy was discontinued due to loss or lack of efficacy. Also, the study cohort was homogeneous in that it consisted of patients who underwent LAR for rectal cancer with the same surgical team and technique, 13 of the 14 patients received neoadjuvant CRT, and all patients had major LARS. Following the test phase, permanent SNM implantation was performed successfully in 13 out of the 14 patients with LARS (92.8%). There was no morbidity or mortality except for wound infection in one patient. The authors' results demonstrated that SNM is a safe and effective treatment for patients with LARS.

The patient selection criteria for SNM therapy and the factors associated with the treatment success are not well defined. Rubio-Perez et al.[19] found that patients who had had previous radiotherapy and fewer anastomoses could have a worse response to SNM therapy. In another study of patients with LARS secondary to rectal cancer surgery, of whom 14 out of 15 underwent neoadjuvant CRT, only 50% of patients received an SNM implant after testing. The authors discussed the effects of radiation and fibrosis in reducing efficacy.[10] In this study, neither previous chemoradiation nor fewer anastomoses (coloanal vs. colorectal) were found to have an impact on success. This may be due to the small number of participants in the study. Age, gender, the ASA score, reported smoking habits, the interval from rectal surgery to a diverting ileostomy closure, or the interval from a diverting ileostomy closure to implantation were not found to be effective in terms of success, in line with the existing literature.[10,19]

The variability in the definition of treatment outcomes, the use of different scoring systems, and the small number of patients are all drawbacks of the studies evaluating SNM therapy for LARS. Various reviews and meta-analyses have pooled published evidence.[11-13,20-22] These studies showed that the SNM implantation technique is not standardized and that there are variations in patient preoperative assessment, intraoperative and postoperative monitoring, as well as QoL evaluation instruments. In the review by Huang and Koh[12], which evaluated 10 studies and included 75 patients with an SNM implant, the CCF-FIS was used to define the response in all studies, whereas the LARS score was used in only three studies.[23-25] A few prospective studies evaluated the efficacy of SNM for LARS, but only one used the LARS score to assess the therapy.[10,23,26] In a prospective study involving 11 patients, D'Hondt et al.[23] demonstrated that all patients exhibited a significant decrease in their CCF-FIS (p=0.0033) and LARS score (p=0.0033) and suggested that the LARS score could be used to evaluate the efficacy of SNM therapy in patients with LARS. In this study, each question of the LARS score was addressed individually, and the authors found that the SNM therapy significantly improved all LARS symptoms.[23] This center published a five-year retrospective study of patients with isolated FI or LARS in 2020. Of the 62 implants, 16 were in patients with LARS. They evaluated the SNM effectiveness with the CCF-FIS and the LARS score and reported that both were associated with treatment success in a similar trend during long-term follow-up. In addition, the authors analyzed the different components of the LARS questionnaire. They confirmed that SNM is effective for all components of LARS.[20]

In this study, the authors evaluated the effectiveness of SNM in patients with LARS using FI episodes, the CCF-FIS, the LARS score, and the FIQoL scale. The authors demonstrated that the SNM treatment significantly improved FI episodes, the CCF-FIS, and the LARS score in the early period compared to baseline and maintained this during long-term follow-up. Similarly, the authors demonstrated that early positive effects on the FIQoL scale persisted over time and reached a plateau. In addition, the impact of SNM on each symptom of the LARS score was analyzed. In contrast to the literature, the authors observed a significant improvement in all LARS symptoms, with the exception of liquid stool incontinence. The authors believe this derives from the score distribution of the second question of the LARS score (LARS 2: accidental leakage of liquid). In this question, patients are presented with three options and three scores. The score distribution for this question is "0" if there is no accidental stool leakage, "3" if there is less than one per week, and "3" if there is at least one stool leakage per week. Giving the same score to two different symptom grades does not provide an appropriate assessment opportunity, even if SNM causes a significant improvement in the symptoms of these patients. The authors know that the LARS score was initially intended as a screening tool for LARS and not as a treatment efficacy evaluation tool. Nevertheless, without a superior alternative, the authors believe that the LARS score could help assess the severity of the symptoms and the response to treatment. However, the LARS score question 2 (LARS 2) may be inadequate for evaluating the outcomes and may show that they are less successful than they are. The authors suggest that SNM efficiency should be considered along with the CCF-FIS and the LARS score in patients with LARS.

