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

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Contact
Bilimsel Tıp Yayınevi
Address : Bükreş Sokak No: 3/20 Kavaklıdere, Ankara, Turkey
Phone : +90 (312) 426 47 47 • +90 (312) 466 23 11
Fax : +90 (312) 426 93 93
E-mail : bilimsel@bilimseltipyayinevi.com
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Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

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Phone: +90 (312) 426 47 47 • +90 (312) 466 23 11
Fax: +90 (312) 426 93 93
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Web: www.bilimseltipyayinevi.com

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2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for other specific parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

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- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Material and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

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Case Reports: There is limited space for case reports in the journal, and reports on rare cases or conditions constituting challenges in diagnosis and treatment, those offering new therapies or revealing insight not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Surgical Methods: Images of remarkable, striking and rare cases that emphasize the basic mechanisms of diagnosis and treatment of diseases, express discrepancies and extraordinary situations and explain new treatment techniques and options are evaluated for publication. Display items are important in this type of manuscripts, and supporting the manuscript with video (in WMV, AVI or MPEG formats) images can facilitate a faster evaluation process and increase the possibility of publication.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The article being commented on must be properly cited within this manuscript.

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Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

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All animal research must have approval from the authors' Institutional Animal Care and Use Committee (IACUC) or equivalent ethics committee(s), and the research must have been conducted according to applicable national and international guidelines. Approval must be received prior to beginning the research.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Manuscripts reporting animal research must state in the Methods section: The full name of the relevant ethics committee that approved the work, and the associated permit number(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why. The author should provide any relevant regulations under which the study is exempt from the requirement of approval.

Tables

Tables should be included in the main document, presented after the reference list, and numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA) should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004. pp. 2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp. 1561-5.

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Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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

Phone: +90 (312) 241 99 90

Fax: +90 (312) 241 99 91

E-mail: editor@turkjsurg.com

Publisher: Bilimsel Tıp Yayınevi

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

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

Fax: +90 (312) 426 93 93

E-mail: bilimsel@bilimseltipyayinevi.com

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FROM THE EDITOR'S DESK

Dear Authors of the Turkish Journal of Surgery,

We have very good news regarding the Journal's performance. It is my great pleasure to inform you that the recently announced "Citescore 2019" of the Turkish Journal of Surgery has increased to 1.0, which is considerably higher than the previous scores. The Journal is now ranked in the 35% percentile. I would rather consider it as the beginning of a new era for the Turkish Journal of Surgery. I would like to take this opportunity to express my deepest gratitude to all the authors and reviewers of the journal, all prior editorial teams, the Turkish Surgical Society, especially our coordinator Dr. Özmen, co-editors Dr. Demirkan and Dr. Ulaş, statistical editors Dr. Güner and Dr. Karanlık, all editorial assistants, and the team members of Bilimsel Tıp Kitabevi and Yazılım Parkı for the great support and the productive teamwork. I am absolutely persuaded that Turkish Journal of Surgery will find its place – undoubtedly with your valuable contributions - among the prominent journals in the surgical field.

Now, you have the third issue of 2020 of the Turkish Journal of Surgery in your hands. This issue addresses a various group of articles that offer something of interest to our diverse readership. These topics include transplantation radiology, endocrine surgery, biliary surgery, proctology, laparoscopic hernia surgery and breast surgery. Moreover there are also some uncommon case reports, which can be very interesting to read.

As the official journal of the Turkish Surgical Society, we feel responsible to open our pages to selected national consensus reports. In this issue, you may find details on the National Consensus of the Turkish Federation of the National Societies for Breast Diseases. Emiroğlu et al. inform about the suggestions on oncoplastic breast conserving surgery in Turkey (1).

Another interesting article of a multinational team from Germany, Switzerland and Sweden is about pilonidal sinus surgery. Doll et al. present their findings about their literature research and conclude that Turkey is the leading country on the pilonidal sinus surgery research (2). A good coincidence with this article is the clinical study of Gündoğdu in this issue on the fasciocutaneous Elliptical Rotation Flap in pilonidal sinus disease (3).

On behalf of the Editorial Board, I would like to thank our authors for their precious efforts. We hope that our readers find the information in the journal beneficial and interesting. We always support our readers to consider submitting to the Turkish Journal of Surgery. We would enjoy to review your original articles.

Please do not hesitate to submit your best work to the Turkish Journal of Surgery.

Kaya SARIBEYOĞLU

Editor,
Turkish Journal of Surgery

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ORIGINAL ARTICLE
Turk J Surg 2020; 36 (3): 241-248

The relation of CT quantified pancreatic fat index with visceral adiposity and hepatic steatosis

Ayşegül Gürsoy Çoruh[1], Çağlar Uzun[1], Zehra Akkaya[1], Atilla Halil Elhan[2]

[1] Department of Radiology, Ankara University School of Medicine, Ankara, Turkey
[2] Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: The purpose of this study was to investigate the relation between pancreatic steatosis and visceral adiposity. Furthermore, the study sought to explore the association between pancreatic steatosis, pancreas volume, hepatic steatosis, age, and sex in adults without prior history of pancreatic disease. The research also served to define a cut-off value of visceral fat tissue area (VFA) predicting fatty pancreas.

Material and Methods: CT scans of 98 living-liver donor transplant patients without prior history of pancreatic disease were evaluated for the presence of fatty pancreas. Pancreas volume, VFA, subcutaneous-total FA, VFA/TFA ratios of the patients with and without fatty pancreas were quantified with a semi-automated model on CT. Coexistence of hepatic steatosis was also recorded.

Results: VFA, TFA and VFA/TFA were significantly greater in the fatty group ($p< 0.001$, $p< 0.001$, $p< 0.001$; respectively), and pancreatic steatosis was moderately correlated with VFA, VFA/TFA and TFA with the highest correlation coefficient with VFA ($r= -0.715$, $r= -0.605$, $r= -0.573$, respectively; $p< 0.001$ for all). A cut-off value of VFA ≥ 107.2 cm^2 estimates pancreatic steatosis with a sensitivity and specificity of 90% (95% CI= 77-96%) and 87.9% (95% CI= 77%-94%), respectively. Pancreas volume was higher in the fatty-group with a mean value of 86.5 ± 17.3 mL (range; 58-119.2 mL, $p= 0.097$). In multiple logistic regression analyses, pancreatic steatosis was significantly associated with VFA and the male sex (OR= 58.2, 95% CI= 12.2-277.1, $p< 0.001$; OR= 11.4, 95% CI= 2.1-63.4, $p< 0.001$; respectively). 77.5% of the fatty pancreas subjects had co-existing hepatic steatosis.

Conclusion: Pancreatic steatosis is related to higher VFA, VFA/TFA and hepatic steatosis. A cut-off value of VFA ≥ 107.2 cm^2 may predict pancreatic steatosis.

Keywords: Pancreas, lipomatosis, liver steatosis, multislice computed tomography, visceral obesity, organ volume

INTRODUCTION

Pancreatic lipomatosis, pancreatic steatosis or fatty pancreas is the accumulation of free fat acids and triglycerides into the pancreatic islet and acinar cells, but preferentially into the interstitium (1-3). The pancreas is a glandular organ, which has both exocrine (acinar and ductal cells) and endocrine (islet cells) functions. Eighty percent of the gland volume is composed of the exocrine component (4). There are various nomenclatures to identify an accumulation of fat including pancreatic lipomatosis, pancreatic steatosis, fatty infiltration, lipomatous pseudohypertrophy, non-alcoholic fatty pancreatic disease, and fatty replacement. However, the term 'fatty replacement' expresses the irreversible damage of glandular islands and the replacement of those with adipocytes (5). Many of those with limited pancreatic steatosis have no major clinical symptoms. In advanced cases, it may lead to exocrine insufficiency and cause clinical symptoms like chronic diarrhea, steatorrhea and weight loss (4). Some studies assume that pancreatic steatosis might cause ductal stones and pancreatitis. In addition, it has been indicated that inflammation due to increased oxidative stress raised by free fat acids metabolism may lead to fibrosis and malignancy in the pancreatic tissue (3,5,6).

There is no single etiologic factor for pancreatic steatosis. It has been assumed that the pathologies related to the pancreas ductal system such as the intraductal calculi and pancreatic tumors may cause fatty pancreas. Pancreatic steatosis also correlates with diabetes mellitus, pancreatitis and the metabolic syndrome, which present the triad of the following features; hyperinsulinemia, hypertension, hyper-

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Corresponding Author
Ayşegül Gürsoy Çoruh
E-mail: draysegulgursoy@gmail.com

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glycemia, hypercholesterolemia, and obesity (4,7). This entity is highly associated with obesity, and it is assumed that visceral fat tissue is a better indicator and predictor of pancreatic steatosis rather than BMI (8).

Computed tomography (CT) is the first line imaging modality used to diagnose suspected pancreas disease. Pancreatic fat index, which shows the difference between mean pancreatic and splenic attenuation (P-S) value and quantified on non-enhanced CT, has been shown to be an indicator of pancreatic steatosis. It has been histologically demonstrated that P–S is significantly correlated with the amount of pancreatic fat component (9). In comparison with other imaging modalities, CT can measure the pancreas volume and amount of abdominal fat component easily and accurately. Instead of two-point measurements, pancreas volume can be measured more accurately with new automatic segmentation models on CT as well as fat tissue quantification. The aim of this study was to investigate the relation between pancreatic steatosis and visceral adipose tissue and to define a cut-off value of visceral fat tissue area on CT, which might show pancreatic steatosis. Additionally, the study also aimed to explore the relation between pancreas steatosis, pancreas volume, hepatic steatosis, age, and sex in adults without prior history of pancreatic disease. To the best of our knowledge, the cut-off value of visceral tissue area for the pancreas steatosis is presented for the first time.

MATERIAL and METHODS

Study Population

This retrospective study was approved by the Clinical Research Ethical Committee of our institution (Ankara University, School of Medicine; ref no: i4-224-20, date: 22.04.2020). CT scans of living-liver donor transplant patients and the institution's radiology information system/picture archiving and communication system (Centricity 5.0 RIS-i, GE Healthcare, Milwaukee, WI) were utilized to identify study population. One hundred and three patients, without chronic alcohol consumption or chronic diseases (diabetes mellitus-DM) in their medical records, examined between December 2016 and December 2018 were included into the study. Patients with acute-chronic pancreatitis, pancreatic tumors, previous pancreatic surgery, ductal dilatation, diffuse or more than one speckled parenchymal calcification or ductal calcifications were excluded from the study. Those etiologic factors were deemed in the literature as factors that induce pancreatic steatosis and affect pancreas volume (4). After addressing all of the exclusion criteria, 98 patients without pancreatic disease were included into the study.

CT Acquisition Parameters and Assessment of Pancreas-Hepatic Steatosis and Volume

All examinations were performed on a 64-detector (Toshiba Aquilion 64, Otowara, Japan) scanner. In our institution, living-liver donor CT protocol consists of non-contrast images followed by arterial, portal, and hepatic venous phases. The post-contrast series were obtained with scan delay times of 30 seconds (arterial phase), 75 seconds (portal phase) and 180 seconds (hepatic venous phase) after the start of IV contrast agent administration. A volume of 1.5-2 mL/kg of intravenous (IV) non-ionic iodinated contrast agent (350 mg/mL Omnipaque; GE Healthcare, Oslo, Norway) and 40 mL of saline were injected via antecubital vein with an 18-gauge cannula at a rate of 4 mL/s. The following CT scan parameters were performed: 120 kVp, collimation of 64 x 0.5, 1 mm section thickness, 0.8 mm reconstruction interval. An automatic exposure control system was used with a range from 100 to 400 mA.

Pancreatic steatosis and hepatic steatosis were assessed by non-enhanced axial CT images (Figure 1). The pancreatic parenchymal attenuation was measured from five different sections (head, corpus, tail, neck and uncinate process) by using an area of 0.5 cm^2 region of interest (ROI). Splenic attenuation was acquired from three different regions by using 1 cm^2 of ROI. Mean CT attenuation value of the splenic-pancreatic parenchyma were calculated by using the average of those measurements. Vascular structures were avoided in the measurements. Care was taken not to involve the peripheral section of the pancreas to avoid partial volume effect. The measurements were performed close to the splenic vein in patients in whom the margins of the pancreas were poorly defined from the adjacent retroperitoneal fat. The difference between the pancreas-splenic attenuation was utilized to determine pancreatic steatosis. Pancreatic steatosis (fatty pancreas group) was defined if the difference was ≤ -5 Hounsfield Unit (HU) (10). The patients with pancreas-splenic attenuation difference > -5 HU comprised the non-fatty pancreas group. Liver attenuation index (LAI), which estimates hepatic steatosis in non-enhanced CT, is the difference between mean hepatic parenchymal attenuation value and mean splenic atten-

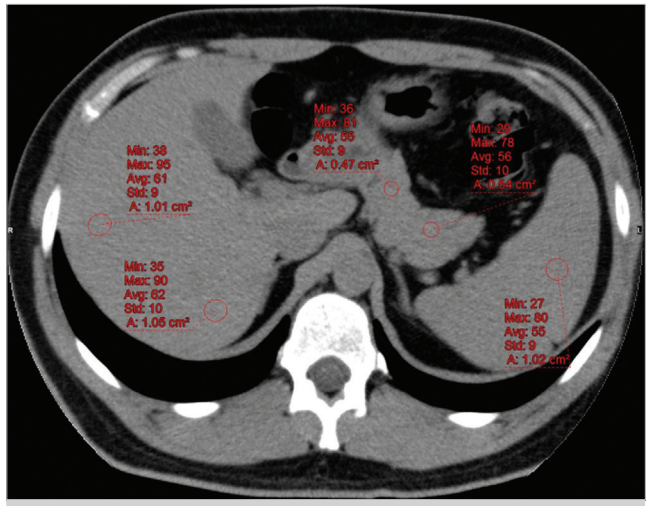

Figure 1. The measurement of mean attenuation values of the liver, spleen and pancreas parenchyma on non-enhanced CT in different sections by using region of interest (ROI).

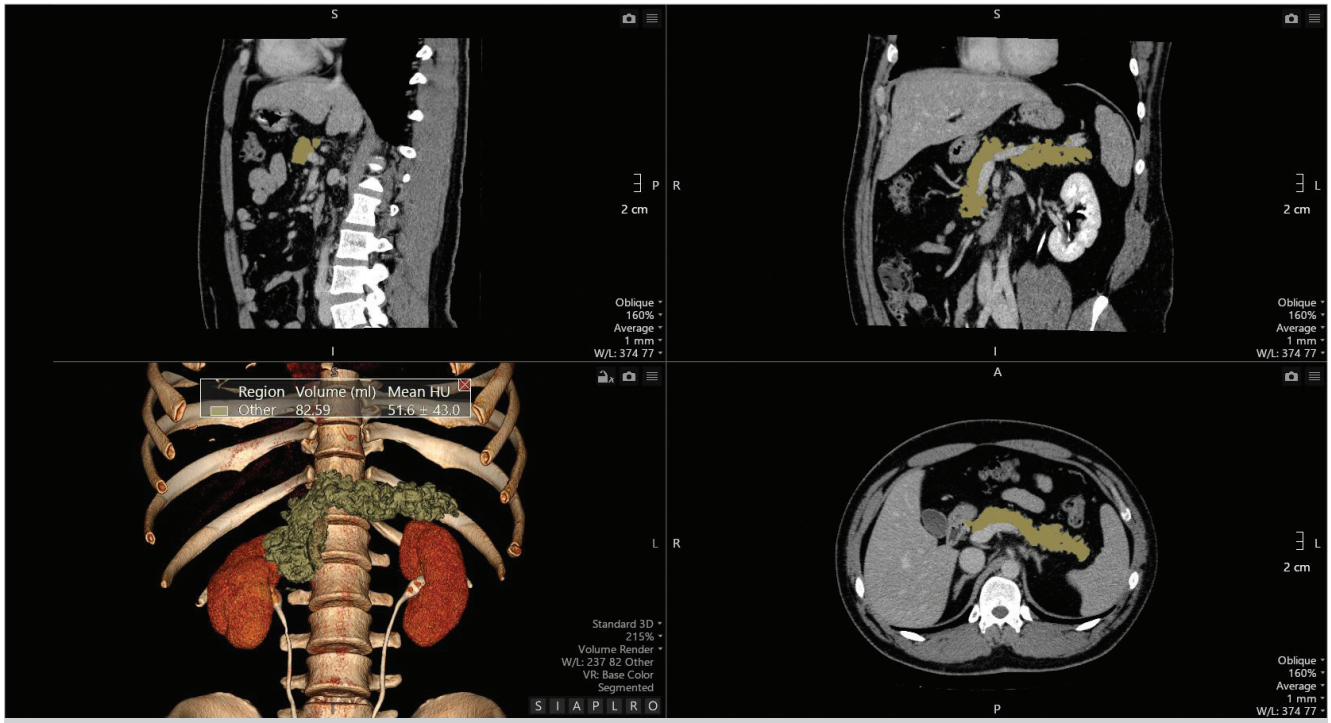

Figure 2. Pancreatic volume measurement by a semi-automated model in a 55-year-old male with pancreatic steatosis. Note that VFA was calculated as 240 cm^2.

uation value. Mean hepatic parenchymal attenuation is calculated by placing 1 cm^2 of ROI in five different regions of the hepatic parenchyma. LAI > 5 HU identifies the absence of significant steatosis (11). The subjects with LAI ≤ 5 HU composed the hepatosteatotic group.

Pancreas volume was calculated on portal venous phase by a semi-automated model (voxel-based volume calculation). In our institution, the axial thickness for non-enhanced series was 5 mm in living-liver donor transplant patients, which is not adequate for pancreatic volume calculation. In this model, threshold-based segmentation algorithms were used facilitating the separation of pancreas parenchyma from the surrounding tissues (12). After selecting a region of interest, pixels of analogous attenuation were highlighted by the software (Figure 2). If the model highlights the surrounding tissues same as the pancreas parenchyma, the erroneously selected structures margins were outlined manually by the radiologists (AGC) on axial images and excluded from the highlighted area. Then the post-processing software (Vitrea Version 7.4, Vital images, Minnetonka, Minnesota, United States) automatically calculated the total parenchymal volume. The mean processing time for pancreatic volume measurement was approximately 19 minutes.

Measurement of Body Fat Composition

The automated fat analysis software program (Vitrea Adcanced Vizualization CT Fat Measurement) quantified the total (TFA), visceral (VFA) and subcutaneous (SFA) fat tissue areas on one axial image at the level of L3-L4 disk. The adipose tissue between the anterior side of the vertebra and abdominal wall muscle was defined as visceral fat, and the area between the skin and abdominal wall was segmented as subcutaneous fat. -30 HU and - 190 HU were arranged as threshold values defining the adipose tissue (13). An area of interest selected the similar pixels of those adjusted attenuation values and then highlighted those adipose tissues separately. The program automatically calculated SFA, VFA, TFA, VFA/TFA and waist circumference.

Statistical Analysis

The difference between the two groups for normally distributed continuous variables were evaluated by Student's t test. Differences between the two groups for nominal variables were analyzed using the Chi Square test. Receiver operating characteristic (ROC) curves were used to describe the performance of diagnostic value of the variables. The area under the corresponding curves was calculated as described by Hanley and McNeil (14). Degree of association between continuous variables was calculated by Pearson's correlation coefficient. In order to define the risk factors of the outcome variable, multiple logistic regression analysis was used, and adjusted odds ratios were calculated. p-values less than 0.05 were considered significant.

RESULTS

Study population consisted of 38 females (38.2%) and 60 males (61.2%) with a mean age of 35.9 ± 8.7 (min-max; 20-59) years.

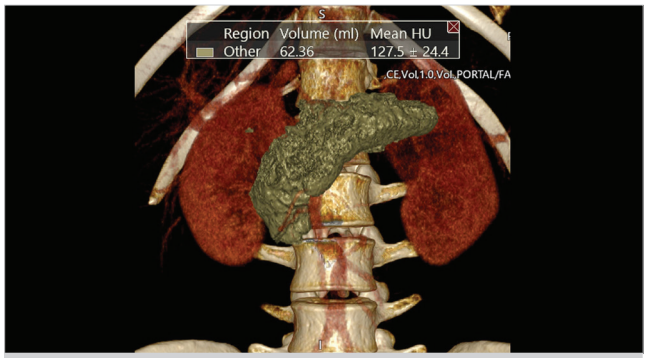

Figure 3. Pancreas volume in a 48-year-old female without fatty pancreas. Pancreas volume was smaller compared to the fatty subject shown as Figure 2. (pancreas volume of the nonfatty pancreatic subject; 62.36 mL, pancreas volume of the fatty pancreatic subject; 82.59 mL).

Fatty pancreas was detected in 40 patients of the study population. There was a statistically significant difference between the two groups in terms of sex (p< 0.001). No statistically significant difference was observed between the two groups in terms of age (p= 0.098). Pancreas volume was lower in the non-fatty group with a mean value of 80.7 ± 16.2 mL (range; 48-114.2 mL), but this difference did not reach statistically significant levels (Figure 3, p= 0.097). Mean VFA value in the fatty group was 173.6 ± 67.6 cm^2, while the mean in non-fatty group was 66.7 ± 46.9 cm2. VFA, TFA and VFA/TFA were significantly larger in the fatty group as compared to the non-fatty group (p< 0.001, p< 0.001, p< 0.001; respectively). Fatty pancreas subjects were found to have higher values of SFA (mean ± SD, 155.8 ± 52.3 cm^2); however, this difference was not statistically significant (p= 0.121). Table 1 summarizes the demographic data and pancreas volume-abdominal fat area measurements of the study population.

