E-ISSN: 2791-8823

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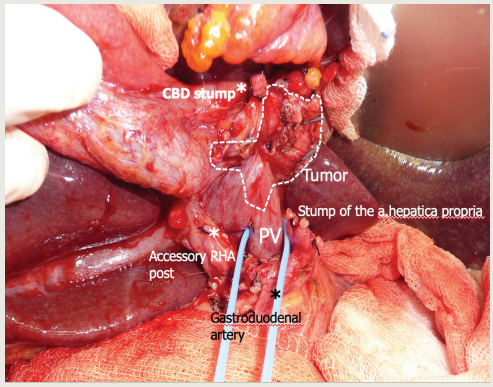
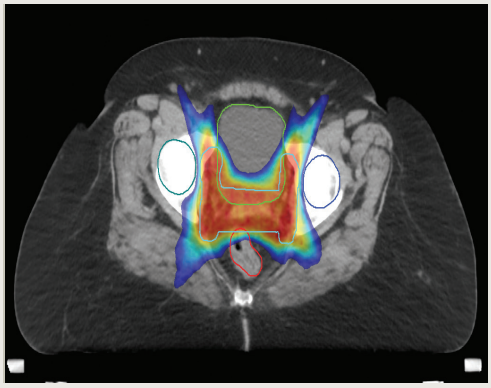
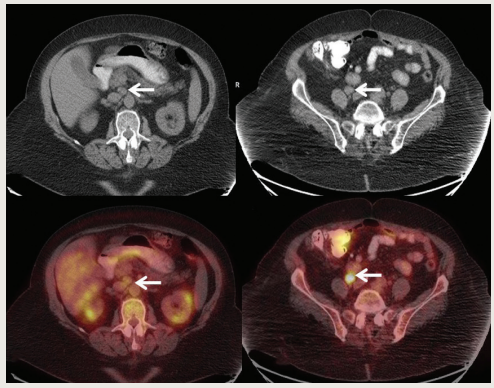
THE JOURNAL OF BAŞAKŞEHİR ÇAM AND SAKURA CITY HOSPITAL







CAM & SAKURA MEDICAL JOURNAL

April
2021 Volume: 1 Issue: 1

galenos Publishing House

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Volume: 1 • Issue: 1 • April 2021

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E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: MetinCopyPlus/Artı Dijital & Baskı Merkezi
Türkocağı Cad. 3/A Türkiye Gazeticiler Cemiyeti Altı
İran Konsolosluğu Karşısı Cağaloğlu, Fatih, İstanbul, Türkiye
Phone: +90 (212) 527 61 81 (PBX) **E-mail:** info@metincopyplus.com
Printing Date: October 2021

E-ISSN: 2791-8823

International scientific journal published quarterly.

CSMJ

Volume: 1 • Issue: 1 • April 2021

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About Us

Cam and Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (March-July-November). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Cam & Sakura Medical Journal publishes original experimental or clinical research, review articles, case reports, technical reports, diagnostic puzzle, clinical images, video article, novel insight, and letters to the editor in the field of general medicine. Review articles will be only prepared by expert academicians upon invitation. The journal's target audience includes academics and expert physicians working in all fields of general medicine.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/) rules.

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In case of a withdrawal of an article by the author/s, they should specify the reason for the withdrawal in detail, and submit it to the Editorial Board with a petition that wet signed by all authors.

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Phone: +90 212 621 99 25

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Instructions to Authors

Editorial, Publication and Peer-review Process

The editorial and publication processes of the journal are established in accordance with the international guidelines. The most important criteria of the manuscripts for publication include originality, scientific quality, and citation potential. The authors should guarantee that the manuscripts have not been previously published and/or are under consideration for publication elsewhere. The scientific and ethical liability of the manuscripts belongs to the authors and the copyright of the manuscripts belongs to CSMJ. Authors are responsible for the contents of the manuscript and accuracy of the references. All manuscripts submitted for publication must be accompanied by the Copyright Agreement and Authorship Acknowledgement Form. The manuscript should be submitted when this form has been signed by all the authors. By the submission of this form, it is understood that neither the manuscript nor the data it contains have been submitted elsewhere or previously published and authors declare the statement of scientific contributions and responsibilities of all authors.

Manuscripts submitted to the CSMJ will be evaluated by a double-blind peer-review process. Each submission will be reviewed by the chief editor, deputy and associate editors and at least two external, independent peer expert reviewers. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The reviewers will be requested to complete review process within 6-8 weeks. Authors will be informed within a period of 8 weeks about the process. Upon review, those manuscripts, which are accepted, shall be published in the journal and issued on the http://www.csmedj.org.

CSMJ does not charge any article submission or processing charges.

General Guidelines

Manuscripts can only be submitted electronically through the Manuscript Manager website (csmedj.manuscriptmanager.net) after creating an account. This system allows online submission and review.

Format: Manuscripts should be prepared using Microsoft Word, size A4 with 2.5 cm margins on all sides, 12 pt Arial font and 1.5 line spacing.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover letter: The cover letter should include statements about manuscript type, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipment (if applicable), approval of language for articles in English and approval of statistical analysis for original research articles.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

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

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

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

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

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

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

Manuscripts are accepted only online and can be submitted electronically through web site (http://csmedj.org) after creating an account. This system allows online submission and review. The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org. The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks are not returned.

All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding. The rules for the title page, references, figures and tables are valid for all types of articles published in this journal. Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Ethical Guidelines

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies. Information about patient consent, the name and approval number of the ethics committee should be stated in the manuscript. Submission which do not have ethical approval will be rejected after editorial review due to the lack of approval.

For experimental studies performed on animals, an approval research protocols by the Ethics Committee in accordance with international

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agreements is required. Also, a statement including measures for prevention of pain and suffering should be declared in the manuscript. For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. The authors have responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be obtained and the publication approval must be provided in the manuscript.

Authors must provide disclosure/acknowledgment of financial or material support, if any was received, for the submitted study. If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, pharmaceutical company. concerned; or specify the type of relationship. Authors must provide conflict of interest statement and provide authorship contributions.

The scientific board guiding the selection of the papers to be published in the Journal consists of elected experts of the Journal and if necessary, selected from national and international authorities. The Editor-in-Chief, Associate Editors, biostatistics expert and language editors may make minor corrections to accepted manuscripts that do not change the main text of the paper.

Plagiarism and Ethical Misconduct

Cam & Sakura Medical Journal is sensitive about plagiarism. All submissions are screened by a similarity detection software (iThenticate by CrossCheck) at any point during the peer-review and/or production process. Authors are strongly recommended to avoid any form plagiarism and ethical misconduct for prevention of acceptance and/or publication processes. Results indicating plagiarism may result in manuscripts being returned for revision or rejected. In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. CSMJ accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

Statistics

Every submission that contains statistical analyses or data-processing steps must explain the statistical methods in a detailed manner either in the Methods or the relevant figure legend. Any special statistical code or software needed for scientists to reuse or reanalyse datasets should be discussed. We encourage authors to make openly available any code or scripts that would help readers reproduce any data-processing steps. Authors are also encouraged to summarize their datasets with descriptive statistics which should include the n value for each dataset; a clearly labelled measure of centre (such as the mean or the median); and a clearly labelled measure of variability (such as standard deviation or range). Ranges are more appropriate than standard deviations or standard errors for small datasets. Graphs should include clearly labelled error bars. Authors must state whether a number that follows the ± sign is a standard error (s.e.m.) or a standard deviation (s.d.). Authors must clearly explain the independence of any replicate measurements, and 'technical replicates' – repeated measurements on the same sample – should be clearly identified. When hypothesis-based tests must be used, authors should state the name of the statistical test; the n value for each statistical analysis; the comparisons of interest; a justification for the use of that test (including, for example, a discussion of the normality of the data when the test is appropriate only for normal data); the alpha level for all tests, whether the tests were one-tailed or two-tailed; and the actual p-value for each test (not merely 'significant' or '$p < 0.05$'). It should be clear what statistical test was used to generate every p-value. Use of the word 'significant' should always be accompanied by a p-value; otherwise, use 'substantial', 'considerable', etc. Multiple test correction must be used when appropriate and described in detail in the manuscript.

All manuscripts elected for full peer review will be assessed by a statistical editor and their comments must be addressed in full.

Preparation of the Manuscript

a. Title Page

The title page should include the full title of the manuscript; information about the author(s) including names, affliations, highest academic degree and ORCID numbers; contact information (adress, phone, mail) of the corresponding author. If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page. If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

For regular article submissions, "**What's known on this subject?**" and the "**What this study adds?**" summaries.

This page should include the title of the manuscript, short title, name(s) of the authors and author information. The following descriptions should be stated in the given order:

1. Title of the manuscript (English), as concise and explanatory as possible, including no abbreviations, up to 135 characters
2. Short title (English), up to 60 characters
3. Name(s) and surname(s) of the author(s) (without abbreviations and academic titles) and affiliations
4. Name, address, e-mail, phone and fax number of the corresponding author
5. The place and date of scientific meeting in which the manuscript was presented and its abstract published in the abstract book, if applicable.
6. The ORCID (Open Researcher and Contributor ID) number of the all authors should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

b. Abstract

The abstract should summarize the manuscript and should not exceed 300 words. The abstract of the original articles consist of the subheadings including "Objective, Methods, Results, and Conclusion". Separate abstract sections are not used in the submission of the review articles, case reports, technical reports, diagnostic puzzle, clinical images, and novel articles. The

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use of abbreviations should be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

c. Keywords

A list of minimum 4, but no more than 6 key words must follow the abstract. Key words in English should be consistent with "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html).

d. Original Article

The instructions in general guidelines should be followed. The main headings of the text should include "Introduction, Material and Methods, Results, Discussion, Study Limitations and Conclusion". The introduction should include the rationale and the background of the study. Results of the study should not be discussed in this part. "Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated. Results should also be given in detail to allow the reproduction of the study. The Discussion section should provide a correct and thorough interpretation of the results with the relevant literature. The results should not be repeated in the Discussion Part. The references should be directly related to the findings of the authors. Study Limitation should be detailed in the section. Conclusion section should provide highlighted and interpreted with the study's new and important findings.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

Original Articles should be no longer than 3500 words and include no more than 6 tables and 7 or total of 15 figures and 40 references. The abstract word limit must be 250.

Introduction

The article should begin with a brief introduction stating why the study was undertaken within the context of previous reports.

Materials and Methods

These should be described and referenced in sufficient detail for other investigators to repeat the work. Ethical consent should be included as stated above.

The name of the ethical committee, approval number should be stated. At the same time, the Ethics Committee Approval Form should be uploaded with the article.

Results

The Results section should briefly present the experimental data in text, tables, and/or figures. Do not compare your observations with that of others in the results section.

Discussion

The Discussion should focus on the interpretation and significance of the findings with concise objective comments that describe their relation to other work in that area and contain study limitations.

Study Limitations

Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion

The conclusion of the study should be highlighted.

e. References

The reference list should be typed on a separate page at the end of the manuscript. Both in-text citations and the references must be prepared according to the Vancouver style. Accuracy of reference data is the author's responsibility. While citing publications, preference should be given to the latest, most up-to-date references. The DOI number should be provided for citation of ahead-of-print publication, Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. All authors should be listed in the presence of six or fewer authors. If there are seven or more authors, the first three authors should be listed followed by "et al." References should be cited in text, tables, and figures should be cited as open source (1,2,3,4) in parenthesis numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. The reference styles for different types of publications are presented as follows:

i) Standard Journal Article

Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340-2348.

ii) Book

Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

iii) Chapter of a Book

Volpe JJ: Intracranial hemorrhage; in Volpe JJ (ed): Neurology of the Newborn, ed 5. Philadelphia, Saunders, 2008, pp 481-588.

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-380.

If more than one editor: editors.

iv) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-1565.

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v) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

vi) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

f. Tables, Graphics, Figures, Pictures, Video:

All tables, graphics or figures should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Figures should be done professionally and no grey colors should be used. Authors are responsible for obtaining permission to publish any figures or illustrations that are protected by copyright, including figures published elsewhere and pictures taken by professional photographers. The journal cannot publish images downloaded from the Internet without appropriate permission.

Figures or illustrations should be uploaded seperately.

Special Sections

Reviews

Reviews will be prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors and subjects will be invited by the journal. All reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

The entire text should not exceed 25 pages (A4, formatted as specified above).

Reviews should be no longer than 5000 words and include no more than 6 tables and 10 or total of 20 figures and 80 references. The abstract word limit must be 250.

Case Reports

Case reports should present important and rare clinical experiences. It must provide novel, and/or rare clinical data, or new insights to the literature. Case reports should consist of an unstructured abstract (maximum 150 words) that summarizes the case. They should consist of the following parts: introduction, case report, discussion. Informed consent or signed releases from the patient the patient or legal representative should be obtained and stated in the manuscript.

Reviews should be no longer than 1000 words and include no more than 200 tables and 10 or total of 20 figures and 15 references. The abstract word limit must be 150.

Clinical Images

The journal publishes original, interesting, and high quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. It can be signed by no more than 5 authors and can have no more than 5 references and 1 figure or table. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Video Article

Video articles should include a brief introduction on case, surgery technique or a content of the video material. The main text should not exceed 500 words. References are welcomed and should not be more than 5. Along the main document, video material and 3 images should be uploaded during submission. Video format must be mp4 and its size should not exceed 100 MB and be upto 10 minutes. Author should select 3 images, as highlights of the video, and provide them with appropriate explanations. Video and images must be cited within main text.

Technical reports

Technical reports are formal reports designed to convey technical information in a clear and easily accessible format. A technical report should describe the process, progress, or results of technical or scientific research or the state of a technical or scientific research problem. It might also include recommendations and conclusions of the research. Technical reports must include the following sections: abstract, introduction, technical report, discussion, conclusions, references. Technical reports should contain less than 20 references.

Diagnostic puzzle

Diagnostic puzzles report unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately. Diagnostic puzzles should include an introduction and answer part. The introduction part should include a brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. Then, the answer part should appear later (maximum 250 words) outlines a brief description of the key diagnostic features of the image, the outcome, and a teaching point.

Diagnostic puzzles will not include more than 5 references. The quality of the image must be at least 300dpi and in TIFF, JPEG, GIF or EPS format. Videos are also welcome and should be in .mov, .avi, or .mpeg format.

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Novel insight

This section will offer an opportunity for articles instead of the traditional category of Case Reports. Submissions to this section should contribute significant new insights into syndromological problems, molecular approach and real novelties on recognized or entirely new genetic syndromes or a new technique. The novel aspect(s) can be in the phenotype and/or genotype, the presentation, and the investigation. Submissions can be based around a single case or serial cases. Manuscripts for this section will go through the usual peer reviewing process. The manuscripts should contain abstract (maximum 150 words), a brief introduction, case report(s) and discussion.

Letters to the Editor

This section welcomes for manuscripts that discuss important parts, overlooked aspects, or lacking parts of a previously published article in this journal. In addition, articles on subjects within the scope of the journal that might have an attraction including educative cases, may also be submitted in the form of a "Letter to the Editor." The manuscripts for this section should be written in an unstructered text including references. The editor may request responses to the letters. There are no separate sections in the text.

Letter to the editors should be no longer than 500 words.

Revision Process

During the submission of the revised version of a manuscript, the authors should submit a detailed "Response to the reviewers and editors" that states point by point how each issue raised by the reviewers and/or editors has been replied and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts should be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue.

LIMITATION TABLE

Type of Manuscript	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review	5000	250	60	6	10 or total of 20 images
Case Report	1000	150	20	200	10 or total of 20 images
Letter to the Editor	500	No Abstract		No tables	No media
Video Article	500		5		
Diagnostic Puzzle	250 (as a brief clinical introduction		5		
Clinical Images	500 (as a brief explanation)		5	1	1
Technical Reports			20		

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Letter From The Chief Physician

Dear Colleagues,

Basaksehir Cam and Sakura City Hospital, a large complex in Istanbul was opened in May 2020. The hospital complex consists of eight special hospitals including six blocks of pediatrics, general medicine, orthopedics & neurology, obstetrics & gynecology, cardiac & vascular surgery and oncology. In addition, there are two adjacent buildings of physical medicine and rehabilitation and psychiatry hospitals. The capacity of the hospital include 725 clinics and 2,682 beds. More than 100 academic staff has been working in our hospital. It has an affiliation with Health Sciences University. Currently, 52 different specialities and subspecialities serve as educational departments for residents and fellows. In addition to training and research activities, we start to publish our official Cam&Sakura Medical Journal (CSMJ) to improve educational facilities. We established a large Editorial Board from all over the world to provide scientific collaboration.

Our primary aim is to establish CSMJ as an indexed journal to share recent improvements from all departments of general medicine. Several kind of manuscripts including invited reviews from experts, experimental and clinical original studies, case reports, letters to the editor, and others will be published in CSMJ. I believe that CMSJ will make important contributions in the scientific literature. Therefore, to achive these goals, we need your help for submission of original manuscripts. I want to thank to all editors and editorial board for their assistance in publication of CSMJ.

I hope you will read the first issue with great interest. I thank to the authors of the manuscripts in this issue. We will be waiting your contributions for the future issues. I wish healthy days for all readers during Covid-19 pandemics.

Mehmet Emin Kalkan
Chief Physician
Cam and Sakura City Hospital

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Editorial

Dear Colleagues and Readers,

It is great honour and pleasure for us to introduce the first issue of Cam & Sakura Medical Journal (CSMJ) with you. CSMJ is designed as an international, scientific, open-access journal. CSMJ is the official publication of the Basaksehir Cam and Sakura City Hospital that will be published three times per year in English. In addition, a special supplement will also be published every year. I especially thank to Chief Physician, Prof. Mehmet Emin Kalkan, for all his efforts during the establishment processes of CSMJ.

As the Editors, Associate Editors and Editorial Board, our primary objective is to include CSMJ in well established national/international indexes and Pubmed in the following years. To achieve this aim as soon as possible, we need your contributions including research articles, case reports, technical reports, diagnostic puzzles, clinical images, video articles, novel insights, and letters to the editor in the field of general medicine designed according to CSMJ submission guidelines.

In this first issue, you can read the interesting review on liver transplantation from a different perspective and you can also find important original articles and a case report. I would like to thank all the authors and reviewers for their contribution to the first issue.

We will be waiting for your valuable assistance for the following issues of CSMJ. We suggest that CSMJ will have an important role in the improvement of medical science in both national and international standards. We welcome all manuscripts from all over the world. Hoping to meet you on the second issue.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Cetinkaya

Editor in Chief

Cam & Sakura Medical Journal

DOI: 10.4274/csmedj.galenos.2021.2021-8-5

REVIEW

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Cam and Sakura Med J 2021;1(1):1-6

CSMJ

Liver Transplantation is Never… Just Liver Transplantation

İlgin Özden

Başakşehir Çam and Sakura City Hospital, Liver Transplantation and Hepatopancreatobiliary Surgery Unit, İstanbul, Turkey

ABSTRACT

Liver transplantation is a unique operation that has not only saved tens of thousands of lives directly, but has also led to dramatic developments in multiple fields of medicine other than surgery.

Keywords: Liver transplantation, cadaveric, living donor, gene therapy, hepatocyte transplantation

Introduction

Liver transplantation (LTx) is indicated for only a small fraction of patients with liver disease. However, this operation has had tremendous direct and indirect effects on not only surgery, but all fields of medicine-hence the title of this paper. Some of its most striking aspects are outlined here, based on the published literature and the author's personal experience at the İstanbul Faculty of Medicine and Çam and Sakura City Hospital.

1- Standard Treatment of End-stage Liver Disease and Acute Liver Failure (ALF) That Does Not Respond to Intensive Care Treatment

LTx is the only definitive treatment for end-stage liver disease and ALF that does not respond to intensive care treatment (1,2,3).

Although the first consistently successful transplants were performed from 1967 onwards (1), the most decisive event was the adoption of LTx as standard treatment by the American National Institutes of Health in 1983 (4). At the time, the 1-month mortality of the recipients varied between 20% and 40% (4). As Starzl (1) noted, *"In 1989, only six years later, a 17-page article divided between the October 12 and October 19 issues of the New England Journal of Medicine began with the following statement: The conceptual appeal of LTx is so great that the procedure may come to mind as a last resort for virtually every patient with lethal hepatic disease".*

The current 1-year patient survival figures vary between 85% and 94% (5). In the published literature, the longest survivor underwent LTx for biliary atresia (BA) as a small child and is alive at 42.7 years posttransplant (1). The program at the İstanbul Faculty of Medicine was established by Koray Acarlı in 1991; some of the patients who received transplants in 1992 are leading active lives as of 2021, corresponding to 29 years of survival. Approximately 35,000 liver transplants were performed around the world in 2018 (6). Centers of excellence have reported large series with near-zero hospital mortality and >95% 1-year survival (7,8).