The permanent SNM device had to be removed in four patients in the authors' series. In one patient, the device was removed after 32 months due to cancer recurrence. The patient underwent abdominoperineal resection and explantation of the SNM device. In patients with an increased risk for local recurrence and the possible need for abdominoperineal excision, SNM treatment may be postponed after the second-year postoperative follow-up if there is no evidence of local recurrence. On the other hand, it may be done as early as possible to improve the patient's QoL during their expected relatively shorter survival time. Balancing the cost of the treatment and the potential increase in QoL may be difficult. In another patient, the authors removed the SNM device because the patient needed lumbar MRI. Widespread use of MRI-compatible devices may be a solution. The authors explanted the SNM device in another patient due to a surgical site infection. The authors removed both the tined lead and IPG and

successfully reimplanted a new SNM device after the resolution of the infection. Finally, the authors replaced one IPG due to an expired battery life after 62 months of operation.

Study Limitations

The authors' study has several limitations, notably its retrospective design and single institutional structure. The study's small sample size may have also diminished the statistical significance of some variables. Moreover, the study lacks a control group for comparison, which may eliminate possible confounding factors. In addition, the cost-effectiveness of the treatment was not considered in the study.

Conclusion

This study's results demonstrate that SNM improves bowel dysfunction and QoL in patients with LARS following rectal cancer surgery and maintains its effectiveness over time. However, further studies are needed to assess the role of SNM in improving LARS symptoms.

Ethics

Ethics Committee Approval: The entire process of this study followed the ethical standards of the Declaration of Helsinki and its later amendments. The Dokuz Eylül University Non-Interventional Research Ethics Committee approved the study (approval number: 2022/28-25, date: 31.08.2022).

Informed Consent: All patients provided written informed consent for the surgery and participation in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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RESEARCH ARTICLE

Experimental Peritoneal Metastasis Model: Which Type of Rodents Should we Choose, and which Method Should we Perform for the Intraperitoneal Inoculation of Tumor Cells?

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ABSTRACT

Aim: This study aimed to create a peritoneal metastasis (PM) model in Wistar albino rats and nude mice and compare PM models and different tumor cell inoculation methods in the two experimental animal types.

Method: There were two main groups: group 1 comprised Wistar albino rats (n=16), and group 2 comprised nude mice (n=16). The group comprising rats was divided into two subgroups (1A and 1B), to which different tumor inoculation methods were applied. Group 2, comprising nude mice, was divided into two subgroups (2A and 2B), to which different tumor inoculation methods were applied. Euthanization was performed on the 7th and 14th days after tumor inoculation. The obtained samples were evaluated macroscopically, microscopically, and biochemically.

Results: Although no PM model was formed in group 1, a PM model occurred in the subjects in group 2 who were euthanized on the 14th day. There was no statistically significant difference between the mean peritoneal carcinomatosis index scores, tumor diameters, and the amount of intra-abdominal ascites in the subgroups (2A vs. 2B), in which the PM model was created by two different methods.

Conclusion: The inoculation of tumor cells with the peritoneal injection method enabled the creation of a PM model that can be used in experimental studies. Although a PM model could not be established in rats, a complete PM model was established in nude mice. In future studies, we plan to evaluate the efficacies of different drugs in the PM models we have created.

Keywords: Peritoneal metastasis model, colorectal cancer, tumor inoculation

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths worldwide. Peritoneal metastasis (PM) has the worst prognosis among all CRC metastases.[1] While an average survival of 1 year can be achieved with systemic chemotherapy in patients with PM due to CRC, 5-year survival rates can reach up to 40-58% with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[2] Therefore, as standard treatment in selected patients, the use of CRS + HIPEC is recommended.[3] Although it is more successful against systemic chemotherapy, there is not enough scientific evidence on CRS + HIPEC. While only hyperthermia has a cytotoxic effect on cancer cells, CRS and HIPEC potentiate each other's effects when combined with chemotherapy.[4] When compared with systemic chemotherapy, intraperitoneal chemotherapy provides a more intense concentration of chemotherapeutic agents on tumor cells, with lower systemic toxicity.[5] Thanks to all these favorable effects, when HIPEC is applied, a 20-50 times more intense tumoricidal effect is achieved compared with using systemic chemotherapy.[6]

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In our study, we created a PM model in Wistar albino rats and nude mice using CC-531 (rat-origin colon adenocarcinoma cell line). We also compared the PM models created in the two different experimental animal types using two different tumor cell inoculation methods. Using the results, we determined the most suitable type of rodent and the most appropriate technique to be used.

Materials and Methods

Our study was conducted at The Experimental Animals Laboratory between January and May 2022 with the approval of the Dokuz Eylül University University Local Animal Ethics Committee (approval number: 53/2019, date: 25.12.2019). In the process of establishing the PM model, 16 male 10-to-12-week- old Wistar albino rats and sixteen 7-to-8-week-old nude mice (athymic mice) bred in the Experimental Animals Laboratory were used. Nude mice caged in groups of four under laboratory conditions in air-filtered laminar flow cabinets were monitored. The mice were fed irradiated food and autoclaved reverse-osmosis-treated water. All treatments were carried out under sterile conditions in a laminar flow hood. The Wistar albino rats were caged in groups of eight.