In ROC analysis, patients with VFA > 107.2 cm^2 (area under the curve [AUC] ± standard error [SE]: 0.920 ± 0.029, p< 0.001) appeared much more likely to have pancreatic steatosis. For this cut-off value (VFA > 107.2 cm^2), sensitivity, specificity, and positive (PPV) and negative predictive values (NPV), as well as their 95% Confidence Intervals (CI), were calculated as 90% (77-96%), 87.9% (77%-94%), 83.7% (95% CI: 70-91.9%), and 92.7% (95% CI: 82.7-97.1%) respectively. Mean VFA/TFA ratio was found to be 0.52 ± 0.09 in the fatty pancreas group. A cut-off value of 0.42 for VFA/TFA in the discrimination of pancreas steatosis was found to allow the appropriate combination of sensitivity 87.5% (73.9-94.5%) and specificity 72.4% (59.8-82.2%), with AUC being 0.856 ± 0.037 (95% CI: 0.784-0.927, p< 0.001). PPV and NPV was 68.6% (55-79.7%) and 89.4% (77.4-95.4%), respectively.

Pearson's correlation analysis demonstrated that the mean attenuation difference of the pancreas-spleen parenchyma negatively correlated with VFA, VFA/TFA and TFA (r= -0.715, r= -0.605, r= -0.573, respectively; p< 0.001 for all). Among the abdominal fat tissue compartments, this relationship is most significant with VFA. However, the attenuation difference was not related with SFA and the pancreas volume (p= 0.086 and p= 0.239). Table 2 demonstrates the correlations between pancreas steatosis (difference of pancreas-splenic mean attenuation value) and abdominal fat tissue compartments and pancreatic volume. Univariate analyses showed that VFA, TFA, waist circumference, and male sex were significant risk factors for pancreas steatosis (Table 3). Multiple logistic regression analyses adjusted for age confirmed that higher VFA (≥ 107.2 cm^2) independently predicted pancreas steatosis (Table 4). No association was found between pancreas steatosis and TFA and SFA in the multivariate analysis.

Out of the 98 patients, 43 had hepatic steatosis (43.9%). Of the 40 patients with pancreatic steatosis, 31 (77.5%) had co-existing hepatic steatosis. Hepatic steatosis was related to fatty pancreas (p< 0.001).

DISCUSSION

Previous studies have shown that fatty pancreas is associated with BMI and visceral fat tissue (10,15). In a later study, the authors have proposed that visceral fat tissue is better indicator and predictor of pancreatic steatosis compared to BMI (8). However, to the best of our knowledge, no cut-off value of VFA

Table 1. Demographic data and pancreas volume-abdominal fat area measurements of the study population

	Fatty Group (P-S ≤ -5 HU)	Non Fatty Group (P-S > 5 HU)
Sex F/M, n	3/37	35/23
Age, mean ± SD, years	37.5 ± 7.5	34.7 ± 9.2
TFA, cm^2, mean ± SD (min-max)	329.4 ± 102.5 (149.6-577.2)	202.9 ± 92.6 (22.3-472.5)
VFA, cm^2, mean ± SD (min-max)	173.6 ± 67.6 (52.8-345.3)	66.7 ± 46.9 (11.7-260.3)
SFA, cm^2, mean ± SD (min-max)	155.8 ± 52.3 (79.8-287.3)	136.1 ± 66.8 (10.6-357.7)
VFA/TFA	0.52 ± 0.09 (0.30-0.70)	0.33 ± 0.14 (0.07-0.61)
Waist circumference	98.3 ± 8.2 (84.2-119.9)	87.8 ± 7.6 (70.8-109.2)
Pancreas volume, mL (min-max)	86.5 ±17.3 (58-119.2)	80.7 ± 16.2 (48-114.2)

F: Female, M: Male, P: Pancreas, S: Spleen, VFA: Visceral fat area, TFA: Total fat area, SFA: Subcutaneous fat area.

Table 2. Correlation coefficients (r) between the variables

	TFA (p)	SFA (p)	VFA (p)	VFA/TFA (p)	Waist Circumference (p)	Pancreas volume (p)
Pancreas-spleen MAV, r	- 0.573 (< 0.001)	-0.174 (0.086)	-0.715 (< 0.001)	-0.605 (< 0.001)	-0.570 (< 0.001)	-0.120 (0.239)
TFA, r		0.781 (< 0.001)	0.866 (< 0.001)	0.348 (< 0.001)	0.903 (< 0.001)	0.084 (0.410)
SFA, r			0.363 (< 0.001)	-0.264 (0.009)	0.613 (< 0.001)	-0.128 (0.208)
VFA, r				0.730 (< 0.001)	0.855 (< 0.001)	0.229 (0.024)
VFA/TFA, r					0.485 (< 0.001)	0.287 (0.004)
Waist Circumference, r						0.259 (0.010)

MAV: Mean attenuation value, VFA: Visceral fat area, TFA: Total fat area, SFA: Subcutaneous fat area.

Table 3. Univariate analyses of the risk factors

	OR	95% CI	p
Age	1.04	0.99-1.09	0.112
Sex (male)	18.76	5.17-68.10	< 0.001
TFA	1.01	1.00-1.02	< 0.001
SFA	1.00	0.99-1.01	0.125
VFA	1.03	1.02-1.04	< 0.001
VFA (≥ 107.2 cm^2)	65.57	17.86-240.71	< 0.001
VFA/TFA (≥ 0.42)	18.37	6.11-55.19	< 0.001
Waist circumference	1.18	1.10-1.26	< 0.001

VFA: Visceral fat area, TFA: Total fat area, SFA: Subcutaneous fat area, OR: Odds ratio, CI: Confidence interval.

Table 4. Multiple logistic regression analyses of the risk factors showing statistically significant difference

	OR	95% CI	p
SEX (male)	11.4	2.1-63.4	< 0.001
VFA (≥ 107.2 cm^2)	58.2	12.2-277.1	< 0.001

OR: Odds ratio, CI: Confidence interval, VFA: Visceral fat area.

quantified on CT has previously been proposed for fatty pancreas.

There are some hypotheses on ectopic fat storage. Ectopic fat accumulation in undesirable sites (such as the liver, the pancreas, the heart) might be due to the dysfunction of subcutaneous fat tissue and as a result, insufficient storage of fat tissue in the subcutaneous fat tissue occurs. The dysfunction of subcutaneous fat tissue signals especially triglycerides to move toward the internal organs (16). Additionally, it has been shown in obese animal models that the dysfunctional visceral adipocyte they present produces inflammation and insulin resistance. Similarly, it has been shown in humans that visceral adipose tissue is metabolically active and secretes enzymes including leptin, endotrophin and inflammatory cytokines such as tumor necrosis factor alpha (TNFα), IL-6, IL-8 and insulin-like growth factor (IGF-1), all of which lead to inflammation. Inflammation within the visceral adipose tissue is associated with systemic insulin resistance and metabolic syndrome (17). As mentioned before, metabolic syndrome is one of the strongest etiologic factors contributing to fatty pancreas. Nevertheless, the pathophysiology of pancreatic steatosis is not as well-understood as it is in the liver (18).

This topic was first investigated by Ogilvie in 1933, where he demonstrated that obese subjects had a higher degree of adiposity in their pancreas compared to controls in his cadaveric study (19). Later, in large autopsies series, the relationship between the amount of pancreatic fat and obesity and age was performed (20). We did not find a correlation between age and pancreas steatosis, but our cohort was younger and limited in a narrow scale (range; 20-59 years) and presented a smaller sample size. This may be the reason why we could not find an association between fatty pancreas and age. Studies in the literature have also defined a correlation between pancreas volume and steatosis and added that pancreatic volume is influenced by steatosis and obesity. They have shown that an incremental increase in the pancreas volume is due to the increase in fat volume in the parenchyma histologically (21). In concordance with their results, we found that pancreas volume was 7% greater in the fatty group. The current study demonstrated that abdominal fat tissue (except subcutaneous fat tissue) and fatty pancreas are related, with the highest correlation being with VFA. In ROC analysis, we defined a cutoff value of ≥ 107.2 cm^2 that estimated fatty pancreas. Similarly, a recent MRI (magnetic resonance imaging) study has shown the highest correlation between fatty pancreas and visceral fat tissue compared to other abdominal fat compartments (22), and the study has also pointed out that BMI is not a good predictor of pancreatic steatosis with a very low correlation coefficient (r) of 0.12. Similarly, Staff et al. have claimed in a pediatric population study that VFA and pancreas fat fraction have a significant association whereas BMI does not (23).

In the current study, 43.9% of the study population had concomitant hepatic steatosis. Of the 40 patients with pancreatic steatosis, 77.5% of the patients demonstrated co-existence of fatty liver, which is quite similar to previous reports in the literature. Our literature review identified citations that demonstrated a positive relationship between nonalcoholic fatty pancreas disease and fatty hepatic disease (10,24,25). The liver and pancreas arise from foregut endoderm in embryologic life. Since the pancreas has the same embryological origin and close anatomical relationships to the liver, fat accumulation might be analogous in the pancreas and liver parenchyma (3). Additionally, the pancreas, liver and visceral fat tissue are controlled by the same vagal neurons (26).

Nonetheless, this study has some limitations. The major limitation of the current study is that pancreas steatosis was not evaluated histologically. However, the study conducted by Kim et al. has assumed that the difference between pancreas and spleen mean attenuation values on CT is significantly correlated with the intrapancreatic fat accumulation histologically (9). They have also added that non-enhanced CT is a useful tool in the non-invasive assessment of pancreas steatosis. The retrospective design of the current study with a limited study population is one of the other limitations. Large scale prospective studies which comprise histopathological evaluation are warranted to strengthen the current study's results. Additionally, we were not able to obtain weight and height data for the study population from the institution's medical records. Therefore, we could not correlate our results with BMI. In the current study, we observed that age was not a risk factor for fatty pancreas. Our cohort was younger and had a smaller sample size, which may explain why we could not find an association between fatty pancreas and age. On the other hand, another study with a larger study population has demonstrated a weak positive correlation between the pancreatic fat fraction and age (r= 0.33, p= 0.01) (22).

CONCLUSION

CT attenuation index, which defines pancreatic steatosis, is moderately correlated with VFA but not with SFA. A cutoff value of VFA ≥ 107.2 cm^2 and VFA/TFA ≥ 0.42 exhibited high specificity and sensitivity ratios to define pancreatic steatosis. Additionally, hepatic and pancreatic steatosis, which are the main ectopic fat accumulation sides, are related to each other. Further large-scale studies are needed to validate the current study findings.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara University Faculty of Medicine Human Research Ethics Committee (2020/İ4-224-20).

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

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ORİJİNAL ÇALIŞMA-ÖZET
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BT ile hesaplanan pankreatik yağ endeksinin viseral obezite ve karaciğer yağlanması ile ilişkisi

Ayşegül Gürsoy Çoruh[1], Çağlar Uzun[1], Zehra Akkaya[1], Atilla Halil Elhan[2]

[1] Ankara Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Ankara, Türkiye
[2] Ankara Üniversitesi Tıp Fakültesi, Biyoistatistik Anabilim Dalı, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Çalışmanın amacı, pankreas yağlanması ile viseral yağ doku miktarı arasındaki ilişkiyi araştırmaktır. Ayrıca, normal yetişkinlerde pankreas yağlanması, pankreas hacmi, karaciğer yağlanması, yaş ve cinsiyet arasındaki ilişkileri de araştırmayı amaçlamaktadır. Aynı zamanda, yağlı pankreası öngören viseral yağ dokusu alanı (VFA) için cutoff değeri bulmayı amaçlamaktadır.

Gereç ve Yöntem: Pankreas hastalık öyküsü olmayan 98 canlı karaciğer nakli vericisinin BT incelemeleri yağlı pankreas varlığı açısından değerlendirildi. BT'de yarı otomatik model ile pankreas hacmi, VFA, subkutan-total FA, VFA/TFA oranları hesaplandı. Eşlik eden karaciğer yağlanması kaydedildi.

Bulgular: VFA, TFA ve VFA/TFA oranları yağlı pankreas grubunda anlamlı olarak daha yüksekti (sırasıyla; p< 0,001, p< 0,001, p< 0,001) ve pankreas yağlanması; VFA, VFA/ TFA ve TFA ile orta derecede korele olup VFA en yüksek korelasyon katsayısına sahipti. (r= -0,715, r= -0,605, r= -0,573; sırasıyla p< 0,001). VFA ≥ 107,2 cm^2 cutoff değeri pankreas yağlanmasını %90 duyarlılık (%95 GA= %77-96) ve %87.9 özgüllükle (%95 GA= %77-94) tahmin eder. Yağlı pankreas grubunda ortalama pankreas hacmi 86,5 ± 17,3 mL (aralık; 58-119,2 mL, p= 0,097) ölçülmüş olup daha yüksek bulundu . Çoklu lojistik regresyon analizinde pankreas yağlanması; VFA ve erkek cinsiyet ile anlamlı derecede ilişkiye sahipti (OR= 58,2, %95 GA= 12,2-277,1, p< 0,001; OR= 11,4, %95 GA= 2,1-63,4, p< 0,001;). Yağlı pankreas grubunun %77,5'inde eşlik eden hepatik steatoz vardı.

Sonuç: Pankreas yağlanması; yüksek VFA, VFA/TFA oranları ve hepatik steatoz ile ilişkilidir. VFA ≥ 107.2 cm^2 cutoff değeri pankreas yağlanmasını öngörebilir.

Anahtar Kelimeler: Pankreas, yağlanma, karaciğer yağlanması, multidedektör bt, viseral obezite, organ hacmi

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The effect of BRAF^{V600E} mutation on lymph node involvement in papillary thyroid cancer

Samet Şahin[1], Gül Dağlar[2], Ebru Menekşe[2], Büşranur Çavdarlı[3], Tolga Bağlan[4]

[1] Department of General Surgery, Muğla Sıtkı Koçman University, Faculty of Medicine, Muğla, Turkey
[2] Clinic of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey
[3] Clinic of Medical Genetics, Ankara City Hospital, Ankara, Turkey
[4] Department of Medical Pathology, Ankara University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: Papillary thyroid cancer (PTC) is the most common well-differentiated thyroid cancer. Lymph node (LN) metastasis is frequently seen in PTC. The effect of BRAF^{V600E} mutation on PTC-associated LN metastasis has not been clearly established. Therefore, we aimed to evaluate the effect of the BRAF^{V600E} mutation in patients with PTC on regional LN metastasis.

Material and Methods: Between January 2013 and 2017, sixty-three PTC patients who underwent central lymph node dissection were included into the study. The patients were divided into two groups according to the pathology results of the LN dissection, and these groups were compared for positive BRAF^{V600E} mutations and other clinicopathological findings.

Results: BRAF^{V600E} mutation was found to be more significant in the pLN1 group (p= 0.005). Multivariate analysis revealed that nodule size, microcalcifications, and BRAF^{V600E} mutation were associated with lymph node metastasis independent of other parameters. ROC analysis also evaluated the adequacy of the BRAF^{V600E} mutation in predicting the presence of LN involvement. AUC: 0.738 (95% CI: 0.6110.866, p: 0.002).

Conclusion: In our study, independent of other parameters, BRAF^{V600E} gene mutation was found to be effective on lymph node involvement.

Keywords: BRAF, Lymph node, involvement, papillary thyroid cancer

INTRODUCTION

Well-differentiated thyroid cancers are the most common endocrine malignancies and are among the world's most common cancers (1). Papillary thyroid cancer (PTC), the most common well-differentiated thyroid cancer, constitutes 80% of all endocrine malignancies (2). Lymph node metastasis, which is directly associated with increased local recurrence (3), is frequently seen in PTC, and its incidence varies between 20% and 90% (4). However, there are opposing views regarding the effect of lymph node metastasis on survival in well-differentiated thyroid cancers. Some previous studies have shown that regional lymph node metastasis has no effect on survival in PTC (5). Other studies, with a sufficiently long follow-up period, for example, 30-year survival in patients with cervical metastases, have shown survival rates to be significantly lower compared to those for patients without cervical metastasis (6).

BRAF^{V600E} is a major oncogenic mutation that promotes PTC development by activating the MAP kinase pathway (7). BRAF^{V600E} mutation, which is an activating mutation of the B isoform of the Raf kinase gene in exon 15, is the most common mutation in PTC, leading to the conversion of valine to glutamic acid at position 600 (8). RAF proteins are serine/threonine protein kinases and play an important role in cell proliferation, differentiation, and programmed cell death (9). RAF proteins act on cell proliferation and differentiation via this pathway by activating the mitogen-activated protein kinase (MAPK) pathway (10). Many studies have demonstrated the association of BRAF^{V600E} mutation with aggressive clinicopathological features of PTC (11). However, the effect of this mutation on PTC-associated lymph node metastasis has not been clearly established. In this study, we aimed to evaluate the effect of BRAF^{V600E} mutation in patients with PTC on regional lymph node metastasis known to be associated with poor prognosis in PTC.

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Corresponding Author
Samet Şahin
E-mail: sametsahin1903@hotmail.com

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MATERIAL and METHODS

Between January 2013 and January 2017, patients whose postoperative pathology specimens indicated PTC at our General Surgery Clinic and who underwent therapeutic or prophylactic central lymph node dissection (CLND) were included into the study. Permission for the study was obtained from Ankara Numune Training and Research Hospital Ethics Committee. The study followed the guidelines and principles of the Declaration of Helsinki. All patients signed informed consents for the use of their clinical data and for genetic analysis.

Our study was organized with the support of medical pathology and medical genetics departments based on surgical approaches. A retrospective examination of the patients showed that total thyroidectomy (TT) was performed for patients whose fine-needle aspiration cytology (FNAC) preoperative results indicated that their specimens fell into one of the following categories: "PTC", "atypia of undetermined significance", "follicular lesion of undetermined significance (FLUS)" or "non-diagnostic" (two times). Fine needle aspiration cytology was performed for patients with lateral pathologic lymph nodes revealed by an ultrasound of the neck. Patients with lymph node metastasis indicated by FNAC and thyroglobulin measurements in the washout of the needle (FNAB-Tg) underwent therapeutic lymph node dissection. Therapeutic CLND was performed on patients with palpable lymph nodes found during TT. Based on the risk factors and tumor characteristics, prophylactic CLND was performed on patients suspected of having a malignancy although pathological lymph nodes were not detected in neck ultrasonography (US). The patients were divided into two groups according to the pathology results of the lymph node dissection, the pLN0 group (patients with no lymph node involvement) and the pLN1 group (patients with one or more lymph node involved). These groups were compared for positive BRAF^{V600E} mutations.

Patients who had their first operation at another center and underwent complementary thyroidectomy and regional lymph node dissection at our clinic and patients who underwent regional lymph node dissection at our clinic after TT at another center were excluded from the study. Patients whose clinical information could not be obtained and patients whose pathology specimens could not be acquired were also excluded from the study. Gaps in information were addressed by contacting the patients by telephone.

One hundred and twenty-three patients were operated on with the diagnosis of PTC and performed right, left or bilateral modified radical neck dissection in addition to TT and prophylactic or therapeutic CLND. A total of 19 patients were excluded since pathology specimens of eight patients could not be reached and clinicopathological data of the remaining eleven patients could not be reached either from them or hospital information management system. The remaining 104 patients were subjected to further processing. From the paraffin blocks of the thyroidectomy material of 104 patients, tumoral tissue sections were obtained. DNA isolation was performed in 104 tissues, and the purity/concentration ratios of 75 patients were seen in the appropriate range. DNA isolation materials of 75 patients were subjected to further treatment. Ten out of the 75 patients were excluded from the study until the sequence analysis due to improper banding on gel electrophoresis and primary duplication and DNA fractures during ExoSAP-cycle step. Two patients were excluded from the study during sequence analysis since one had "forward repeat", and the other had a "reverse repeat". Ultimately, sixty-three patients were included into the study. Hospital records indicating age, sex, thyroid and neck US results (number of nodules, nodule size, echogenicity status, cystic or solid state of the nodule, the presence of microcalcifications, increase in nodal blood flow, border irregularity in nodules), FNAC results regarding malignancy (the presence of nuclear elongation, discohesive cells, nuclear notching, irregular nucleus, cytoplasmic clarification, inclusion body, oncocytoid morphology, histiocytic giant cells), postoperative pathology specimen results (tumor size, multicentricity status, the presence of capsule invasion or neurovascular invasion), the number of metastatic and total lymph nodes removed during neck dissection, and the results of BRAF^{V600E} mutation data analysis were obtained and evaluated.

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 20 (SPSS, Inc., IBM, Armonk, NY, USA). Continuous variables were evaluated for normality using the Kolmogorov–Smirnov test. Normally distributed variables expressed as mean ± standard deviation were compared using the Student's t test. Non-parametric variables expressed as median (interquartile range) were compared using the Mann–Whitney U test. Nominal variables were compared using the Pearson's chi-squared test or Fisher's exact test. Univariant and multivariant analyses were conducted to determine if any of the variables were associated with lymph node involvement. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic ability of BRAF in determining lymph node involvement. $P < 0.05$ was determined as being significant.

RESULTS

Mean age of the 63 patients was 42.9 ± 13.3 years. Of these, 45 were females (71.4%) and 18 were males (28.6%). TT and CLND were performed on 38 patients (60.3%), 29 (46%) for prophylactic purposes and 9 (14.3%) for therapeutic purposes. TT, CLND, and modified radical neck dissection (MRND) were performed on 25 (39.6%) patients (Table 1). Based on the postoperative pathology specimens, fifty of the 63 patients had classic PTC (79.4%), 12 had follicular variant (FV) of PTC (19.1%), and 1 had the tall cell variant

Table 1. Numerical distribution of operations according to FNAB results

	TT + CLND		TT + MRND
	Prophylactic	Therapeutic	
Non-diagnostic	4	1	6
AUS	3	6	3
FLUS	-	-	1
Malignancy Suspicion	3	2	5
PTC	19	0	10

N: Number, PTC: Papillary thyroid cancer, AUS: Atypia of undetermined significance, FLUS: Follicular lesion of undetermined significance, TT: Total thyroidectomy, CLND: Central lymph node dissection, MRND: Modified radical neck dissection.

Table 2. Lymph node metastasis according to post-operative pathology results

	pLN0	pLN1
Classic type PTC	23 (46%)	27 (54%)
FV-PTC	6 (50%)	6 (50%)
TCV-PTC	-	1

LN: Lymph node, PTC: Papillary thyroid cancer, FV-PTC: Follicular Variant Papillary thyroid cancer, TCV-PTC: Tall Cell Variant Papillary thyroid cancer, pLN0: patients without lymph node involvement, pLN1: Patients with lymph node involvement.