Address for Correspondence: İlgin Özden Prof. MD, Başakşehir Çam and Sakura City Hospital, Liver Transplantation and Hepatopancreatobiliary Surgery Unit, İstanbul, Turkey
Phone: +90 532 415 08 87 **E-mail:** iozden@hotmail.com **ORCID ID:** orcid.org/0000-0001-7360-628X
Received: 18.01.2021 **Accepted:** 14.02.2021

2- An Indelible Understanding of Acute Liver Failure

ALF is a life-threatening condition defined by the acute onset of jaundice, coagulopathy and encephalopathy in a patient with no previous liver disease. LTx is the only hope of survival in patients who do not respond to intensive care treatment (2,3). Although prognostic criteria have been proposed, none can represent the grim reality of ALF better than operative findings. The liver of a patient with ALF is shown in Figure 1a. At first glance, everything looks normal. However, the pallor and multiple areas of "dimpling" on the normally smooth capsule (caused by collapse due to necrosis) cannot escape the trained eye. In fact, the entire organ is necrotic. Figure 1b shows one of the small islands of liver tissue which, with the support of the excellent intensive care team, enabled the patient to survive until an organ for transplant became available.

3- An Intergral Part of Hepatology Training

There are established indications and criteria for referring patients to liver transplant units and placing them on liver transplant lists (9,10). For example;

"BA patients who are post hepatoportoenterostomy (HPE) should be promptly referred for LT evaluation if the total bilirubin is greater than 6 mg/dL beyond 3 months from HPE (1-B); liver transplant evaluation should be considered in BA patients whose total bilirubin remains between 2-6 mg/dL (1-B)" (10).

If LTx are performed at the same institution, the residents and fellows will have opportunities to observe the entire course of the patient's treatment. If not, the patient will have to be referred to a transplant center. Although this is a good arrangement for the patient, it inevitably creates a huge gap in the education of the trainees because their exposure to patients with liver dysfunction beyond a particular level becomes extremely limited. The maxim "What does not kill you, makes you stronger" holds for all forms of training. Exposure to complicated clinical problems under proper supervision not only provides the fellows with excellent education, but also inculcates a judicious self-confidence that is vital for a successful professional life. Therefore, gastroenterology and hepatology fellows should attend a 3-month rotation at a high-volume liver transplant unit prior to graduation. Since the increasing number of long-term survivors makes it impossible and impractical for the transplant center to follow all patients directly, having an increased number of fellows on rotation would also be beneficial for patients. Some form of holistic collaboration with gastroenterologists, hepatologists and family physicians would be mandatory, at least for patients without major complications (11).

4- Enhancement of Radiology Training

Any type of major surgery is impossible without strong support from diagnostic and interventional radiology. Living donor LTx (LDLTx) requires accurate delineation of the intrahepatic anatomy for the safe division of a vital organ for transplantation. Expertise in ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) are vital. In most centers, patients who receive grafts from living donors undergo Doppler USG examinations twice a day during the first week and once a day during the second. In teaching institutions, this is performed by senior residents under the general supervision of attending radiologists and the transplant surgeon; there is a general understanding that serial examination by a properly supervised junior

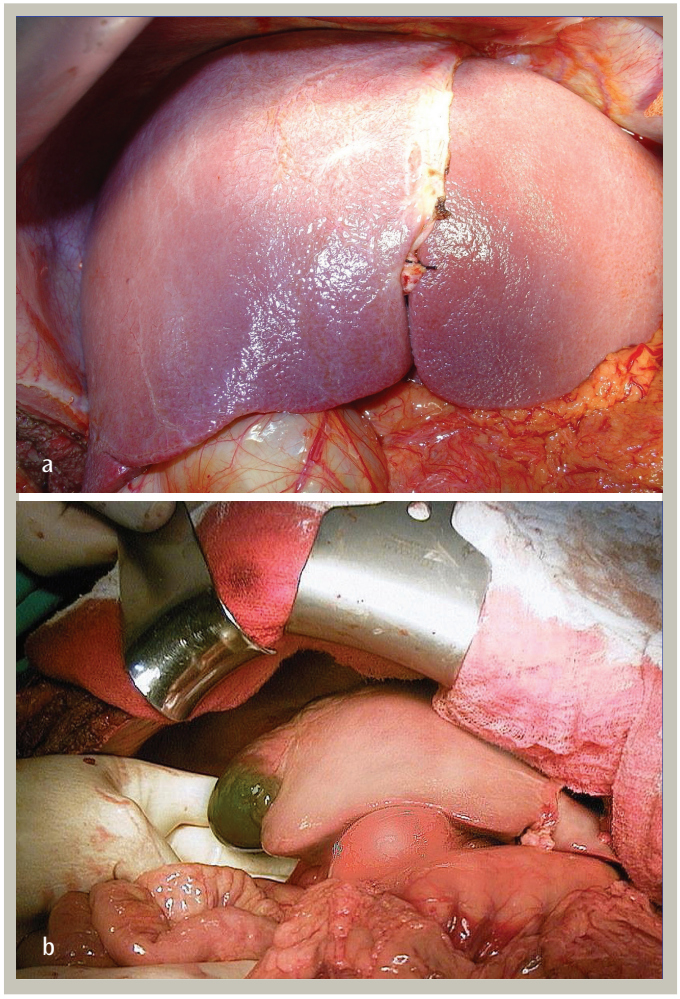

Figure 1. a) Operative photograph of an ALF patient who underwent liver transplantation; the pallor and multiple areas of "dimpling" on the normally smooth capsule are signs of extensive necrosis, b) one of the remaining small islands of viable liver tissue (brown)

physician is more reliable in detecting subtle but important changes, compared to examinations performed by multiple, more senior radiologists. This daily duty provides excellent radiology training with remarkable results, as shown in the following example from the İstanbul Faculty of Medicine.

A 34-year-old patient had attended various institutions over three years due to inability to walk in a coordinated manner, dysarthria and non-convulsive fainting episodes that lasted up to 30 minutes and were followed by complete recovery. Episodes of orientation loss and aggression (1-2/month) were reported by his relatives. The results of the standard liver function tests and USG were within normal limits except for increased ammonia levels, noted occasionally. A low-protein diet was partially effective for symptom control. The neurology resident and her supervisor felt that the liver imaging was incomplete without a Doppler USG. The radiology resident who was assigned to the initial examination happened to be physician who had completed her one-month liver transplant rotation. She diagnosed a congenital shunt between the left portal vein and the left hepatic vein by herself and informed her supervisor. A CT angiography confirmed her diagnosis (Figure 2).

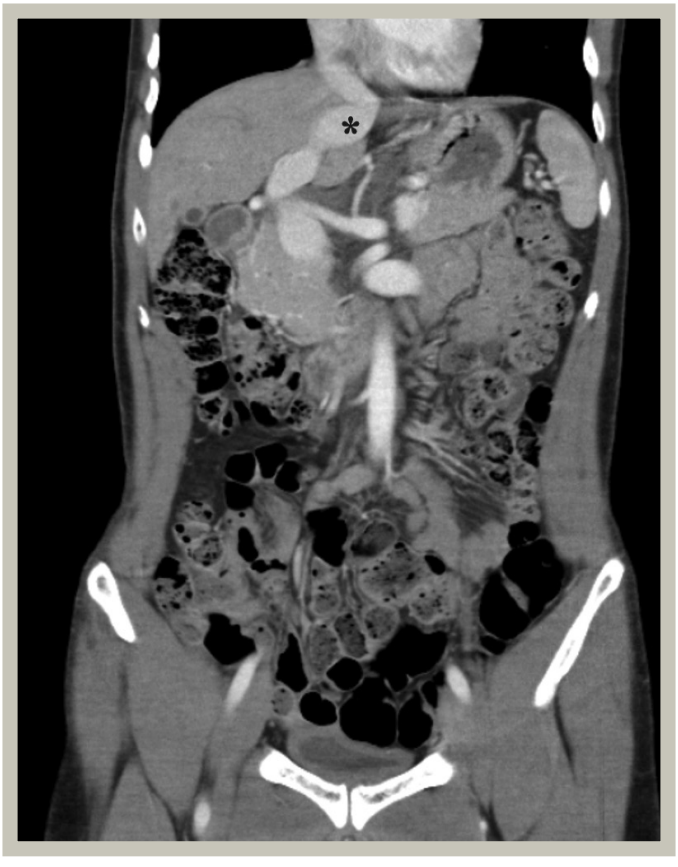

Figure 2. The congenital shunt (asterisk) between the left portal vein and the left hepatic vein

5- Enhanced Infectious Disease Training

The rate of development of new antibiotics cannot keep up with the increasing rates of multidrug resistance (MDR). Consequently, infections due to MDR organisms (MDRO) have become important causes of hospital mortality (12,13). One of the most problematic fields is LTx because of the high risk of colonization due to multiple infections during the waiting period. Colonization is the most important risk factor for infection and carries a very high risk of mortality (14). An institution hosting a successful liver transplant program must have established practices for hospital hygiene, quarantine, antibiotic stewardship, and the monitoring and control of colonization, as well as early diagnosis and aggressive treatment of infections due to MDRO. A successful institutional response to this challenge lays an excellent foundation for training residents and fellows in infectious diseases. Of course, LTx is not the only clinical field affected by this problem, but fellows training in gastroenterology and hepatology will certainly reap the benefits listed above.

6- Clues to the Recovery Capacity of the Brain

The prognostication of neurological recovery after transplantation for ALF is a very challenging issue. The available criteria are inadequate for determining which patients will recover without sequalae and which will not (15,16,17). A previously reported case demonstrates that the recovery capacity of the brain may, in some instances, challenge even the basic principles of neurologic examination (18):

"A 9-year-old boy underwent cadaveric transplantation for mushroom poisoning after 5 days of endotracheal intubation. During hilar dissection, after ligation and division of the hepatic arteries and the common hepatic duct, the anesthesiologist reported that pupillary reflex disappeared and the pupillae had become fixed and dilated. A decision whether to abort or proceed had to be made. The liver from a 72-year-old donor had been sent by plane from a distant city and taken to the operation table. It was unlikely that the liver could be used in another recipient. The operation was continued. The graft showed good early function. However, the pupils remained dilated until 10 hours after abdominal closure. Then dilation started to resolve and the pupillary reflex returned. He regained consciousness and was extubated on the 4th postoperative day. However, he was tetraparesic. He was admitted to the ward on the 7th postoperative day. Full functional recovery could be achieved with 4 weeks of intense physical rehabilitation and he was discharged to his home on the 40th postoperative day"…

"Of course, if the disappearance of the light reflex had been noted in the intensive care unit, transplantation would have been cancelled".

7- Reciprocal Enhancement of Liver Transplantation and Non-transplant Hepatobiliary Surgery

The examples below show that LTx and hepatobiliary surgery should be considered parts of a whole.

LTx is indicated in some patients with hepatocellular carcinoma either as a primary or secondary procedure (salvage operation for intrahepatic recurrence after a hepatectomy) (19). In a situation analogous to the exposure of fellows to patients with moderate-to-severe dysfunction, hepatopancreatobiliary surgery fellows in institutions that do not provide LTx should participate in a 3-month rotation at a high-volume liver transplant unit before graduation.

LDLTx requires a very high level of expertise on intrahepatic and hilar anatomy. This can be attained not by experience in whole-organ cadaveric transplantation but in complex hepatectomies and hepatobiliary resections for oncological surgery. In this sense, hepatobiliary surgery sets the stage for success in LDLTx, as has occurred in countries in the Far East. Conversely, experience in LDLTx enables a team to perform aggressive hepatobiliary surgery precisely and safely, as illustrated in the following example. The MRI and CT angiography of the patient with perihilar cholangiocarcinoma (İstanbul Faculty of Medicine) are shown in Figure 3. The tumor had divided the biliary tree into at least three compartments, encased the left portal vein and invaded the left and possibly right hepatic arteries. The patient had an accessory right posterior artery that the tumor had not involved. Upon laparotomy, the tumor was

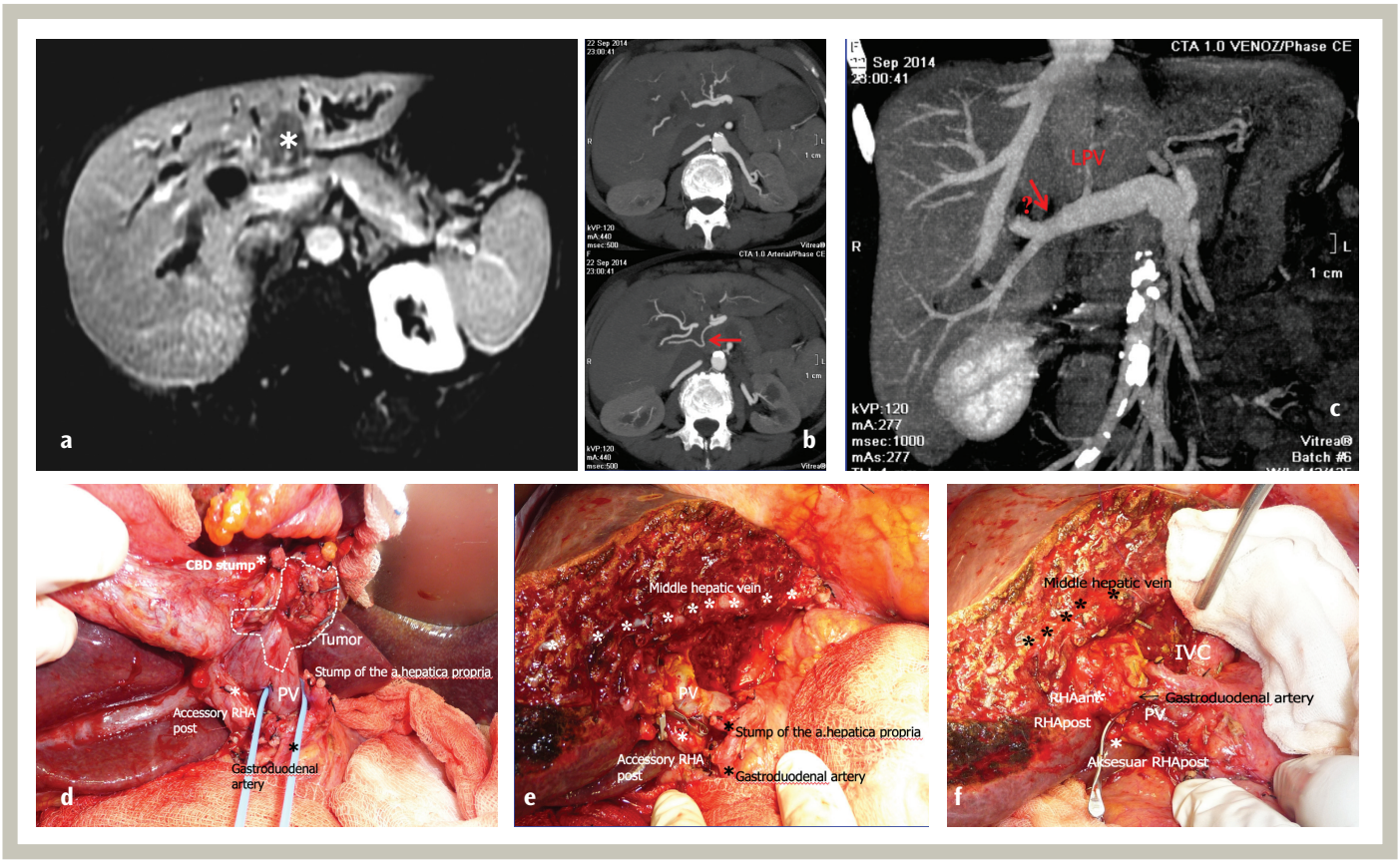

Figure 3. a) Perihilar cholangiocarcinoma (asterisk), b) Involvement of the left and middle hepatic arteries; there is an accessory right posterior hepatic artery (arrow). c) Encasement of the left portal vein branch, suspected involvement of the right branch (arrow). d) The right and left hepatic arteries, the posterior wall of the main portal vein and the left portal vein branch were involved; the accessory right posterior hepatic artery (RHA post) was not. e) Doppler USG showed arterial signals in the right posterior section only. The vascular clips are on the right anterior and posterior branches of the right hepatic artery, f) anastomosis to the branching area would entail risk of thrombosis; the right anterior hepatic artery was reconstructed using the gastroduodenal artery (arrow)

USG: Ultrasonography

found to have invaded the main portal vein and right and left branches of the hepatic artery. The accessory artery was preserved. Left hepatectomy, caudate lobectomy and resection & reconstruction of the portal vein were performed. The right hepatic artery had to be cut at a point that was very close to the division of the anterior and posterior branches; reconstruction near this bifurcation was deemed to carry a high risk of thrombosis. Doppler USG showed arterial signals in segments 6 and 7 (posterior section) but not in 5 and 8 (anterior section). The posterior branch of the bifurcation was sacrificed (since the accessory artery was already providing adequate arterial perfusion) to achieve a "cylindrical" inflow. There was a gap between the main hepatic artery and the right anterior branch and also a size discrepancy. The gastroduodenal artery was divided and used to provide inflow to the right anterior section. The patient survived for 4 years and 9 months. Of course, this type of operation can be performed by a team that is not active in transplantation. However, our team's extensive experience in LDLTx enabled us assess the preoperative situation, use the intraoperative Doppler USG to make a final decision on the intrahepatic arterial perfusion and implement it without hesitation, because such decisions are common in LDLTx.

A much lesser known but extremely powerful approach is the possibility of keeping transplantation as a backup procedure during a complicated hepatectomy. While this has been reported with a cadaveric donor (20), the availability of a living donor offers much greater versatility. For example, a 2-year-old boy attended the Çam and Sakura City Hospital with extensive hepatoblastoma limited to the liver; he had undergone intensive chemotherapy with a good response (Figure 4a). However, the lesion looked marginally resectable on imaging; it extended into the right lobe and invaded the pedicle of the right anterior section near its origin (Figure 4b). It had involved the middle and left hepatic veins and regression of the tumor under chemotherapy had caused traction of the suprahepatic part of the inferior vena cava (Figure 4c). The caudate lobe surrounded the vena cava completely. A left trisectionectomy was planned; maximum effort had to be spent to preserve the enlarged right inferior hepatic vein, because there was a possibility that the right superior hepatic vein would have to be sacrificed (due to traction of the vena cava by the tumor). His mother was prepared as a living donor. The tumor was resected by our team (Erdem Kınacı, Melih Akın, İlgin Özden) with negative surgical margins in an 8-hour operation. If the tumor had been evaluated as inoperable or if we had encountered an intraoperative catastrophe, we would have immediately switched to transplantation. He has had no evidence of recurrence at 3 months.