The group of rats was divided into two separate subgroups (1A and 1B), in which two different tumor inoculation methods were applied separately. Group 2, consisting of nude mice, was divided into two subgroups (2A and 2B), each of which received a different tumor inoculation method. In the animals in groups 1A and 2A, tumor cell inoculation was performed by intraperitoneal injection, while in the animals in groups 1B and 2B, it was performed after peritoneal irritation via a laparotomy incision (Table 1). The mean weights of the Wistar albino rats and nude mice were 300 (±50) g and 32 (±2) g, respectively.

Intraperitoneal inoculation of tumor cells: Cancer cells from the CC531 colon adenocarcinoma cell line were harvested during the logarithmic growth stage by incubation at 37 °C under a humidified 5% CO_2 atmosphere. Cells were then resuspended in phosphate-buffered saline (PBS) for intraperitoneal injection. The suspended cells were administered to the animals in groups 1A and 2A by intraperitoneal injection using 16 mm long and 0.45 mm diameter needles. After sterilization of the abdominal area, the abdominal wall was passed by entering the abdominal midline from the right lateral at a 90° angle using a 16 mm needle. Then, a 1-2 mm needle was advanced at an angle of 45°. It was confirmed by aspiration that there was no intestinal content or bleeding. After these steps, tumor cells were injected into the abdominal cavity.

Table 1. Groups and tumor cell inoculation method

Groups	Subgroups (tumor cell inoculation method)
Group 1 (n=16) Wistar albino rat	Group 1A (inoculation by intraperitoneal injection)
	Group 1B (inoculation with laparotomy)
Group 2 (n=16) Nude mouse	Group 2A (inoculation by intraperitoneal injection)
	Group 2B (inoculation with laparotomy)

Diethyl ether inhalation anesthesia was applied to the animals in groups 1B and 2B, and the abdominal skin was cleansed with povidone-iodine solution. The necessary sterilization conditions were provided by covering the mice or rats with sterile surgical drapes. A midline abdominal incision of approximately 5 mm in length was made, and the abdominal cavity was entered (Figure 1). Peritoneal irritation was performed with the help of sterile fine-tipped forceps, and peritoneal cells were inoculated into the abdomen. The midline incision was closed primarily with 4/0 prolene sutures. Intraperitoneal inoculation of $5x10^6$ cells (0.3 cc in 200 µL PBS) was performed in all groups in line with referenced studies.[4]

Follow-up, euthanization, and evaluation of subjects: The animals were followed up daily. Laparotomies were performed under diethyl ether inhalation anesthesia in four animals from each group on the 7th and 14th days to evaluate the results obtained. Those with macroscopic PM findings were scored according to the peritoneal carcinomatosis index (PCI). The PCI was calculated according to the largest tumor diameter obtained from the experimental model, the number of organs involved, and the presence of intra-abdominal acid, with scores from two adjusted points (small bowel, peritoneum, diaphragm, ascites, and other organs).[4] Peritoneal cancer indices were determined, and scoring totaling 8 points was performed with consideration of the organ involved and the tumor diameter.

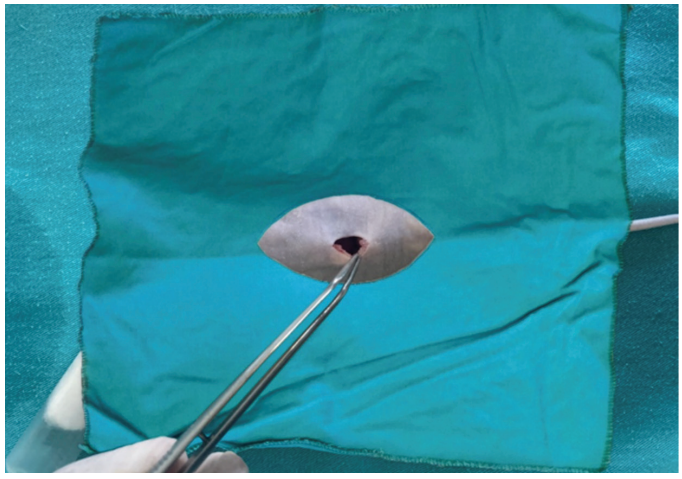

Figure 1. Tumor cells were inoculated into the intraperitoneal area by making an incision of approximately 5 mm

The results were evaluated as follows: small bowel and/or mesenteric involvement: 1 point; peritoneal involvement: 1 point; diaphragmatic involvement: 1 point; ascites (+): 1 point; involvement of other organs: 1 point. Tumor diameters were measured and scored as follows: no tumor growth: 0 points; nodule diameter ≤2 mm: 1 point; nodule diameter 2-5 mm or >5 tumor nodules: 2 points; nodule diameter ≥5 mm or >10 tumor nodules: 3 points (Figure 2). Ascites fluid was aspirated and quantified. Intra-abdominal lavage was performed using saline solution, and the examination of the samples retrieved did not reveal the presence of macroscopic tumors.