(TCV) of PTC (1.5%) (Table 2). $BRAF^{V600E}$ mutation was detected in 21 (33.3%).

Lymph node metastasis was found in 34 patients (53.9%), based on post-operative pathology results. In classic type PTC, 23 of 50 the patients, in FV-PTC, 6 of the 12 patients and 1 TCV-PTC patient had lymph node involvement.

Mean age of the pLN0 group was 43.9 ± 12.9 years, and mean age of the pLN1 group was 42 ± 13.8 years, and there was no significant difference between the two groups (p= 0.583). Lymph node involvement was higher in males than in females (p= 0.005) (Table 3).

When preoperative US parameters were compared between the groups, only the nodule size (p = 0.004) and the presence of microcalcifications (p= 0.009) were found to be more significant in the pLN1 group (Table 3).

The results of fine needle aspiration cytology showed no significant difference between the two groups (p> 0.05 for both) (Table 3).

When the $BRAF^{V600E}$ result was compared between the groups, BRAF mutation was found to be more significant in the pLN1 group (p= 0.005) (Table 3).

Multivariate analysis revealed that nodule size, the presence of microcalcifications, and the presence of the $BRAF^{V600E}$ mutation were associated with lymph node metastasis independent of other parameters, which were significantly higher in the pLN1 group according to the univariate analyses (Table 4).

$BRAF^{V600E}$ mutation was detected in 3 (10.3%) of the 29 patients in the pLN0 group, while gene mutation positivity was found in 18 (52.9%) of the 34 patients in the pLN1 group (p< 0.001). ROC analysis to assess the adequacy of $BRAF^{V600E}$ mutation in predicting the presence of pathologic lymph node involvement was calculated as AUC: 0.738 (95% CI: 0.611-0.866, p: 0.002) (Figure 1).

DISCUSSION

In this study, the effect of $BRAF^{V600E}$ mutation on lymph node metastasis in PTC was evaluated, and lymph node mutation was found to be significantly higher in individuals with the gene mutation. $BRAF^{V600E}$ mutation was detected in 31.7% of our patients. In addition to being the most common mutation in PTC, the incidence of $BRAF^{V600E}$ has also increased (12,13). According to the literature, the frequency of $BRAF^{V600E}$ mutation in patients with PTC ranges from 18%-87% (14,15). In a study by Kurtulmuş et al. (16), $BRAF^{V600E}$ mutation rate has been found to be 36.4%, and the rate in our study was similar. The frequency of lymph node metastasis in PTC also ranges widely from 30%-90%) (17-19). In our study, lymph node metastasis was observed in 34 patients (53.9%) according to postoperative pathology results, which is consistent with the literature.

Although preoperative ultrasonographic evaluation is routine in the management of thyroid diseases and is a valuable examination on PTC, its adequacy in predicting lymph node involvement is limited, and there are opposing views in the literature. According to Schlumberger et al. (20), US is the most sensitive test to detect metastatic lymph nodes. However, Kim et al. (21) have found that the sensitivity of US during the preoperative period is lower when not combined with other imaging methods. In evaluating the relation between preoperative US findings and lymph node involvement in our patient group, the presence of microcalcification in the thyroid nodule and increased nodule size indicated a significant increase in lymph node involvement, but no difference was found between other ultrasonographic findings and lymph node metastasis. While 11 of the 26 patients with lymph node involvement were not identified based on US, lymph node involvement was observed in the specimens. However, there was no lymph node involve-

Table 3. Comparison of preoperative demographic, ultrasonographic parameters, FNAC and sequence results of the groups

	pLN 0	pLN 1	p
Age	43.9 ±12.9	42 ±13.8	0.583*
Sex			**0.005**
Female	26 (89.7%)	19 (55.9%)	
Male	3 (10.3%)	15 (44.1%)	
Ultrasonographic parameters			
Number of nodule	2 (1-3)	3 (2-3)	0.132ǂ
Nodule size (mm)	13 (7.5-18)	18 (13.8-22.3)	**0.004ǂ**
Echogenicity			0.154†
Hypoechogenous	20 (69%)	16 (47.1%)	
Isoechogenous	2 (6.9%)	7 (20.6%)	
Mixed	7 (24.1%)	11 (32.4%)	
Cystic-solid construction			0.861†
Cystic	2 (6.9%)	2 (5.9%)	
Solid	17 (58.6%)	18 (52.9%)	
Mixed	10 (34.5%)	14 (41.2%)	
Microcalcification			**0.009†**
(-)	18 (62.1%)	10 (29.4%)	
(+)	11 (37.9%)	24 (70.6%)	
Blood supply of nodule			0.268†
(-)	13 (44.8%)	20 (58.8%)	
(+)	16 (55.2%)	14 (41.2%)	
Border regularity			0.251†
Regular	17 (58.6%)	15 (44.1%)	
Irregular	12 (41.4%)	19 (55.9%)	
LN metastasis			0.097†
(-)	15 (51.8%)	11 (32.3%)	
(+)	14 (48.2%)	23 (67.7%)	
FNAC results			
Nuclear elongation			0.681†
(-)	8 (27.6%)	11 (32.4%)	
(+)	21 (72.4%)	23 (67.6%)	
Discohesive cell			0.859†
(-)	13 (44.8%)	16 (47.1%)	
(+)	16 (55.2%)	18 (52.9%)	
Nuclear notching			0.758†
(-)	10 (34.5%)	13 (38.2%)	
(+)	19 (65.5%)	21 (61.8%)	
Irregular nucleus			0.231†
(-)	7 (24.1%)	13 (38.2%)	
(+)	22 (75.9%)	21 (61.8%)	
Cytoplasmic clarification			0.080†
(-)	9 (31%)	18 (52.9%)	
(+)	20 (69%)	16 (47.1%)	
Intranuclear inclusions			0.512†
(-)	8 (27.6%)	12 (35.3%)	
(+)	21 (72.4%)	22 (64.7%)	
Oncocytic morphology			0.233†
(-)	11 (37.9%)	18 (52.9%)	
(+)	18 (62.1%)	16 (47.1%)	
Multinuclear histiocytic giant cell			0.572†
(-)	15 (51.7%)	20 (58.8%)	
(+)	14 (48.3%)	14 (41.2%)	
BRAF^{V600E}			**0.005†**
(-)	25 (86.2%)	18 (52.9%)	
(+)	4 (13.8%)	16 (47.1%)	

*: mean ± SD and Student's t test
†: number and Fisher's exact test or Pearson chi square test
ǂ: median (IQR) and Mann Whitney U test
LN: Lymph node, pLN0: Patients with lymph node involvement, pLN1: Patients with lymph node involvement.

Table 4. Multivariate analysis of the factors associated with the pLN1 group

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Male sex	6.48 (1.73-27.02)	0.006	6.12 (0.89-42.1)	0.066
Microcalcification (US)	3.93 (1.37-11.25)	0.011	1.16 (1.05-1.29)	0.004
Nodule size, mm (US)	1.10 (1.02-1.18)	0.013	10.11 (1.97-51.85)	0.006
$BRAF^{V600E}$	9.75 (2.48-38.44)	0.001	6.41 (1.25-32.8)	0.026

OR: Odd ratio, CI: Confidence interval, US: Ultrasonography.

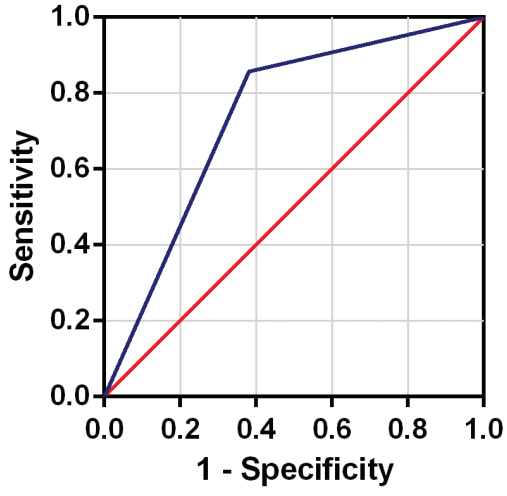

Figure 1. Revised roc curve for the ability of $BRAF^{V600E}$ mutation to demonstrate lymph node metastasis.

ment in the specimens of 14 of the 37 patients with pathologic lymph nodes identified using US. This result shows that US is not sufficient to predict lymph node metastasis in the preoperative period and that the evaluation of lymph node involvement should be supported by non-subjective preoperative data.

Although FNAC is a gold standard method for detecting the presence of malignancy in thyroid nodules (22,23), our study concluded that none of the cytopathological parameters in FNAC were different in patients with or without lymph node metastasis. Each of the cytopathological parameters evaluated in our study are diagnostic findings for PTC. From this point of view, it is noteworthy that FNAC was not associated with lymph node metastasis in the diagnosis of PTC.

In a study by Dong et al. (24), the authors have found that $BRAF^{V600E}$ gene mutation is not associated with all PTC subgroups with regional lymph node metastasis but with lymph node metastasis in patients with classic PTC. In a study in which the factors affecting cervical lymph node metastasis in patients with Delphian lymph node metastasis were examined, tumor size, multifocality, extrathyroidal spread, and $BRAF^{V600E}$ mutation in pathology specimens have been found to be independent risk factors related to each metastasis (25). In another study in which patients with metastatic thyroid cancer but no primary tumor were evaluated, it has been observed that the patients with metastatic thyroid cancer had a statistically significant $BRAF^{V600E}$ mutation than the patients without metastatic thyroid cancer (26). In a study by Kurtulmuş et al., the presence of the gene mutation has been associated with regional lymph node metastasis (16). In our study, the presence of $BRAF^{V600E}$ mutation was found to be effective in predicting lymph node involvement using ROC curve analysis.

According to the American Thyroid Association (ATA), $BRAF^{V600E}$mutation was identified for the first time in 2002 even though it was not described in the 2009 guidelines. The first time this mutation was described as being useful in risk classification is in the 2015 guidelines (19). The role of gene mutation has been better elucidated by means of systematic meta-analyzes published in subsequent years (27,28). In the 2009 ATA guidelines, TT without the need for SLND was recommended if no lymph node metastasis was clinically detected in T1-2 tumors (29). Also, according to the 2015 ATA guidelines, BRAF review is not routinely recommended in the first postoperative risk classification of the DTK, since knowing the BRAF mutation contributes a very small prognostic contribution to the clinico-pathological staging system (weak suggestion, moderate evidence) (19). However, in our study, $BRAF^{V600E}$ mutation was found to be associated with lymph node metastasis independent of other pre-operative clinicopathological findings. The high cost of the genetic kit we used in our study had an impact on the limited number of patients. This situation is seen as the limitation of our study. Further studies involving mostly patient groups are needed to support the routine use of BRAF gene mutation analysis in predicting lymph node metastasis.

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ORİJİNAL ÇALIŞMA-ÖZET
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Papiller tiroid kanserli hastalarda BRAF^{V600E} mutasyonunun bölgesel lenf nodu tutulumuna etkisi

Samet Şahin[1], Gül Dağlar[2], Ebru Menekşe[2], Büşranur Çavdarlı[3], Tolga Bağlan[4]

[1] Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Muğla, Türkiye
[2] Ankara Numune Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Ankara, Türkiye
[3] Ankara Şehir Hastanesi, Tıbbi Genetik Kliniği, Ankara, Türkiye
[4] Ankara Üniversitesi Tıp Fakültesi, Tıbbi Patoloji Anabilim Dalı, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Papiller tiroid kanseri (PTK) iyi diferansiye tiroid kanserleri içinde en sık görülen tiptir. Lenf nodu (LN) metastazı PTK'de sıklıkla görülür. BRAF^{V600E} mutasyonunun PTK ile ilişkili LN metastazı üzerindeki etkisi kesin olarak belirlenememiştir. Bu nedenle çalışmamızın amacı PTK'li hastalarda BRAF^{V600E} mutasyonunun bölgesel LN metastazı üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Ocak 2013-2017 arasında santral lenf nodu diseksiyonu yapılan 63 hasta çalışmaya dahil edildi. Hastalar LN diseksiyonunun patoloji sonuçlarına göre pLN0 ve pLN1 olmak üzere iki gruba ayrıldı. Gruplar BRAF^{V600E} mutasyon varlığı açısından ve diğer klinikopatolojik bulgular ile karşılaştırıldı.

Bulgular: BRAF^{V600E} mutasyonu, pLN1 grubunda anlamlı yüksek saptandı. (p= 0,005). Yapılan çok değişkenli analizde nodül büyüklüğü, mikrokalsifikasyon ve BRAF^{V600E} mutasyonunun diğer parametrelerden bağımsız olarak lenf nodu metastazı ile ilişkili olduğunu ortaya koyuldu. ROC analizi ile BRAF^{V600E} mutasyonunun LN tutulumunun varlığını öngörmedeki yeterliliği de anlamlı olarak saptandı [AUC: 0,738 (%95 CI: 0,61-0.86, p= 0,002)].

Sonuç: Çalışmamızda diğer parametrelerden bağımsız olarak BRAF^{V600E} gen mutasyonunun lenf nodu tutulumu üzerinde etkili olduğu bulundu.

Anahtar Kelimeler: Braf, lenf nodu tutulumu, papiller tiroid kanser

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ORIGINAL ARTICLE
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Platelet-rich fibrin can accelerate the healing of common bile duct anastomosis in a rat

Necdet Özçay[1], Ali Özant[1], Kalbim Arslan[1], Hanife Özkayalar[2], Hasan Besim[1]

[1] Department of General Surgery, Faculty of Medicine Near East University, Nicosia, Cyprus
[2] Department of Medical Pathology, Faculty of Medicine Near East University, Nicosia, Cyprus

ABSTRACT

Objective: This study aimed to evaluate the effect of platelet-rich fibrin (PRF) concentrate on the bile duct anastomosis healing process in rats.

Material and Methods: Thirty male Sprague Dawley (SD) rats were used for the study. The animals were allocated into three groups: Group I Control Group (n= 10): Anastomosis to the common bile duct (CBD) with a stent. Group II PRF Group (n= 10): Anastomosis to the CBD with a stent and covered with PRF. Group III Sham Group (n= 10): Preparation of the common bile duct, no anastomosis. The animals were followed up for 1 month, then sacrificed. Study parameters were adhesions around the anastomosis, thickness of the bridging bile duct tissue over the stent, and histopathologic examination of the bridging bile duct tissue.

Results: CBD anastomosis using a stent caused severe adhesion around the anastomosis, bridging bile duct tissues were weak and histopathologically, healing was incomplete in most of the control animals. However, PRF application significantly reduced the adhesions, increased the quality of the bridging bile duct tissues, and caused complete healing histologically.

Conclusion: PRF is an autologous, easily prepared membrane. The present study findings show that PRF prevents local complications and increases the healing capacity of the bile duct after CBD anastomosis. Therefore, it might be a new treatment option for preventing complications following common bile duct anastomosis in liver transplantation patients.

Keywords: Platelet-rich fibrin, biliary complications, biliary reconstruction, liver transplantation

INTRODUCTION

The bile duct and the vascular endothelium are vulnerable to the damaging effects of ischemic, immunologic, and preservation injuries. The regenerative capacity of the biliary tract is also poor and is often compromised further due to ischemic injury (1). Therefore, independent from surgical techniques, biliary complications following hepatobiliary operations and liver transplantation are common and remain a major source of morbidity. Biliary leaks and strictures are the most common complications after liver transplantation, with an incidence of 5%-32% (2). The effective management of biliary complications is difficult and always requires additional medical or surgical treatments. Unfortunately, even with advanced interventional or surgical treatments, treatment results are not satisfactory (3).

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate which was first developed by Choukroun et al. (4-5). PRF is a fibrin matrix in which platelets are trapped massively and may be released after a certain time and could serve as an autologous membrane. Fibrin and platelets play crucial roles during the gastrointestinal wound healing process. The formation of fibrin seal on the outer part of the bowel is essential for the early integrity of the anastomosis (6). The fibrin matrix covers the injured tissue and affects the metabolism of inflammatory cells. Fibrin also plays a role as the natural guide of angiogenesis (5). Platelets are anucleate cytoplasmic fragments and contain many granules in which a large amount of growth factors as well as inflammatory and healing cytokines exist. Platelet growth factors are a well-known source of healing, and they also have synergetic effects on healing processes (7). PRF has some advantages over other platelets concentrates, such as easy and quick preparation without any complex manipulations or additives, and prolonged action. These technical advantages and unique structures of PRF have led to the hypothesis that using PRF could accelerate the healing of common bile duct anastomosis.

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Corresponding Author
Necdet Özçay
E-mail: necdetozcay@gmail.com

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The authors believe that the prevention of biliary tract complications is more important than treatment. Promoting the healing process and increasing the regenerative capacity of the biliary system might play an important role in preventing biliary complications following hepatobiliary operations and liver transplantation. PRF has been used to accelerate the healing of skin autografts, oral and maxillofacial tissue and hand wounds with encouraging results for many years (8-12). In this study, it was aimed to investigate the effects of platelet-rich fibrin on the bile duct healing process in rats.

MATERIAL and METHODS

Animals

This study was approved by Başkent University Ethical Committee for Experimental Research on Animals (project no: DA16/08). Thirty male outbred Sprague Dawley (SD) rats weighing 250-300 grams were purchased from the experimental animals breeding center at Başkent University in Ankara, Turkey. The animals were housed in the Başkent University Experimental Research Center (Ankara, Turkey) in accordance with the guidelines established by the Turkish Government. Food and water were not restricted from the animals. The rats were anesthetized with an intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). The abdomen was cleansed with povidone iodine, and laparotomy was performed via a midline incision. The study groups were designed as follows:

Group I (n= 10): Anastomosis with stent (Control); Laparotomy, transection of the common bile duct, end-to-end anastomosis with silicon stent, followed-up 1 month, sacrificed.

Group II (n= 10): Anastomosis with stent and PRF; Laparotomy, transection of common bile duct, end-to-end anastomosis with silicon stent, placement of the PRF membrane around the stent, followed-up 1 month, sacrificed.

Group III (n= 10): Sham group; Laparotomy, preparation of the common bile duct, followed-up 1 month, sacrificed.

Preparation of the PRF

The PRF was prepared as previously described by Dohan at al. (4). Briefly, one ml of blood samples was obtained before the surgical procedures from each animal by cardiac puncture, and poured into a glass centrifuge tube without anticoagulant. The tubes were then immediately centrifuged at 3,000 revolutions per minute (rpm) for 10 minutes in a centrifuge machine (Nüve NF 415). Three centrifugation strata were obtained: a fibrin clot (PRF) in the middle of the tube, between the red corpuscles at the bottom and the acellular plasma at the top. The platelets were trapped in large numbers in the fibrin meshes. The upper straw-colored layer was removed and the middle fraction was collected. A resistant autologous fibrin membrane was then obtained by driving out the serum from the clot.

Surgical Model

An operating microscope (Carl Zeiss OPMI 9-FC, Germany) was used for the surgical model. A laparotomy was performed via a midline incision. The hepatic hilum was dissected to free the common bile duct (CBD). Then, the CBD was transected at the middle. The CBD was reconstructed by duct–to-duct anastomosis with a stent: the stent was inserted into both ends of the bile duct and was secured with a 7/0 Prolene purse-string suture. The distance between the two sutures was 10 mm. This bare stent area was left between the two sutures to observe migration of the bile duct tissue. The PRF membrane covered the stent and the two ends of the PRF were attached to each other with a 7/0 Prolene suture to prevent sliding of the PRF in the treatment group (Figure 1). The hepatic hilar was dissected to free the CBD in the sham group of animals. The animals were followed-up daily for 1 month, then sacrificed.

Study Parameters

Gross findings at necropsy

The anastomotic area of the CBD was quantitatively evaluated by an experienced surgeon in a blinded manner during necropsy. Firstly, adhesions around the CBD anastomosis were evaluated. Anastomotic adhesions were graded from 0-to-III, as modified from Nair et al. (13): Grade 0: No adhesion; Grade I (mild adhesion): A single organ, omentum, duodenum or liver, adherent to the anastomosis; Grade II (moderate adhesion): Two organs adherent to the anastomosis; Grade III (severe adhesion): More than two organs adherent to the anastomosis. Secondly, the bridging bile duct tissue over the silicon catheter was qualitatively evaluated and graded as follows: Grade 0: Catheter completely visible and there is no bridging bile duct tissue; Grade I: Catheter partially visible and there is partial bile duct tissue over the catheter; Grade II: Catheter is not visible,

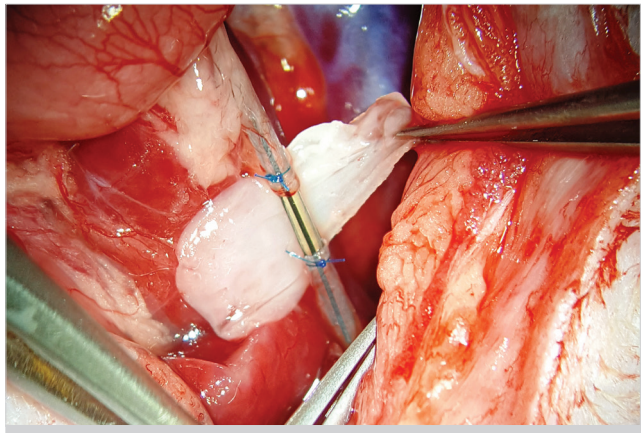

Figure 1. Common bile duct reconstruction by duct–to-duct anastomosis with a stent and application of the PRF membrane. After the PRF membrane covered the stent, the two ends of the PRF were attached to each other with a suture to prevent sliding of.

complete but thin bridging bile duct tissue exists; Grade III: Catheter is not visible and is covered with thick and strong bile duct bridging tissue. The scores from each of the groups were then totaled and averaged to give a median macroscopic score for each group. Stenosis and/or dehiscence of the anastomosis and CBD dilatation were also recorded during necropsy.

Histopathology

Full-thickness sections of the CBD anastomosis were obtained at necropsy, fixed in 10% buffered formalin, embedded in paraffin, cut into 4-to-5 µm-thick sections and stained with hematoxylin and eosin. Sections were also stained with Masson's trichrome for the assessment of collagen deposition. A pathologist examined the tissue sections under light microscopy in a double-blinded fashion. Epithelization, cellular infiltration, collagen deposition and neovascularization were graded from 0-2 (0= absent, 1= mild to moderate, 2= marked) as modified from Greenhalgh et al. (14).