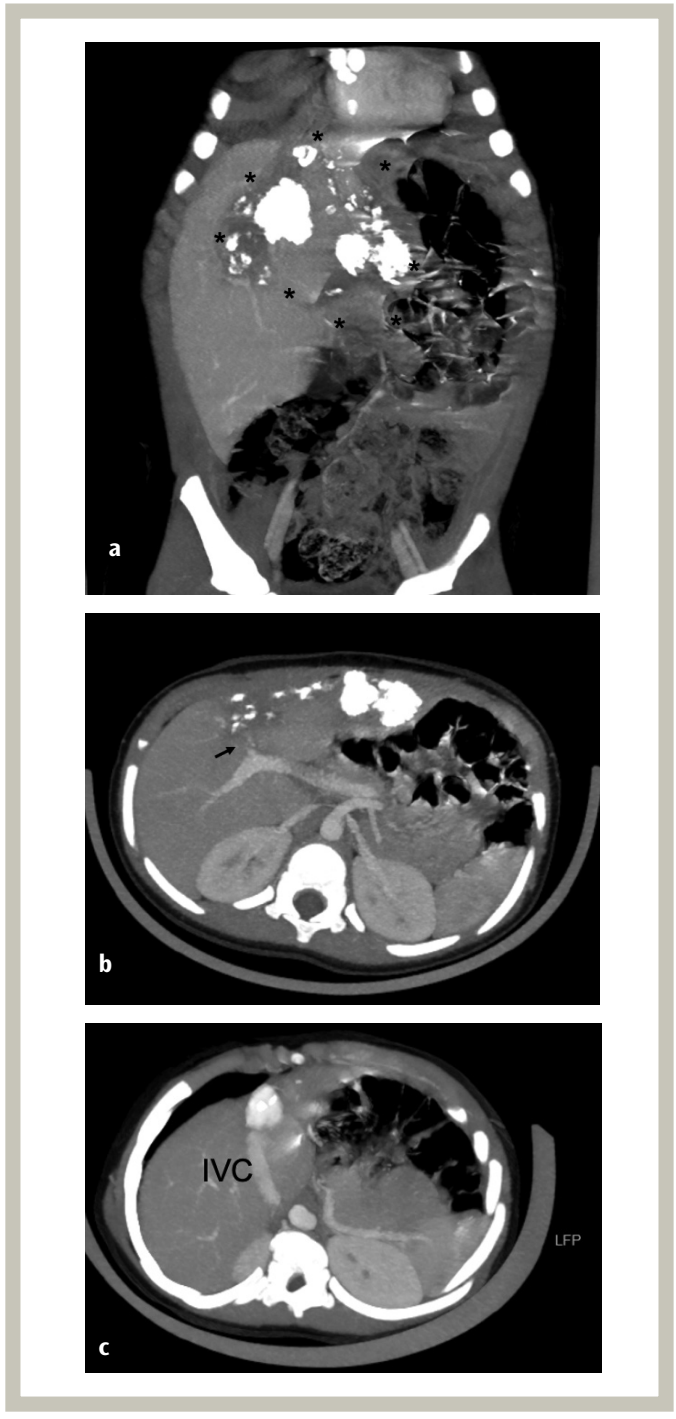

Figure 4. a) A 2-year-old boy who had hepatoblastoma (outlined with asterisks) that was still locally advanced even after a good response to chemotherapy, b) the left lobe tumor extended into the right lobe and involved the right anterior section pedicle near its origin. c) The tumor involved the middle and left hepatic veins extensively and had pulled the suprahepatic section of the inferior vena cava toward itself during regression under chemotherapy

IVC: Inferior vena cava

8- Bridge to the Future

LTx as we know it has saved and will continue to save tens of thousands of lives every year. However, it has a very basic philosophical weakness that will eventually relegate it to history: For the physician to save a life by LTx, somebody must die (cadaveric donor) or be exposed to the risk of living donor mortality. More practical alternatives, such as gene therapy for monogenic diseases (21), antifibrogenic agents to arrest the progression to, and even reverse, cirrhosis (22,23), and hepatocyte transplantation (24) are in various stages of development. LTx will have to serve as a "salvage" procedure for the failures during the development of the alternatives (24), only to be replaced by them in the long run.

Ethics

Peer-review:Externally and internally peer-reviewed.

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

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DOI: 10.4274/csmedj.galenos.2021.2021-8-4

ORIGINAL ARTICLE

7

Cam and Sakura Med J 2021;1(1):7-13

CSMJ

Is Hypomagnesemia a Risk Factor for Atherogenic Dyslipidemia in Patients with Chronic Kidney Disease?

Sümeyye Kılıç[1], Osman Maviş[2], Banu Böyük[3]

[1]Cizre Selahattin Cizrelioğlu State Hospital, Clinic of Internal Medicine, Şırnak, Turkey
[2]University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
[3]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Internal Medicine, İstanbul, Turkey

What is known on this subject?

Atherosclerosis is an important cause for increased morbidity and mortality in chronic renal failure. Magnesium may have possible positive effects on the cardiovascular system due to endothelial-mediated vasodilatation, improved lipid metabolism, reduced inflammation, and inhibition of the platelet functions.

What this study adds?

This study demonstrated that there was no relationship between magnesium levels and atherogenic dyslipidemia in patients with chronic kidney disease.

ABSTRACT

Objective: Atherosclerosis, which starts from early stages of chronic kidney disease (CKD), is an important cause for increased morbidity and mortality. We aimed to investigate whether hypomagnesemia is a marker of increased atherogenic dyslipidemia in patients with CKD with a glomerular filtration rate (GFR) <60 mL/min/1.73 sq m.

Material and Methods: In our study, a total of 80 patients who did not receive renal replacement therapy with GFR <60 mL/min/1.73 sq m, who were diagnosed with CKD and abided by the study entry criteria were retrospectively studied. Patients' gender, age, presence of comorbid disease(d), medications being used, and laboratory findings were recorded. Urea, creatinine, serum electrolytes [calcium, phosphorus, magnesium (Mg)], uric acid, fasting blood glucose, glycosylated hemoglobin, albuminuria/creatinine in spot urine, creatinine clearance, and lipid profile levels were examined.

Results: A total of 36 (45%) male and 44 (55%) female patients were included in the study. The average age was 62.79±14.08 years. Diabetes mellitus was present in 32 (40%) patients, hypertension in 53 (66.25%) patients, and hyperlipidemia in 14 (17.50%) patients. The mean Mg value of our patients was 1.83±0.35. Average for lipid levels were total cholesterol (174.59±57), triglycerides (TG) (173.59±86.85), low-density lipoprotein-C (102.42±43.61), high-density lipoprotein cholesterol (HDL-C) (38.68±12.28), non-HDL-C (134.75±49.72), TG/HDL-C (4.93±3.09), and atherogenic index in plasma (0.61±0.28). Patients were divided into two groups according to their Mg levels. Patients whose Mg levels were <1.7 mg/dL were in group A, and patients whose Mg levels were ≥1.7 mg/dL in group B. When the parameters were compared between the groups, the difference between the two groups was not statistically significant (p>0.05).

The 20th National Congress of Internal Diseases (10-14, October 2018, Belek-Antalya) was presented as a poster.

Address for Correspondence: Banu Böyük MD, University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Internal Medicine, İstanbul, Turkey

Phone: +90 505 262 91 25 **E-mail:** banuilk@gmail.com **ORCID ID:** orcid.org/0000-0001-7794-4411

Received: 25.01.2021 **Accepted:** 21.03.2021

CAM & SAKURA MEDICAL JOURNAL

ABSTRACT

Conclusion: In this study conducted in patients with CKD, there was no relationship between Mg levels and lipid parameters. There is a need for larger, more comprehensive, prospective studies on this issue.

Keywords: Chronic renal disease, magnesium, total cholesterol, triglyceride, HDL-C, LDL-C

Introduction

Chronic kidney disease (CKD) is characterized by irreversible and progressive nephron loss and is an important public health problem with increasing prevalence and high morbidity-mortality (1). Atherosclerosis beginning in the early stage of CKD is an important cause for increased morbidity and mortality (2). Increased oxidative stress in CKD accelerates atherosclerosis. Oxidative stress causes peroxidation of atherogenic lipids that play an important role in cardiovascular disease (3).

Abnormalities in lipid metabolism are known to be very important in the development of atherosclerosis. A variety of lipid abnormalities like increased serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) levels, and reduced high-density lipoprotein cholesterol (HDL-C), clearly increase the risk of coronary heart disease (CHD). Experimental and clinical studies revealed that one of the major changeable causes of atherosclerosis is hyperlipidemia (HL). Antihyperlipidemic medication and medical nutrition treatments are recommended to correct lipid metabolism disorders in patients to prevent complications linked to atherosclerosis like CHD, cerebrovascular events, peripheral artery disease, and hypertension (HTN) (4).

Kidneys play a very important role in serum magnesium (Mg) concentration and homeostasis (5). There has been focus on possible positive effects of Mg on the cardiovascular system due to endothelial-mediated vasodilatation, improved lipid metabolism, reduced inflammation, and inhibition of platelet functions by Mg. Low Mg levels in circulation are associated with increased blood pressure, atherogenic dyslipidemia, clotting disorders, inflammatory burden, oxidative stress, carotid wall thickness, and increased CHD (6,7).

In this study, the aim was to investigate the correlation between serum Mg levels and serum lipid parameters among patients with CKD.

Material and Methods

Patients attending the internal medicine clinic as outpatients were investigated. The study retrospectively assessed 80 patients who were not receiving renal replacement therapy with glomerular filtration rate (GFR) <60 mL/min/1.73 m², a diagnosis of CKD, and who abided by the study criteria. Exclusion criteria for the study included those receiving renal replacement therapy like hemodialysis, peritoneal dialysis, or kidney transplant; those using Mg; and those with a history of CHD, malignancy, acute-chronic infection or inflammatory diseases, cirrhosis, pregnancy, or the presence of any hematologic disease. The patients' gender, age, comorbid diseases, medications used, and laboratory results were recorded.

Urea, creatinine, serum electrolyte levels (calcium, phosphorus, Mg), uric acid, fasting blood glucose, glycosylated hemoglobin (HbA1c), albuminuria/creatinine in spot urine, creatinine clearance, and lipid profile levels were investigated. All biochemical tests were studied with a Beckman Coulter Chemistry Analyzer AU680 (AC 208/220/230/240 V, SN: 2017025450). When calculating the serum TC, HDL-C, and triglycerides (TG) levels, an autoanalyzer with a spectrophotometric measurement method was used. LDL-C was calculated using the Fridewald formula as a routine. In the presence of TG >400 mg/DL, the spectrophotometric measurement method with an autoanalyzer was used. The Fridewald formula was LDL-C=[TC - (HDL-C + TG/5)]. Non-HDL-C=TC - HDL-C and atherogenic index of plasma (AIP)=Log (TG/HDL-K) were also calculated. The GFR was calculated based on the Modification of Diet in Renal Disease Study Group (MDRD) formula. The MDRD study group formula is [186 × (serum creatinine) - 1.154 × (age) - 0.203 × (0.742 if female) × (1.21 if African descent)]. All patients had spot albumin/creatinine measured in the first morning urine.

This study was performed according to the guidelines of the Declaration of Helsinki, and it was approved by the Ethics Review Committee of İstanbul Taksim Training and Research Hospital (date: 07.02.2018, number: 66).

Statistical Analysis

Descriptive statistics were used for continuous variables (mean, standard deviation, minimum, median, maximum). Comparison of more than two independent variables abiding by the normal distribution used the Kruskal-Wallis test. For

comparison of two independent variables without normal distribution, the Mann-Whitney U test was used. To analyze the relationship between two continuous variables without normal distribution, Spearman's rho correlation was used. Statistical significance was set at $p<0.05$. Analyses were completed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program.

Results

Out of all the patients included in our study, total of about 36 were male (45%) and 44 were female (55%). The patients were aged from 25 to 85 years with a mean age of 62.79±14.08 (median: 66). When assessed in terms of chronic diseases, 32 patients had diabetes mellitus (DM) (40%), 53 had HTN (66.25%), and 14 had HL (17.5%). When the medication use of patients is investigated, 15 patients used antihyperlipidemics (18.75%), 33 patients used diuretics (41.25%), five patients used oral antidiabetic medication (OAD) (6.25%), 45 patients used antihypertensives (57.5%), and 30 patients used insulin (37.5%).

The mean Mg levels of patients were 1.83±0.35 mg/dL (minimum: 1.24 mg/dL, maximum: 3.2 mg/dL) (Table 1). There were 39 patients (48.75%) with Mg level <1.7 mg/dL and 41 patients (51.25%) with ≥1.7 mg/dL, and these were named group A and group B, respectively. Comparisons were performed between the two groups in terms of age, gender, epidermal GFR (eGFR) level, urea, creatinine, uric acid, albuminuria/creatinine in spot urine, LDL-C, TG, TC, HDL-C, non-HDL-C AIP, diagnoses (DM, HTN, HL), and medications used (Table 2).

There were no significant differences between groups A and B when compared in terms of age, gender, diabetes and HTN, diuretic medication and antidiabetic medication (OAD and insulin) use ($p>0.05$). There were three patients in group B (7.32%) and 11 patients in group A (28.21%) with HL diagnosis, and this difference was statistically significant ($p=0.014$). There were four patients in group B (9.76%) and 11 patients in group A (28.21%) using antilipidemic medication, and this difference was statistically significant ($p=0.035$). Antihypertensive medication use was present among 18 patients in group B (43.90%) and 27 patients in group A (71.79%). The difference was identified to be statistically significant ($p=0.012$) (Table 3).

When examined in terms of biochemical parameters, the LDL-C levels measured in groups A and B had mean values of 99.05±51.01 g/dL and 105.63±35.55 g/dL, and the difference was not found to be statistically significant ($p=0.513$). The mean values for non-HDL-C levels measured in groups B and A were 140.59±41.63 g/dL and 128.62±56.92 g/dL, and the difference was not significant ($p=0.289$). When examined in terms of plasminogen activator inhibitor (Log TG/HDL), the mean values in groups B and A were 0.62±0.24 and 0.6±0.32, and the difference was not statistically significant ($p=0.789$) (Table 2).

Table 1. Laboratory characteristics of the patients

Parameters	Mean ± standard deviation
Glucose	125.24±56.99 107 (75-401)
HbA1c	7±1.73 6.4 (4-11.9)
Urea	103.43±42.61 96.5 (40-261)
Creatinine	2.84±1.01 2.65 (1.14-6.2)
Uric acid	7.5±3.05 7.02 (2.9-25.7)
eGFR	29.81±13.36 26.28 (9.09-59)
Total cholesterol	174.59±57 173.5 (64-324)
TG	173.59±86.85 151 (32-462)
LDL-C	102.42±43.61 106 (20-229)
HDL-C	38.68±12.28 36.5 (15-74)
Non-HDL-C	134.75±49.72 131.5 (41-267)
AIP	4.93±3.09 4.05 (0.76-15.9)
Magnesium	1.83±0.35 1.8 (1.24-3.2)
Calcium	8.66±0.87 8.9 (5.8-11.2)
Phosphorus	4.29±1.24 4.11 (1.83-8.3)
Calcium x phosphorus	36.98±11.08 34.6 (15.9-82.1)
Albuminuria/creatinine	972.8±1658.43 518.3 (5-7809)
AIP	0.61±0.28 0.61 (-0.12-1.2)

Student's t-test p, Mann-Whitney U test p. HbA1c: Glycosylated hemoglobin, eGFR: Epidermal glomerular filtration rate, TG: Triglycerides, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, AIP: Atherogenic index of plasma

Groups B and A were compared in terms of eGFR in our study. In groups B and A, the mean eGFR values were identified as 29.35±13.27 mL/min/1.73 m² and 30.3±13.6 mL/dk/1.73 m². There was no difference in statistical terms between these values (p=0.825). When albumin/creatinine in spot urine were examined, the mean values in groups A and B were 1001.44±1665.39 and 951.03±1687.12, and the difference was not accepted as statistically significant (p=0.804) (Table 2).

There was no statistically significant correlation between Mg and any parameter (Spearman's rho p>0.05) (Table 4).

Discussion

Much evidence obtained from *in vitro* studies, animal models, and observational studies show that low Mg levels are associated with endothelial dysfunction, atherosclerosis, and vascular calcification (8). Hypomagnesemia may be associated with increased cardiovascular mortality in CKD and more rapid reduction in kidney functions (9). There are many studies showing inadequate Mg intake and/or hypomagnesemia increase inflammation, oxidative stress, insulin resistance, and HL (8).

Van Laecke et al. (9) researched whether there was a correlation with the prognostic significance between serum Mg level, and mortality linked to all causes in patients with CKD diagnosis who were not receiving renal replacement treatment. In this study including 1.650 patients, at the end of mean 5.1 years follow-up duration, a total of 284 deaths were observed. Mean serum Mg level was found to be 2.09±0.27 mg/dL. They compared two groups with serum Mg level <1.8 mg/dL and >2.2 mg/dL. In the hypomagnesemia group, the mortality risk linked to all causes was observed to increase by 61% (9).

A study by Lacson et al. (10) investigated whether there was a relationship between serum Mg level and mortality linked to all causes in 27,554 patients receiving hemodialysis treatment. Patients included in the study were divided into seven groups according to the serum Mg level, and the mean serum Mg level for all patients was identified as 1.86±0.32 mg/dL. At the end of 2 year follow-up, a total of 4.531 deaths were observed. Mortality linked to all causes was identified to be highest in the group with the lowest serum Mg level (Mg <1.30 mg/dL). Moving from the group with the lowest Mg level to the next highest group (Mg >2.50 mg/dL), mortality linked to all causes appeared to reduce (10). As stated above, in studies by Van Laecke et al. (9) and Lacson (10), mean serum Mg levels were 2.09±0.27 mg/dL and 1.86±0.32 mg/dL, respectively. In our study, serum Mg levels were identified to be close to the

Table 2. Comparison of patient groups according to the parameters

	A group	B group	p
Total cholesterol	169.23±65.22 164 (64-324)	179.68±48.18 182 (66-285)	0.420
Triglyceride	177.03±102.08 146 (32-462)	170.32±70.53 159 (54-407)	0.679
LDL-C	99.05±51.01 95.5 (20-229)	105.63±35.55 107.5 (34-197)	0.513
HDL-C	38.23±12.69 37 (15-72)	39.1±12.02 36 (17-74)	0.773
Non-HDL-C	128.62±56.92 112 (41-267)	140.59±41.63 138 (45-242)	0.289
TG/HDL	5.05±3.37 4.03 (0.76-15.6)	4.81±2.83 4.1 (1.24-15.9)	0.795
eGFR	30.3±13.6 26.5 (15.5-59)	29.35±13.27 25.89 (9.09-58)	0.825
Age	63.44±12.41 65 (30-85)	62.17±15.63 68 (25-84)	0.765
Albuminuria/creatinine	1001.44±1665.39 477.5 (5-7010)	951.03±1687.17 541 (15.8-7809)	0.804
AIP	0.6±0.32 0.61 (-0.12-1.19)	0.62±0.24 0.61 (0.09-1.2)	0.789

Student's t-test p, Mann-Whitney U test p. LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, eGFR: Epidermal glomerular filtration rate, AIP: Atherogenic index of plasma

Table 3. Comparison of patient groups according to various parameters

		A group		B group		p
		N	%	N	%	
Gender	Male	18	46.15	18	43.90	0.840
	Female	21	53.85	23	56.10	
HTN	No	11	28.21	16	39.02	0.306
	Yes	28	71.79	25	60.98	
DM	No	21	53.85	27	65.85	0.273
	Yes	18	46.15	14	34.15	
HL	No	28	71.79	38	92.68	0.014$^{\beta}$
	Yes	11	28.21	3	7.32	
Antilipidemic	No	28	71.79	37	90.24	0.035$^{\beta}$
	Yes	11	28.21	4	9.76	
Diuretic	No	22	56.41	25	60.98	0.678
	Yes	17	43.59	16	39.02	
Antihypertensive	No	11	28.21	23	56.10	0.012$^{\beta}$
	Yes	28	71.79	18	43.90	
OAD	No	36	92.31	39	95.12	0.671
	Yes	3	7.69	2	4.88	
Insulin	No	21	53.85	29	70.73	0.119
	Yes	18	46.15	12	29.27	

Pearson chi-square, $^{\beta}p<0.05$, HTN: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, OAD: Oral antidiabetic medication

Table 4. Correlation between magnesium with other laboratory parameters

Parameters		Magnesium correlation
Total cholesterol	R	0.181
	P	0.108
TG	R	0.097
	P	0.394
LDL-C	R	0.119
	P	0.300
HDL-C	R	0.079
	P	0.486
Non-HDL-C	R	0.201
	P	0.073
TG/HDL	R	0.080
	P	0.483
eGFR	R	0.012
	P	0.918
Age	R	0.047
	P	0.681

Spearman's rho β p<0.05. TG: Triglycerides, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, eGFR: Epidermal glomerular filtration rate

lower limit of 1.83±0.35 mg/dL. When examined from this aspect, mean serum Mg levels in our study were like those of the study by Lacson et al (10).

A study by Dey et al. (11) investigated the correlation between hypomagnesemia and atherogenic dyslipidemia. In this study, they compared 90 patients with grade 2-5 CKD, and hypomagnesemia with 90 people from the healthy population. In the group with hypomagnesemia, TC (p<0.001), LDL-C (p<0.001), and non-HDL-C (p<0.001) values were identified to be higher, and this difference was found to be statistically significant. However, they did not identify any statistical difference for very low-density lipoprotein cholesterol (VLDL-C), HDL-C, and TG levels. At the same time, all these parameters were correlated with the severity of CKD (11). In this study by Dey et al. (11), the patient group with CKD and hypomagnesemia were compared with a healthy population. The significant difference in the results of their study might have been due to the difference in the demographic characteristics between the two groups included in the study. In our study, CKD patients with hypomagnesemia were compared to CKD patients without hypomagnesemia.