After the retrieval of samples from the small intestine, peritoneum, intra-abdominal fluid, and blood, the animals were euthanized, and the tissue and intra-abdominal fluid samples were evaluated histopathologically and biochemically. The tissue samples were fixed in 10% formaldehyde, cassetted, and embedded in paraffin blocks after tissue follow-up. Frozen sections of 5 µm in thickness were prepared from the optimal surface area of the sections. The sections were then stained with hematoxylin and eosin and examined under an Olympus x50 light microscope.

Tissue samples were evaluated for the presence of tumors, tumoral pattern, differentiation, apoptosis, mitosis, and necrosis. An evaluation was made by calculating the total number of mitoses in 10 different tumor areas by magnifying the field of vision 400 times under a light microscope with a 40x objective. The number of apoptotic cells was calculated by evaluating 5,000 cells and determining their percentage in 1,000 cells. The tissue samples were evaluated for evidence of tumor necrosis. Supernatants remaining after the centrifugation of the mice's intra-abdominal fluid samples were studied using lysyl oxidase-like protein 1 (LOXL1) and TWIST transcription factor (TWIST) mouse-compatible ELISA kits. Vascular endothelial growth factor (VEGF) levels in the diluted fluid samples were calculated, taking into account the mouse-compatible ELISA kit application steps. According to the absorbance values obtained from the standards, standard graphs of each test were created. Concentrations were expressed by calculating the absorbance values of the samples. The measuring range and the measurement sensitivity of the LOXL1 ELISA kit were 78-5,000 and 29 pg/mL, respectively. The measuring range and the measurement sensitivity of the TWIST test kit were 0.156-10 and 0.056 ng/mL, respectively. The measuring range and the measurement sensitivity of the VEGF test kit were 15-1,000 and 9,375 pg/mL, respectively.

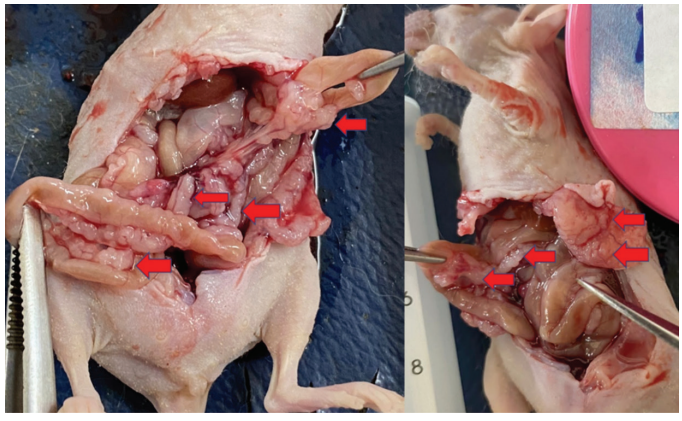

Figure 2. Metastatic nodules (shown with red arrows). The peritoneal metastasis model was scored macroscopically using the peritoneal cancer index

Statistical Analysis

Before the study, the number of experimental animals was determined by a power analysis. The maximum number of animals allowed by the animal experimentation ethics committee was used to ensure statistically significant results. Statistical analyses were performed using IBM's SPSS 24.0 statistics software program. The significance of differences was assessed using the Kruskal-Wallis test. Continuous variables were compared using an independent-samples t-test. Descriptive statistics were presented in the median (25^{th}-75^{th} percentile) format. Fisher's exact test, the chi-squared test, and t-tests were used for the analysis of qualitative data, and descriptive statistics were shown in the form of frequencies. A value of $p<0.05$ was defined as statistically significant.

Results

None of the rats in group 1 were lost during the experiment and follow-up. However, wound infection/dehiscence occurred in two animals in the group in which tumor inoculation was performed by laparotomy. No macroscopic or microscopic evidence of tumors was found in the evaluation performed after the euthanization of the experimental animals, and no PM developed in the Wistar albino rats.