Statistical Analysis

The results are expressed as mean ± standard deviation (SD). Differences between the groups were analyzed by the Kruskal-Wallis test, followed by the Mann-Whitney U test. Probability values $p< 0.05$ were considered significant. The SPSS 17.0 (SPSS Ver. 17.0, Chicago IL, USA) program was used for analysis.

RESULTS

Surgery was successful in all of the cases. Cardiac puncture for obtaining blood samples did not cause any problem in animals. Animals were followed up daily for a month according to their general condition, and none of the animals experienced any problems during the study period. All animals reached the end point of the study in a healthy status.

Gross Findings at Necropsy

There was neither bile leakage nor stent obstruction in the study groups. Only four animals in Group I (control group) had proximal common bile duct dilatation although the lumen of the stents were open.

Intraabdominal Adhesion

The adhesion scores of the groups are shown in Table 1. Animals in the control group (Group I) showed mild to severe adhesion around the CBD stent; three animals had mild adhesion in which the liver was adherent to anastomotic region. Five animals had moderate adhesion in which the liver and duodenum were adherent, and two animals had severe adhesion in which the liver, duodenum and omentum were adherent to the anastomotic region. Mean adhesion score of the animals in Group I was 1.9 ± 0.7. Gross findings during necropsy following 1 month after the operations revealed that all intra-abdominal organs were normal in Group II animals. PRF application dramatically reduced the adhesions around the anastomosis region; seven of the ten animals in this group had no adhesion and three animals had mild adhesion around the CBD stent. The adhesion score of Group II was statistically different to Group I ($p< 0.001$). The animals in Group III (sham group) largely showed no adhesion or very limited adhesion around the CBD; four animals had no adhesion, four animals had mild adhesion in which the liver was adherent to the CBD, and only two animals in this group had moderate adhesion in which the liver and duodenum adherent to the CBD. The adhesion scores of the PRF group and the sham group were not statistically different ($p= 0.422$).

Bridging Bile Duct Tissue

Evaluation of the bridging tissue over the plastic stent revealed that only three of the ten animals in Group I developed fully covered tissue. Five animals had very thin bridging tissue around the plastic stent, and in two animals, the plastic stents were visible, which meant that there was very weak healing in these two animals. The bridging bile duct tissue scores of the groups are shown in Table 2.

Table 1. Adhesion scores of the groups (0-to-3)

Group	n	Mean ± SD	Median	Min-Max
I (Control)	10	1.9 ± 0.7	2	1-3
II (PRF)	10	0.3 ± 0.5*	0	0-1
III (Sham)	10	0.6 ± 0.7	0.5	0-2

*Group II was significantly statistically different when compared with Group I (< 0.001). There were no statistical differences between Group II and Group III (p= 0.422).

Table 2. Bridging bile duct tissue scores of the groups (0-to-3)

Group	n	Mean ± SD	Median	Min-Max
I (Control)	10	1.9 ± 0.5	2	1-2.5
II (PRF)	10	2.8 ± 0.3*	3	2-3
III (Sham)	10	N/A	N/A	N/A

*Group II was significantly statistically different when compared with Group I (p= 0.002).

Table 3. Histologic scores of the groups (0-to-8)

Group	n	Mean ± SD	Median	Min-Max
I (Control)	10	4.9 ± 0.8	5	4-6
II (PRF)	10	6.7 ± 0.8*	6.5	6-8
III (Sham)	10	4.3 ± 0.6	4	3-5

*Group II was significantly statistically different when compared with Group I (p= 0.002).

Most of the animals in Group II developed very thick and dense bridging tissue around the CBD stent; eight of the ten animals had complete and thick coverage of the stent, whereas the other two had complete but relatively thin coverage of the stent. The difference between the PRF and control groups for bridging tissue was statistically different (p= 0.002).

Histopathologic Evaluation

Histopathologic examination of the bridging tissue showed incomplete healing of the animals in the control group (Group I); the mucosa was a single layer of tall columnar epithelium and the pili and crypt structures were not fully developed (Figure 2a). In the lamina propria, congested vessels and mixed type inflammatory cells infiltrated with polymorphonuclear leukocytes were observed. Cellular infiltration and neovascularization were graded mild to moderate in this group of animals. Most of the control group animals also had weak granulation tissue and collagen deposition. Thin discrete collagen fibers are seen in Figure 2b with Masson's trichrome staining. Mean histologic score of the control group was 4.9 ± 0.8 (total of 8).

The animals in the PRF group (Group II); however, had almost complete healing one month after the operation. The PRF membranes were not visible and were completely dissolved from the serosal surface of the anastomoses in the PRF treatment group. The mucosa was lined by a single layer of tall columnar epithelium, and the epithelialization, pili and crypt structures were precisely developed. Dense mixed inflammatory cell infiltrated with polymorphonuclear leukocytes, congested and proliferated vessels were observed in the lamina propria (Figure 2c). Similarly, in the macroscopic observations, most of the animals showed very thick granulation tissue in their bridging tissue. Almost all animals in this group had marked epithelization, cellular infiltration, neovascularization and collagen deposition. Multiple thick collagen bundles can be seen in Figure 2d with Masson's trichrome staining. The histologic score of the PRF group was significantly higher than the control group (p= 0.002).

The sham group of animals had no CBD anastomosis, and therefore there was no healing process in this group. Histopathologic examination of this group showed normal histologic appearance of the CBD. The mean histologic score of the sham group of animals was 4.3 ± 0.6. The histopathologic scores of the groups are shown in Table 3.

DISCUSSION

PRF is a second-generation autologous platelet concentrate with simplified processing without biochemical blood handling. Use of bovine thrombin and anticoagulants is not required during the preparation. It has significant capacity to support cell migrations and healing processes, and therefore, it has been described as a completely usable healing concentrate by Dohan et al. (7). It is well known that platelets play a prominent role in wound healing (1). PRF is a rich source of platelets containing endogenous growth factors, cytokines and several other wound-healing stimulating factors (15-18). Platelets release cytokines and growth factors during clot formation at the wound site. Platelet activation in response to tissue damage results in the secretion of biologically active proteins from the α-granules. These include platelet-derived growth factor (PDGF), transforming growth factor β-1 (TGF β-1), interleukin (IL)-1, vascular endothelial growth factor (VEGF), platelet-derived angiogenesis factor (PDAF), epidermal growth factor (EGF), insulin-like growth factor (IGF), epithelial cell growth factor (ECGF), osteonectin, osteocalcin, fibrinogen, vitronectin, fibronectin, and thromboplastin (7). These secretory proteins simultaneously support angiogenesis, immunity, and epithelial cover during healing. Fibrin matrix of PRF also plays an important role during the healing process. Fibrin is the natural guide for angiogenesis, and it also stimulates the metabolism of epithelial cells and fibroblasts (5). Thus, with all these mechanisms, PRF accelerates healing, increases the development of microvascularization and also guides epithelial cell migration to the stent surface (19).

The improvement of healing by the placement of autologous PRF concentrate at the site of tissue injury is supported by previous studies. There are studies that provide evidence that the use of PRF has some beneficial effects in certain types of wounds and causes an increase in hard- and soft-tissue wound healing; For example, Visser et al. (20) have used PRF to enhance the healing process in the patellar tendons of dogs and found that PRF increases the amount of tissue reconstruction. Inchingolo et al. (21) have used PRF in sinus lift procedures and demonstrated a significant increase in peri-implant bone density and implant stability.

PRF has been mainly used for many years by dentists for oral and maxillofacial surgery and plastic surgeons for facial plastic procedures and skin autografts with promising results (8,22-24).

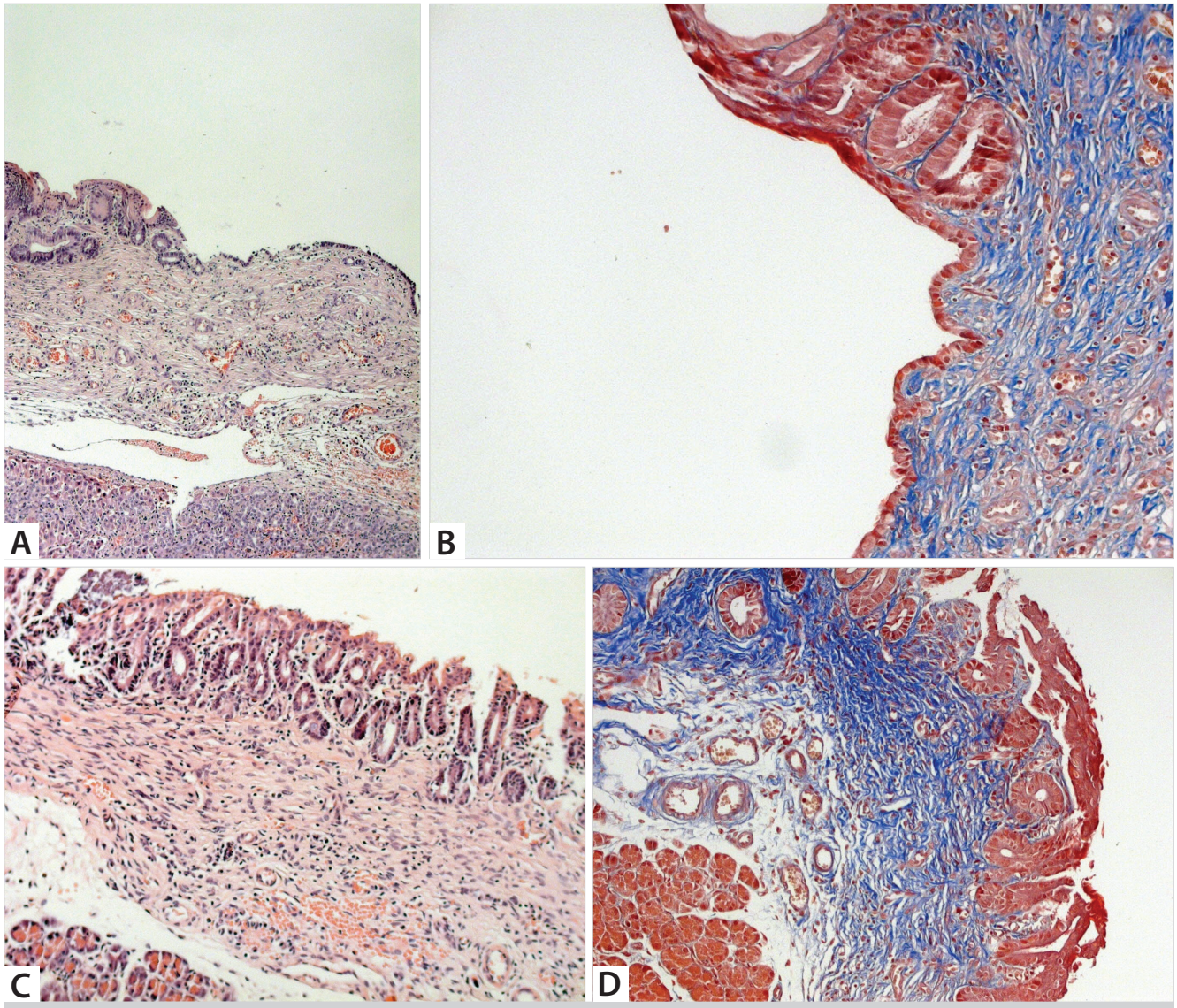

Figure 2. a. The junction of the common bile duct and the bridging tissue in the control group. A single layer of columnar epithelium is seen in the biliary mucosa, while pili and crypt development are not evident at the bridging tissue site (Hematox). **b.** Thin discrete collagen fibers of a control group animal (Masson's trichrome, X20). **c.** The bridging tissue histological view of the experimental (PRF) group. A single layer of biliary epithelium with fully developed pili and crypt formation is seen, while the lamina propia has dense mixed inflammatory infiltrate (Hematoxylin) **d.** Thick collagen bundles of a PRF group animal (Masson's trichrome, X20).

However, there is no clinical data about intra-abdominal usage of PRF in the literature. One of the reasons for that might be due to concerns about its fibrin content, which may cause adhesion when used intra abdominally. However, a recently published experimental study demonstrated that intra-abdominal usage of PRF is very safe and does not cause any adhesion in the abdominal cavity (25). Moreover, PRF reduces the adhesion and accelerates the intestinal anastomosis wound healing. This result supports our observation in this study as one of the main findings in our study was decreased adhesion around the CBD anastomosis site when PRF was applied. There was a significant difference between the PRF and control group adhesion scores in our study. Most of the animals in the PRF group had an almost complete lack of adhesion, whereas most of the control animals had severe adhesion. Manipulation of the CBD, suture materials, and silicon catheter cause adhesion around the anastomosis. However, PRF application efficiently prevents this effect, possibly because it is an autologous and degradable material.

One of the other main findings of the present study was the increased regenerative capacity of the biliary tract when PRF was applied. Macroscopic observations revealed that the application of PRF significantly increased bridging tissue thickening

over the plastic stent. There was complete and thick bridging tissue coverage around the anastomosis in most of the animals. This observation was supported by histopathological examinations: histologically, these bridging tissues had almost the same structure as the bile duct; dense collagen deposition and bile duct gland proliferation were observed in the anastomosis one month after operation. There were tall, uniform columnar cells in the epithelium with mucosal longitudinal folds. The sub-epithelial regions were also very similar to CBD and had dense, hypocellular connective tissue with few lymphocytes. It is well known that the biliary tissue can migrate along the surface of synthetic materials (26). Our findings indicate that PRF application increases tissue migration and proliferation of the cells. The mechanism of this effect might be mechanical rather than promoting wound healing. However, regardless of the mechanism, PRF has a beneficial effect on the bile duct healing process.

The main advantages of PRF over other platelet concentrates are that it is not necessary to add bovine thrombin or other anti-coagulants, thus it is completely safe, easy to use and requires standard preparation and handling by clinicians. The only disadvantage of PRF might be the amount of material required. It is not suitable for large surfaces, such as the abdominal cavity, since only a small amount of PRF could be obtained from the limited volume blood sample. However, CBD anastomosis or any type of biliary-enteric anastomosis sites are small areas and PRF concentrates are sufficient to cover these areas.

PRF preparation is very simple and does not require anticoagulant or bovine thrombin. Around 5 ml of whole venous blood collects in each of the two sterile vacutainer tubes of 6 ml capacity without anticoagulant. The tubes should then be placed in a centrifugal machine as quickly as possible. Blood collection and transfer to the centrifuge must be completed within minutes, because without the anticoagulant, the blood sample will begin to coagulate almost immediately on contact with the glass tube. Quick handling is the only way to obtain a clinically usable PRF clot. The tubes centrifugate at 3.000 rpm for 10 minutes, after which it settles into the following layers: the red lower fraction contains red blood cells, the upper straw-colored cellular plasma and the middle fraction contains the fibrin clot. The upper and lower layers are removed and the middle fraction can be collected, which is the PRF. The PRF membrane is then cleaned using physiological saline to remove blood clots and after that, it is ready for use. In this technique, fibrinogen combines with the circulating thrombin due to centrifugation to form fibrin. Thus, the use of anticoagulant and the addition of bovine thrombin to promote conversion of fibrinogen to fibrin is avoided. This preparation could be performed in the operating theatre during the operations and the PRF membrane could be applied immediately after preparation onto the CBD anastomosis sites.

One of the main problems in hepatobiliary surgery and liver transplantation is biliary complications (27-30). Biliary leaks and strictures are still very common and cause major morbidity and mortality after these operations. Refined surgical methods have decreased the bile duct anastomosis complications; however, they are not eradicated. Since the bile duct is a vulnerable organ, it is very sensitive to ischemic injury and also has low regenerative capacity. Therefore, regardless of the surgical technique, the possibility of bile duct anastomosis problems will always exist for surgeons. Accelerating healing and increasing the regenerative capacity of the bile duct might be solutions to prevent these complications. This study evaluated the effect of PRF on the bile duct healing process with some macroscopic and microscopic parameters. According to our findings, it could be said that PRF has some beneficial effects on the bile duct healing process. There is no data available in the literature regarding PRF application on bile duct anastomosis healing process. Therefore, the results of this original study may help surgeons to prevent bile duct complications. However, the mechanism of these effects and biochemical changes such as liver function tests or cytokines levels have not been studied. These represent the main limitations of the present study. Further studies are necessary to answer these questions.

CONCLUSION

PRF is a safe, autologous and degradable material which contains high amounts of platelets and fibrin. Preparation is very simple and only requires a 10 ml venous blood sample from the patient as well as a centrifuge machine. Preparation of the PRF only takes a few minutes and could easily be done in the theatre during the operation. The present study results indicate that PRF application reduced the adhesion around the anastomosis and increased the healing. Therefore, it could be said that PRF is an alternative solution to prevent complications following common bile duct anastomosis in liver transplantation patients.

Ethics Committee Approval: Ethic committee approval was received for this study from Başkent University Ethical Committee for Experimental Research on Animals (DA 16/08; 15.02.2016/16-09).

Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Trombositten zengin fibrin sıçanlarda safra yolu anastomoz yara iyileşmesini hızlandırabilir

Necdet Özçay[1], Ali Özant[1], Kalbim Arslan[1], Hanife Özkayalar[2], Hasan Besim[1]

[1] Yakın Doğu Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Lefkoşa, Kıbrıs
[2] Yakın Doğu Üniversitesi Tıp Fakültesi, Tıbbi Patoloji Anabilim Dalı, Lefkoşa, Kıbrıs

ÖZET

Giriş ve Amaç: Trombositten zengin fibrin (PRF) konsantresinin sıçanlarda ana safra yolu anastomoz yara iyileşmesi üzerine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışma için otuz adet Spraque-Dawley cinsi erkek sıçan kullanıldı. Çalışma grupları şu şekilde dizayn edildi: Grup I, Kontrol grup (n= 10): Plastik stent üzerinden ana safra yolu (ASY)' na anastomoz. Grup II, PRF Grubu (n= 10): Plastik stent üzerinde ASY'ye anastomoz ve PRF ile anastomoz bölgesinin kaplanması. Grup III, Sham grubu (n= 10): ASY orta kısmının preparasyonu, anastomoz yapılmadı. İşlem sonrası hayvanlar 1 ay takip edildi ve çalışma sonlandırıldı. Çalışma parametreleri; anastomoz bölgesindeki yapışıklıklar, stent üzerindeki köprü dokunun kalınlığı ve bu dokunun histopatolojik incelenmesi ile yara iyileşmesinin durumu değerlendirildi.

Bulgular: Kontrol grubundaki hayvanların çoğunluğunda anastomoz bölgesinde yoğun yapışıklık saptandı. Ayrıca bu hayvanların stent üzerindeki köprü dokuları ince görünümlü idi ve histolojik olarak da bu bölgede tam yara iyileşmesi olmadığı görüldü. Buna karşın PRF uygulanan hayvanların çoğunluğunda anastomoz bölgesinde hiç yapışıklık yoktu, stent üzeri oldukça kalın bir köprü doku ile kaplıydı ve bu bölgenin histolojik incelenmesinde tam yara iyileşmesi olduğu görüldü.

Sonuç: Bu çalışmamızda PRF uygulamasının ana safra yolu anastomozlarında yapışıklık gibi lokal komplikasyonları önlediği ve aynı zamanda yara iyileşmesini de artırdığı saptandı. Bu nedenle PRF uygulaması, ana safra yolu cerrahi işlemleri gerektiren karaciğer nakli veya diğer bu bölge ameliyatlarından sonra görülen komplikasyonların önlenmesi amacıyla kullanılabilir.

Anahtar Kelimeler: Trombositten zengin fibrin, karaciğer transplantasyonu, yara iyileşmesi, safra yolu yaralanması

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ORIGINAL ARTICLE
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Comparison of the effectiveness of two treatment modalities for chronic anal fissure: Botox versus sphincterotomy

Coşkun Çakır[1], Ufuk Oğuz İdiz[1], İbrahim Aydın[2], Deniz Fırat[3], Abdulhakim İbrahim Ulusoy[4], Pınar Yazıcı[5]

[1] Clinic of General Surgery, Istanbul Training and Research Hospital, Istanbul, Turkey
[2] Clinic of General Surgery, Avicenna Hospital, Istanbul, Turkey
[3] Clinic of General Surgery, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey
[4] Clinic of General Surgery, Okmeydani Training and Research Hospital, Istanbul, Turkey
[5] Clinic of General Surgery, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: Anal fissure is a common health problem that affects the quality of life of young patients. The aim of our study was to benchmark results of lateral internal sphincterotomy (LIS) and botulinum toxin injection in the treatment of chronic anal fissure.

Material and Methods: This multi-center, retrospective study used data from 135 chronic anal fissure patients. Patients' demographic features, clinical findings, fissure characteristics, post-defecation pain score, rectal bleeding or pruritus, and treatment satisfaction scores were recorded. Patients' data were collected from the hospital records and patients with all of this data available were called and invited to the hospital for examination.

Results: Seventy-four LIS and 61 botulinum toxin applied patients were included. Symptom duration, hospitalization period, and duration of remission of complaints after the treatment were significantly higher in the LIS group ($p< 0.001$). However, pruritus in anus and relapses were found to be higher in the botulinum toxin group ($p= 0.04$ and $p= 0.043$, respectively). Abscess and fistula were observed in one patient's perianal region in the LIS group, and an abscess was observed in one patient in the botulinum toxin group. There was no significant difference in treatment satisfaction rates and postoperative complications.

Conclusion: Botulinum toxin yields satisfying results that are comparable to LIS. Patient selection may help mitigate this disease and allow it to be considered a good alternative option to surgery.

Keywords: Chronic anal fissure, botulinum toxin, lateral internal sphincterotomy, incontinence

INTRODUCTION

Anal fissure is a common and major problem that affects the quality of life of the patients. Generally, pain and bleeding, both during and after defecation, are among the most frequent symptoms.