Robles et al. (12) performed a study to investigate whether there was a positive correlation between Mg levels and serum

lipid parameters in patients receiving hemodialysis treatment. In the study including 25 non-diabetic CKD patients receiving hemodialysis treatment, there were positive correlations identified between Mg with TC ($p<0.001$), LDL-C ($p<0.01$), VLDL-C ($p<0.001$), and apolipoprotein E ($p<0.01$) (12).

Ansari et al. (13) performed a study to investigate whether there was a positive correlation between serum Mg levels with dyslipidemia in patients with end-stage renal failure receiving hemodialysis treatment. In this study comprising 50 patients, there were clear positive correlations identified between serum Mg level with lipoprotein a ($p<0.007$), serum HDL ($p<0.01$), and serum TG ($p<0.005$) (13).

Baradaran and Nasri (14) performed a study to investigate whether there was a correlation between serum Mg level with dyslipidemia among hemodialysis patients. In this study including 36 patients, clear positive correlations were identified between serum Mg with lipoprotein a ($p<0.05$) and serum TG ($p<0.05$). There were no correlations identified between serum Mg with TC, HDL-C, and LDL-C ($p>0.05$) (14).

We completed our study in patients with CKD who were not receiving renal replacement treatment. As stated in detail above, though these three studies identified correlations between serum Mg level with a variety of lipid parameters, in our study, despite the lack of a significant correlation between hypomagnesemia and lipid parameters, there were higher rates of HL diagnosis, antihyperlipidemic, and antihypertensive medication use rates in the hypomagnesemia group. Based on these findings, we think hypomagnesemia may be associated with dyslipidemia and HTN development.

A study divided 144 patients with type-2 diabetic nephropathy and 311 patients with non-diabetic CKD into two classes according to serum Mg levels (≤1.8 and >1.8 mg/dL). Among diabetic nephropathy patients, the group with low serum Mg was found to have a 2.12-fold higher risk of end-stage renal disease compared to the group with high serum Mg levels. In this study, it was proposed that Mg supplementation may have a renoprotective effect in type-2 diabetic nephropathy patients (15).

Many studies found that hypomagnesemia was associated with a reduction in kidney functions. In our study, there was no correlation between serum Mg level with eGFR in the correlation study. We connect the lack of identification of a significant correlation between these parameters to the lack of prospective examination in our study, and the lack of follow-up for progression in the patients.

Study Limitations

The most important limitation of our study is that patients had chronic diseases like HTN, DM, and HL in addition to CKD diagnosis, and for this reason used, medications that may affect Mg and lipid levels. This may have affected the results of the study.

Conclusion

In our study on patients with CKD, there was no correlation between Mg levels with lipid parameters. However, those with hypomagnesemia had higher antihyperlipidemic and antihypertensive medication use rates, which led to the consideration of a correlation between hypomagnesemia with dyslipidemia and HTN development. There is a need for large scale, broad scope, prospective studies investigating this topic.

Ethics

Ethics Committee Approval: This study was performed according to the guidelines of the Declaration of Helsinki, and it was approved by the Ethics Review Committee of İstanbul Taksim Training and Research Hospital (date: 07.02.2018, number: 66).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: B.B., Design: B.B., Data Collection or Processing: S.K., Analysis or Interpretation: O.M., B.B., Literature Search: S.K., O.M., B.B., Writing: S.K., O.M., B.B.

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

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

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DOI: 10.4274/csmedj.galenos.2021.2021-8-9
Cam and Sakura Med J 2021;1(1):14-23

CSMJ

Diagnostic Accuracy of Preoperative Metabolic ^{18}F-FDG PET/CT Parameters for Patients with Endometrial Cancer Treated with Postoperative Radiation Therapy

Sedef Dağ[1], Ayşe Kutluhan Doğan[1], Emel Canaz[2], Nazmiye Deniz Arslan[1], Burçak Yılmaz[3]

[1]University of Health Sciences Turkey, Yedikule Chest Disease and Toracic Surgery Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Gynecologic Oncology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Nuclear Medicine, İstanbul, Turkey

CAM & SAKURA MEDICAL JOURNAL

What is known on this subject?

The known is that pre-operative ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) can be used for staging in endometrial cancer patients.

What this study adds?

^{18}F-FDG PET/CT is not standart diagnostic image in endometrial cancer (EC). According to our results, we found out that the metabolic parameters on ^{18}F-FDG PET/CT, for prediction of lymph node metastases increase diagnostic accuracy for EC.

ABSTRACT

Objective: This study aimed to evaluate the diagnostic accuracy of preoperative ^{18}F-fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) metabolic parameters for the prediction of risk factors and detection of lymph node metastasis (LNM) in patients with endometrial cancer.

Material and Methods: This study included 26 patients with endometrioid carcinoma who underwent preoperative PET/CT and treated with adjuvant local radiotherapy. The maximum standard uptake value of the tumor (SUV_{max}-T), SUV_{max} of the pelvic and/or para-aortic LNs, metabolic tumor volume (MTV), and tumor lesion glycolysis (TLG) with cut-off values of 30-40% were calculated. International Federation of Gynecology and Obstetrics stages 3 and 4, high-grade disease, lymphovascular invasion (LVI), cervical involvement (CI), and myometrial invasion (MI) ≥50% were established as high-risk features. Disease-free survival and overall survival were analyzed in comparison with ^{18}F-FDG PET/CT parameters.

Results: SUV_{max}-T was only associated with tumor diameter (p=0.01). It was not correlated with MI, high-grade disease, CI, or LNM. With SUV_{max}-P ≥2.81 as a cut-off value, the sensitivity,

Address for Correspondence: Sedef Dağ MD, University of Health Sciences Turkey, Yedikule Chest Disease and Toracic Surgery Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 212 409 02 00 **E-mail:** ozdemirzedef@hotmail.com **ORCID ID:** orcid.org/0000-0002-8595-2929
Received: 24.02.2021 **Accepted:** 25.03.2021

ABSTRACT

specificity, and accuracy in the detection of LNM were high (90%, 83.3%, 71.4%, respectively). For LNM, the mean MTV-30 (p=0.021), TLG-30 (p=0.030), and SUV_{max}-P (p=0.009) were significant predictors. According to the regression analysis, MTV-40 (p=0.043) was an independent predictor of LNM, and LVI (p=0.037) was the only significant predictor of MI. MTV-30 was a significant predictor of CI (p=0.04).

Conclusion: SUV_{max}-P, MTV, and TLG cut-off values, to predict LN metastases, increase diagnostic accuracy for EC.

Keywords: Brachytherapy, endometrial cancer, FDG-PET/CT, metabolic parameters

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with adenocarcinoma as the most common histologic type (1). The majority of patients with EC are diagnosed at an early stage with the disease confined to the primary site (67%). However, the spread to regional organs and lymph nodes (LNs) (21%) and distant metastases (8%) are less frequent (2). Although EC staging is performed with surgery, the identification of disease extent before surgery is very important for treatment planning.

Imaging modalities play an important role for staging and treatment planning of patients with EC. ^{18}F-fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) combines morphology with physiology and is the preferred imaging modality, especially in clinical oncology. Its accuracy of staging and determination of the aggressiveness of EC have also been investigated (3,4). The maximum standardized uptake value (SUV_{max}) of the tumor, the most widely used PET parameter, was considered an important indicator that reflects tumor aggressiveness, such as myometrial invasion (MI), cervical involvement (CI), LN metastases (LNM), and high-risk disease in EC (4,5). The metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were reported to have prognostic effect on several cancers, including cervical, ovarian, and lung cancer; however, data regarding EC are limited (6,7,8).

In this study, we aimed to evaluate the prognostic importance and diagnostic accuracy of preoperative ^{18}F-FDG PET/CT metabolic parameters of the local tumor and pelvic and/or para-aortic LN SUV_{max} of patients with EC treated with intracavitary brachytherapy (ICRT) and/or pelvic external beam radiation therapy (EBRT) postoperatively and to examine the correlation of results with histopathology.

Material and Methods

Patients

The study was approved as a retrospective study by the İstanbul Training and Research Hospital Clinical Research Ethics Committee (decision no: 1447, date: 28.09.2018), and the requirement to obtain informed written consent was abandoned. A total of 90 patients with histopathologically verified EC treated with three-dimensional high dynamic range (3D HDR) ICRT and/or pelvic EBRT at a single center between August 2016 and October 2019 were analyzed. Of those, 26 patients who underwent preoperative ^{18}F-FDG PET/CT were included in this study. Patients with previous or concurrent diagnosis of any other primary malignancy, patients with follow-up duration <6 months, patients without pretreatment ^{18}F-FDG PET/CT, and patients without adequate surgical staging (total abdominal hysterectomy and bilateral salpingoopherectomy, pelvic- para-aortic LN dissection) were excluded from the study.

Patients with EC were surgically staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) (9). Tumor histopathologic types were classified as endometrioid endometrial carcinoma (grades 1, 2 and 3), serous carcinoma, mixed-type endometrial carcinoma, and carcinosarcoma. The estimated 3-year NFS, DFS, and overall survival rates were 84.2%, 86.1%, and 87.5%, respectively.

^{18}F-FDG PET/CT Image Acquisition and Analysis

All ^{18}F-FDG PET/CT records were retrospectively analyzed by the investigators without knowledge of patients' clinical and histopathological information. Imaging of patients who fasted for at least 6 h before intravenous administration of 5-6 MBq/kg ^{18}F-FDG and whose blood glucose concentrations were <180 mg/dL was perfromed using an integrated PET/CT system. Combined image acquisition began approximately 60

min after [18]F-FDG injection from the vertex to the mid-thigh. Sagittal, coronal, and transaxial images and fused images were analyzed on workstation (Syngo.via Siemens Molecular Imaging).

Qualitative and quantitative (or semi-quantitative) image analyses were performed by an experienced nuclear medicine physician (B.Y.) with significant experience in reading [18]F-FDG PET/CT scans (average 140 reads/month individually). Pretreatment FDG uptake in both local tumor and LNs was quantitatively assessed using SUV_{max}. For each FDG PET/CT study, SUV_{max} values of the most FDG-avid pelvic and/or para-aortic and inter-aortocaval LNs were measured.

The volume of interest (VOI) was defined over the primary tumoral lesion. The tumor contours were semi-automatically delineated by using thresholds of 30% and 40% of the SUV_{max} within the lesion to calculate MTV (7,8). MTV values were used to calculate TLG by multiplying the mean SUV within the VOI both for 30% and 40% thresholds. In the pretreatment PET/CT for the primary tumor area, SUV_{max}-of the tumor (T), MTV-30, MTV-40, TLG-30, and TLG-40; for pelvic LNs SUV_{max}-P, for para-aortic LNs SUV_{max}-PA, for interaortocaval LNs, SUV_{max}-invasive adenocarcinoma (IAC) were recorded (Figure 1). In addition, any suspicious distant metastatic site was noted and verified by other imaging modalities.

Treatment and Follow-up

3D HDR ICRT was delivered once a week in three or five fractions, and D90 ≥5.5 Gy or 7 Gy was prescribed for the planning target volume (PTV) in all patients. The PTV was defined as the upper 1/3 and 5 mm deep of the vagina using a cylinder applicator on the same-day CT scan and a new plan in each brachytherapy fraction. Twelve (46.2%) patients received pelvic intensity modulated radiation therapy (IMRT) technique with Rapid Arc in 1.8 Gy daily fractions, five times a week, for a median total dose of 45 Gy (range, 45-50.4). Para-aortic radiation was delivered to cases with para-aortic LN histopathological involvement (n=3), with a dose up to 45 Gy with one isocenter field in field IMRT. Adjuvant chemotherapy (cisplatin and paxlitaxel, 4-6 cycles) was only administered to patients with high-risk EC (30.8%; n=8).

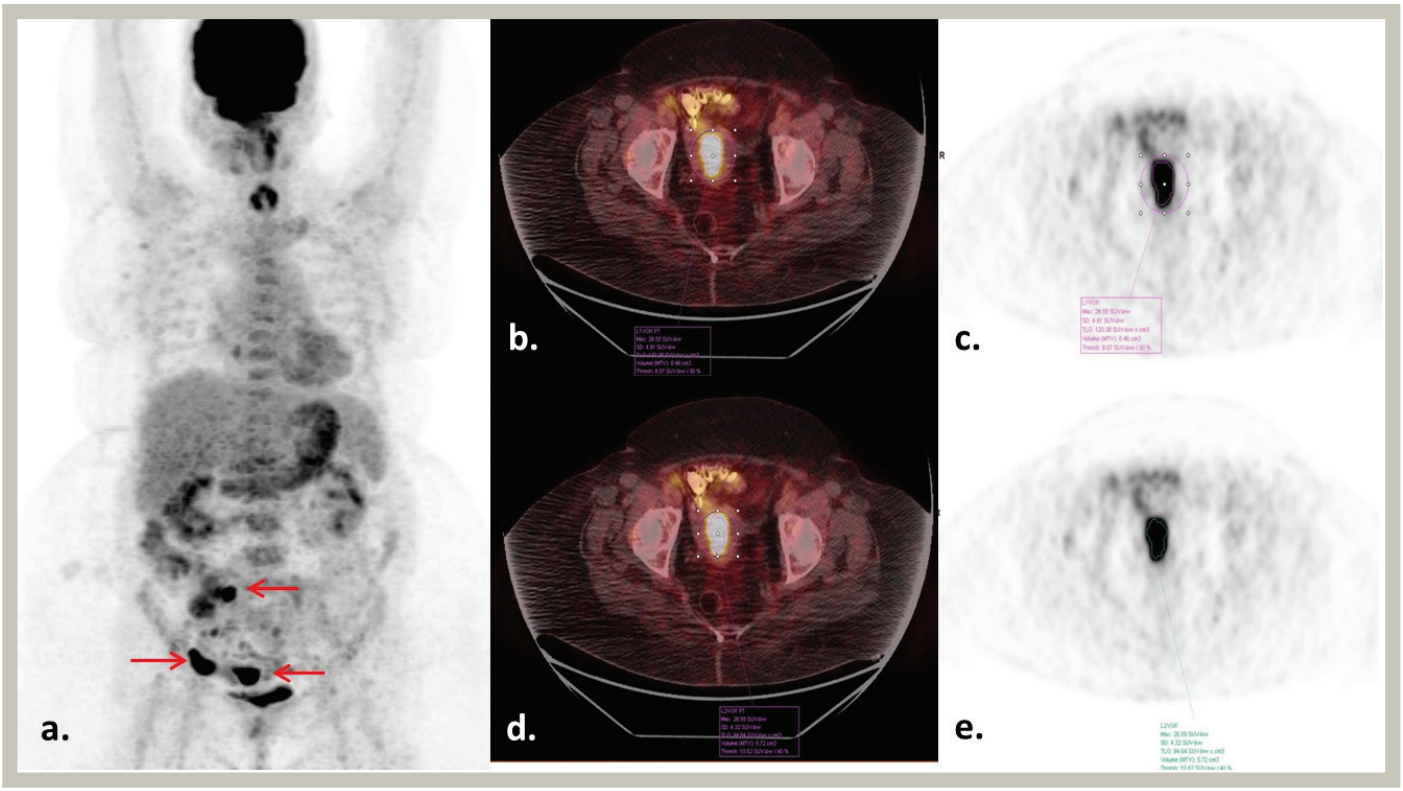

Figure 1. Pretreatment [18]F-FDG PET/CT images of a 52-year-old patient with high-risk EC. a) MIP image with primary tumor and lymph node metastases (arrows). b, d) Axial fused pretreatment PET/CT image of the pelvis with endometrial tumor demonstrating high FDG uptake and different threshold values of MTV and TLG. c, e) Axial PET images with different threshold levels of MTV and TLG

[18]F-FDG:[18]F-fluoro-deoxy-glucose, PET/CT: Positron emission tomography/computed tomography, MIP: Maximum ıntensity projection, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, EC: Endometrial cancer

During follow-up patients underwent bimanual pelvic examination and speculum examination. Serum CA-125 levels were measured and imaging studies were performed every 3 months for 2 years, every 6 months from 2 to 5 years, and annually thereafter.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 15.0; SPSS Inc.), with $p<0.05$ considered significant. Descriptive data are expressed as mean ± standard deviation and percentages. Student's t-test was used to compare the mean values between two independent groups, and the chi-square test was used to compare nominal values between two groups. The metabolic parameters among the groups were compared using the Mann-Whitney U test. Correlations among the PET parameters were analyzed using Spearman rank correlation analysis. With respect to SUV_{max}, MTV, and TLG, receiver-operating characteristic (ROC) curve analysis was performed to determine the cut-off values for predicting LNM and clinicopathologic characteristics. The optimal cut-off values of SUV_{max}, MTV, and TLG were those giving the highest sensitivity and specificity.

The sensitivity, specificity, and area under the curve (AUC) values of the ^{18}F-FDG PET/CT were also calculated. Multivariate logistic regression analysis was performed to determine the independent variables associated with LNM and clinicopathologic characteristics by including all significant factors ($p<0.25$) from the univariate analysis.

Results

Patient Characteristics

Patient's clinicopathological findings were summarized according to risk stratification (Table 1). The median age was 63 (range, 45-84) years, and the median follow-up time was 22 (range, 9-36) months. Sixteen patients had FIGO stage I disease, and 22 patients were found to have endometrioid histology. While 14 patients had intermediate-risk EC, 12 patients had high-risk features. Moreover, 26 patients had pelvic LN dissection, and 15 patients underwent further para-aortic LN dissection, of which 888 LNs were retrieved. Six (23.1%) patients had LNM on pathologic examination (Figure 2).

Correlation of Preoperative ^{18}F-FDG PET/CT Metabolic Parameters with Clinicopathological Factors

According to the presence of LNM, metabolic parameters of PET and clinicopathological findings are shown in Table 2. The mean TLG-30, TLG-40, and SUV_{max}-T were significantly higher in patients with tumor diameter ≥2.5 cm ($p<0.01$), and only TLG-40 was significantly related with high-grade EC ($p=0.045$). The mean TLG-30, TLG-40, MTV-30, and MTV-40 of the local tumor were significantly higher in patients with locally advanced disease ($p<0.03$) (Table 3). Meanwhile, the mean SUV_{max}-P for LNM was significantly higher in the node-positive group than in the node-negative group ($p=0.009$). By contrast, SUV_{max}-T could not predict pelvic and/or para-aortic LNM. Moreover, no significant difference was found for SUV_{max}-T between endometrioid and non-endometrioid subtypes, with mean SUV_{max} of 13.02 and 13.68, respectively ($p>0.05$). Besides, the mean SUV_{max}-PA and SUV_{max}-IAC were not higher in patients with para-aortic LN metastases ($n=3$; $p<0.05$).

Cut-off Values of PET Parameters for Predicting Risk Factors

The ROC curve for SUV_{max}-P for discriminating LNM is shown in Figure 3 (AUC 0.900; 95% confidence interval (CI) 0.729-1.000; $p=0.003$). Using 2.81 as a cut-off value of SUV_{max}-P, the specificity, accuracy, sensitivity, positive predictive value, and negative predictive value of ^{18}F-FDG PET/CT in the detection of LNM in all patients ($n=26$) were 95%, 83.3%, 88.5%, 94.7%, and 71.4%, respectively (Table 3). The relationship between SUV_{max}-P and DFS and OS was not significant ($p=0.3$; $p=0.5$, respectively). The cut-off values of SUV_{max}-T, SUV_{max}-PA, and SUV_{max}-IAC were not significant to discriminate LNM, high-grade tumor, MI, or CI. For the prediction of LNM, MTV-30 and MTV-40 with cut-off values of 11.9 cm^3 and 24.8 cm^3 yielded sensitivity and specificity of 83.3-60% ($p=0.021$; AUC 0.817) and 66.7-100% ($p=0.051$; AUC 0.767), respectively.

For the prediction of CI and MI, cut-off values of metabolic PET parameters were also evaluated with ROC curve analysis (Figure 4, 5). For CI prediction, MTV-30 and MTV-40 with cut-off values of 20.7 cm^3 and 14.3 cm^3 yielded sensitivity and specificity of 75-88.9% ($p=0.006$; AUC 0.844) and 75-88.9%, respectively ($p<0.006$; AUC 0.819).