In group 2, wound infection/dehiscence developed in three animals in the subgroup in which tumors were inoculated by laparotomy, one of whom exited on the 4^{th} postoperative day. On day 7, four subjects from both subgroups were euthanized. No macroscopic tumor or intra-abdominal ascites was detected. However, microscopic tumor cells were found in the intra-abdominal lavage fluid. On day 14, four experimental animals from each subgroup were euthanized. Macroscopic tumors and intra-abdominal ascites were detected in all subjects. Diffuse intra-abdominal ascites and widespread tumor implants were observed in the small intestines and peritoneum. In groups 2A and 2B, in which the PM model was created by two different methods, there was no statistically significant difference between the

mean PCI scores, tumor diameters, and the amount of intra-abdominal ascitic fluid [PCI: 7.50 (±0.57) vs. 7.25 (±0.50); tumor diameter: 3.75 (±1.70) mm vs. 3.50 (±1.29) mm; ascitic fluid: 3.50 (±1) mL vs. 3.37 (±0.85) mL] (Table 2).

Microscopic findings: When the tissue samples harvested from the intestinal system, peritoneum, and liver after euthanization were evaluated under a microscope, tumor cell infiltration was observed in all tissues. There were nodular and undifferentiated tumor samples. There was no statistically significant difference between groups 2A and 2B in terms of mitotic and apoptotic cell counts (Table 3).

Biochemical findings: There was no statistically significant difference between groups 2A and 2B in terms of the mean VEGF, LOX1, and TWIST values of intra-abdominal ascites (Table 4).

Table 2. There was no statistically significant difference between the mean PCI scores, tumor diameters, and the amount of intra-abdominal ascites in the subgroups (group 2A vs. group 2B), in which the PM model was created by two different methods

Mean ± SD	Group 2A	Group 2B	p-value
PCI	7.50±0.57	7.25±0.50	0.537
Tumor diameter (mm)	3.75±1.70	3.50±1.29	0.823
Ascites (mL)	3.50±1	3.37±0.85	0.855

Kruskal-Wallis test, t-test, PCI: Peritoneal carcinomatosis index, PM: Peritoneal metastasis, SD: Standard deviation

Table 3. The means of tumor tissues in the groups, mitosis counts, and apoptosis counts

	Mitosis count (40x)	Apoptosis count/1,000 cells
Group 2A Inoculation by intraperitoneal injection	12,250 (std 2.06)	6.75 (std 2.21)
Group 2B Inoculation with laparotomy	13,000 (std 1.41)	6.00 (std 2.70)
p-value	0.570	0.683

Kruskal-Wallis test, t-test, std: Standard deviation

Discussion

Experimental models created for the treatment of patients with PM will enable the realization of preclinical studies and new treatment options in the future. Studies based on mouse models allow researchers to learn about diseases with highly complex and dynamic pathophysiologies, such as cancer.[7,8] Clinical advances in cancer research in recent years have been associated with the efficient use of preclinical tumor models. They have also provided us with the opportunity to understand tumor growth, physiology, and interactions with the tumor microenvironment. Models created by grafting tumor cells into genetically engineered mouse models (nude/athymic mice) constitute useful and usable experimental tools in cancer research.[9,10] In our study, we used Wistar albino rats and genetically engineered nude mice, a species routinely used in experimental trials. We evaluated the relevant differences between both species. We also compared rats that were more suitable in terms of both size and endurance during surgical procedures and follow-up with much smaller and fragile immunosuppressive nude mice, in which the performance of surgical procedures could be more difficult. A suitable PM model could not be established using rats; however, we were able to create a suitable PM model in nude mice that could be used in experimental studies.

The most common cell lines used to induce the development of PM in mouse models include MC38 and CT26 (colon adenocarcinoma cell lines).[11-16] We used the CC531 rat colon adenocarcinoma cell line in our study, which enabled us to create an effective model for use in experimental studies. Peritoneal inoculation can be performed by intraperitoneal injection or via a laparotomy approach directly into the peritoneal cavity. The desired number of cells for the peritoneal inoculation model is determined according to the tumor cell line used and the degree of aggression (i.e., MC38: 2-5x10^5 cells and ID8 (epithelial ovarian cell line): 5-10x10^6 cells). For this reason, the number of cells used for peritoneal inoculation and the volume of cells suspended both for peritoneal inoculation and the wider dissemination of cells throughout the peritoneal cavity are of critical importance.[11-13,17] In our study, 5x10^6 cells were resuspended

Table 4 VEGF, LOX1, and TWIST values in intra-abdominal fluid

	VEGF	LOX1	TWIST
Group 2A	377,382 (std ± 174,620)	496,250 (std ± 166,851)	1,241 (std ± 0.205)
Group 2B	335,535 (std ± 128,002)	510,000 (std ± 140,059)	1,165 (std ± 0.219)
p-value	0.712	0.904	0.629

Kruskal-Wallis test, t-test, VEGF: Vascular endothelial cell growth factor, LOX1: Lysyl oxidase-like protein 1, TWIST: Twist transcription factor, std: Standard deviation

(0.3 cc, 200 µL PBS) and injected into the intraperitoneal area of all groups. Two different methods were used to inoculate cells intraperitoneally: either intraperitoneal injection or peritoneal irritation through a laparotomy approach under anesthesia, with the cells released directly into the peritoneal area. In both groups of different species of rodents, post-procedural morbidities (wound infection/dehiscence) were observed in the groups that underwent laparotomy using these two different methods. One animal died in the nude mouse group. The morbidity rate was 25% (n=2) in group 1B (Wistar albino rats), and the morbidity and mortality rates in group 2B (nude mice) were 50% (n=4) and 12.5% (n=1), respectively.