In etiopathogenesis, there are usually sphincter spasms and mucosal ischemia based on the mucosal defect that occur following local trauma of the squamous lining in the anal channel (1,2). Although they are usually located in the posterior midline, their atypical localization should bring to mind inflammatory bowel disease, tuberculosis, trauma, and other malignancies (3).

In the treatment of chronic anal fissure, many medical and surgical treatment modalities have been identified. Although surgical treatment modalities are the golden standard, botulinum toxin injection is considered an effective treatment modality (4,5). Among the surgical treatment modalities, Lateral Internal Sphincterotomy (LIS) has a success rate of up to 96% and a recurrence rate of 2.3-3% in the treatment of chronic fissures (6,7). In spite of these high success rates, it has complications such as bleeding, pain, and incontinence (5). After LIS, fecal and/or intestinal gas incontinence rates as high as 10%-30% have been reported (8,9).

Thus, alternative treatment methods to surgical treatment are being developed to protect patients from the adverse effects of LIS. For example, topical nitroglycerin ointment, injection of botulinum toxin and oral or topical calcium chan-

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Corresponding Author
Ufuk Oğuz İdiz
E-mail: oguzidiz@yahoo.com

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nel blockers reduce the sphincter pressure temporarily and reversibly until the fissure recovers (10,11). Botulinum A toxin has been used since the late 20th century in the treatment of anal fissure. It shows its effect by blocking acetylcholine neuromuscular transmitter activity, ensuring that a temporary chemical sphincterotomy is obtained (12,13).

In the literature, there are studies comparing LIS and botulinum toxin injection, but these studies' limited numbers of patients draw attention (5). In this study, regarding the treatment of chronic anal fissure, patients to whom LIS and botulinum toxin injection had been applied were compared, and their satisfaction states were evaluated.

MATERIAL and METHODS

This retrospectively designed study received approval from the Local Human Ethics Committee (March 2016 with the no: 631). One hundred thirty-five patients to whom lateral internal sphincterotomy or botulinum toxin injection was applied to treat chronic anal fissure at five different hospitals between 01.01.2014 and 01.06.2015 were included in this study after obtaining informed consents of patients. The inclusion criteria for the study were as follows: being between the ages of 18 to 80, having received LIS or BTI to treat chronic anal fissure, and having at least 12 months of follow-up. The exclusion criteria for the study were as follows: having a complicated anal fissure (stenosis, abscess, fistula or hemorrhoid) having an acute anal fissure, having been treated by another treatment modality except for LIS or BTI, having immune deficiency, being infected sexually, having an inflammatory bowel disease, having tuberculosis, having a diagnosis of leukemia, having large bowel malignancy, or being pregnant. The progression of complications in the postoperative period included postspinal headache, perianal abscess and fistula, and temporary or permanent intestinal gas or fecal incontinence. Recurrence was evaluated as a separate criterion. LIS treatment was applied if recurrence was observed in BTI-applied patients.

According to the treatment modality, the patients were separated into two groups: the LIS group and the BTI group.

LIS

The LIS procedure was carried out in a jackknife position for patients in whom spinal anesthesia was not contraindicated and in the lithotomy position for patients in whom spinal anesthesia was contraindicated (those with improper posture or cardiac problems). Lateral internal sphincterotomy was performed with a 10 mm incision at the level of the dentate line and at the 3 o'clock level of the anal channel.

Botox Injection

The BTI procedure was carried out by a 25 IU botulinum toxin injection to the internal anal sphincter at 3 o'clock and 9 o'clock levels (50 IU in total) while the patients were in a semi-jackknife position.

All patients were discharged with a medication regimen of 500 mg cefuroxime axetil (Enfexia, Bilim Ilac, Istanbul, Turkey) twice daily for 10 days. Additionally, postoperative stool softener and Sitz baths were advised for all patients for three weeks to avoid constipation and reduce infection, pain, and bleeding.

Patient age, sex, locations of the anal fissures, pre-treatment durations of the patients' complaints, whether any treatment had previously been applied due to anal fissure, treatment modality applied (LIS or BTI), treatment dates, hospitalization periods, and the days of the treatment on which the complaint was completely terminated, were determined from the patients' hospitalization and outpatient clinic application files. Patients with all of this information available were called and invited to the hospital for control purposes. Their current symptoms were noted, and an anorectal examination was administered. Their current post-defecation pain was scored according to a visual analogue scale (VAS) ranging from 0 to 10 (0: no pain, 10: unable to bear pain), on whether they had bleeding, whether they had pruritus in anus, and the Five-Point Horizontal Scale (FPHS) to assess their satisfaction level for the applied treatment (Table 1).

Statistical Analysis

SPSS 15.0 (Armonk, NY, USA) for Windows program was used for statistical analysis. Descriptive statistics were given as number and percentage for categorical variables and as average, standard deviation, and median for numeric variables. For comparisons between two independent groups, the Mann-Whitney U test was applied since numeric variables did not provide a normal distribution. Categorical values were tested via the Chi-Square test and Fisher exact test in the groups. Statistical significance level was set as $p< 0.05$.

RESULTS

Seventy-four LIS (mean age 37.1 years, F/M: 67/6) and 61 BTI (mean age: 39.5 years, F/M: 29/32) patients were included into the study (Figure 1). In both groups, there was no statistically

Table 1. Five-point horizontal scale (FPHS)

Points	Definition
1	Very Unsatisfied
2	Somewhat Unsatisfied
3	Neither Satisfied nor Unsatisfied
4	Somewhat Satisfied
5	Very Satisfied

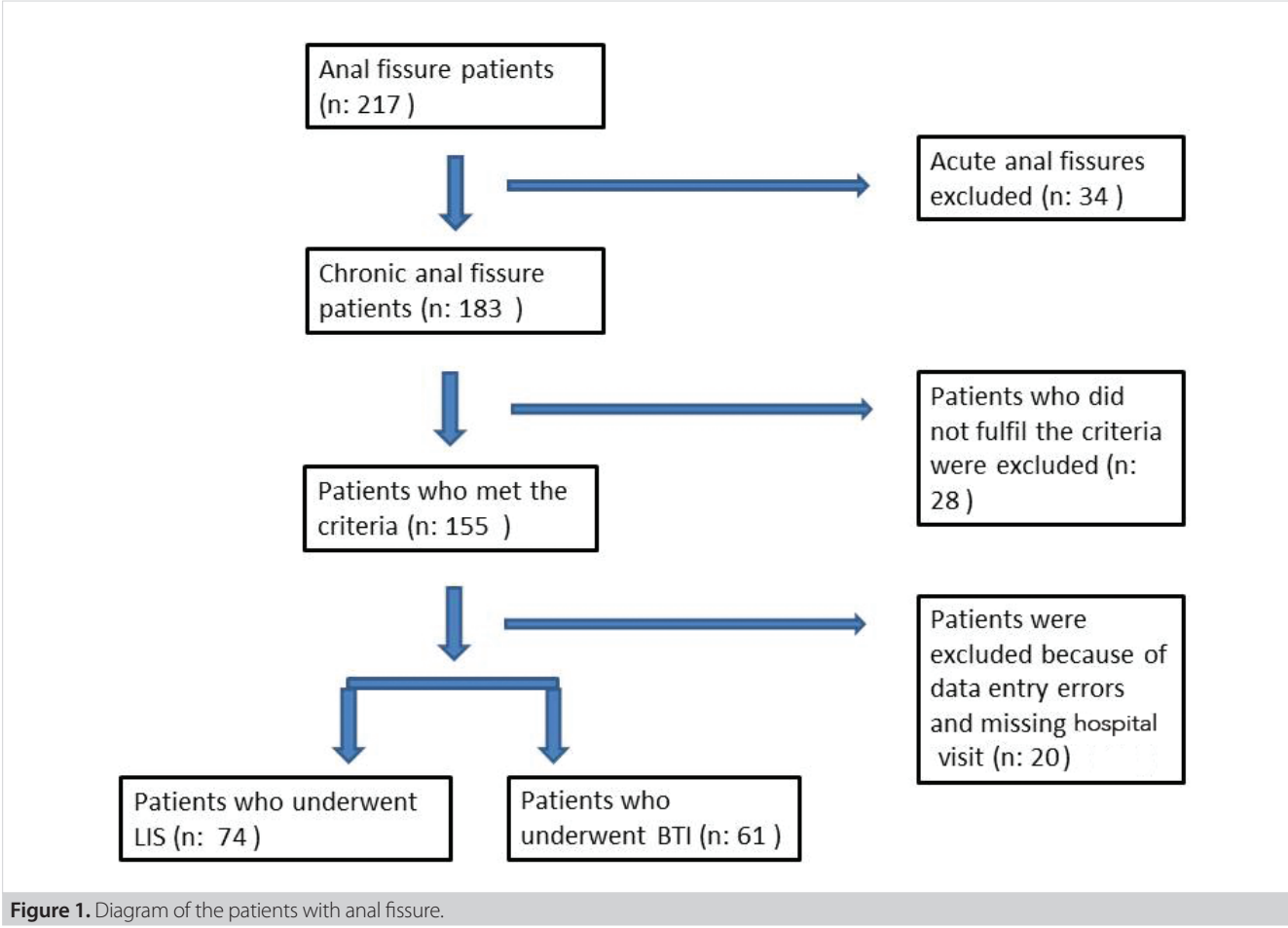

Figure 1. Diagram of the patients with anal fissure.

significant difference in age (p= 0.356). However, the male ratio of the patients to whom Botulinum Toxin Injection was applied was found to be statistically significantly higher than the patients to whom LIS was applied (p< 0.001).

Symptom duration, hospitalization period, and duration of remission of the complaints after treatment of the LIS group were statistically and significantly higher than those of the BTI group (p< 0.001). Abscess and fistula development in 1 patient's perianal region were observed, as was postspinal headache in 2 patients to whom LIS was applied, and an abscess was observed in 1 patient from the BTI group.

No statistically significant differences were determined between the groups at VAS pain score or FPHS treatment satisfaction rates during defecation (p= 0.579 and p= 0.861, respectively) (Table 2).

When symptom and complication rates were examined in control visits, pruritus in anus was found to be statistically higher among BTI-applied patients (p= 0.04).

In the long-term follow-ups in the LIS group, permanent intestinal gas and fecal incontinence in 1 patient, temporary intestinal gas and fecal incontinence in 1 patient (recovered at the fifth month), and temporary intestinal gas incontinence in 1 patient were observed. In the BTI group, temporary intestinal gas incontinence was observed in only 1 patient. When total complications were observed, no statistically significant difference was found between the groups (p= 0.290) (Table 2). When recurrence rates of the groups were evaluated, the number of recurrences was statistically higher in the BTI-applied patients than the LIS-applied patients (p= 0.043).

BTI patients were separated into two groups according to recurrence. There were no statistically significant differences between the groups in age and sex (p= 0.957 and p= 0.450, respectively). However, the patients who had a longer pre-treatment symptom duration had a significantly higher recurrence rate, and it was observed that all of the patients with a growing relapse had fissure with posterior localization (p< 0.001 and p: 0.016, respectively). Additionally, in patients with a growing relapse, the VAS score was higher, the FPHS rates were lower, and the patients had more rectal bleeding and pruritus among their anus complaints (p= 0.001) (Table 3).

Table 2. Comparison of Lateral internal sphincterotomy (LIS) and Botulinum toxin injection (BTI)

	BTI (n: 61)	LIS (n: 74)	P
Age (years), (mean ± SD)	39.5 ± 11.9	37.1 ± 11.4	0.356
Sex Female, n (%) Male, n (%)	 29 (47.5) 32 (52.5)	 67 (91.8) 6 (8.2)	< 0.001
Location of fissure Anterior, n (%) Posterior, n (%)	 26 (42.6) 35 (57.4)	 28 (38.4) 45 (61.6)	0.616
Duration of symptoms (months) (mean ± SD)	21.6 ± 12.5	13.0 ± 4.0	< 0.001
Anesthesia (%) Spinal General Local	 6 (9.8) 0 (0.0) 55 (90.2)	 63 (86.3) 8 (11.0) 2 (2.7)	< 0.001
Length of hospital stay, (hours) (mean ± SD)	2.8 ± 3.8	24.8 ± 5.0	< 0.001
Recovery time of complaints (days) (mean ± SD)	1.9 ± 0.6	7.2 ± 3.1	< 0.001
Pain score during defecation (VAS)*(mean ± SD)	0.46 ± 0.81	0.37 ± 0.71	0.579
Patient satisfaction (FPHS)** (mean ± SD)	4.4 ± 1.0	4.5 ± 0.9	0.861
Rectal bleeding during follow-up period n (%)	7 (11.5)	2 (2.7)	0.079
Pruritus ani during follow-up period n (%)	10 (16.4)	4 (5.5)	0.040
Temporary flatus incontinence n (%)	1 (1.6)	2 (2.7)	0.625
Temporary fecal incontinence n (%)	0 (0.0)	1 (1.4)	1.000
Persistent flatus incontinence n (%)	0 (0.0)	1 (1.4)	1.000
Persistent fecal incontinence n (%)	0 (0.0)	1 (1.4)	1.000
Postoperative perianal infection n (%)	1 (1.6)	1 (1.4)	1.000
Postoperative complication n (%)	2 (3.3)	6 (8.2)	0.290
Recurrence rate n (%)	8 (13.1)	2 (2.7)	0.043

*Visual analog score (VAS) was applied.
** Five-point horizontal scale (FPHS) was applied).

DISCUSSION

The most frequently applied treatment modality for chronic anal fissure is LIS, which is acknowledged as the golden standard (14). Complications such as fecal incontinence, abscess, and intestinal gas incontinence observed after LIS have provided a basis for applying less invasive treatment modalities. Topical nitroglycerin ointment, injection of botulinum toxin and oral or topical calcium channel blockers are some non-surgical treatment modalities (10,11).

There are many studies comparing defined treatment modalities for anal fissure. In a randomized study in which LIS and topical nitroglycerin ointment were compared in 54 patients, at the end of a 10-week treatment and follow-up period, a 100% recovery in LIS patients and an 89% recovery in topical nitroglycerin ointment patients was observed. However, when the complications were evaluated, the incidence rate of minor fecal incontinence drew attention as being 44% in patients to whom LIS was applied and 0% in patients to whom topical nitroglycerin ointment was applied. After a 2-year follow-up, residual fecal incontinence was observed in 15% of the LIS-applied patients (15). Also, in the literature, the rate of incidence of fecal incontinence is between 3% and 16% after LIS treatment (4).

In studies carried out on botulinum toxin injection, which is a less invasive treatment modality than LIS but has a higher rate of recurrence compared to surgical treatment options, there is a decrease in complication rates, especially in that of incontinence (16). In a randomized study, botulinum toxin (n: 15) and saline (n: 15) injection to the internal anal sphincter were compared in 30 patients with chronic anal fissure. In the 2nd month, compared with the controls after treatment, a statistically significant recovery was observed in the botulinum toxin-applied group. In this patient group, re-injection was required for some patients, and no relapse was observed in any of them over an approximately 16-month follow-up (17). In a randomized study in which botulinum toxin injection and LIS were compared, Botox was applied to 61 patients and LIS was applied to 50 pa-

Table 3. Demographics and clinical features of the patients who underwent Botulinum toxin injection in terms of recurrence

	Recurrence		
	No	**Yes**	**p**
Age (years), (mean ± SD)	39.3 ± 11.4	40.6 ± 15.8	0.957
Sex Female, n (%) Male, n (%)	 24 (45.3) 29 (54.7)	 5 (62.5) 3 (37.5)	0.460
Location of fissure Anterior, n (%) Posterior, n (%)	 26 (49.1) 27 (50.9)	 0 (0.0) 8 (100)	0.016
Duration of symptoms (months) (mean ± SD)		18.5 ± 4.5	< 0.001
Recovery time after treatment (day) (mean ± SD)	1.8 ± 0.6	2.1 ± 0.4	0.133
Pain score during defecation* (VAS) (mean ± SD)	0.21 ± 0.45	2.13 ± 0.64	< 0.001
Patient satisfaction score (FPHS) **(mean ± SD)	4.8 ± 0.5	2.3 ± 0.7	< 0.001
Rectal bleeding during follow-up period n (%)	0 (0.0)	7 (87.5)	< 0.001
Pruritus ani during follow-up period n (%)	2 (3.8)	8 (100)	< 0.001
Temporary flatus incontinence n (%)	1 (1.9)	0 (0.0)	1.000
Postoperative perianal infection n (%)	1 (1.9)	0 (0.0)	1.000
Total complication rate n (%)	2 (3.8)	0 (0.0)	1.000

*Visual analog score (VAS) was applied.
** Five-point horizontal scale (FPHS) was applied).

tients. In the Botox-applied group, recovery rates of 73.8% were obtained in the 2nd month, and after the second injection, this rate reached 86.9%. A success rate of 94% was achieved in the LIS-applied patients, but the success rate in the Botox group remained at 75%. When the complication rates were observed, temporary anal incontinence was determined to be present in 16% of the LIS-applied patients, whereas no anal incontinence was reported for the Botox-applied patients. Additionally, for the patients, the duration until starting to perform daily activities was significantly lower in Botox-applied patients than in the LIS-applied ones (18). In another study evaluating 100 patients who received Botox treatment due to chronic anal fissure, after the 6-month follow-ups, total recovery was observed in 79% of the patients, and recurrence was observed in 8%. Additionally, temporary fecal incontinence was observed in 7% of the patients (19).

In our study, total complication rates were higher in the LIS group, but there were no significant differences. Additionally, temporary intestinal gas or fecal incontinence rates were higher in the LIS group, but there were no significant differences. Permanent incontinence was observed in only 1 patient who received LIS treatment. There was no serious incontinence problem in the BTI group, except for only 1 of the patients who had temporary intestinal gas incontinence. In the BTI group of our study, after a 12-month follow-up, complete recovery rate was 86.9%, whereas recurrence was determined in only 8 patients. In studies that include longer follow-up periods, recurrence rates have been determined to be significantly higher (41%) (20), but in our study, the follow-up period was approximately 14.2 months, and long-term follow-ups will be evaluated again. In the literature, etiological factors for high recurrence rates have been reported as follows: the time interval between symptom onset and surgery, the need for re-injection or high-dose botulinum toxin, and a minimum decrease in anal sphincter pressure after treatment (20). In our study, the recurrences observed in the Botox-applied patients were specifically related, with fissure being with posterior localization and a longer interval between symptom onset and surgery.

In conclusion, among many treatment modalities that have been defined for anal fissure treatment, LIS, which is acknowledged as the gold standard, is both more invasive and has higher complication rates than other modalities. Botulinum Toxin Injection, which is one of the less invasive modalities, has higher recurrent rates but can be accepted as an alternative treatment modality for select patients due to its low complication rates. Observing recurrence more frequently in patients with a long-term disease and in patients with posterior localization shows that patient selection is an important issue. BTI may be applied as a first-step treatment modality to patients who have a low risk of recurrence.

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ORİJİNAL ÇALIŞMA-ÖZET
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Kronik anal fissür tedavisinde iki modalitenin karşılaştırılması: Botoks ve sfinkterotomi

Coşkun Çakır[1], Ufuk Oğuz İdiz[1], İbrahim Aydın[2], Deniz Fırat[3], Abdulhakim İbrahim Ulusoy[4], Pınar Yazıcı[5]

[1] İstanbul Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye
[2] Avicenna Hastanesi, Genel Cerrahi Bölümü, İstanbul, Türkiye
[3] Bursa Yuksek Ihtisas Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Bursa, Turkey
[4] Okmeydanı Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye
[5] Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Anal fissür, genç hastaların yaşam kalitesini etkileyen yaygın bir sağlık problemidir. Çalışmamızın amacı, kronik anal fissür tedavisinde lateral internal sfinkterotomi (LİS) ve botulinum toksin enjeksiyonu sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Bu çok merkezli, retrospektif çalışma 135 kronik anal fissür hastasının verilerinin kullanılması ile hazırlanmıştır. Hastaların demografik özellikleri, klinik bulguları, fissür özellikleri, dışkılama sonrası ağrı skoru, rektal kanama veya pruritus ve tedavi memnuniyet skorları not edildi. Hasta bilgileri hastane bilgisayar sistemlerinin taranması ile toplandı ve araştırılan kayıtları taşıyan hastalar telefon ile aranılarak muayene için hastaneye davet edildi.

Bulgular: Yetmiş dört LİS ve 61 Botulinum Toksini uygulanmış hasta çalışmaya dahil edilmiştir. Semptomların süresi, hastanede kalış süresi ve tedavi sonrası remisyon süresi LiS grubunda anlamlı olarak yüksek bulundu ($p< 0.001$). Ancak, anal kaşıntı ve rekürrens botulinum toksin grubunda daha yüksek olduğu bulundu (sırasıyla, $p= 0.04$ ve $p= 0.043$). Bir hastanın perianal bölgesinde LİS uygulanan gruptaki bir hastada perianal apse ve fistül, botulinum toksin enjeksiyonu uygulanan grupta bir hastada perianal apse gözlendi. Tedavi memnuniyet oranları ve postoperatif komplikasyonlar arasında anlamlı bir fark yoktu.

Sonuç: Botulinum Toxininin, LiS ile karşılaştırıldığında tatmin edici sonuçlara sahip olduğu görülmektedir. Hasta seçimi botulinum toksininin tedavisinde cerrahiye iyi bir alternatif olarak görülmesine yardımcı olacaktır.

Anahtar Kelimeler: Kronik anal fissür, botilinum toksin, lateral internal sfinkterotomi, inkontinans

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ORIGINAL ARTICLE
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National consensus on oncoplastic breast conserving surgery in Turkey: position paper for the standardization of surgical practice

Mustafa Emiroğlu[1], Cem Karaali[1], Mehmet B. Öztop[2], Bahadır M. Güllüoğlu[3]

[1] Clinic of General Surgery, Izmir Tepecik Education and Research Hospital, İzmir, Turkey
[2] Izmir Provincial Health Directorate, Health Directorate, İzmir, Turkey
[3] Department of General Surgery, Marmara University School of Medicine, Istanbul , Turkey

ABSTRACT

Objective: The algorithms that define most of the application of oncoplastic breast conserving surgery (OBCS) in breast cancer patients are not clearly defined. Therefore, a consensus survey was conducted between the leading and experienced breast surgeons and oncoplastic breast surgeons in Turkey on the controversial areas of oncoplastic breast surgery.