Table 1. Patient characteristics

		Intermediate risk (n=14)	High risk (n=12)
Histology n (%)	Adeno Ca	14 (100)	8 (66.7)
	Others	(-)	4 (33.3)
Tumor diameter mean ± SD (min-max)		3.07±1.3 (0.8-5.5)	3.8±2.3 (1-9)
≤2.5 cm; n (%)		7 (50)	4 (33.3)
>2.5 cm; n (%)		7 (50)	8 (66.7)
Grade, n (%)	1-2	12 (85)	5 (42)
	3	2 (15)	7 (58)
LVI n (%)	-	2 (14.3)	5 (41.7)
Myometrial invasion n (%)	<1/2	10 (71.4)	0
	>1/2	4 (28.6)	12 (100)
Cervical involvement n (%)	-	0	8 (66.7)
FIGO stage n (%)	1A	10 (71.4)	0 (0.0)
	1B	4 (28.6)	2 (16.7)
	2	-	4 (33.3)
	3c1	-	3 (25)
	3c2	-	3 (25)
Lymph node metastases; n (%)	-	0	6 (100)
Left pelvic LN mean ± SD (min-max)	-	12.1±7.4 (3-30)	13.6±7.5 (5-29)
Right pelvic LN mean ± SD (min-max)	-	10.8±4.5 (2-22)	10.6±4.75 (2-20)
Para-aortic LN mean ± SD (min-max)	-	6.9±13.3 (0-51)	12.5±7.5 (0-24)
Presacral LN mean ± SD (min-max)	-	1.05±2.64 (0-9)	0.5±1 (0-3)
SUV_{max}-T mean ± SD (min-max)	-	12.8±7.4 (0.8-5.5)	13.62±7.5 (1-9)
SUV_{max}-P mean ± SD (min-max)	-	2.11±0.45 (1.5-3.1)	2.57±0.95 (1.1-4.24)
SUV_{max}-PA mean ± SD (min-max)	-	0.57±1 (0-2.9)	0.61±0.92 (0-2.44)
SUV_{max}-IAC mean ± SD (min-max)	-	0.34±1.29 (0-4.8)	0.28±0.68 (0-2.1)
MTV-30 mean ± SD (min-max)	-	11.69±6.9 (3.67-33.1)	36.5±36.4 (2.8-120.1)
TLG-30 mean ± SD (min-max)	-	79.1±72.6 (19.2-290.3)	243.3±351.7 (17-1314)
MTV-40 mean ± SD (min-max)	-	7.9±4.6 (2.7-21.3)	23.8±24.4 (1.74-85.5)
TLG-40 mean ± SD (min-max)	-	61.5±55.3 (13.8-211)	189.5±286.6 (13.1-1067)

LVI: Lymphovasculer invasion, FIGO: International Federation of Gynecology and Obstetrics, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, SD: Standard deviation, min: Minimum, max: Maximum, LN: Lymph node, IAC: Invasive adenocarcinoma

The area under the ROC plot for detecting LNM using TLG-30 with a cut-off value of 99.09 g/mL cm^3 was 0.792 (sensitivity 83.3%; specificity 75%; p=0.033). Additionally, the AUC of TLG-30 with a cut-off value of 82.06 g/mL cm^3 was 0.788 (sensitivity 68.8%; specificity 80%; p=0.015) and the AUC of TLG-40 with a cut-off value of 49.01 g/mL cm^3 was 0.781 (sensitivity 75%, specificity 70%, p=0.018), and they were significant predictors of MI. Furthermore, mean tumor diameter and lymphovascular invasion had significant relation with MI.

Multiple Logistic Regression Analysis

According to the regression analysis, MTV-40 [p=0.043; odds ratio (OR) 1.123; 95% CI 1.004-1.258] was an independent predictor of LNM, and the lymphovascular invasion (p=0.037; OR 64.006; 95% CI 1.291-3172.4) was the only significant predictive factor of MI. In addition, MTV-30 was a significant predictor of CI (p=0.04; OR 1.108; 95% CI 1.005-1.223; Table 4).

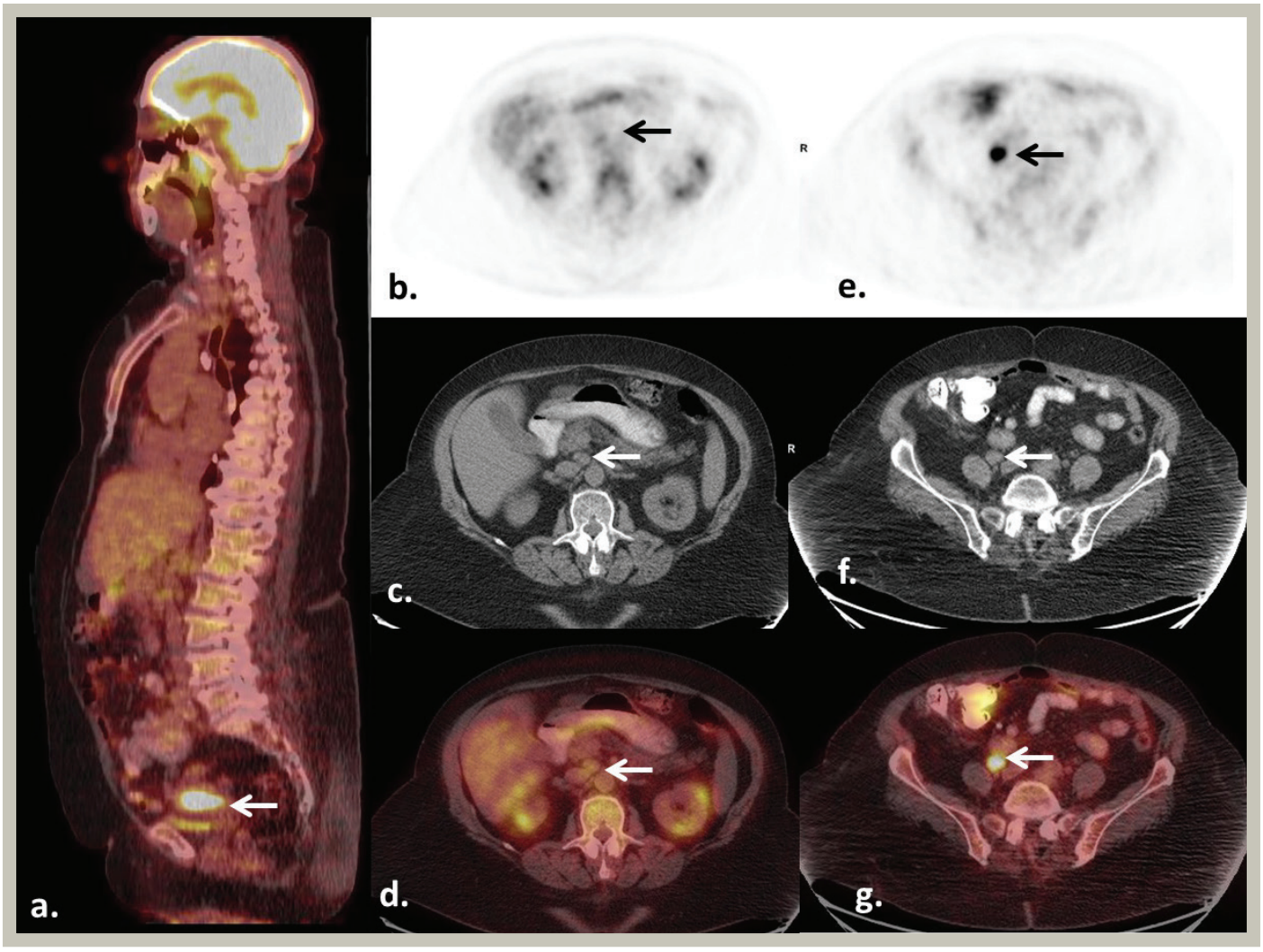

Figure 2. Pretreatment [18]F-FDG PET/CT images of a 62-year-old patient with high-risk EC. a) Sagittal fused image of pretreatment PET/CT demonstrates high FDG uptake of the primary tumor (arrow). b, c, d) Axial PET, fused, and CT images of interaortocaval lymph node metastasis (arrows). e, f, g) Axial PET, fused, and CT images of right common iliac lymph node metastasis (arrows)

[18]F-FDG:[18]F-fluoro-deoxy-glucose, PET/CT: Positron emission tomography/computed tomography, EC: Endometrial cancer

Table 2. PET parameters according to lymph node metastases

	Lymph node metastases [n=6 (23%)]	
	Yes	p
SUV_{max}-T mean ± SD (median)	13.2±5.5 (12.8)	0.972
SUV_{max}-P mean ± SD (median)	3.28±0.81 (346)	**0.009**
SUV_{max}-PA mean ± SD (median)	0.94±1.08 (0-2.44)	0.264
MTV-30 mean ± SD (median)	52.9±45.6 (39.5)	**0.021**
TLG-30 mean ± SD (median)	357.8±479.3 (179.8)	**0.033**
MTV-40 mean ± SD (median)	35.1±30.6 (29.9)	0.051
TLG-40 mean ± SD (median)	279.9±391.9 (143.4)	0.051

p<0.05 is significant. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, PET: Positron emission tomography, SD: Standard deviation

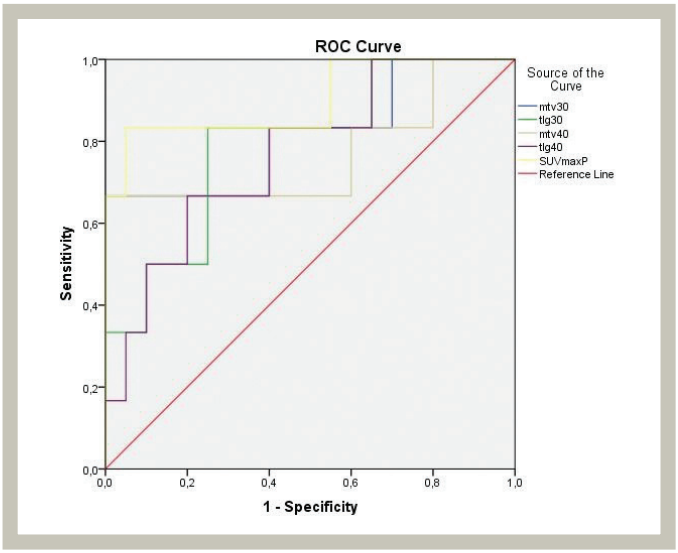

Figure 3. ROC curve associated with the metabolic parameters on ^{18}F-FDG PET/CT in predicting lymph node metastases

ROC: Receiver-operating characteristic, ^{18}F-FDG: ^{18}F-fluoro-deoxy-glucose, PET/CT: Positron emission tomography/computed tomography, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, SUV_{max}: Maximum standardized uptake value

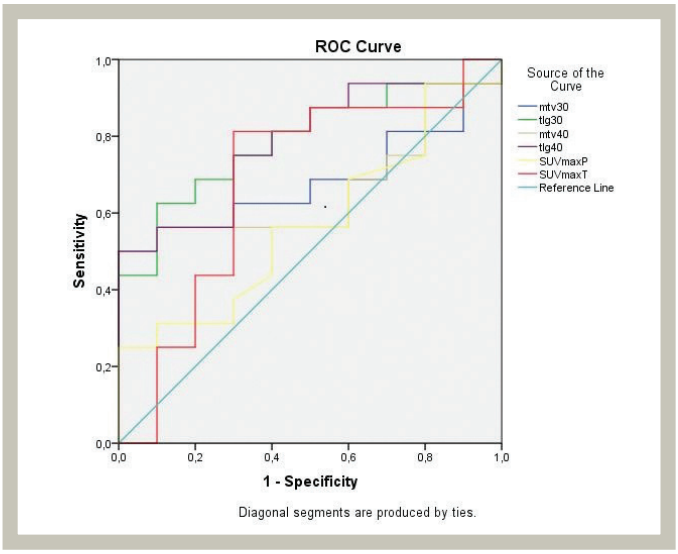

Figure 4. ROC curve analysis for the diagnostic value of maximum standardized uptake value of the primary tumor and metabolic parameters in predicting deep myometrial invasion

ROC: Receiver-operating characteristic, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, SUV_{max}: Maximum standardized uptake value

Discussion

In accordance with the literature, we found that SUV_{max}-P, MTV-30, and TLG-30 were significantly correlated with LNM in patients with EC. Moreover, we found significant correlation between these metabolic parameters and MI and CI, which are well-known prognostic factors to predict LNM in EC.

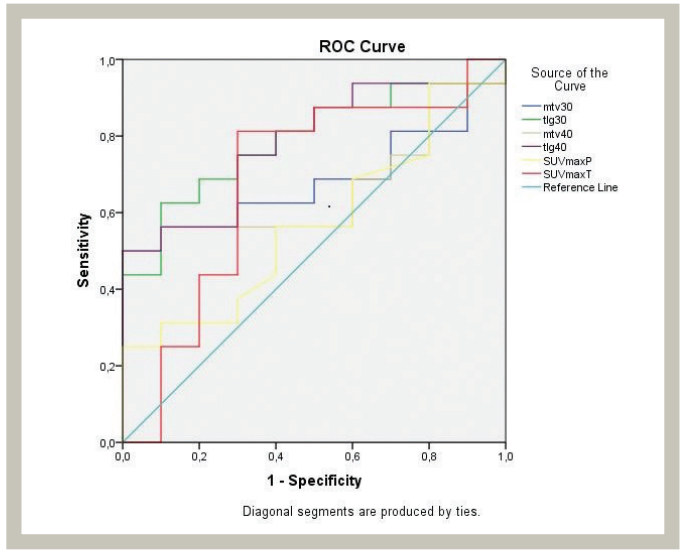

Figure 5. ROC curve analysis for the diagnostic value of maximum standardized uptake value of the primary tumor and metabolic parameters in predicting cervical invasion

ROC: Receiver-operating characteristic, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, SUV_{max}: Maximum standardized uptake value

In patients with inoperable EC, primary radiotherapy is the preferred treatment (10). By contrast, adjuvant radiotherapy is widely used, depending on the individual risk factors, including histological subtype, grading, lymphovascular-stromal invasion, MI and CI, tumor size, and LNM (9). While these prognostic factors were previously determined through surgery and pathological examination, nowadays, imaging modalities allow evaluation of tumor size, MI and CI, and LNM to some extent.

Patients with EC with early stage, grade 1, and grade 2 endometrioid histology, preoperative imaging usually does not significantly change the baseline management or prognosis. However, staging of patients with high-risk EC with ^{18}F-FDG PET/CT has become more common gradually. This is an important issue because LNM is a major factor in treatment planning and prediction of prognosis. However, few studies have examined the diagnostic accuracy of PET/CT for the detection of LNM in EC, and available results show variable accuracy (11). Studies have reported that ^{18}F-FDG PET/CT have high specificity in detecting metastatic nodes; however, its sensitivity was only modest and affected by the size of the metastatic deposit (12,13). In our study, we found high sensitivity, specificity, and accuracy of SUV_{max}-P with a specific cut-off value in the detection of LNM, and this finding was diffferent from those of previous studies.

Table 3. Sensitivity, specificity, area under the curve, and p value of metabolic parameters on ^{18}F-FDG PET/CT for detecting lymph node metastases

	Sensitivity	Specificity	AUC	95% CI	p value
SUV_{max}-P ≥2.81	83.3	95	0.900	0.729-1000	0.003
MTV-30 ≥11.89	83.3	60	0.817	0.586-1000	0.021
TLG30 ≥99.09	83.3	75	0.792	0.583-1000	0.033
MTV-40 ≥24.82	66.7	100	0.767	0.489-1000	0.051
TLG-40 ≥62.18	83.3	60,0	0.767	0.552-0.981	0.051

p<0.05 is significant. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycosis, AUC: Area under the curve, CI: Confidence interval, ^{18}F-FDG: ^{18}F-fluoro-deoxy-glucose, PET/CT: Positron emission tomography/computed tomography

Table 4. Results of multiple logistic regression analysis

		Lymph node metastases		
	p	**OR**	**95% CI**	
MTV- 40	0.043	1.123	1.004	1.258
		Myometrial invasion		
	p	OR	95% CI	
LVI	0.037	64.006	1.291	3172.464
TLG-30	0.075	1.013	0.999	1.028
Tumor diameter	0.103	2.533	0.828	7.748
		Cervical invasion		
	p	**OR**	**95% CI**	
Histology	0.056	22.058	0.928	524.149
MTV-30	0.040	1.108	1.005	1.223

p<0.05 is significant. MTV: Metabolic tumor volume, LVI: Lymphovascular invasion, TLG: Total lesion glycosis, OR: Odds ratio, CI: Confidence interval

Previous studies have demonstrated that high SUV_{max}-T can be associated with the aggressiveness of EC (3,4), although its effect on overall survival or locoregional relapse remains controversial (5,11). Yahata et al. (13) reported that a high SUV_{max}-T was predictive of risk factors, such as deep MI, locally advanced stage, and node metastasis in EC. In contrast to these studies, the present study showed that SUV_{max}-T had significant relation only with tumor diameter in patients with EC.

In recent years, several metabolic parameters of PET/CT, besides the SUV_{max}, were reported to be useful in EC. Kitajima et al. (14) demonstrated that the MTV and TLG of local tumors were correlated with pathological features and were suggested useful for differentiating high- from low-risk EC. Consistently, Chung et al. (8) reported that MTV was an independent prognostic factor for disease recurrence in EC, and Husby et al. (15) reported that MTV was useful to classify patients with high-risk EC. Lee et al. (16) showed that preoperative TLG was related with disease recurrence in 28 patients with carcinosarcoma. Additionally, Shim et al. (17) stated that preoperative MTV and TLG could be independent prognostic factors to predict EC recurrence. In the present study, we found that MTV and/or TLG may be a new tool to assess well-established surrogate markers for poor outcome: High-grade disease, advanced FIGO stage, CI, and LNM. Therefore, we evaluated potential cut-offs to help identify patients at a higher risk of having these markers. For CI and LNM prediction, we found specific cut-off values for MTV-30 and MTV-40. Additionally, TLG-40 was a significant predictor of high-grade tumors, and TLG-30 and TLG-40 were higher in patients with EC with high FIGO stages. Our results also suggest the potential importance ofMTV and TLG for the preoperative classification of patients with high-risk status and improve the ability to tailor surgical and systemic therapies accordingly. Our results are similar with those of previous studies (15,17) that emphasize MTV and TLG as significant predictors of several clinicopathologic characteristics and superior to SUV_{max}-T in differentiating patients with high-risk status from those with low-risk status.

However, we could not achieve significant cut-off values for SUV_{max}-T, SUV_{max}-PA, and SUV_{max}-IAC to predict LNM, deep MI, CI, and high-grade EC. As SUV_{max}-T only represents the

single greatest point of metabolic activity within the tumor, it cannot evaluate the entire metabolic tumor burden (18). Meanwhile, MTV and TLG can evaluate metabolic activity throughout the tumor volume. Therefore, these parameters could reflect tumor histology, prognosis, and treatment response more precisely than SUV_{max}-T.

Study Limitations

This study has some limitations. First, it was a retrospective study. Second, the study was conducted with a relatively small number of patients. Third, the study cohort was composed of patients with intermediate- or high-risk status and these findings do not represent those with low-risk status. Prospective studies with a larger number of patients and longer follow-up periods are required to confirm our findings. The potential added value of ^{18}F-FDG PET/CT as a predictive biomarker is promising but requires further evaluation.

Conclusion

SUV_{max}-P, MTV, and TLG cut-off values on ^{18}F-FDG PET/CT for the prediction of LNM increase the diagnostic accuracy and aid pretreatment identification of patients with high-risk status. Especially, SUV_{max}-P can be useful in deciding the extent of LN dissection and radiation therapy field for patients with medically inoperable intermediate-high-risk EC or for patients with inadequate surgical staging.

Ethics

Ethics Committee Approval: The study was approved as a retrospective study by the İstanbul Training and Research Hospital Clinical Research Ethics Committee (decision no: 1447, date: 28.09.2018).

Informed Consent: The requirement to obtain informed written consent was abandoned.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., A.K.D., E.C., B.Y., N.D.A., Concept: S.D., B.Y., Design: S.D., B.Y., Data Collection or Processing: S.D., A.K.D., E.C., B.Y., N.D.A., Analysis or Interpretation: S.D., B.Y., Literature Search: S.D., B.Y., Writing: S.D., B.Y.