In different studies, a PM model was created between the 7th and 40th days, depending on the type of cells given after intraperitoneal inoculation.[4,18,19] In our study, the experimental animals divided into groups after the inoculation of tumor cells were euthanized on the 7th and 14th days. No tumors were detected macroscopically or microscopically in the animals in group 1. In group 2, extensive peritoneal tumors were observed in the group that was euthanized on the 14th day. On the 7th day, tumor cells were observed in the cytological samples obtained by intra-abdominal lavage, but no macroscopic tumors were observed.

There are significant differences between the peritoneums of rodents and humans. The most important difference is related to the omentum, which is a highly vascularized organ critical to the development of PM in humans; however, the mouse omentum is hypovascular and does not play the same role in mice.[20-22] Due to the complexity of cancer pathophysiology, it is very difficult to establish an ideal PM model. Therefore, results in mice should always be carefully evaluated and interpreted. However, rodents belong to a species suitable for simulating PM in experimental studies. Considering all these facts, PM models are applicable and suitable models for testing different chemotherapeutic agents for application to the peritoneal cavity.

Study Limitations

In our study, two different species produced by us in the animal experiments laboratory were used. The diversity of rodent species can be increased.

Conclusion

In our study, a suitable PM model was developed that can be used in studies performed with nude mice. We determined that intraperitoneal injection is the most appropriate method for the intraperitoneal inoculation of tumor cells. Using this method, a PM model can be created with acceptable morbidity and mortality rates. In future studies, we plan to use this model for intraperitoneal therapeutic approaches.

Ethics

Ethics Committee Approval: Our study was conducted at The Experimental Animals Laboratory between January and May 2022 with the approval of the Dokuz Eylül University University Local Animal Ethics Committee (approval number: 53/2019, date: 25.12.2019).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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LETTER TO THE EDITOR

Non-Traumatic Small Intestine Perforation

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Keywords: Non-traumatic, perforation, small intestine

Dear Editor,

We read through two reviews published in this journal about the occurrence of non-traumatic small bowel perforation (NTSBP) during two different periods: 2009-2019 and 2016-2019.[1,2] Dal et al.[1] compared the surgical management between two groups of patients with NTSBP based on their status of survival (group 1, n=25) or mortality (group 2, n=17) at 90 days of the postoperative period. The mean age (54 vs. 61 years) and percentage of male patients (48% vs. 76.5%) were higher in group 2. Among the patients, 42% underwent previous abdominal surgery, and 30% had antecedent malignancies. Moreover, the most common sites of perforation were the jejunum (64.7%) in group 2 and the ileum in group 1 (68%). The authors stressed that the morbidity and mortality of patients treated for NTSBP were high and that previous diseases and hypoalbuminemia played a role, unlike the perforation site and time of admission to the hospital.[1] More recently, Muniandy et al.[2] performed a retrospective study on the outcomes of 42 patients with non-traumatic jejunum and ileum perforation (NTJIP). Their mean age was 55.7 (±19.3) years, and 29 patients (69%) reported symptoms within a 3-day period.[2] The mean hospitalization time was 10 days, the post-operative ileus was 21%, the surgical site infection was 23%, the anastomotic leak was 23%, and the mortality rate was 36%. Moreover, the peritonitis index was a reliable predictor of mortality. The authors emphasized radiation and vascular etiologies as the most common identifiable causes of NTJIP.[2]

It seems appropriate to add short comments about three case studies of Brazilian patients with perforated jejunal diverticulitis, which was not a highlighted cause in the above-mentioned studies.[3] An 80-year-old woman had abdominal symptoms 5 days prior to admission, and an imaging study showed pneumoperitoneum, duodenal and colonic diverticula, and inflammatory changes at the proximal jejunum. Moreover, the laparotomy revealed a perforated diverticulitis at 60 cm of the Trietz angle, which was managed via enterectomy (20 cm) with primary anastomosis, and the patient had an uneventful postoperative course.[3] An 80-year-old man was admitted due to severe abdominal pain, with 24 hours of duration, and the exploratory laparoscopy converted to laparotomy revealed a diagnosis of perforated diverticulitis at the level of the jejunoileal transition. A segmental enterectomy with primary anastomosis was then performed. The patient recovered without complications and was discharged home on the sixth postoperative day.[3] A 72-year-old man was admitted with abdominal pain for one day, and an imaging study revealed inflammatory changes at the jejunoileal transition besides the pneumoperitoneum, and the laparoscopy showed perforated jejunal diverticulitis, which was managed via enterectomy (30 cm) with an end-to-end anastomosis. The patient was discharged on the eighth postoperative day, accepting the diet and experiencing normal intestinal transit.[3] The authors emphasized that perforated jejunal diverticulitis is an uncommon condition, is rarely included in differential diagnoses of acute abdomen, and is often incidentally detected by abdominal imaging studies. They also highlighted that case studies contribute to enhancing the index of suspicion about this rare entity.[3]