Material and Methods: This consensus survey was carried out on-line through the Consensus software program (www.consensuss.com) under the roof of Turkish Federation of National Societies for Breast Diseases (TFNSBD). After finalizing each proposition, web-based remote access consensus process was performed on the Likert scale using Delphi method with the Consensus (www.consensuss.com) software program. Through the related software, an invitation was sent to 111 people who had at least 5 years of general surgery expertise in Turkey, and who devoted more than 50% of their daily clinical practice to the treatment and surgery of breast diseases.

Results: Sixty-two out of 111 people accepted to participate in the panel and made an on-line evaluation. According to the consensus results; Lumpectomy area should be done by placing the clips on at least four walls of the cavity, if the margin of the tumor is clear in central tumors, the distance between the tumor and the nipple is not significantly important, oncoplastic techniques may be used in patients with locally advanced breast cancer after neoadjuvant chemotherapy, in patients who have macromastia with ductal carcinoma in situ or breast cancer, OBCS techniques can be performed, and OBCS should be evaluated in terms of breast aesthetics. After OBCS, re-excision can be performed at a re-do setting in cases with involved surgical margins.

Conclusion: Our consensus results may provide a basis for the development of some standards in OBCS.

Keywords: Oncoplastic breast conserving surgery, standardization, consensus

INTRODUCTION

Oncoplastic breast conserving surgery (OBCS) is one of the significant procedural innovations in the surgical treatment of breast cancer. This recent change in surgical practice is the result of a patient-centered trend of treatment (1).

Clinical guidelines are written documents to which physicians and other care providers frequently refer for better health care. Guidelines are required to be evidence-based (2). However, when considering patient care pathway in a certain health problem or practice such as surgical treatment of breast cancer, it is unfortunate that not every time the evidence is straightforward. For those instances, consensus procedure is recommended in which expert opinion is collected to guide the care. Consensus is advised to be sought when there is no satisfactory evidence for the aforementioned issue. This happens when there is no reported data on the issue or there are more than one but contradictory to each other or when the collected data is not applicable for the respective population (3).

So far, no regional or global comprehensive OBCS practice guideline or consensus has been released. Therefore, today, surgeons empirically shape their practice in line with their own knowledge and experience (1,4,5). Standards of practice related to OBCS are not explicitly defined. Neither national nor international consensus has been reached on all aspects of surgical practice on this field yet.

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Corresponding Author
Cem Karaali
E-mail: cemkaraali@gmail.com

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Therefore, currently there is a pressing need for a contemporary OBCS guideline. Here in this position paper, we report the results of a consensus procedure on OBCS by collecting opinions from eminent Turkish breast surgeons who have considerable amount of experience on the field. All recommendation statements for voting were formulized from those issues with no satisfactory evidence, hence regarded as gap-of-knowledge.

MATERIAL and METHODS

Consensus procedure was structured according to the Delphi method (6). We used a commercially available consensus software program (www.consensuss.com; Pleksus, Istanbul, Turkey) to run the whole procedure on-line.

Turkish Federation of the National Societies for Breast Diseases (TFNSBD) fully endorsed and sponsored the consensus process.

As the initial step, a consensus development committee (CDC) was constituted. Twelve breast surgeons who were among the executive members of TFNSBD at the time were assigned as CDC members. CDC initially drafted 14 statements as clinical recommendations in areas where they regarded there is gap of knowledge. After rigorous review of these statements, they were lowered to 10.

All regulatory preferences of the consensus procedure were decided a priori and necessary instructions were given accordingly to the user interface of the programme.

Candidate panelists were chosen from Turkish Society of Surgery's Members Registry according to the criteria as described below:

a. Surgical oncologists who have experience on breast surgery for at least 10 years.

b. Having experience on OBCS (those currently performing OBCS or ad previous certification on OBCS).

c. Currently working or recently worked at a surgical oncology unit in tertiary hospitals for minimum 5 years.

d. Currently practicing breast surgery at minimum 50% of his/her clinical time.

E-mail invitation was sent to those surgeons who fulfilled the above criteria in which the aim, scope and the structure of the procedure was explained. Those who accepted to attend the on-line sessions were assigned as "Panelist".

Structurally, consensus voting was performed by using a 9-item Likert scale where 1, 2, 3 represented "I agree", 7, 8, 9 represented "I disagree" and 4, 5, 6 represented "abstained" for the asked recommendation.

Criteria for decisions on recommendations were as follow:

"Quorum": Threshold of overall voting (attendance) rate for reaching a decision on any recommendation was determined to be 80%, regardless of the voting result.

"Consensus Reached-Endorsed as a Recommendation": If 70% or more panelists voted for "I agree", that recommendation was regarded as "endorsed" by the consensus panel.

"Consensus Reached-Rejected as a Recommendation": In case of having less than 70% "I agree" voting, if 25% or more panelists voted for "I disagree", that recommendation was regarded as "rejected" by the consensus panel. If votes for both "I agree" and "I disagree" exceeded the thresholds of 70% and 25%, respectively, the decision was regarded according to the one whichever has the majority.

"Consensus Not Reached-Inconclusive": In those recommendations where less than 80% of the panelists sent their opinion after overall 2 rounds, the decision was regarded as "consensus not reached-inconclusive". Also, if both votes for "I agree" and "I disagree" did not exceed the thresholds of 70% and 25%, respectively, the decision was again regarded as "consensus not reached-inconclusive".

In each round, the set of recommendations was sent by e-mail to all panelists who accepted to attend the on-line consensus. In each round, one week duration was given to the panelists to complete their voting. In those recommendations where a decision was not reached according to the criteria, next round of voting was done. Total rounds of voting were determined to be 2. If any of the a priori determined thresholds was reached in any round, the consensus process was regarded to be completed for that particular recommendation. On the other hand, if any decision was not reached at the end of second round, result was regarded as "consensus not reached-inconclusive" for that recommendation. No statistical analysis was done. Only descriptive voting results were given as raw data.

RESULTS

The invitation for on-line consensus procedure was sent to 111 surgeons who fulfilled the selection criteria. Sixty-two (56%) agreed to participate in the consensus voting (Table 1). Consensus panel was commenced on 4 July 2016 100 and finished on 12 August 2016.

The panelists reached a consensus on 7 recommendations after the first round, 2 after the second. Only for one recommendation, the panelists did not reach a consensus due to under threshold voting counts for both "I agree" and "I disagree" options despite having the quorum until the final second round.

Voting Results

Recommendation no 1: "For breast boost irradiation following OBCS, marking the lumpectomy cavity should be done by placing clips on at least four walls of the cavity."

First round: 62 (100%) panelists attended the voting and 37 (60%) of them favored the recommendation, whereas 10 (16%) disagreed and 15 (24%) remained abstain.

Table 1. The panelists participating in the panel are listed below in 346 alphabetical order

Abut Kebudi	Fatih Altıntoprak	Mustafa Emiroğlu
Ali Uğur Emre	Fatih Aydoğan	Necati Özen
Ali Uzunköy	Göktürk Maralcan	N. Zafer Cantürk
Alper Akcan	Güldeniz Karadeniz	Ömer Bender
Arzu Akan	Günay Gürleyik	Ömer Cengiz
Ayfer Kamalı Polat	Gürsel Soybir	Ömer Harmancıoğlu
Baha Zengel	H. Özgür Aytaç	Öner Menteş
B. Bülent Güngör	Hakan Mersin	Orhan Veli Özkan
Bahadır M. Güllüoğlu	Hande Köksal	Orhan Yalçın
Bekir Kuru	Hasan Karanlık	S. Turay Yazıcı
Belma Koçer	Hedef Özgün	Sadullah Girgin
Betül Bozkurt	Jülide Sağıroğlu	Semih Görgülü
Beyza Özçınar	Kemal Atahan	Semra Günay
Bülent Alıç	Levhi Akın	Serap Erel
Can Başaran	Lütfi Doğan	Serdar Özbaş
Cem Karaali	Mehmet Ali Gülçelik	Serdar Saydam
Ceyhun İrgil	Mehmet Ali Koçdor	Sibel Özkan Gürdal
Cihan Uras	Mehmet Eser	Tamer Çolakoğlu
Erol Aksaz	Metehan Gümüş	Teoman Coşkun
Ertuğrul Gazioğlu	Münire N. Akçay	Vahit Özmen
Fatih Ağalar	Murat Çalıkapan	

Second round: 57 (92%) panelists attended the voting and 45 (79%) of them favored the recommendation, whereas 3 (5%) disagreed and 9 (16%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 2: "For centrally located tumors, the distance between the tumor and nipple-areola complex (NAC) should not be considered as a selection criterion for OBCS as long as the surgical margin is tumor-free after intraoperative frozen section histological assessment."

First round: 62 (100%) panelists attended the voting and 43 (70%) of them favored the recommendation, whereas 16 (26%) disagreed and 3 (4%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 3: "OBCS can be performed in patients with locally advanced breast cancer (LABC) when they are downstaged after receiving neoadjuvant systemic treatment (NST)."

First round: 62 (100%) panelists attended the voting and 51 (82%) of them favored the recommendation, whereas 2 (3%) disagreed and 9 (15%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 4: "Performing concomitant breast reduction is appropriate in breast cancer patients with macromastia."

First round: 62 (100%) panelists attended the voting and 55 (89%) of them favored the recommendation, whereas 4 (6%) disagreed and 3 (5%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 5: "OBCS techniques can be performed in patients with ductal carcinoma in-situ (DCIS) when safe margins are provided."

First round: 62 (100%) panelists attended the voting and 61 (98%) of them favored the recommendation, whereas only 1 (2%) disagreed and no panelist remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 6: "Outcome of OBCS should be assessed routinely for cosmetic outcome."

First round: 62 (100%) panelists attended the voting and 52 (84%) of them favored the recommendation, whereas 2 (3%) disagreed and 8 (13%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 7: "Aesthetic assessment of the breasts after OBCS should be done earliest at 6 months after completing all adjuvant treatments except hormonal treatment."

First round: 62 (100%) panelists attended the voting and 51 (82%) of them favored the recommendation, whereas only 1 (2%) disagreed and 10 (16%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 8: "After OBCS, re-excision can be performed at a re-do setting in cases with involved surgical margins."

First round: 62 (100%) panelists attended the voting and 47 (76%) of them favored the recommendation, whereas 2 (3%) disagreed and 13 (21%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 9: "For surveillance of young breast cancer patients with dense tissue who have undergone volume displacement and/or replacement surgery, breast magnetic resonance imaging (MRI) should be supplemented to standard mammography (± breast ultrasonography) for routine imaging of the breasts."

First round: 62 (100%) panelists attended the voting and 33 (53%) of them favored the recommendation, whereas 14 (23%) disagreed and 15 (24%) remained abstain.

Second round: 57 (92%) panelists attended the voting and 46 (81%) of them favored the recommendation, whereas 6 (11%) disagreed and 5 (9%) remained abstain.

Result: Consensus Reached-Endorsed as a Recommendation.

Recommendation no 10: "In those breast cancer patients planned to undergo OBCS, breast volume should be measured before surgery."

First round: 62 (100%) panelists attended the voting and 34 (55%) of them favored the recommendation, whereas 6 (10%) disagreed and 22 (35%) remained abstain.

Second round: 57 (92%) panelists attended the voting and 32 (56%) of them favored the recommendation, whereas 5 (9%) disagreed and 20 (35%) remained abstain.

Result: Consensus Not Reached-Inconclusive.

DISCUSSION

In this first consensus from Turkey on OBCS, ten statements were voted. All statements were formulized from controversial issues chosen from breast cancer patients' care pathway by the CDC assigned by the National Federation (TFNSBD). As a result, nine statements were favored by the majority of 62 opinion leaders who are dedicated and experienced breast surgeons authenticated by their case load and academic level. Only in one statement the voters did not reach a consensus.

This is the first consensus on OBCS in Turkey and as far we know, one of the few in the world. We used a contemporary methodology for the whole process, as described previously (3). We established strict criteria for panelist nominations, and all attendants were expert surgical oncologists with adequate expertise on this particular field and whose names were in agreement overall. Due to the practicability of the software package, the consensus went uneventful and fast. All of the terms of the consensus procedure were decided a priori and due to technical aspect of the on-line voting system, all the results were obtained automatically therefore, decreasing human error. Almost all decisions were reached at the end of the first round. Only one recommendation was needed to be voted in two rounds but could not reach a consensus at the end.

In this consensus procedure, we had certain limitations. We could not discuss all controversial issues for OBCS and put them for voting. Furthermore, although they are also the part of the team, plastic and reconstructive surgeons were not invited for the voting process. Another potential limitation was the low acceptance rate after sending the initial invitation to all breast cancer-related surgical oncologists. Although more than half of the invited surgeons attended the voting, the overall representation rate may be considered low.

Since its first conceptual description in the early 1990s, many different OBCS techniques have been described and classified in different terminology (1,4,7,8). Currently, variations in surgical practice do not get any widely accepted standardization. This still causes nonuniform practice among surgeons and lack of common language (7,9,10). One of the gaps-in knowledge for OBCS is the adequate marking of the resection cavity since local recurrences after lumpectomy are usually in the field of lumpectomy.

Furthermore, boost irradiation of the tumor bed in addition to whole breast has been found to decrease local recurrence (11). However, tumor area is significantly being displaced with OBCS. Marking the cavity may become a challenging issue especially during OBCS, such as wise pattern reductions. Discussions still continue on how many walls should be clipped after lumpectomy before reshaping (9,10,12). Despite different practice patterns, some surgeons find adequate to place only one clip on the base of the cavity (13). Here in our panel, opinion leaders reached a consensus with the majority favoring the recommendation for marking the cavity by placing clips on minimum 4 walls.

Preservation of the NAC during breast cancer surgery is still a matter of debate. There are surgeons who advocate NAC-sparing surgery if intraoperative frozen section assessment does not reveal tumor involvement at the retro-areolar resection margin without taking the distance between the tumor and the NAC complex under consideration (10). On the other hand, some suggest that NAC sparing surgery should not be attempted if the distance is less than a certain length (14). In this consensus, the surgeons were in agreement for the feasibility of performing NAC-sparing surgery where the distance between the tumor and NAC should not be considered as a selection criterion as long as the surgical 241 margin is tumor-free after intraoperative histologic evaluation.

Again, another controversial issue is the safety of BCS in those patients with tumors down-staged after NST. Previous reports have shown that up-front OBCS techniques can safely be performed to resect large tumors which are not feasible for conventional BCS (15,16). Therefore, OBCS also seems to be a relevant choice for patients who receive NST for locally advanced cancer. It has been shown that OBCS can be performed safely in patients after NAC without an increased complication risk or adjuvant treatment delays (17). Furthermore, OBCS has been found to provide satisfactory breast cosmetic outcome in these patients (18). Along with these individual findings, also in our consensus panel, most surgeons supported the statement in which OBCS is recommended as one of the valid options in patients with locally advanced cancer who received NST and downstaged.

Apart from its association with shoulder and neck pain in patients (19), dose distribution problems during whole breast irradiation make macromastia to be regarded as one of the relative contraindications for BCS (20). Therefore, OBCS such as tumor resection with a reduction mammoplasty technique in patients with macromastia would obviate such limitations. One of the gaps-in-knowledge in this context is the essentiality of performing concomitant bilateral reduction at both sides including contralateral healthy breast. It is reasonable to expect that macromastia-related symptoms may be corrected as a whole by such intervention on both sides. It has been previously shown that unilateral wise-pattern reduction mammoplasty improves patient-related outcomes such as patient satisfaction and quality-of-life measures in breast cancer patients (12,21). However, it is not clear yet if bilateral reduction mammoplasty provides any better patient-related outcome in patients with unilateral breast cancer. In this consensus panel, the panelists voted overwhelmingly favoring concurrent contralateral breast reduction in patients with unilateral breast cancer and bilateral macromastia.

There are controversial findings of the clinical outcome of OBCS techniques in DCIS patients. Findings of some studies do not support implementing oncoplastic surgery in these patients (22,23), whereas in others it has been found that OBCS techniques with larger resections can be safely performed without compromising oncological outcome (4,10,24). In our panel, the recommendation which advocates performing OBCS in DCIS patients as long as the margin clearance is provided was endorsed with consensus.

It has been suggested that the outcome of OBCS should also be assessed from aesthetic perspective. Breasts are gender-specific organs which represent feminity and provide the integrity of sexual well-being in women. Most think that along with survival, aesthetic outcome after breast cancer surgery has paramount importance (9,10). Also, some authors think that the assessment should be done when edema and swellings are minimum after surgery (25,26). However, there is still a controversy regarding the necessity of routine aesthetic evaluation and its timing after OBCS (9,10,25,26). Therefore, in this current consensus, we also asked breast surgeons for their opinions whether making aesthetic evaluation a standard component of outcome after OBCS is necessary. The panel overwhelmingly agreed that aesthetic assessment should be done after surgery as one of the treatment outcome indicators. In further voting, the panelists agreed that this assessment should not be done until all adjuvant radiotherapy and chemotherapy are completed and not before postoperative 6th month.

Margin positivity is one of the most significant determinants of local recurrence after lumpectomy in breast cancer patients (27). However, despite every effort to obtain clear margins, permanent pathology assessment may reveal tumor involvement at surgical margins. In this circumstance, some advocate performing total mastectomy (5,9,28). On the other hand, in order to maintain the integrity of the breast, re-resection of cavity walls was also recommended in suitable cases (10,19,29). Therefore, in order to clarify this issue in OBCS patients, we asked the panel their opinion on this issue. As a result, the majority endorsed re-resection of the involved margins where it seems appropriate and feasible.

Young patients commonly have breast tissue with high-density. This is particularly important when assessing the breasts in patients after partial mastectomy for in-breast local recurrence screening (30). Since OBCS includes breast re-modelling with volume replacement and displacement which are more complex and extensive techniques than conventional BCS, fibrosis and fat necrosis have been found to occur more commonly especially when those patients receive irradiation (31). Therefore, ruling out cancer recurrence has upmost importance in these patients. Interpretations of mammography and ultrasonography have been reported to be challenging after OBCS as well (32). Therefore, the role of breast MRI in young patients undergoing OBCS is not clear (21,32). However, in this consensus, the majority of the panelists agreed to advocate using breast MRI in young breast cancer patients for surveillance after treatment.

In the current panel, there was only one recommendation that did not attain an agreement amongst the panelists. It is believed that tumor size to breast volume ratio is important for determining the type of surgery. In those patients, when the resection volume is expected to be greater than 20%, OBCS, instead of conventional BCS, seems to be a valid option to avoid mastectomy (10,33). Also, associated macromastia may affect the surgeon's choice for oncoplastic technique (10,12). However, there is no generally accepted practice for measuring the breast volume before the surgery. Most surgeons perform breast surgery by estimation of the breast volume and its ratio

to the tumor size either empirically or by various non-uniform methods (34). After two rounds of voting, the consensus panel did not reach a majority either for endorsement or rejection of performing routine measurement of breast volume at both sides before the surgery. So, this issue remained inconclusive in the current panel.

CONCLUSION

According to the current consensus results, Turkish surgeons were in agreement for almost all of the chosen controversial issues in OBCS. The simplicity and speed of the consensus methodology and its results showed that many controversial issues may be discussed and solved by collecting expert opinions with electronic tools such as ours. The current panel which gathered significant amount of experts' opinions on-line provided temporary solutions to some of the controversial issues on OBCS until having satisfactory further evidence from clinical studies.

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Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (3): 271-277

Türkiye'deki onkoplastik meme koruyucu cerrahi uygulamaları hakkında ulusal konsensüs: cerrahi pratik uygulamaların standardizasyonu için öneriler

Mustafa Emiroğlu[1], Cem Karaali[1], Mehmet B. Öztop[2], Bahadır M. Güllüoğlu[3]

[1] İzmir Tepecik Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İzmir, Türkiye
[2] İzmir İl Sağlık Müdürlüğü, İzmir, Türkiye
[3] Marmara Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Meme kanseri hastalarında onkoplastik meme koruyucu cerrahi (OMKC) uygulamalarının çoğunu tanımlayan algoritmalar net değildir. Bu nedenle ülkemizin önde gelen ve konularında deneyimli meme cerrahları ve onkoplastik meme cerrahları arasında onkoplastik meme cerrahisindeki tartışmalı alanlar hakkında bir konsensüs düzenlenmiştir.

Gereç ve Yöntem: Bu konsensüs Türkiye Meme Hastalıkları Dernekleri Federasyonu (TMHDF) çatısı altında on-line Consensuss (www.consensuss.com) yazılımı aracılığı ile gerçekleştirildi. Her bir önermeye son şeklinin verilmesinden sonra Consensuss (www.consensuss.com) yazılım programı ile web tabanlı uzaktan erişimli konsensüs işlemi Delphi metodu kullanılarak Likert skalası üzerinden gerçekleştirildi. Türkiye'de çalışan en az 5 yıllık genel cerrahi uzmanı olup günlük klinik uygulamalarının %50'sinden fazlasını meme hastalıklarının tedavisine ayıran 111 kişiye ilgili yazılım aracılığı ile davet yollandı.

Bulgular: Davet edilen 111 kişiden 62'si panele katılmayı kabul etmiş ve on-line değerlendirme yapmıştır. Konsensüs sonuçlarına göre; lumpektomi kavitesine en az dört klps konulmalıdır, santral tümörlerde temiz cerrahi sınır elde edilmesi yeterlidir, neoadjuvan kemoterapi sonrası OMKC uygulanabilir, OMKC kanserli veya duktal karsinoma in-situ hastalığına sahip makromastili hastalara uygulanabilir, OMKC estetik sonuçları açısından değerlendirilmelidir. OMKC sonrası pozitif sınır gelmesi durumunda re-eksizyon yapılabilir.

Sonuç: Konsensüs sonuçlarımız OMKC'de bazı standartların gelişmesine temel oluşturabilir.