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

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

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DOI: 10.4274/csmedj.galenos.2021.2021-8-14
Cam and Sakura Med J 2021;1(1):24-7

CSMJ

Evaluation of Survival of Patients Who Underwent Decompressive Craniectomy: Clinical Series

Erkan Kutlu Ekiz, Ozan Barut, Ozan Haşimoğlu, Yusuf Kılıç

University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Turkey

What is known on this subject?

Rapid emergency surgical treatment is important in patients with intracranial hematoma.

What this study adds?

When the Glasgow Coma scale score is 10 and below, rapid surgical treatment is not important.

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ABSTRACT

Objective: This study aimed to examine the parameters thought to reduce the mortality of patients with epidural-subdural hemorrhage, basal ganglia hemorrhage, edema with compression effect due to intracerebral ischemic infarction, and hemorrhage from infarcts and to find significant relationships accordingly.

Material and Methods: The demographic and clinical characteristics of patients, pre-operative Glasgow Coma scale (GCS), duration of the operation after the development of the first event, length of stay in intensive care units (ICUs), infection and antibiotic therapy rates developed during their hospitalization, and long-term follow-up were recorded. The survival of the patients were compared statistically.

Results: In 38 patients with GCS less than 10 points, pre-operative GCS, length of stay in ICUs, duration of mechanical ventilator support, infection, and need for antibiotic therapy were examined. All patients were divided into four groups; subdural-epidural hematoma, intracerebral hematoma, intracerebral ischemic infarction, and post-infarction hemorrhage groups. The relationship between their data and mortality were studied. The pre-operative GCS scores in the four groups were 6.16, 6.73, 7.13, and 6.28, respectively. The pre-operative GCS in these four dead groups were 5, 6.6, 7, and 6, respectively. There was no difference between the variables and mortality.

Conclusion: No correlation was found between all clinical data and survival rates. The benefits of an early surgery shown in previous studies were not associated with mortality in this study. Studies with larger case series are needed for more significant relationships.

Keywords: Cerebral ischemic stroke, decompressive craniectomy, epidural hemorrhage, intracerebral hemorrhage, mortality, subdural hemorrhage

Address for Correspondence: Erkan Kutlu Ekiz MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Neurosurgery, İstanbul, Turkey
Phone: +90 532 671 71 31 **E-mail:** ekutlue@hotmail.com **ORCID ID:** orcid.org/0000-0002-5661-8892
Received: 27.01.2021 **Accepted:** 09.03.2021

Introduction

Decompressive craniectomy (DC) aims to reduce intracranial pressure, which is increased due to epidural-subdural hematoma, intracerebral hematoma, and ischemia. The effects of cell loss due to increased intracranial pressure and low cerebral perfusion caused by blood and inflammatory mediators on mortality and morbidity are already known (1). DC reduces intracerebral pressure (ICP), but its effect on mortality and morbidity is uncertain (2). However, DC is the most commonly used surgical treatment for increased ICP after trauma, hemorrhage, or ischemia. This study aimed to investigate the effects of demographic and clinical features on the survival of patients who underwent DC for traumatic or non-traumatic reasons.

Material and Methods

Patients who underwent DC in our clinic between 2016 and 2017 due to traumatic intracerebral hematoma, subdural/epidural hematoma, hypertensive basal ganglia hemorrhage, and post-acute ischemic/hemorrhagic infarct edema and hematoma were included in the study. Frontoparietal DC was performed on the shifted side in all patients. The bone was placed in a subcutaneous pocket in the abdomen. The bone was placed back after six months of healing. Demographic and clinical features, Glasgow Coma scale (GCS) scores, the time between the incident and surgery, period of stay in intensive care units (ICUs), infections, and antibiotic treatments were recorded. These data were compared statistically with the survival of the patients retrospectively. These data were obtained from the Bakırköy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatric, Neurologic, and Neurosurgical Diseases database.

Exclusion Criteria

Patients under 12 years of age and those who underwent DC for reasons other than traumatic intracerebral hematoma, subdural/epidural hematoma, hypertensive cerebral hemorrhage, and acute ischemic/hemorrhagic infarction were excluded in this study.

Statistical Analysis

Physiological measurements within groups were analyzed by the Student's t-test for paired data and Pearson's chi-square test for independent samples (two-tailed) using a statistical software (SPSS version 10.0, Chicago, IL). $P<0.05$ was considered statistically signficant.

Results

Thirty-eight patients, 10 female and 28 male, were included in this study. Eight patients had hypertensive intracerebral hematoma, seven had post-infarction hematoma, 11 had extensive ischemic infarction, and 12 had subdural/traumatic hematoma. The mean GCS score of all patients on admission to the operation was 6.73. The mean GCS score of patients who died during follow-up on admission was 6.00. Moreover, 74% of the patients were discharged with recovery.

The mean GCS score of patients with ischemic infarction who underwent DC was 7.13. The mean operation time was 66.76 h. The mean operation time of patients who died was 38.23 h. Early surgery was not found to be significant in this group in terms of mortality. The mean ICU follow-up was 31.5 days. The mean follow-up time with a mechanical ventilator was 19.09 days. The mean GCS score of patients who died was 7. The mean ICU follow-up was three days, and the mean follow-up time with a mechanical ventilator was 3.3 days. No significant difference was found between the variables and survivalm rates of these groups.

In patients with post-infarction hematoma, the average GCS score was 6.28. The mean ICU follow-up was 11.4 days, and the mean follow-up with a mechanical ventilator was 4.8 days. The mean admission GCS score of patients who died was 6, the mean number of ICU follow-up duration was 9, and the mean follow-up with a mechanical ventilator was 6 days. No significant difference was found between the variables and survival rates of these groups.

In patients with subdural/traumatic hematoma, the mean GCS score of all patients was 6.16. The mean follow-up period was 35.35 days, and the mean follow-up with a mechanical ventilator was 8.4 days. Of the six patients who died, the mean GCS score was 5.00, the mean ICU follow-up duration was 48.50, and the mean follow-up with a mechanical ventilator was 7.4 days. No significant difference was found between the variables and survival rates of these groups.

Eight patients with hypertensive intracerebral hematoma were included in this study. The mean GCS score of all patients with intracerebral hematoma was 6.73. The mean ICU follow-up time was 18.74 days, and the mean mechanical ventilator follow-up time was 11.24 days. The GCS score of deceased patients was 9. The number of ICU follow-up days was 41, and the follow-up period with a mechanical ventilator was 35 days. No significant difference was found between the variables and survival rates of these groups.

The number of patients who received prophylactic antibiotic therapy was 34, while 25 patients developed an

infection and received systemic antibiotics. Six of these patients died. There was no significant difference between the infection and survival All data are summarized in Table 1.

Discussion

This DC case series was reviewed retrospectively from a group of patients with long-term follow-up period. Patients who underwent DC for subdural hematoma, intracerebral hematoma, post-infarction hematoma, and ischemic infarction were included in this study. The relationship between the clinical features of these patients and their mortality was compared statistically. No correlation was found between their mortality values, demographic characteristics, clinical features, initial GCS scores, duration of operation after the development of the first event, length of stay in ICUs, and infection. In this study, all patients who underwent DC had a GCS score of <10. The GCS score at the time of entry to the operation did not contribute to mortality. In STICH and STICH II trials, which allow a multicenter meta-analysis, the survival and clinical outcome scores of the patients who underwent surgical intervention when the GCS scores ≥12 increased (3,4). The subject of rapid surgery was included in this study. However, since there was no patient with a GSC score >10 points, this study produced a different result from that in other studies. These studies suggest that the rapid surgical intervention, which has a positive effect on mortality, is not suitable for patients with a GCS score of ≤10.

The aim of the treatment and follow-up in patients with acute subdural hematoma and intracerebral hematoma was to reduce brain damage due to bleeding, to stop the progression of rapid neurological regression, and to reduce the elevated intracranial pressure and mass effect. However, the postoperative clinical results of patients with subdural and intracerebral hematoma are not satisfactory. Nevertheless, DC is considered superior to the maximum conservative treatment (5).

The most common causes of intracerebral hematomas are hypertensive, vascular, and hemorrhages secondary to amyloid deposition (5). Although the use of a minimally invasive hematoma drainage treatment for hypertensive hematomas can be observed in the basal ganglia, which generally causes low GCS scores, serious neurological deficits, and very poor prognosis, DC is still the most used method worldwide (6). In intracerebral hematomas, perihematomal edema increases by 75% in the first 24 h (6). One of the reasons why DC is the most preferred method for the surgical treatment of intracerebral hematoma is because of its effectiveness in eliminating the compression effect regardless of the location of the hematoma (6). Despite this, there is still no clear consensus on regulations that will increase their survival. No statistically significant survival parameter was found in this study.

DC is also widely used in diffuse intracerebral edema that develops after an ischemic stroke that causes a compression effect. An impaired cerebral perfusion and cerebral oxygenation due to edema increases the amount of edema, creating a vicious circle (7). In previous studies, in patients who needed DC after an ischemic stroke, it has been reported

Table 1. Patient who had decompressive craniectomy clinica follow-up data

				All patients			
	Female/male	Age	Initial GCS	ICU follow-up days	Mechanical ventilator follow-up days	Infection	Antibiotic treatment
Subdural hematoma	4/8	59.9	6.16	35.3	8.4	5/12	10/12
Infarction	5/13	61.6	6.94	23.7	13.5	12/18	14/18
Hypertensive ICH	3/12	57.7	6.73	18.7	11.2	8/15	11/15
Post-infarction ICH	2/5	64.5	6.28	11.4	4.8	4/7	5/7
				Ex patient			
	Female/male	**Age**	**Initial GCS**	**ICU follow-up days**	**Mechanical ventilator follow-up days**	**Infection**	**Antibiotic treatment**
Subdural hematoma	3/3	65.5	5	48.5	7.4	2/6	4/6
Infarction	2/5	62.8	6.42	6.4	4.5	3/7	4/7
Hypertensive ICH	1/4	54.8	6.6	15.4	11.4	3/5	3/5
Post-infarction ICH	1/3	63.5	6.0	9.0	6.0	2/4	2/4

GCS: Glasgow Coma scale, ICU: Intensive care unit

that an early planning for surgery is effective in improving neurological deficits and preserving other brain functions (8). In our study, no data were found to show the positive effects of an early surgery on mortality.

In this study, the ICU period, infection, need for antibiotic therapy, and duration of mechanical ventilator use were examined. Most of the patients included in this study needed mechanical ventilators. In addition, they received an antibiotic therapy due to infections that developed in various locations in the body outside the surgical area. However, no significant difference was found between these variables. It was also shown that the rate of infection after DC increases the risk of mortality (9).

Study Limitations

The main limitation of the study was the small number of patients, which was less than the population prevalence, and the short examination time for the follow-up group. In addition, because all patients were under different surgeons and neurologists, the timing of surgery may have been decided subjectively. A significant level of evidence on this subject has not yet been reached (10). In addition, in this study, the operation times were not recorded, and the patients were operated on quickly after the event occurred, except for the ischemic infarct group. To improve the survival after DC, it would be beneficial to work with more standardized and larger patient groups.

Conclusion

In this study, no correlation was found the between the clinical features and mortality of the patients who underwent DC. The relationships between these variables can be shown more clearly in future large case series.

Ethics

Ethics Committee Approval: Approval was obtained from the Başakşehir Çam and Sakura Hospital Clinical Research Ethics Committee (protocol no: 2021-182).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K.E., O.H., O.B., Y.K., Concept: E.K.E., O.H., Design: E.K.E., O.H., Data Collection or Processing: O.B., Y.K., Analysis or Interpretation: O.B., Y.K., Literature Search: E.K.E., O.H., Writing: E.K.E., O.H.

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

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

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DOI: 10.4274/csmedj.galenos.2021.2021-8-11
Cam and Sakura Med J 2021;1(1):28-36

CSMJ

Monte Carlo-based Volumetric Arc Radiation Therapy vs. Helical Tomotherapy in Terms of Tumor Control Probability and Normal Tissue Complication Probability for Endometrial Cancers

Sümeyra Can, İlknur Harmankaya, Özge Atilla, Ayben Yentek Balkanay, Didem Karaçetin

University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Radiation Oncology, İstanbul, Turkey

What is known on this subject?

The dose range providing uncomplicated cure for gynecological cancers, especially in the presence of a gross disease, is narrow. Even though the provision of high-quality dose-response analysis for external radiotherapy of gynecologic carcinomas is not possible, analyses of tumor sites present an important correlation between the radiotherapy dose and probability of controlling macroscopic diseases. The treating doses used for lymph node metastases of gynecological cancers come with a limitation to reveal a significant relationship between dose and tumor response. A routine 60 Gy administration of radiotherapy to lymph node metastases with intensity modulated radiation therapy (IMRT) and image-guided radiation therapy leads to a significant decrease in the rate of intra-field paraaortic nodal recurrence to less than 5%. These results offer a very significant relationship between the dose of radiotherapy and the tumor control probability (TCP). At the same time, the possibility of normal tissue complications for critical organs has gained importance in the evaluation of radiotherapy in recent years. For the same reason, the evaluation of normal tissue complication probability (NTCP) based on different methods for endometrial cancers has come to light in recent studies.

What this study adds?

The great importance of Monte Carlo (MC) dose calculation algorithm in protecting critical structures is determined in recent studies. Therefore, in this study, MC-volumetric arc radiation therapy (VMAT) plan was compared with the dose volume-helical tomotherapy (HT) plan to evaluate plan effectiveness in reducing the radiation dose causing toxicity and the quality of the plan was analyzed for both approaches in terms of dosimetric results, TCP and NTCP. For the analysis, two different approaches were considered for plan quality evaluation and the equivalent uniform dose (EUD) based TCP and NTCP model, proposed by Niemierko, was taken advantage of for analysis in this study. In previous studies, dosimetric analysis was done to evaluate critical structures' dose. However in the present study MC based VMAT plan HT plan in terms of EUD based TCP and norma tissue complication probability.

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Address for Correspondence: Sümeyra Can MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 553 686 7040 **E-mail:** sumeyracn@gmail.com **ORCID ID:** orcid.org/0000-0003-1991-9474
Received: 26.01.2021 **Accepted:** 29.03.2021

ABSTRACT

Objective: This study aimed to compare the effectiveness and to plan parameters of the Monte Carlo (MC)-based volumetric arc radiation therapy (VMAT) plan, which was devised using the equivalent uniform dose concept for endometrial cancers, to the dose volume (DV)-based helical tomotherapy (HT) plan. Additionally, both approaches were evaluated in terms of tumor control probability (TCP) and normal tissue complication probability (NTCP).

Material and Methods: The study comprised ten patients diagnosed with endometrial cancer, and treated with radixact tomotherapy unit. The target volumes (PTV) and organs at risks (OARs) were contoured through an accuracy planning system. All plans were devised to receive a total of 50.4 Gy in 28 fractions with the fractional dose to be 1.8 Gy for patient treatment. Monaco 5.51 planning system hosted all planning computed tomography images to devise MC-based VMAT plans. Both plans were analyzed in terms of TCP and NTCP.

Results: DV-HT plans (CI: 1.1) came with the more conformal plan while the difference between both approaches was <1% for HI. Based on the results of the analyses, no statistical difference between DV-HT plan of MC-VMAT for the dose values of 2%, 30%, and 40% of rectal volume ($p>0.05$) was observed. The same results were obtained for the dose values of 2% and 30% of the bladder volume ($p>0.05$). The $D_{5\%}$ of the femoral heads were 7 Gy which is < MC-VMAT plan compared to DV-HT plan. The NTCP values of all OARs were <1% in both approaches.

Conclusion: Statistically, similar results were obtained in MC-VMAT and DV-HT plans for OAR's doses when the treatment dose was given to PTV. Both approaches had no significant difference for NTCP statistically; however, the possibility of bone marrow complications to be investigated as well was concluded, so as to evaluate hematological toxicity.

Keywords: Endometrial cancer, Monte Carlo, NTCP, tomotherapy, TCP, VMAT

Introduction

Endometrial cancers (ECs) are among the most common forms of gynecological cancers worldwide (1). Predicted standard surgical treatment is by total abdominal hysterectomy (TAH) and bilateral salpingo-oopherectomy (2). Identification of lymph node-positive patients is recognized through lymphadenectomy compelling adjuvant therapy. However this therapy is not required in low-risk ECs (i.e., stage-1, grade I-II, ½< myometrial invasion, and no lymph vascular invasion) (3,4,5). Based on the results of the GOG-249 study, pelvic external beam radiation therapy (EBRT) should use as the standard therapy in patients with high-intermediate and high-risk stage I-II EC (grade III, and deep invasion and/or lymph vascular space invasion, unfavorable histology, and unfavorable molecular factors) (6,7). In the long run, EBRT increases the rise of morbidity; however, the pelvic region's acute and late toxicity is reduced by taking advantage of intensity modulated radiation therapy (IMRT) (8,9,10). Additionally, a new dimension for IMRT is defined as the provision of highly conformal dose distribution within the target volume with helical tomotherapy (HT). Dose volume [(DV)-HT] planning is proven to be superior to a traditional linac-based IMRT in providing dose homogeneity and protecting the organs at risks (OARs) (11). One of the main advantages of IMRT compared to conformal radiation therapy (3D-CRT) is its ability to rapidly decrease provision in the dose between target volume (PTV) and OARs (12,13,14). Nonetheless, controlling the low-dose region in the modern IMRT is proven to be difficult. Consequently, the risk of developing secondary malignancies in normal tissues is available. To avoid the problem, volumetric arc radiation therapy (VMAT) was developed; thus, the high dose area around the normal tissues was reduced at the same time by providing a homogeneous dose distribution in PTV. Meanwhile, controlling the low-dose zone with VMAT is easier (15,16,17).

The Monaco treatment planning system (TPS) offers various optimizations for VMAT treatment (18). Unlike the DV-based TPS, Monaco TPS requires using three different biological functions for dose optimization, which are the poisson statistical cell kill model, serial, and parallel complication model (19,20). Although the poisson statistical cell kill model is mandatory for target volumes, biological and physical function may be selected for OARs. In Monaco TPS, dose optimization takes place in two stages with beam segmentation performed in the first stage, as well as dose optimization in the second stage using the Monte Carlo (MC)-based virtual source model (21,22).

Undoubtedly, the foundation of radiotherapy is to provide maximum level of protection for the OARs, while delivering the prescription dose to the PTVs. On the same ground, being aware of the exact amount of absorbed dose plays an important role in escalating the chances of the success of the treatment, while protecting patients against radiation damage. Being aware of the tumor control probability (TCP) and normal tissue complication probability (NTCP), equivalent uniform dose (EUD) is the key to optimal plan design providing information about the treatment outcomes

(23,24,25). In recent years, the concept of EUD has gained importance in biological based treatment planning, since it reveals information about the organ function, whether serial or parallel (26,27).

Considering the abovementioned concept, evaluating the effectiveness and plan parameters of MC-VMAT plan, which was created using the EUD concept, was aimed through comparing with DV-HT plan for ECs. Additionally, analyzing both approaches in terms of TCP and NTCP was aimed.

Material and Methods

Patient Selection

A total of ten patients diagnosed with ECs were selected for this retrospective study. All patients received adjuvant radiotherapy who were treated with Radixact Tomotherapy Unit in Basaksehir Cam, Sakura City Hospital Radiation Oncology Clinic between February 2021 and April 2021. All TAH, bisalpingo oophorectomy, and pelvic lymph node dissection were performed. Detailed information concerning the patients is presented in Table 1.

Simulation and Contouring

The planned computed tomography (CT) images were obtained by scanning the patients in the supine position with a slice of 3-mm thickness using a Philips Big Bore CT (Philips Healthcare, Andover, MA, USA). According to our defined protocol, all patients were asked to drink 1 L of water 45-60 minutes before the CT scan. At the same time, enemas were applied to the patients before the procedure, and the extraction was ensured with an empty rectum. All planned CT images were transferred with the Accuracy Precision of 2.0.0.1 TPS to contour the PTV and OARs. The radiation Oncology Group-0418 (RTOG) study atlas was used to control the nodal target volumes. Provided pelvic radiotherapy or common iliac, external, and internal iliac, obturator lymph nodes, parametrium, upper vaginal/paravaginal tissue, and presacral lymph nodes (in patients with cervical involvement) were observed, and they were included in the residual; in other ways, they were added in an operation lodge. A 1-cm wide vaginal volume was added laterally and caudally to the clinical target volume (CTV). A 7-mm margin was added to the periphery of the pelvic vessels, internal, external, and common iliac nodes. PTV was created by giving a 7-mm margin to the CTV. The bladder was contoured from the base to the dome. The rectum was contoured as the part between the ano-rectal line and the recto-sigmoid component. The peritoneal cavity was contoured up to 5 cm above the PTV. The femoral heads were contoured from the apex of the hip joint to the lower border of the lesser trochanter.