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Therefore, the literature included herein may increase awareness among healthcare workers.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: V.M.D.S., L.A.M.D.S., Design: V.M.D.S., L.A.M.D.S., Data Collection or Processing: V.M.D.S., L.A.M.D.S., Analysis or Interpretation: V.M.D.S., L.A.M.D.S., Literature Search: V.M.D.S., L.A.M.D.S., Writing: V.M.D.S., L.A.M.D.S.

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LETTER TO THE EDITOR

Structured Robotic Training Programs for Colorectal Trainees: is it Time?

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Keywords: Colorectal, robotic, surgery, training

Dear Editor,

The past few decades have seen a paradigm shift from a conventional open approach to minimally invasive surgery (MIS) for abdominal surgery. The concept of MIS has made its way into various specialties where it provides an alternative to the open approach for various indications. The benefits of MIS for colorectal resections have been recognized and gradually accepted over time. As published evidence has shown better short-term outcomes and oncological equivalence compared with open surgery, MIS has taken a central role in the management of colon and rectal surgery. This concept was further validated by several landmark randomized controlled trials;[1-4] currently, laparoscopy is considered and offered as the first option to most patients for both benign and malignant conditions in colorectal surgery. However, this transition is marked by resistance from the surgical community, which is largely due to the longer learning curve, skill gap, and increased capital cost. Bridging the skill gap requires various initiatives from both health departments and industry-funded fellowships for senior trainees to improve the skills of practicing colorectal surgeons. The LAPCO program in the United Kingdom (UK) was a government initiative that led to the increased uptake of laparoscopy in many laparoscopic colorectal units throughout the country. The adoption of laparoscopic resections in the UK remains at approximately 72%.[5] These figures drop when rectal cancer surgery is considered due to the obvious perceived technical difficulties associated with rectal cancer surgery. Various factors can be identified as causes of the limited uptake of laparoscopy, even after the country-wide and government-sponsored training program. The main reason is likely a steep learning curve, which puts established open surgeons off the idea of MIS. Other factors and limitations reported include a lack of tactile feedback, issues with exposure, and difficulty working in confined spaces. These concerns are mostly secondary to the lack of proper training and assessment before laparoscopic resections are undertaken.

Robot-assisted MIS was introduced approximately two decades ago, and surgeons in various specialties were able to report significant benefits of the newer technology. The innovative system had the advantage of a stable three-dimensional magnified view, with the arms allowing 7 degrees of movement, 180 degrees of articulation, and 540 degrees of rotation in confined spaces. Although these advantages made robot-assisted MIS the preferred choice for surgeons, the presence of certain disadvantages hindered its wider acceptance. The lack of a structured training program, financial implications, and the selective availability of the technology to a limited group of surgeons are the main reasons for the reduced uptake of this modality in surgical practice.

The European Association of Urologists and the British Association of Urology Surgeons, followed by the Society of

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Gynaecology Robotic Surgeons, were the first to formulate a structured curriculum and objective assessment before the certification of the surgeons to undertake procedures. These structured training pathways lead to improved outcomes, and the respective specialties were able to show the significant gains of robot-assisted MIS for certain disorders. Although marginal benefits have been reported by expert hands, especially in high-risk patients, training in robotic colorectal surgery remains in its infancy. However, it is anticipated that the introduction of structured training programs in robotic colorectal surgery will bring the necessary changes by proving the significant benefits of robot-assisted MIS for colorectal disorders.

At present, the Fundamentals of Robotic Surgery in the United States and the European Association of Robotic Colorectal Surgery in Europe are evaluation-based training programs.[6-8] A structured training curriculum for modular training using a dual robotic console for added patient safety is recommended. This is followed by an objective assessment using the Global Assessment Score across different variables, including robot docking, colonic dissection, total mesorectal excision, resection, and anastomoses.[9] The evidence supports that the transition from open to robotic surgery has a shorter learning curve than the transition to laparoscopic surgery and is safe and effective.[10] Moreover, it has been established that 10 cases through structured training are sufficient to perform robotic rectal resection competently, which is very unlikely with lap-assisted MIS.