Anahtar Kelimeler: Onkoplastik meme koruyucu cerrahi, standardizasyon, konsensüs

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ORIGINAL ARTICLE
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Laparoscopic repair of lateral sided trocar site hernias

Hasan Ediz Sıkar[1], Kenan Çetin[1]

[1] Clinic of General Surgery, Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objective: Repair of trocar site hernia (TSH) has been mentioned in a limited number of studies. Trocar site hernias are mostly located in the umbilical region with a small size. Laparoscopic repair could be a choice due to the appearance of large defects and requirement of mesh repair for lateral sided TSH. We aimed to share our experience with laparoscopic repair of lateral sided trocar site hernia (LRTSH) with a long term follow up.

Material and Methods: Twenty-three patients who underwent LRTSH between March 2013 and July 2015 were included in our study. Four edges of the mesh were fixed with pre-tied 2/0 polypropylene suture for 9 patients initially (Group 1). Unexpected complication of chronic pain in 3 patients led us to revise our method and we avoided to position the mesh with transabdominal sutures for the rest of the patients (Group 2).

Results: Nineteen (82.6%) female and 4 (17.4%) male patients, with a mean age of 50.9 years underwent laparoscopic repair. Following the revision and avoiding transabdominal sutures to position the mesh, no complaint of chronic pain was observed, and the difference was statistically significant between the groups ($p< 0.05$).

Conclusion: Previous laparoscopic surgery indicates the lack of obstacle in laparoscopic repair of TSH, and LRTSH can be considered as first option in treatment. Shorter mean operative time in obese patients and lack of recurrence in our series support this view. Using transabdominal sutures should be avoided to prevent chronic pain in LRTSH.

Keywords: Incisional hernia, laparoscopy, surgical mesh

INTRODUCTION

The increase in the number of laparoscopic operations has undesirably led to a rise in trocar site hernias (TSH). Most of the studies consist of the causes and etiology of TSH (1-6). Repair of TSH has been mentioned in a limited number of studies (7,8). Trocar site hernias are mostly located in the umbilical region with a small size, and open approach could be the first choice of treatment for these patients (9-11). In contrast, most of the patients with lateral sided TSH had a defect with a diameter of more than 3 cm in our series. Blunt dissection with retractors to insert the optical trocar and insufficient closure of the abdominal wall could be the possible cause of this situation (12).

Trocar site hernias are incisional hernias, and laparoscopic repair is one of the treatment options for incisional hernias with decreased recurrence rates and morbidity (13). Laparoscopic repair could be a choice due to the appearance of large defects and requirement of mesh repair for lateral sided TSH. Although there are some case reports for laparoscopic repair of TSH, there is data missing in the literature about this specific topic (14). We aimed to share our experience with laparoscopic repair of lateral sided trocar site hernia (LRTSH) with a long-term follow up.

MATERIAL and METHODS

Regarding the literature, hernias located laterally from the lateral margin of the rectus sheath are defined as lateral hernias. Thus, hernias located between the lateral borders of the rectus muscle sheath -which were not located over linea alba- were excluded. Twenty-three patients who underwent LRTSH between March 2013 and July 2015 were included in our study. Ultrasonography was used to evaluate the remaining trocar sites before the operation. All operations were performed by the same surgeon in our clinic. The study was approved by our hospital's ethics com-

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Corresponding Author
Hasan Ediz Sıkar
E-mail: hasan.sikar@me.com

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mittee (reg. 5141092, 2018). Medical records were reviewed retrospectively from our clinic's database collected prospectively with a follow-up form including patient characteristics and demographics, TSH occurrence time, previous surgery, defect size, mesh size, mesh type, operative time, conversion rate, complications, recurrences and follow-up time.

The patients were positioned supine, and the arm of the opposite side was tucked. All operations were performed with three ports and a 30-degree laparoscope. Ports were placed as far away as from the TSH, in the opposite side of the abdominal wall. The optical port was an 11-mm trocar and was inserted using an open approach. Following the creation of the pneumoperitoneum, two additional trocars of 6 mm were inserted under direct vision to form a triangle. Most of the patients required adhesiolysis for peritoneal adhesions due to previous operations. Following the measurement of the hernia size, the closest available size of the mesh was used for sufficient overlap in most of the cases – about 5 cm all around the defect. Parietene Composite (PPC) Mesh (Covidien, Mansfield MA, USA) was used for laparoscopic repair. The mesh was shaped in defects smaller than 4 cm to avoid unnecessary use. Four edges of the mesh were fixed with pre-tied 2/0 polypropylene suture for 9 patients initially (Group 1). Unexpected complication of chronic pain in 3 patients led us to revise our method, and we avoided positioning the mesh with transabdominal sutures for the rest of patients (Group 2). Titanium helical tacks were used to fix the mesh with double-crown technique for all patients (Figure 1).

All cases were controlled on the postoperative 10th day, sixth week, third month, sixth month and annually. Also, patients with symptomatic seroma were controlled in 8th and 10th week to decide aspiration. Patients were examined with ultrasonography for both hernia site and trocar site annually.

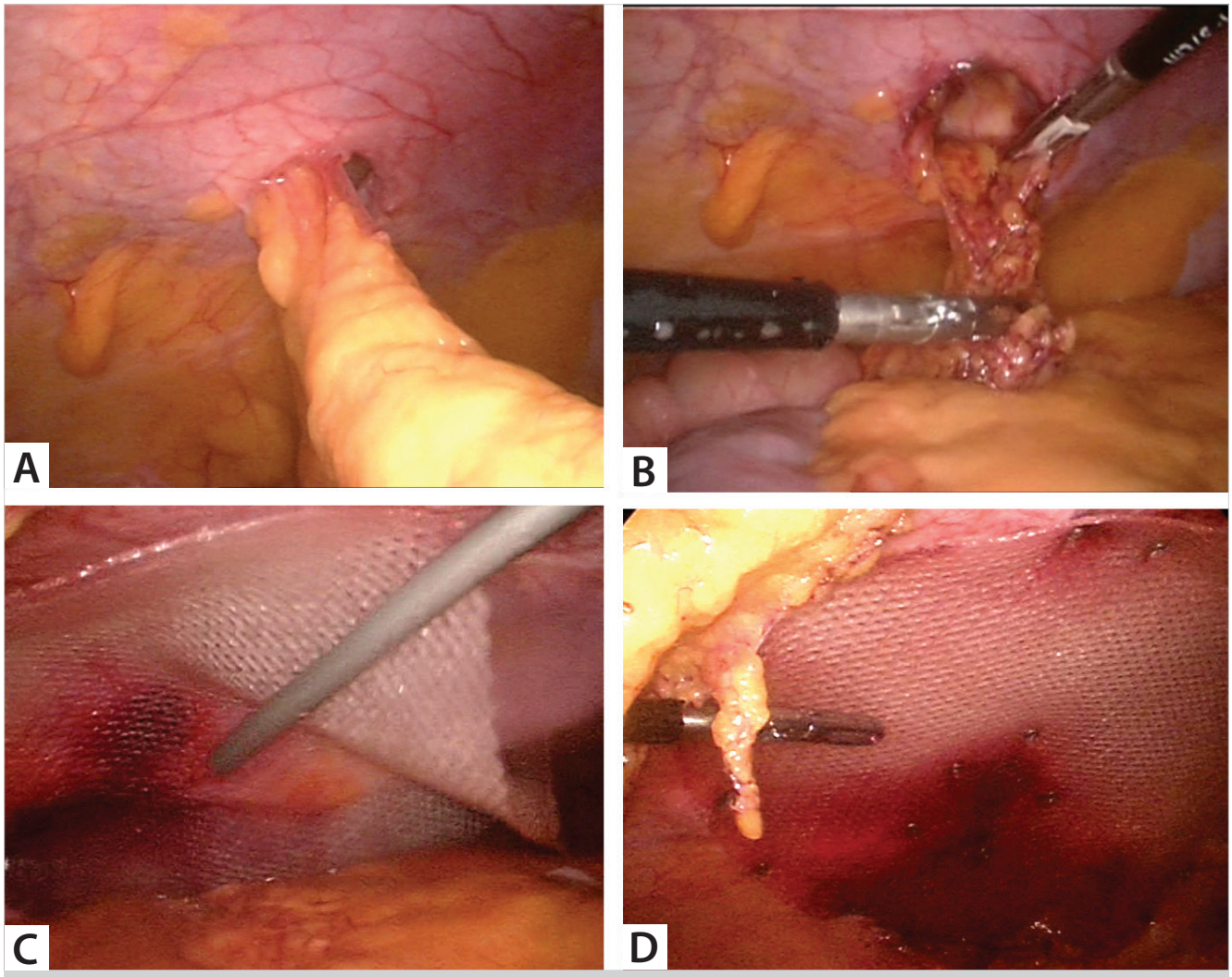

Figure 1. a. Right-sided trocar site hernia following laparoscopic hernia repair, b. Reducing the contents of the hernia, c. Positioning the mesh, d. Double-crown technique.

An Excel worksheet (Microsoft Corp., Redmond, WA) was used to enter the data. Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation, frequency, percent, minimum and maximum) were used to evaluate the study data. Mann-Whitney U test was used to compare quantitative variables without normal distribution. Pearson Chi-square test and Fisher's exact test were used to compare qualitative data. Based on the results of the analyzes, p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 23 patients, 19 (82.6%) females and 4 (17.4%) males, with a mean age of 50.9 years underwent laparoscopic repair. Most of the patients were obese, and mean BMI was 30.7 kg/m^2. Mean number of previous operations was 2.1. All patients were admitted with symptoms within 1 year following surgery, and mean TSH occurrence time was 6.1 months. Twenty-two (95.7%) of the TSH had occurred from 10 mm or larger trocars. The patient with hysterectomy had 2 hernias side by side that occurred from 5 mm trocars. Operation notes were examined, and insertion of large drain tubes from both trocars could be explanatory for this atypical condition. Nine (39.1%) of the patients had previous laparoscopic surgery in our clinic. Most common type of previous operation was laparoscopic abdominal hernia repair (LAHR) - 8 (34.8%) of the patients. Characteristics of the patients and operative findings are presented in Table 1.

Table 1. Characteristics of the patients

Parameter	Value
Age	50.9 ± 10.3
Sex (female/male)	19 (82.6%)/4 (17.4%)
BMI (kg/m^2)	30.7 ± 4.8
Smoking	3 (13.1%)
Comorbid disease	17 (73.9%)
Region (right/left)	12 (52.2%)/11(47.8%)
TSH occurrence time (months)	6.1 ± 2.2
Follow up time (months)	50.5 ± 7
Defect size (cm^2)	16.3 ± 12.3
Mesh size (cm^2)	219.8 ± 58.2
Operative time (min)	51.5 ± 7.4
Number of previous operations	2.1 ± 1.4
Type of previous operation	
LAHR	8 (34.8%)
Colorectal	5 (21.7%)
Bariatric	3 (13%)
Nephrectomy	3 (13%)
Splenectomy	2 (8.7%)
Adrenalectomy	1 (4.3%)
Hysterectomy	1 (4.3%)

*BMI: Body mass index; TSH: Trocar site hernia; LAHR: Laparoscopic abdominal hernia repair.

There was no recurrence, and TSH occurrence during the follow-up period of 50.5 months. Complications occurred in 4 (17.4%) of the patients. One patient (4.3%) had symptomatic seroma and required aspiration twice on the 8th and 10th weeks. Three patients (13%) had chronic pain, all at the same region. Oral analgesics were sufficient, clinical improvement was observed about 4 months following surgery, and no additional intervention was required.

Following the revision and avoiding transabdominal sutures to position the mesh, no complaint of chronic pain was observed, and the difference was statistically significant between the groups (p< 0.05). Comparison of the groups is shown in Table 2. Mean follow-up time was significantly higher in Group 1 – 56.6 ± 5.1 months vs. 46.5 ± 4.8 months (p< 0.001). There was no statistically significant difference regarding age, sex, BMI, smoking, comorbid disease, region, TSH occurrence time, defect size, mesh size, operative time, number of previous operations, and mean hospital stay.

DISCUSSION

Incisional hernias remain one of the major complications following abdominal surgery with a high ratio (12,13). TSH incidence is rare in comparison with incisional hernias following conventional surgery (10-12). However, the number of TSH has increased due to the high ratio of laparoscopic surgery. Although the exact incidence of lateral sided TSH in our department is unknown, 743 patients have undergone laparoscopic surgery (LAHR, colorectal surgery, bariatric surgery, splenectomy, and adrenalectomy) at the same interval, and 9 (1.2%) of these patients have been admitted with lateral sided TSH–operations without 10 mm trocar entry located laterally to the rectus muscle, such as laparoscopic cholecystectomy, TAPP, appendicectomy and remaining operations, were excluded. Following the division of branches in our department, laparoscopic approach has become the first choice of treatment for incisional hernias in the division of hernia surgery, and laparoscopic repair has been used initially for all patients with TSH. Umbilicus was the most common localization and most of the cases with midline localization had a fascial defect under 3 cm in our series. Open approach for exploration and to repair the edges of the aponeurosis with slight enlargement of the skin incision could be applicable for most of the cases with midline localization in our daily practice. Also, a simple mesh repair could be adequate for this type of hernias (9). All existing reasons led us to abandon laparoscopic approach for TSH with midline localization following initial cases. On the other hand, most of the cases with lateral sided TSH had a fascial defect of 3 cm or more and content of a sliding colon segment with adhesions was present -due to proximity- in the

Table 2. Comparison of the groups

	Group 1 (n= 9)	Group 2 (n= 14)	p
Age	48.6 ± 10.9	52.3 ± 9.9	0.504
Sex (female/male)	9 (39.1%)/0	10 (43.5%)/4 (17.4%)	0.127
BMI (kg/m^2)	30.8 ± 5.3	30.5 ± 4.5	0.975
Smoking	0	3 (13%)	0.253
Comorbid disease	6 (26.1%)	11 (47.8%)	0.643
Region (right/left)	6 (26.1%)/3 (13%)	6 (26.1%)/8 (34.8%)	0.4
TSH occurrence time (month)	5.6 ± 2.6	6.4 ± 1.9	0.504
Follow up time (month)	56.6 ± 5.1	46.5 ± 4.8	< 0.001
Defect size (cm^2)	21.1 ± 13.2	13.1 ± 10.9	0.064
Mesh size (cm^2)	225 ± 64.9	216.4 ± 55.7	0.765
Operative time (min)	54.2 ± 7.6	49.8 ± 7.1	0.175
Number of previous operations	2.3 ± 1.4	1.9 ± 1.4	0.296
Hospital stay (day)	1	1	1.0
Complications			
Seroma	-	1	1.0
Chronic pain	3	-	< 0.05

*BMI: body mass index, TSH: trocar site hernia.

hernia sac for most of the cases (Figure 2). Disintegrated fibers of the muscles with blunt dissection and insufficient closure due to insufficient identification of lateral borders of the incision have been found to be associated with lateral sided trocar site hernia (12). Considering the methods to prevent lateral sided TSH occurrence, there is a requirement of an extended skin incision to repair disintegrated fibers of muscles. In addition, there is a requirement of an extended skin incision to repair disintegrated fibers of muscles in case of open approach for lateral sided TSH (12).

Obesity, age, defect size, smoking or an asymptomatic hernia could be the reasons not to operate for some surgeons and also, some surgeons refrain from laparoscopic repair concerning preexisting comorbidities (15). All of the patients were admitted with symptoms within 12 months - following laparoscopic surgery - in our series. Depending on recent time and type of the previous operation, we believe that all patients could undergo laparoscopic repair for TSH. Lambertz et al. have reported an extensive series of TSH with a recurrence rate of 9% and 3 ± 4 days of mean hospital stay following conventional repair (7). In addition, Kwon et al. have reported a recurrence rate of 29.4% following TSH repair (8). Although it is not a scientific data, we should point out a statement for our series: patients with TSH following laparoscopic hernia repair are stressful to the possibility of recurrence, and it is the main issue that these patients focus on. The absence of recurrence and 1 day of mean hospital stay in our series could be supportive findings for laparoscopic repair of TSH. TSH occurrence has been reported higher in obese patients before (3,4,12). Lambertz et al. have reported that patients with mesh repair had higher BMI and mean operative time – 32 ± 9 of BMI and 83 ± 47 minutes of mean operative time (7). Technical difficulties could explain this condition. Most of the cases were obese or overweight in our series. Despite a similar level of BMI, mean operative time seems to be shorter in our series – 30.7 ± 4.8 of BMI and 51.5 ± 7.4 minutes of mean operative time. Regarding the technical difficulties in obese patients, laparoscopic repair of TSH could be a choice of treatment to shorten mean operative time.

Chronic pain was the major complication, and 3 cases had complaints about pain for more than 3 months in our series. All patients had the same complaint at the same region - around the superior edge and near costal margin of the transabdominal suture. Although oral analgesics were sufficient, depending on patients' complaints around the transabdominal sutures, we avoided using transabdominal sutures to position the mesh for subsequent cases. The absence of chronic pain in the revised group and the statistically significant difference was supportive to avoid using transabdominal sutures in lateral sided TSH patients. Furthermore, there was no recurrence or an unexpected complication in Group 2 patients due to the absence of transabdominal sutures on follow-up. Observational design was the major limitation of our study, patients in Group 1 were the first cases and the difference between mean follow-up time was a result of this condition. In spite of the statistically significant difference, all of the patients were followed for more than 36 months in our series, and mean follow-up time of 46.5 months

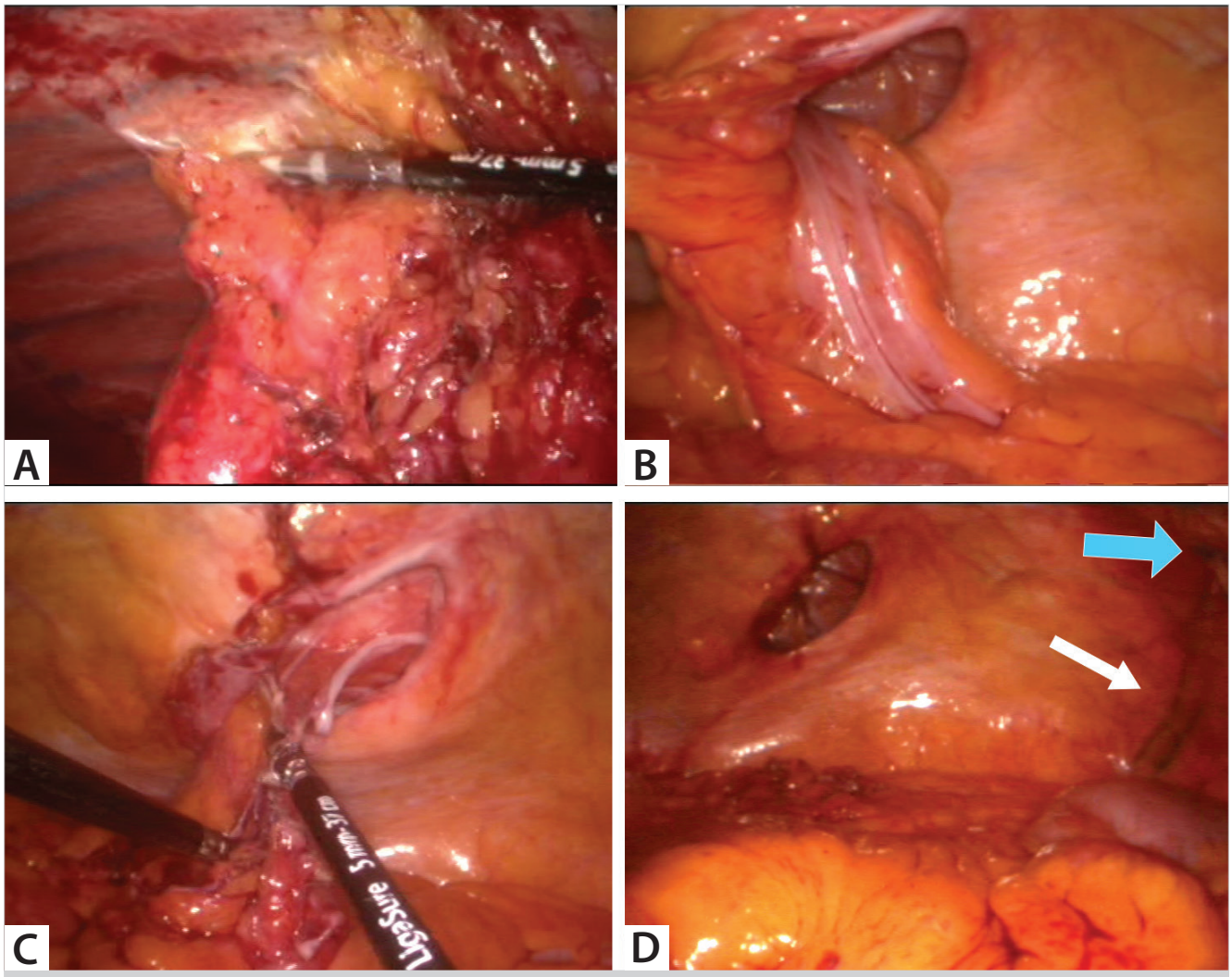

Figure 2. Left-sided trocar site hernia following laparoscopic hernia repair a. Adhesiolysis of previous laparoscopic hernia repair, b. Sliding colon segment, c. Reduction of colon segment, d. Appearance following adhesiolysis and reduction (blue arrow indicates the edge of the previous mesh, white arrow indicates inferior epigastric vessels).

in Group 2 patients could be considered as a notable duration from most of the studies in the literature. Kwon YH et al. have reported the mean duration between TSH repair and first recurrence as 32 months - in a range between 20-49 months - and have recommended examination annually for the first two years to detect recurrence (8). Due to lack of recurrence following LRTSH and lack of lateral sided TSH occurrence after postoperative year 1, we can recommend an examination for the first year and longer intervals more than a year to prevent unnecessary controls.

CONCLUSION

In conclusion, previous laparoscopic surgery indicates the lack of obstacle in laparoscopic repair of TSH, and laparoscopic repair of lateral sided TSH can be considered as the first option in treatment. Shorter mean operative time in obese patients, lack of recurrence, and shorter mean hospital stay in our series support this view. As a technical detail, the use of transabdominal sutures should be avoided to prevent chronic pain in LRTSH.