Table 1. Patient characteristics

Patient characteristics	Number of patients
Myometrium invasion <50%	1
Myometrium invasion >50%	9
Grade I	1
Grade II	4
Grade III	5
Endovascular invasion	5
TAH + BSO + PLND	7
TAH + BSO + PLND + PALND	3
Peryton sampling (+)	0
Peryton sampling (-)	5
Peryton sampling (0)	5
Stage IB	6
Stage II	2
Stage IIIA	2
Adenocarcinoma	9
Carcinosarcoma	1

TAH: Total abdominal hysterectomy, BSO: Bisalphingo-oophorectomy, PLND: Pelvic lymph mode dissection, PALND: Paraaortic lymph node dissection

Treatment Planning

Taking advantage of Radixact Tomotherapy TPS, namely Accuracy Precision Version 2.0.0.1, DV-HT plans were devised (Tomotherapy Inc. Madison, WI). A total of 50.4 Gy to PTV in 28

Table 2. Summary of parameters used in all treatment plans

Energy	6 MV
Grid spacing (cm)	0.3
Algorithm	Pencil Beam and Monte Carlo
Statistical uncertainty	1% per calculation
Min. CT number	-600
Auto flash margin (cm)	0.2
Surface margin (cm)	0.6
Beamlet width (cm)	0.3
Target margin	Normal (8 mm)
Avoidance margin	Normal (8 mm)
Maximum number of arcs	2
Maximum control points	720
Minimum segment width (cm)	0.3
Fluence smoothing	Low

fractions with the 1.8 Gy fractional dose was delivered during the treatment plans. The field width was determined as 2.5 cm, pitch factor as 0.250, and the modulation factor was selected as 3-3.5 in all plans. All contoured CT images were transferred to Monaco 5.51 TPs for the purpose of generating VMAT plans. Based on the biological optimization, EUD concept was used in MC-VMAT plans. The couch angle was 0° and two arcs for a single arc with a fixed collimator rotational position at 0° for all plans. The grid spacing, beamlet width, and minimum segment width were 0.3 cm. In the first step, the pencil beam algorithm was used for rapid modeling, and the final dose optimization was done with the MC algorithm. The list of parameters used in all treatment plans is shown in Table 2. EUD-based functions for PTV and OARs were defined, and the list of functions used is presented in Table 3.

Dosimetric Analysis

Indices of conformity (CI) and heterogeneity (HI) were used in this study to evaluate the plan quality. In addition, the $D_{95\%}$, $D_{98\%}$, and $D_{2\%}$ values which are the doses received by 95%, 98%, and 2% of PTV, respectively, and the mean dose (D_{mean}) were analyzed. The volume receiving 107% of the treatment was considered to evaluate the maximum dose (D_{max}). The reference protocol for dose criteria of OARs was defined to be RTOG-0615 protocol. The D_{max} for the femoral heads, and the dose that received 5% of its volume ($V_{5\%}$) were taken into account. The dose received by 2%, 30%, and 40% of the rectum and bladder volumes ($D_{2\%}$, $D_{30\%}$, $D_{40\%}$), as well as the volume receiving 40 Gy (V_{40Gy}) and D_{mean} were evaluated as well. Data from the DV histograms of all plans were used to determine the difference between the two approaches.

Table 3. The cost functions and isoconstraints that define the OARs and target

	MC-VMAT plan	
Structure	Cost function	Isoconstraints
PTV	Target penalty	PD: 5040 cGy
	Quadratic overdose	MD: 5400 cGy RMS: 2 cGy
Bladder	Parallel	RD: 3500 cGy MOD: 40% PLE: 3.5
	Serial	EUD: 3500 cGy PLE: 15
Rectum	Parallel	RD: 2800 cGy MOD: 20% PLE: 3.5
	Serial	EUD: 2800 PLE: 15
Femoral heads	Quadratic overdose	MD: 2000 cGy RMS: 2 cGy
Bowel	Quadratic overdose	MD: 4000 cGy RMS: 50 cGy

MD: Maximum dose, EUD: Equivalent uniform dose, RD: Reference dose, PLE: Power low exponent, MOD: Mean organ damage, RMS: Root mean square, MC: Monte Carlo, OARs: Organs at risks, VMAT: Volumetric arc radiation therapy, PTV: Target volumes

Biological Model

As Niemerko suggests, EUD-based TCP and NTCP were taken advantage of in radiobiological model response evaluation. To evaluate biological effectiveness, target dose distribution was performed based on a generalized EUD. The EUD was calculated according to the equation given below (28):

$$gEUD = (\sum_i v_i D_i^a)^{1/a} \quad \text{.....(1),}$$

where D_i is the dose, v_i, the fractional organ volume that received the dose, and a is the tissue-specific parameter that describes the DV effect (4).

In this study, a = -10 was defined as the target volume. Additionally, biologically equivalent dose (EQD), which is the physical dose of 2 Gy, was considered for the purpose of comparison. EQD was defined as

$$EQD = D \times \frac{\frac{\alpha}{\beta} + \frac{D}{n_f}}{\frac{\alpha}{\beta} + 2} \quad \text{.....(2),}$$

where n_f is the fraction number, and α/β is linear quadratic parameter which is tissue-specific for organs (29). TCP, which is the probability of tumor cells controlling the radiation dose, was considered as well. TCP was calculated based on the equation

$$TCP = \frac{1}{1+(\frac{TCD_{50}}{EUD})^{\gamma_{50}}} \quad \text{.....(3),}$$

where TCD_{50} is the dose to control 50% of the tumor when the radiation is delivered to the tumor homogeneously. Based on the linear quadratic model, NTCP was defined as a function of the delivered dose and normal tissue volume which was irradiated. NTCP was calculated as

$$NTCP = \frac{1}{1+(\frac{TD_{50}}{EUD})^{\gamma_{50}}} \quad \text{.....(4),}$$

where TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval, and γ_{50} is a dimensionless parameter which defines the slope of the dose response curve (30). All coefficient used for EUD, EQD, TCP, and NTCP calculation are listed in Table 4.

Table 4. Parameters used to calculate EQD-based EUD and EUD-TCP and NTCP

Structure	100% Dpf	n_f	A	α/β (Gy)	γ_{50}	TCD_{50} (Gy)	TD_{50} (Gy)	Dpf (Gy)
Tumor	1.8	28	-10	1.2	2.2	28.34	-	2
Rectum	1.8	28	8.33	3.9	3.63	-	80	2
Bladder	1.8	28	2	8	2.66	-	80	2
Femur heads	1.8	28	4	0.85	4	-	65	2

EQD: Biologically equivalent dose, EUD: Equivalent uniform dose, TCP: Tumor control probability, NTCP: Normal tissue complication probability, n_f: Number of fractions, TCD_{50}: The tumor dose to control 50% of the tumor, TD: Tolerance dose, Dpf: Dose per fraction

Statistical Analysis

The dosimetric comparison occurred in two parts: Firstly, the radiation dose for PTV and ORAs were analyzed based on the aforementioned criteria. In the second part, both the approaches were evaluated through EQD, EUD, TCP, and NTCP comparisons. The statistical differences of each parameter obtained through all plans were examined by SPSS statistical software (SPSS, Statistics v22, Chicago, IL, USA). For statistical analysis, the test of the significance between two plan parameters was first applied to check whether the variables assume normality. Provided that the differences were distributed normally, paired-samples t-test were applied, or else, two related-samples test was applied. A p value <0.05 was considered statistically significant for both tests.

Results

Dosimetric Comparison for Target Volume

To evaluate the superiority of each approach in terms of PTV coverage, the MC-VMAT plan and DV-HT plan were compared based on the abovementioned criteria. Based on the results, no statistical difference between DV-HT plan and MC-VMAT plan was observed in terms of $D_{98\%}$, $D_{95\%}$, $V_{107\%}$ ($p>0.05$) along with the percentage difference between both approaches for the parameters was obtained lesser than 1.5%. On the one side, the $D_{2\%}$ value was 1.12% higher in MC-VMAT plan compared to DV-HT plan, which was statistically significant ($p<0.05$). On the other side, both treatment approaches showed similar results in delivering prescription dose to the target as well as providing a target volume coverage based on the statistical analysis. CI and HI values were considered to assess the plan quality. Even though a more conformal dose distribution was achieved by the DV-HT plan than expected (CI: 1.1), the difference between HI values was <1%. The planning data of target volume are listed in Table 5.

Dosimetric Comparison for OARs

The required dose of OARs was gained through a comparison between the MC-VMAT plan and the DV-HT plan. The two approaches revealed no statistical difference in the dose values of $D_{2\%}$, $D_{30\%}$, and $D_{40\%}$ which received 2%, 30%, and 40% of the rectal volume and the V_{40Gy} value, which was the volume receiving 40 Gy ($p>0.05$). In the DV-HT plan, the D_{mean} of the rectum was approximately 4 Gy lower. For the bladder, the difference between both plans was <1% for D_2 and V_{40Gy} values. On the other hand, D_{mean} and $D_{40\%}$ were 3 Gy and 4 Gy higher, respectively, in the MC-VMAT plan compared to DV-HT plan. For the femoral heads, the $D_{5\%}$ value in the MC-VMAT plan was 7 Gy lower than the DV-HT plan, and the MC-VMAT plan was more effective in reducing the femoral heads dose. In addition, D_{max} was approximately 6 Gy and 3 Gy less for the right and left femoral heads, respectively, in the MC-VMAT plan, and the difference between the approaches was statistically significant ($p>0.05$). The critical organ doses obtained from both plans along with their comparisons are presented in Table 5. Additionally, half dose distributions of the MC-VMAT plan and DV-HT plan were shown in Figure 1.

Biologic Model Evaluation

With the aiming gaining an awareness of the response of target volume and normal tissues to radiation, EUD-based TCP and NTCP calculations were performed. The mean EQD and EUD in MC-VMAT plan were 1.73 Gy and 48.6 Gy, respectively, while these values were 1.76 Gy and 49.3 Gy in the DV-HT plan. No statistically significant difference between the EUD values for both approaches ($p>0.05$) was observed. EUD-based TCP was calculated for PTV according to Niemierko model. Although TCP values in the MC-VMAT plan were <1% compared to the DV-HT plan, this result caused a statistically significant difference ($p<0.05$). In addition, NTCP calculation was performed for the rectum, bladder, and femoral heads. NTCP values were <1% in both approaches and no statistical difference was observed between the values ($p>0.05$). EUD, EQD, TCP, and NTCP values calculated for both approaches are shown in Table 6.

Table 5. Summary of evaluated dosimetric values for target and organs at risk

		MC-VMAT plan	DV-HT plan	p (<0.05)
PTV 50.4	$D_{2\%}$ (Gy)	53.19±0.25	52.59±0.37	0.016
	$D_{98\%}$ (Gy)	48.10±0.31	48.77±0.31	0.050
	$D_{95\%}$ (Gy)	49.27±0.15	49.72±0.19	0.050
	D_{mean} (Gy)	51.27±0.16	51.07±0.29	0.022
	$V_{107\%}$ (%)	0.23±0.25	0.10±0.07	0.083
	CI	0.52±0.28	1.11±0.08	0.000
	HI	1.07±0.00	1.09±0.01	0.050
Rectum	D_{mean} (Gy)	28.07±8.346	24.98±6.39	0.037
	$D_{2\%}$ (Gy)	51.46±1.48	51.62±1.65	0.444
	$D_{30\%}$ (Gy)	36.06±12.11	35.09±11.21	0.203
	$D_{40\%}$ (Gy)	31.63±11.52	28.59±10.61	0.114
	$V_{40\ Gy}$ (%)	29.10±17.22	26.68±14.03	0.445
Bladder	D_{mean} (Gy)	34.40±8.76	31.55±8.94	0.022
	$D_{2\%}$ (Gy)	52.23±0.66	51.97±0.77	0.139
	$D_{30\%}$ (Gy)	41.74±9.35	40.47±10.06	0.047
	$D_{40\%}$ (Gy)	38.25±0.11	34.94±12.00	0.017
	$V_{40\ Gy}$ (%)	43.48±27.29	41.55±26.16	0.169
Right femur	$D_{5\%}$ (Gy)	20.54±5.11	27.76±6.53	0.005
	D_{max} (Gy)	30.97±8.74	36.10±8.98	0.799
Left femur	$D_{5\%}$ (Gy)	21.15±4.28	28.02±5.98	0.007
	D_{max} (Gy)	33.94±7.82	36.61±7.29	0.095

MC: Monte Carlo, VMAT: Volumetric arc radiation therapy, DV: Dose volume, HT: Helical tomotherapy, CI: Indices of conformity, CI: Heterogeneity

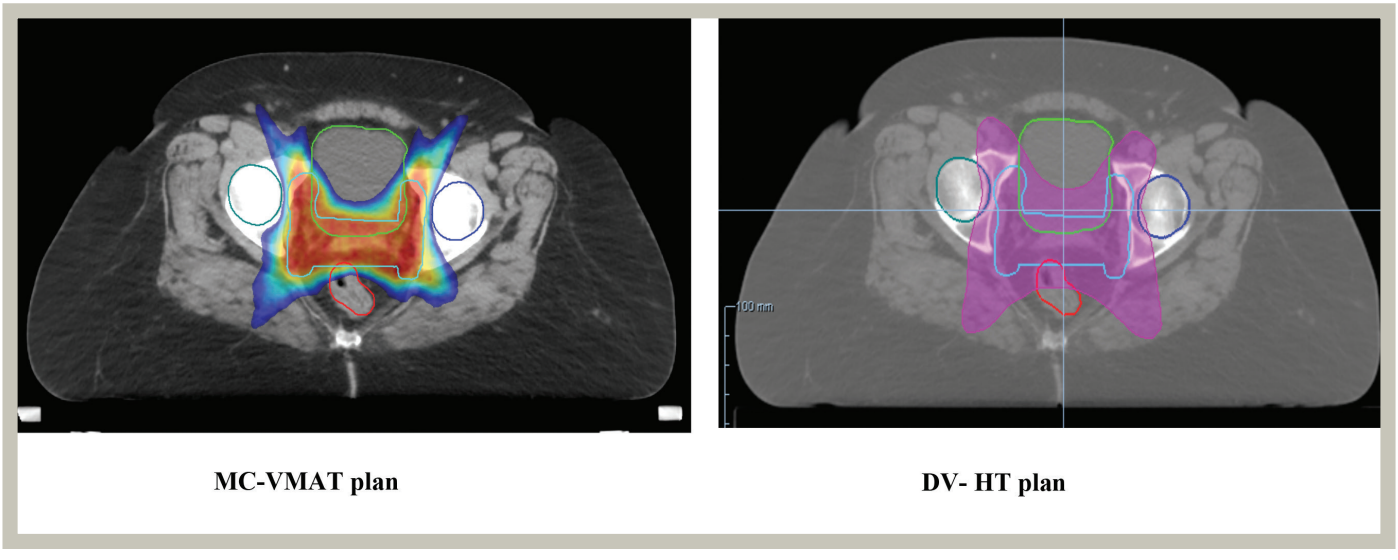

Figure 1. The half dose distribution in both approaches for the selected case

MC: Monte Carlo, VMAT: Volumetric arc radiation therapy, DV: Dose volume, HT: Helical tomotherapy

Table 6. Calculated EQD, EUD, TCP, and NTCP for both treatment planning

	MC-VMAT plan	DV-HT plan	p (<0.05)
$EQD_{(PTV)}$ (Gy)	1.735	1.760	0.008
$EUD_{(PTV)}$ (Gy)	48.60	49.30	0.277
TCP (%)	76.62	77.19	0.008
$NTCP_{(Rectum)}$ (%)	0.065	0.047	0.107
$NTCP_{(Bladder)}$ (%)	0.073	0.053	0.070
$NTCP_{(Right\ Femur\ Head)}$ (%)	0.003	0.014	0.646

EQD: Biologically equivalent dose, EUD: Equivalent uniform dose, TCP: Tumor control probability, NTCP: Normal tissue complication probability, TCD: The tumor dose to control, DV: Dose volume, HT: Helical tomotherapy

Discussion

The dose range providing an uncomplicated cure for gynecological cancers, especially in the presence of a gross disease, is narrow. Even though the provision of high-quality dose response analysis for external radiotherapy of gynecologic carcinomas is not possible, analyses of tumor sites present an important correlation between the radiotherapy dose and probability of controlling macroscopic diseases. The treating doses used for lymph node metastases of gynecological cancers come with a limitation to reveal a significant relationship between dose and tumor response. A routine 60 Gy administration of radiotherapy to lymph node metastases with IMRT and image-guided radiation therapy leads to a significant decrease in the rate of intra-field paraaortic nodal recurrence <5%. These results offer a very significant relationship between the dose of radiotherapy and the TCP. At the same time, the possibility of normal tissue complications for critical organs has gained importance in the evaluation of radiotherapy in recent years. For the same reason, the evaluation of NTCP based on different methods for ECs has come to light in recent studies.

Jodda et al. (31) compared NTCP values of bone marrow in ECs for different radiotherapy techniques and planning strategies. Data from 50 patients over three different treatment plans were analyzed. While evaluating the dose criteria for PTV, the rectum, bladder, bone marrow, bowel, and femoral heads, NTCP was compared for bone marrow only using the Lyman-Kuther-Burman-NTCP (LKB-TCP) model with the Bazan method (31).

Brent S. Rose et al. (25) tested whether the pelvic bone marrow radiation dose causes hematological toxicity in cervical patients, and the NTCP model was tried to be developed. In this study, the relationship between hematological subsets and V_{10Gy} and V_{20Gy} along with the volume of a bone marrow receiving 10 Gy and 20 Gy, respectively, during chemoradiotherapy were analyzed. Based on the obtained results, hematological toxicity increased depending on the radiation dose received by the pelvic bone marrow volume (25).

Duman et al. (32) evaluated different treatment modalities, including 3D-CRT, field in field, and seven-field IMRT for patients with endometrial and cervical cancer. In their study, dosimetric comparisons were made for critical organs, and NTCP values were calculated for OARs. Additionally, they used LKB-NTCP models for the small intestine, rectum, and bladder; NTCP was <1% for the rectum and bladder (32).

On the other hand, two different approaches were considered for plan quality evaluation and the EUD-based TCP and NTCP model proposed by Niemierko was taken advantage of for analysis in this study. The great importance of MC dose calculation algorithm in protecting critical structures is determined in recent studies. Therefore, in this study, MC-VMAT plan was compared to the DV-HT plan to evaluate plan effectiveness in reducing the radiation dose causing toxicity, and the quality of the plan was analyzed for both approaches in terms of dosimetric results for TCP and NTCP. NTCP values of OARs were <1% in both approaches, and there was no statistically significant difference between MC-VMAT and the DV-HT plan. However, this study does not consider bone marrow volume in the optimization process while hematological toxicity values were not included in the plan comparison.

Conclusion

This study compared the MC-VMAT plan to the DV-HT plan for EC. The plan parameters were analyzed in terms of TCP and NTCP. In the Monaco 5.51 TPS, VMAT plans were made using the MC algorithm and biologically based EUD concept. Similar TCP and NTCP values were obtained with MC-VMAT plan as well as DV-HT plan. As a result of the analysis, both approaches achieved success in protecting OARs while

delivering the prescription dose to PTV. On the other hand, the DV-HT plan was superior to the MC-VMAT plan in obtaining a more conformal dose distribution, and the MC-VMAT plan was superior to the DV-HT plan in reducing the D_{max} and $D_{5\%}$ doses for the femoral heads. However, for a more detailed analysis, both approaches should be evaluated in terms of hematological toxicity.

Ethics

Ethics Committee Approval: Ethics Committee Approval is not required for dosimetric studies.

Informed Consent: Informed Consent form is not needed for dosimetric studies.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.C., Design: İ.H., A.Y.B., D.K., Data Collection or Processing: S.C., Ö.A., Analysis or Interpretation: S.C., İ.H., D.K., Literature Search: S.C., Ö.A., İ.H., Writing: S.C.