Before a candidate enters a structured training program, it should be mandatory for them to have attained some non-technical and technical skills. The non-technical skills revolve around leadership, teamwork, and communication skills. An operating surgeon oversees the robotic surgery theatre and is responsible for communicating effectively with other medical and non-medical personnel present. The scrub nurse, bedside assistant, and anesthetist work in coordination with the operating surgeon, who is away from the patient cart, and each relies on commands from their team members. This theatre setup minimizes the risks to others, and having effective control of the situation in case of an emergency requires other attributes to be learned before surgical skills.

Technical skills, including e-learning about the robotic system, simulation-based training, attendance at short courses to learn safe docking and undocking, and case observations, are always helpful in the training process. The curriculum should be designed according to the needs of the individual, as it involves two tiers of trainees, i.e., practicing consultant surgeons and trainee registrars.

The common training opportunities available in robotic colorectal surgery include various global short-term courses and some cadaver courses, which are mainly offered by the industry. The issue with the short-term courses is that the candidates experience simulator-based training in dry labs for a couple of days in a robotics institute, watch highly edited videos over the duration of the course, and then return to a real-world environment in which there is no opportunity to practice the skills they have learned. The issue with the cadaver courses run by the industry is that there is limited availability, the selection of the candidates is recommendation-based, and the course is expensive. These courses aim to provide insight into the philosophy of operating a robotic machine over a period of one to two days. Fellowships in robotic colorectal surgery constitute the most popular platform for senior trainees who are awaiting consultant appointments. After 6 months to 1 year of training in robotic colorectal surgery, an appointment in an institute where a robot is available is not guaranteed. Importantly, these courses and fellowships lack an objective assessment and certification.

There may be a place for training pathways in which trainee surgeons will be placed in centers where robotic systems are available to give trainees adequate practical experience at the beginning of their surgical training. The learning process of these trainees may be followed by teaching the use of tools such as Kolb's learning cycle, which is based on concrete experience, reflective observation, abstract conceptualization, and active experimentation. This cycle repeats itself at every training module of robotic colorectal surgery and continues during the entire training. The process may be a way forward for developing surgeons of the future with competence in robot-assisted surgery.

Robotic colorectal surgery may seem like a novelty at present, but it is believed that the marginal gains that have been observed after robot-assisted colorectal surgery, especially in high-risk patients, will become more pronounced, making it a necessity of the future. Laparoscopy will no doubt retain its place in colorectal surgery, but difficulties encountered with straight instruments and a steep learning curve will likely shift the balance toward robot-assisted MIS.

It remains the responsibility of the colorectal surgical faculty to provide structured, assessment-based training pathways to help train surgeons wishing to learn robotic colorectal surgery. It should be done independently from and uninfluenced by the industry, with quality being the focus of skill acquisition.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.A.N., A.P., Design: M.A.N., A.P., Concept: V.M.D.S., L.A.M.D.S., Data Collection or Processing:

M.A.D., N.Z.A., Analysis or Interpretation: M.A.D., N.Z.A., M.A.N., Literature Search: M.A.D., N.Z.A., Writing: M.A.D., N.Z.A., A.P.

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ERRATUM

The start date of the study mentioned in the publication of the article titled 'Effectiveness of Different Local Anesthesia Application Methods in Postoperative Pain Control in Laparoscopic Appendectomies: A Randomized Controlled Trial,' published by Anıl Ergin and colleagues in September 2022, has been provided incorrectly.

Turkish Journal of Colorectal Disease, (Turk J Colorectal Dis 2022;32:170-177, DOI: 10.4274/tjcd.galenos.2022.2021-11-9).

For the study, after obtaining ethical approval, the research commenced immediately, and the dates mentioned in the "Abstract (Method) and Main Document (Materials and methods)" section, originally stated as September 2018 and 2019, have been updated to December 2018 and 2019.

*** The sentences under the heading "Abstract (Method) on page 170 and Main Document (Materials and Methods)" on page 171 have been changed.**

Incorrect;

ABSTRACT
Method: Overall, 160 patients who underwent laparoscopic appendectomy for uncomplicated acute appendicitis between September 2018 and September 2019 were included.

Correction;

ABSTRACT
Method: Overall, 160 patients who underwent laparoscopic appendectomy for uncomplicated acute appendicitis between December 2018 and 2019 were included.

Incorrect
Materials and Methods
In this double-blind, randomized, controlled study, we included 160 patients aged 16-74 years who underwent laparoscopic appendectomy for acute appendicitis between September 2018 and 2019.

Correction;
Materials and Methods
In this double-blind, randomized, controlled study, we included 160 patients aged 16-74 years who underwent laparoscopic appendectomy for acute appendicitis between December 2018 and 2019.