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

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

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DOI: 10.4274/csmedj.galenos.2021.2021-8-6
Cam and Sakura Med J 2021;1(1):37-42

CSMJ

Regression of Hypermetabolic Splenic Granulomata Mimicking Metastases Following Non-targeted Effect of Radiotherapy for Uterine Cervical Carcinoma

Nazmiye Deniz Arslan[1], Sedef Dağ[1], Ayşe Kutluhan Doğan[1], Nesrin Gürçay[2], Hüseyin Özkurt[3], Burçak Yılmaz[4]

[1]University of Health Sciences Turkey, Yedikule Chest Disease and Toracic Surgery Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Atatürk Chest Disease and Toracic Surgery Training and Research Hospital, Clinic of Pathology, Ankara, Turkey
[3]University of Health Sciences Turkey, İstanbul Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Radiology, İstanbul, Turkey
[4]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Nuclear Medicine, İstanbul, Turkey

What is known on this subject?

If there are any suspicious or atypical findings, histopathological verification is mandatory, and the treatment should be arranged accordingly.

What this case report adds?

The systemic effects of radiation therapy in non-irradiated area might influence active granulomatous reactions. Such effects have not been described in the literature before and needs further investigation.

ABSTRACT

Cervical carcinoma (CC) is one of the most common cancers in women. Unfortunately, false-positive imaging findings can be reported, which may change the treatment plans. In this case report, we describe a patient with CC and incidentally detected splenic lesions mimicking metastases, seen on magnetic resonance imaging, ultrasonography, and 2-(^{18}F)-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography. Histopathology confirmed a granulomatous infection. Although the patient did not receive any therapy for the infection, the splenic lesions almost disappeared on follow-up imaging, possibly due to the non-targeted immunological effect of radiation therapy.

Keywords: Cervical cancer, MRI, FDG-PET/CT, false positive, non-targeted effect

Address for Correspondence: Nazmiye Deniz Arslan MD, University of Health Sciences Turkey, Yedikule Chest Disease and Toracic Surgery Training and Research Hospital, Clinic of Radiation Oncology, İstanbul, Turkey
Phone: +90 544 668 15 49 **E-mail:** denizsaracoglu@hotmail.com **ORCID ID:** orcid.org/0000-0003-0080-2284
Received: 02.02.2021 **Accepted:** 18.03.2021

CAM & SAKURA MEDICAL JOURNAL

Introduction

Despite using screening methods and vaccinations, cervical carcinoma (CC) is the third most common cancer and the leading cause of cancer-related death in women (1,2). To understand the locoregional extension of the disease and pretreatment assessment of prognostic factors such as tumor diameter, parametrial invasion, and lymph node metastases, magnetic resonance imaging (MRI) is the preferred imaging modality (3,4). For detecting distant metastases, 2-(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) (1).

CC metastases tend to commonly occur through direct local invasion and lymphatic dissemination. Hematogenous metastases are infrequent and usually occur in advanced tumors or uncommon pathologic types (5). Common distant metastatic sites are lungs, bones, and liver (6). Splenic metastasis of squamous cell carcinoma of the uterine cervix is extremely rare (7,8,9,10,11). In such rare cases, if a metastatic splenic lesion is suspected based on one imaging modality, then this can be further evaluated by other modalities for optimal staging and diagnosis and minimizing the rate of false-positive findings (12).

A non-targeted effect of radiation therapy (out-of-field tumor response, abscopal effect, and bystander effect) means that the localized irradiation induced systemic antitumorigenic effects, inducing shrinkage of a tumor distant from the radiation field (13). It is suggested that irradiated cells may start to affect nearby or distant non-irradiated cells (14).

In this case report, we present a patient with spleen lesions with false-positive findings on MRI, ultrasonography (USG), and ^{18}F-FDG-PET/CT. This suggests CC metastases, with a near total regression of splenic lesions after radiation therapy without any anti-infectious treatment.

Case Report

A 52-year-old postmenopausal Syrian woman (height: 150 cm; body weight: 53 kg) presented to our hospital with abnormal vaginal bleeding and pelvic pain for one year. Previous medical and surgical history was negative. There was no family history of cancer. Her vital signs were normal. On the gynecological examination, a bulky cervical tumor extending into the upper vaginal wall with left parametrial invasion was observed. Colposcopy was planned, and cervical punch biopsies revealed moderately differentiated minimally keratinized large cell squamous cell carcinoma of the cervix (Figure 1). Her laboratory tests included the following: Leukocyte 12.15x10^/uL (4.5-10.5), neutrophil 8.51x10^/uL (1.56-6.13), hemoglobin 10.2 g/dL (11.5-15.5), c reactive protein 10.35 mg/L (0-5), parathormone 568.6 pg/mL, calcium 8.53 mg/dL (8.6-10.2), phosphor 2 mg/dL (2.6-4.5), and 25-OH vitamin D <3.0 ng/mL. Brucella agglutination test and tumor markers including CEA, CA-125, and CA 15-3 were negative.

For evaluating the locoregional extension of the disease, the patient underwent abdominopelvic MRI with intravenous gadolinium-diethylenetriamine-pentaacetic acid contrast agent. On MRI, there was a 53 mm mass in the uterine cervix with extension into the urinary bladder anteriorly and rectum posteriorly, in addition to multiple right iliac, left paraaortic, and mesenteric enhancing lymph nodes. Incidentally detected on MRI were widespread splenic lesions, which were hypointense on T2 weighted images without contrast enhancement. Because of the clinical history of a known malignancy, the lesions in the spleen were interpreted as suspicious of metastases (Figure 2).

^{18}F-FDG-PET/CT scan was then performed for evaluating the distant metastatic disease. In the uterine cervix, the known mass had a maximum standardized uptake value (SUV_{max}) of 24.5. There were multiple FDG-avid metastatic lymph nodes with SUV_{max} up to 3.6, seen in the paraaortocaval, bilateral iliac chain, and bilateral parametrial regions. PET/CT also demonstrated widespread heterogeneously hypermetabolic lesions with SUV_{max} of 13.0 in the spleen (Figure 3).

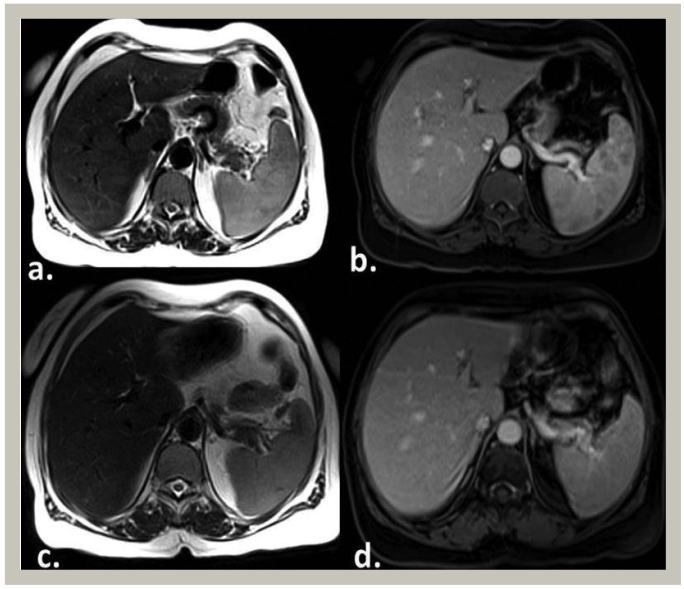

Figure 1. a) Squamous cell carcinoma of the uterine cervix infiltrating stroma with a significant pleomorphism (HE, 10X). b) Minimal caseification and necrosis in the center and epithelioid histiocytes and multinucleated giant cells in the surrounding of granuloma in spleen parenchyma (H&E, 200X)

H&E: Heosin and eosin

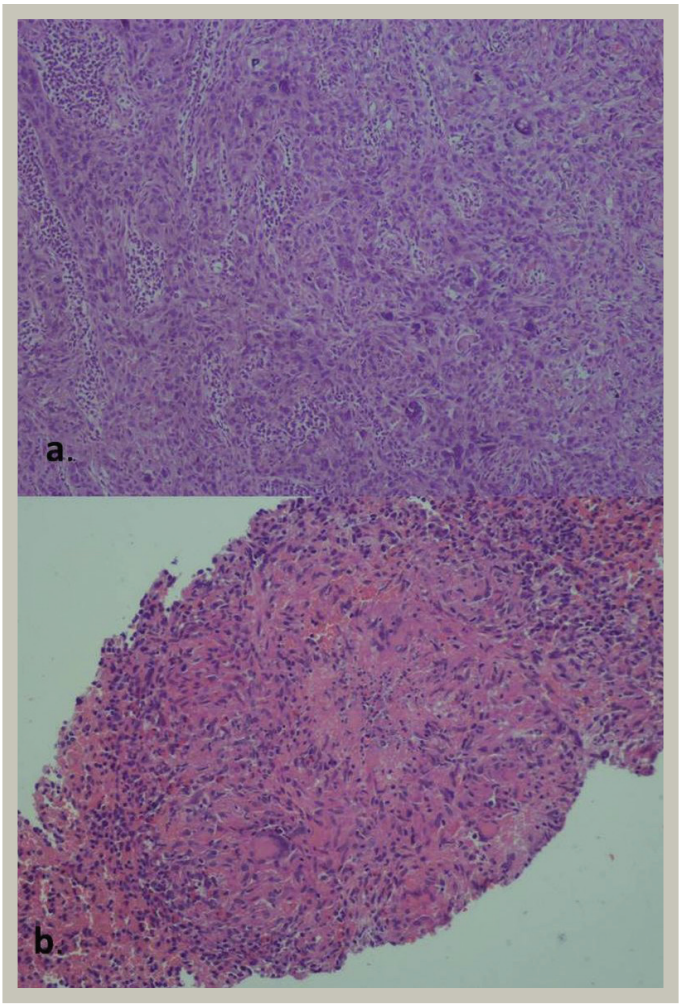

Figure 2. a) Pretreatment axial T2-weighted MR image demonstrates slightly hypointense multiple lesions, significant in the anterior spleen parenchyma. b) Pretreatment axial postcontrast T1-weighted image demonstrates hypointense multiple lesions. c, d) Axial T2-weighted and axial postcontrast T1-weighted images three months after radiation therapy demonstrate significant regression of spleen lesions

MR: magnetic resonance

With the suspicion of splenic metastases, USG guided biopsy was planned. USG detected hypoechoic lesions with fuzzy contours in some lesions of the spleen. A tru-cut biopsy was performed. Histopathology was consistent with granuloma without any neoplasm subsequently (Figure 1).

Following the imaging and laboratory tests, the disease was classified as stage IIB according to the International Federation of Gynecology and Obstetrics staging system. The treatment plan was concurrent chemotherapy and whole-pelvic and paraaortic FDG-PET/CT-based external beam radiation therapy (EBRT) followed by 3D-image-guided high-dose-rate intracavitary radiation therapy (3D-HDR-ICRT). The patient received weekly cisplatin (40 mg/m^2) with premedication (steroid and antiemetic) and 50.4 Gy EBRT to the pelvis in 28 fractions following paraaortic field radiotherapy with a dose of 45 Gy in daily fractions of 1.8 Gy.

Three months after radiation therapy, ^{18}F-FDG/PET and MRI were performed to evaluate the treatment effects. ^{18}F-FDG/PET imaging detected residual FDG-avid disease in the left side of the uterine cervix with SUV_{max} of 5.0 and decreased size and FDG activity within the lymph nodes described on the initial PET/CT with SUV_{max} up to 1.2, previously 3.6. There was no abnormal FDG uptake in the spleen (Figure 3). On MRI, residual cervical tumoral lesions with decreased size and subcentimetric iliac chain lymph nodes were reported, with the regression of the splenic lesions (Figure 2). At the start of the initial therapy, the patient did not receive any treatment for infection. After the follow-up examinations, adjuvant chemotherapy was planned.

Discussion

A detailed analysis of previous imaging and clinical history and a multidisciplinary approach of clinicians and experienced radiologists/nuclear medicine physicians help decide which further investigations should be performed for an exact diagnosis in suspicious conditions (15).

In CC, the most common sites of metastases are the lungs, bones, liver, supraclavicular nodes, and paraaortic nodes (5). Uncommon metastatic sites of CC have been reported in the skin and soft tissue (16), breast (7), pericardium (17), umbilical region (18), vulva (19), thyroid gland (20), oral cavity (21), skeletal muscle (22), intestine (5), ovaries (23), brain (24), and spleen (7,8,9,10,11). Uterine CC is a rare source of splenic metastasis. Splenic metastases of squamous cell carcinoma of the cervix have been reported to be 15.3% of distant metastasis (25).

When splenic metastasis is detected, surgery is not indicated (11). Our patient had paraaortic lymph node metastases with a locoregional extension of the disease. In this clinical setting, the presence of multiple splenic lesions has been interpreted as metastatic, with knowledge of its rarity. The clinicians were aware that the patient came from a war zone, with limited resources for self-hygiene, and they highly suspected an underlying infectious process. Therefore, USG-guided biopsy of the splenic lesions was performed for therapy planning. The pathology was consistent with granuloma. Similar to our patient, many infectious agents involve the spleen, such as pyogenic abscess, fungal abscess, parasitic disease, and granulomous infections (26).

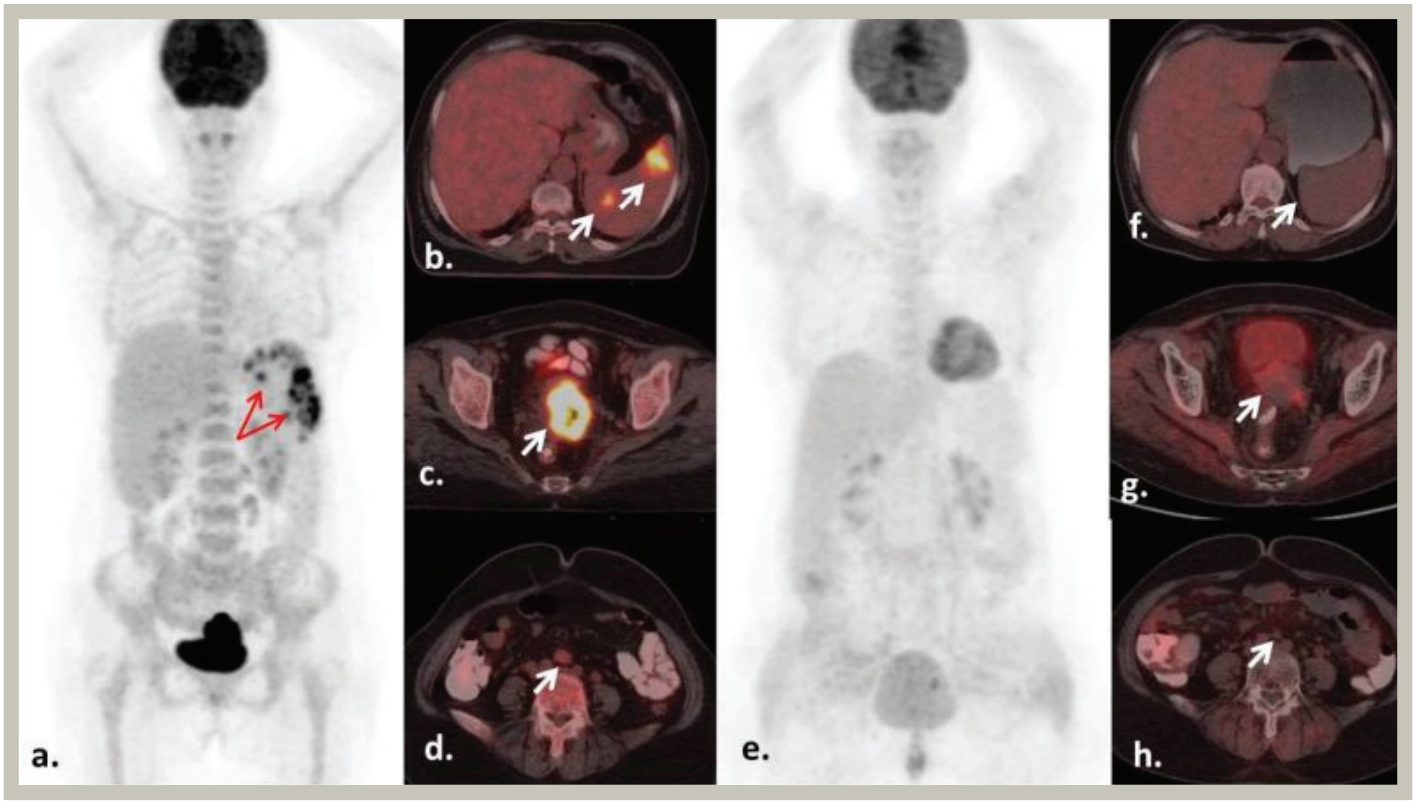

Figure 3. Pretreatment FDG-PET/CT images. a) MIP image showing multiple hypermetabolic spleen lesions. b) Fusion axial PET/CT image showing hypermetabolic spleen lesions. c) Fusion axial PET/CT image showing hypermetabolic primary uterine cervix carcinoma. d) Fusion axial PET/CT image showing slightly hypermetabolic paraaortic metastatic lymph node. FDG-PET/CT images three months after radiation therapy. e) MIP image showing no abnormal FDG uptake in the spleen. f) Fusion axial PET/CT image showing total regression of hypermetabolic splenic lesions. g) Fusion axial PET/CT image showing slightly hypermetabolic residual tumoral lesion on the left side of the uterine cervix. h) Fusion axial PET/CT image demonstrating metabolic and anatomical regression of mildly hypermetabolic paraaortic metastatic lymph node

FDG: 2-(18F)-fluoro-2-deoxy-D-glucose, MIP: Maximum intensity projection, PET/CT: Positron emission tomography/computed tomography

Concerning ^{18}F-FDG-PET/CT, FDG uptake is not only seen in malignancy but also in infection and inflammation, due to increased glucose metabolism. False-positive FDG uptake has been reported in abscesses, postsurgical changes, granulomatous diseases, foreign body reactions, diverticulitis, gastritis, and arteriosclerosis (27). More than 25% of PET/CT studies in patients with cancer have been declared to estimate a non-physiological benign FDG uptake. Almost 50% of incidentally detected foci of FDG uptake outside the primary region of the tumor area are related to benign pathological situations, unrelated to the primary tumor (28,29).

Conversely, USG is cheap and easily accessible, but inferior to MRI for detection of focal lesions (30). However, MRI have some drawbacks; periportal eosinophilic infiltration, abscess, granuloma, and peripheral edema due to parasitic infiltration may cause small, ill-defined, oval or elongated nodules on dynamic images similar to other types of granuloma or inflammatory lesions (31).

In our patient, the infectious agent was unidentified, and she did not get any specific therapy for infection. Surprisingly, on the follow-up examinations, splenic lesions have had almost resolved. The patient only received concurrent chemoradiotherapy. Systemic chemotherapy with steroid premedication induces immunosuppression. Therefore, theoretically, it should have caused worsening of the infectious process. Another possible explanation is that the patient had an atypical form of sarcoidosis, with isolated splenic involvement. This explanation is also unlikely as chemotherapy usually causes flaring of sarcoidosis. One possible explanation is an interval improvement in an infectious process due to the "non-targeted effect of radiation therapy", which suggests that local radiotherapy initiates

and promotes systemic immunological responses (14,32). This effect is still under investigation; several potential mechanisms are possible, including distant effects on p53, elaboration of inflammatory agents including cytokines, and secondary immune mechanisms (33). After total abdominal or total-body irradiation of mice, the radiation-induced systemic inflammatory reaction and cytokine and chemokine production were increased (34). In our patient, the splenic non-metastatic lesions resolved after radiation therapy, without any anti-infectious treatment. From this perspective, we hypothesize that systemic effects of radiation therapy in non-irradiated area might influence active granulomatous reactions. Such effects have not been described in the literature before and needs further investigation.

Knowledge of patients' clinical status and key facts in their medical and social history and careful evaluation of imaging findings will increase the diagnostic confidence of radiologists and nuclear medicine physicians and help avoid misinterpretation. Multimodality imaging is preferred to make specific diagnoses. Different imaging modalities can be complimentary and may help clinicians in therapy planning. Awareness of pitfalls that can cause false-positive imaging findings, like in our patient, may prevent inappropriate patient management. In such patients, if there are any suspicious or atypical findings, histopathological verification is mandatory. Besides, non-targeted systemic effects of radiation therapy may induce anti-inflammatory response in non-irradiated area. However, this speculation needs further prospective research.

Ethics

Informed Consent: Patient consent has been obtained

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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

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