Ethics Committee Approval: Ethics committee approval was received for this study from Kartal Dr. Lütfi Kırdar Training and Research Hospital Clinical Research Ethics Committee (2018/514/139/2).

Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Lateral yerleşimli trokar yeri fıtıklarının laparoskopik onarımı

Hasan Ediz Sıkar[1], Kenan Çetin[1]

[1] Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, Istanbul, Türkiye

ÖZET

Giriş ve Amaç: Trokar yeri fıtığının (TYF) onarımı az sayıda çalışmada bildirilmiştir. TYF çoğunlukla küçük ve göbek bölgesinde yerleşimlidir. Laparoskopik onarım, geniş defektler ve yama onarımı gerektiren lateral yerleşimli TYF'ler için seçenek olabilir. Çalışmamızda laparoskopik onarım uygulanan TYF'lerinde (LOTYF) uzun dönem takip sonuçlarımızı sunmayı amaçladık.

Gereç ve Yöntem: Mart 2013-Temmuz 2015 tarihleri arasında LOTYF uygulanan 23 hasta çalışmaya dahil edildi. İlk 9 hastaya yamanın dört kenarından 2/0 prolen transabdominal dikiş uygulandı (Grup 1). Grup 1'deki 3 hastada beklenmeyen kronik ağrı komplikasyonu gelişmesi nedeniyle sonraki hastalarda ameliyat yöntemi değiştirilerek yamanın pozisyonu için transabdominal dikiş kullanılmadı (Grup 2).

Bulgular: Ortalama 50,9 yaşında, 19 (%82,6) kadın ve 4 (%17,4) erkek hastaya laparoskopik onarım uygulandı. Yöntem değişikliği sonrasında transabdominal dikiş uygulanmamasını takiben hiçbir hastada kronik ağrı şikayeti gözlenmedi ve gruplar arasında istatistiksel açıdan anlamlı fark saptandı ($p< 0,05$).

Sonuç: Geçirilmiş olan laparoskopik cerrahi prosedür, LOTYF uygulanmasına engel bir durum olmadığını göstermektedir. Bu nedenle LOTYF tedavi için ilk seçenek olarak değerlendirilebilir. Obez hastalarda ameliyat süresinin kısa olması, nüks izlenmemesi bu görüşümüzü destekler niteliktedir. LOTYF hastalarında, transabdominal dikişten, olası kronik ağrı şikayetinin önlenmesi için kaçınılmalıdır.

Anahtar Kelimeler: İnsizyonel fıtık, laparoskopi, cerrahi yama

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ORIGINAL ARTICLE
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Turkey is leading in the 21st century pilonidal sinus disease research

Dietrich Doll[1], Verena Stauffer[2], Maja Diekmann[1], Pieter Van Wyk[3], Markus M Luedi[4]

[1] Department of Procto-Surgery, St. Marienhospital, Vechta, Germany
[2] Department of Emergency Medicine, Lindenhofgruppe, Bern, Switzerland
[3] Karolinska University Hospital, Division of Trauma and Acute Care, Stockholm, Sweden
[4] Bern University Hospital, University of Bern, Department of Anaesthesiology, Bern, Switzerland

ABSTRACT

Objective: Pilonidal sinus disease (PSD) has been a recognized pathology for the past 188 years. We studied whether scientific interest in this common disease has grown or declined over time. Our investigation included analysis of the world literature between 1833 and 2018.

Material and Methods: A PubMed search was conducted to identify all publications on pilonidal sinus disease, broken down by country, year of publication and number of patients included or described.

Results: The number of patients studied has been increasing, with date of more than 10,000 patients published per decade since 1970, and the total number of affected patients exceeding n= 40.000 in 2010 and Turkey leads the research, contributing 39% of the Mediterranean patients and 18% of the patients globally, while Italy provides 26% of the Mediterranean patients and 12% of the global total. Flap studies have increased, whereas primary open treatment studies have decreased from 40% in 1940 to less than 10% at present. Twenty percent of the studies performed today report primary median approaches, and the number of randomized controlled trials has increased.

Conclusion: Surgeons in Turkey currently publish the lion´s share of the pilonidal sinus literature.

Keywords: Hair, pilonidal sinus, surgery, recurrence rate, publications, study size

INTRODUCTION

Pilonidal sinus disease research began in 1847 with Dr. AW Anderson, who removed tufts of hair from a non-healing wound on the "back" of a young man. Shortly thereafter the wound healed, and the cure was published (1). Since then, there have been thousands of publications, ranging from case reports to studies containing several thousand patients. At the time, open wound treatment was considered the standard of care as this was a septic wound. This became a problem during World War II, when more than 70.000 soldiers were temporarily decommissioned due to open wound treatment for PSD, amassing 47.000 sick leave days in 1941 alone (2). Primary closure was attempted as early as 1933 (3), but wound complications were high in the pre-antibiotic era. Several subsequent publications focused on surgical methods, including H-like (4) and Star-like (5-7) incisions, partial closure, obliteration of dead space using metal wires (8-10) or cotton rolls (11-13), and even perceived advantages and disadvantages of surgical drains (14,15). Roentgen irradiation, radioactive substances and obliterating substances were tried. When antibiotics finally became available to the surgical community (16) and asymmetric flap procedures increased, results improved-and research took off.

Contemporary work still mentions a number of therapeutic options, possibly either due to lack of comprehensive knowledge or to therapeutic negligence. In order to evaluate historical and current research efforts, we analyzed all publications addressing pilonidal sinus disease, from the first description up to the present literature, focusing on the number of patients treated and the number of articles published.

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Corresponding Author
Dietrich Doll
E-mail: ddoll@gmx.de

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MATERIAL and METHODS

We built a database with all of the literature found in a systematic search for the NCBI Medical Subject Heading (MeSH) term "pilonid*", as well as "dermoid" AND "cyst" in MEDLINE, PubMed, PubMed Central, Scopus, Ovid, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), as described previously by Stauffer (17) and Doll (18). In brief, all randomized, non-randomized, prospective, retrospective, and observational studies such as cohort, case-control, and cross-sectional studies, and case reports published between 1833 and 2017 were included. Figure 1 displays the results of the systematic search for evidence regarding recurrence and long-term follow-up data associated with common surgical procedures in PSD, based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Specific details of data collection, data extraction and quality assessment, as well as grouping of therapeutic procedures and statistical analyses, can be found in the papers by Stauffer (17) and Doll (18).

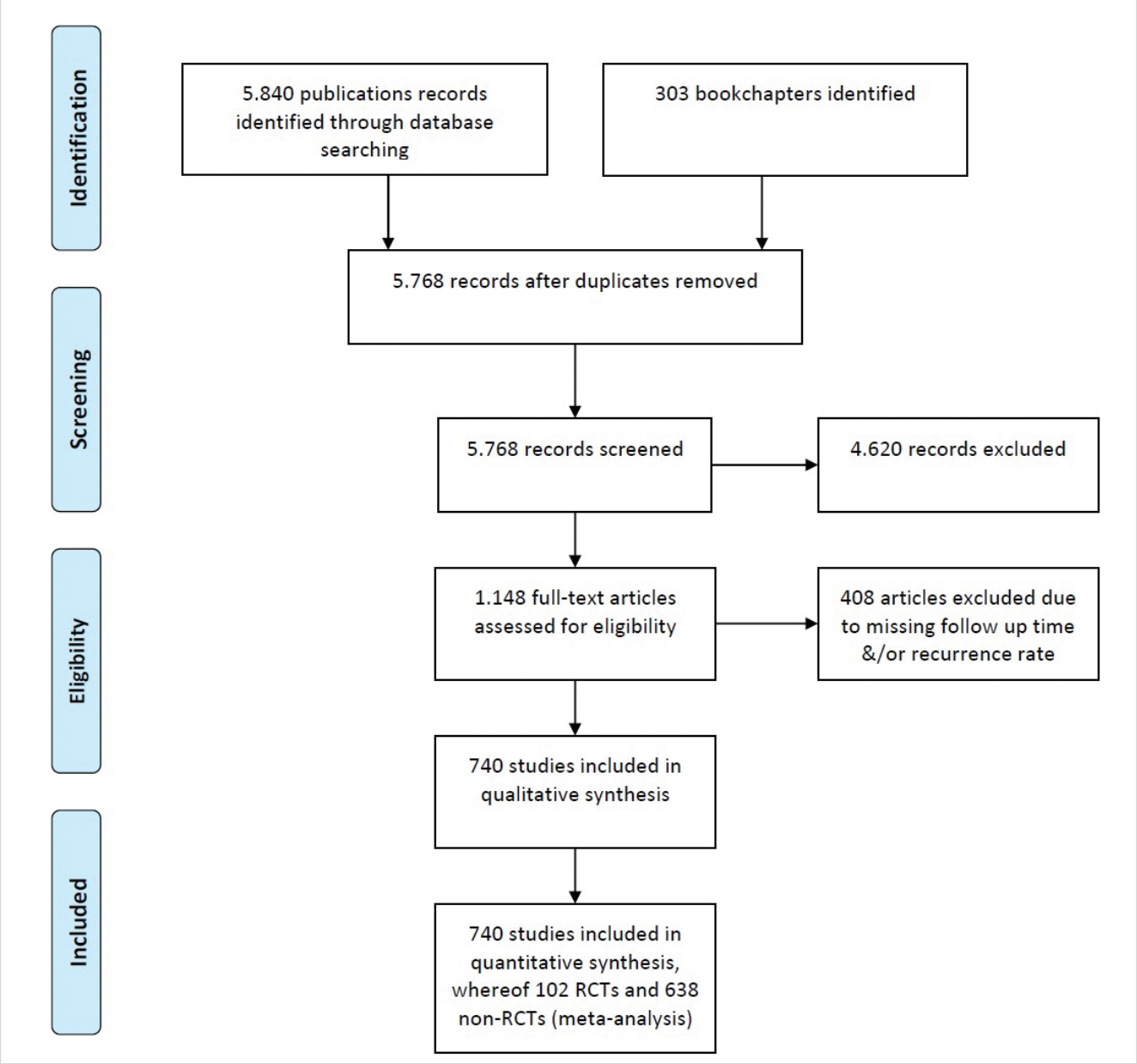

Figure 1. Flow diagram based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) illustrating the systematic search for evidence regarding recurrence and long-term follow-up data associated with common surgical procedures in PSD.

RESULTS

The average sample size was n= 73 patients (mean n= 33 ± 8 patients), with 60% of all studies published between 1833 and 2018 containing fewer than 50 patients (Figure 2). Thirty percent of the publications contained between 50 and 149 patients. Ultimately, 90% of all studies reported fewer than 150 patients on average. Sample size did not increase over time between 1940 and 2010, as illustrated by Figure 3. Here, the sample size over time was depicted from 1930 to 2010 (earlier publications are too scant to calculate a meaningful average). Please note that the values are given in mean ± SEM (standard error of the mean).

Interestingly, the sample size per publication did not increase over time, and has remained between n= 50 patients and n= 100 patients over the past 8 decades. In order to analyze whether interest in PSD has grown over time, we investigated the total study population over time. Adding up all publications over time in decades, another picture arose (Figure 4). As Figure 4 illustrates, the total number of PSD patients mentioned in pilonidal sinus publications has been increasing significantly since the 1940's. Significant interest in the disease first arose during World War II due to the temporary decommissioning of more than 78.000 soldiers with PSD between 1941 and 1945 (19). Soldiers were absent for weeks and sometimes even months following surgery and primary open treatment. A more than fourfold increase could be seen during the first post-millennial decade.

While publications from North America (Canada and the USA) initially dominated between 1940 and 1950, interest seems to have decreased there, with cumulative numbers plateauing in the past 30 years (Figure 5). Conversely, interest from Northern Europe and the Mediterranean has shown a persistent increase over the

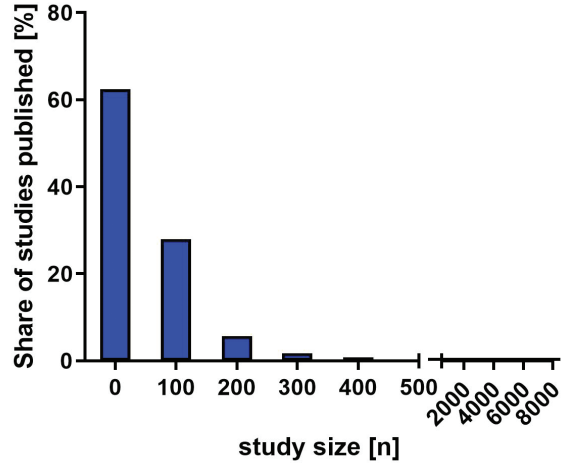

Figure 2. Histogram of pilonidal sinus disease (PSD) study sizes from 1833 to 2018.

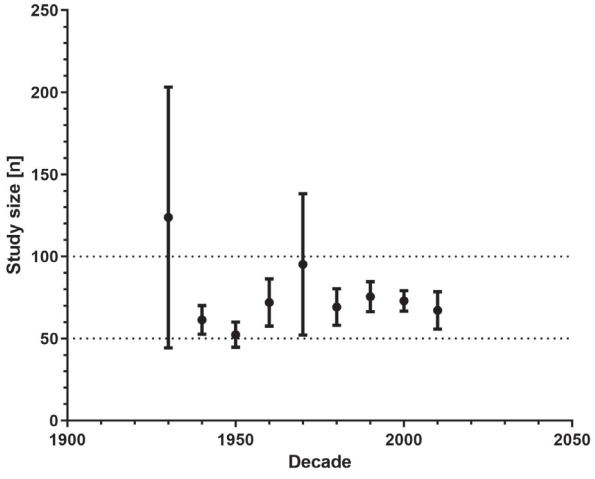

Figure 3. Size of published pilonidal sinus studies over time between 1930 and 2010, given as mean ± SEM. Data from 1920 and earlier are too few to calculate average values ± SEM.

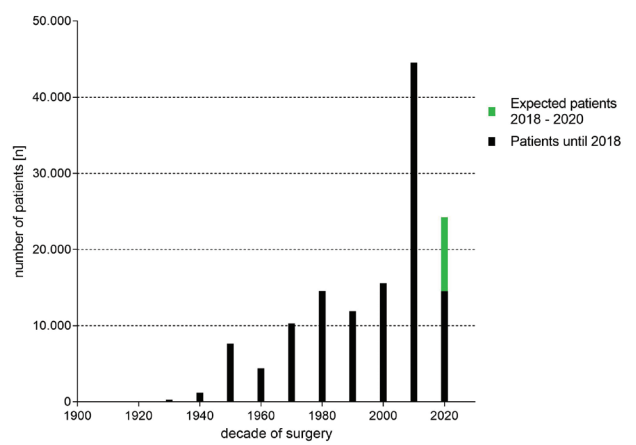

Figure 4. Number of published PSD patients according to decade of surgery. Please note that the 2020 value is estimated.

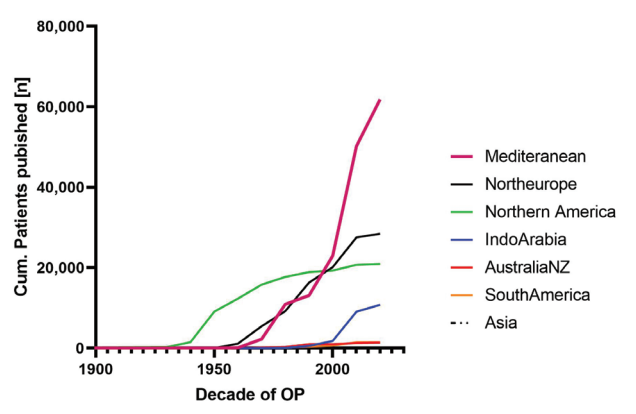

Figure 5. Number of pilonidal sinus disease (PSD) patients in research published between 1833 and 2018, by decade of surgery in different land groups (smoothed over 4 decades).

Table 1. Distribution of Mediterranean pilonidal sinus disease (PSD) patients in research published between 1833 and 2018

Country	Number of patients [n]	% Mediterranean	% worldwide
Turkey	23,998	38.56%	18.00%
Italy	16,088	25.74%	12.07%
Egypt	3,995	6.39%	3.00%
Spain	1,391	2.23%	1.04%
Israel	6,496	10.39%	4.87%
Greece	9,667	15.47%	7.25%
Lebanon	257	0.41%	0.19%
Croatia	100	0.16%	0.08%
Bosnia-Herzegovina	90	0.14%	0.07%
Morocco	14	0.02%	0.01%
Serbia	127	0.20%	0.10%
Portugal	8	0.01%	0.01%
Total	62,231	100%	46.67%

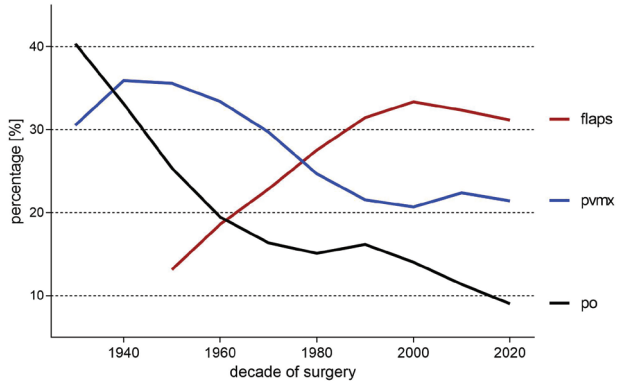

Figure 6. Percentage use of therapeutic methods by decade of surgery (Percentage depicts percentage of patients with certain therapy; smoothed over 4 decades).

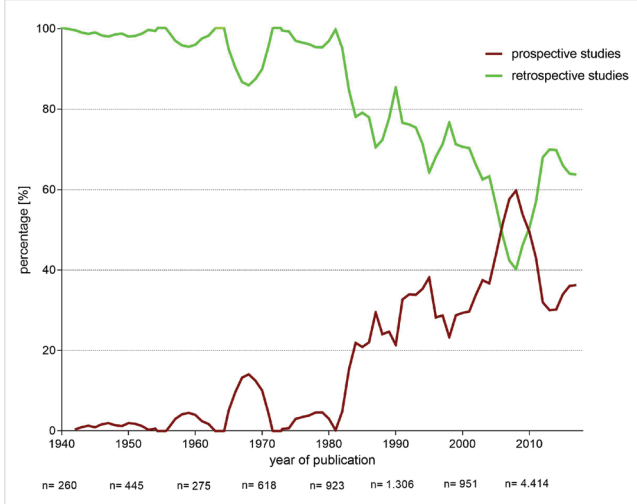

Figure 7. Percentage of prospective vs. retrospective PSD studies by year of publication, smoothed over 4 decades.

past 6 decades. The Indo-Arab region started publishing study results from 2000 onwards. Asian patients are scant, and to our knowledge, there are still no studies from Africa. With the exception of isolated case reports, the disease seems to be practically non-existent among Africans.

In the Mediterranean region, Turkey and Italy are clearly the largest contributors to knowledge of PSD (Table 1). Italy contributed 25% of the Mediterranean patients, and 12% of the global total published between 1833 and 2018. Turkey heads the field, with 39% of Mediterranean and 18% of world PSD patients studied and published within this time frame.

Interest in primary open treatment seems to be decreasing (Figure 6). Flap surgeries are at the forefront, having been used in more than 30% of the studies. Twenty percent of the studies still appear to include primary midline closure, which is characterized by prohibitive long-term recurrence rates (17).

Recent literature reveals a 30:60 ratio of retrospective to prospective studies, with a clear decrease in the number of retrospective studies since the 1980's. Despite being more laborious in terms of effort and resources, the perceived benefits and superiority of prospective studies are possible explanations (Figure 7).

DISCUSSION

Our study shows that a large body of knowledge on pilonidal disease has accumulated in the past decades, and the numbers of both publications and patients recruited are still increasing.

Evidence for new surgical techniques has emerged over the past two decades, with flap techniques being studied much more often compared to primary open or midline technique. It is mindboggling that 20% of the patients studied were still treated with midline closure in 2010 despite prohibitively high recurrence rates. This was impressively shown by Stauffer et al., who analyzed the same patient data as we did (17). With a 32% recurrence rate at 10 years, midline closure is only surpassed by limited excision, with 34% recurrence at 10 years of follow-up (17). These techniques both exceed by far the currently accepted standard of care, delivering acceptable recurrence rates of 1% (good result) to 2% per year of follow up (20).

Most of the contemporary PSD research derives from the Mediterranean. Turkish surgeons have contributed a large body of evidence over the past 40 years, and the share is still rising. There are many potential reasons, including the large case load in the civilian and military populations (both overt and silent disease) (21-23), greater awareness of the disease among surgeons, and scientific interest.

There is increasing evidence that geographical location may contribute to recurrence rate and therapy efficacy (18), as well as social and familial factors (24-27). The large burden of patients has encouraged Turkish surgeons to publish research on the factors contributing to greater PSD incidence (23), such as cut hair removal (28-30) as well as regular showering (31,32). New methods have been proposed (33-35), classifications defined, systematic reviews compiled (36) and rarities published (37-41). It is therefore understandable that-of all the general surgical articles in Turkey-15.4% cover pilonidal sinus disease and its treatment (42). More and more surgeons understand that the recurrence rate is a function of time, and while a rate of 2% per year of follow-up (i.e., 4% RR at 2 years) is acceptable, it can be lower (i.e., 5% at 3 years of follow-up) (20,43,44).

This goes hand in hand with an increased willingness to strive for more precise results through prospective randomized studies, which are shown to be increasing. Randomized controlled trials are generally conducted by large private and university-affiliated hospitals with specialized staff and research facilities. Nevertheless, small to midsize hospitals are the main location for pilonidal sinus surgeries, and the expertise of all surgeons involved in the treatment of pilonidal sinus disease is most welcome for inclusion in studies and publications.

We are aware of the limitations of our study, inherent in this type of epidemiological research. First, not all treated patients are included in published studies, and it would in fact be interesting to investigate this relation. Second, texts written in languages other than English, Spanish, French and German are lacking. Third, articles not indexed in PubMed, not published in larger journals, and not accessible via the Internet were not identifiable using our research algorithm. Fourth, there is a certain lag period between therapy, research, publication and the condensation of extended therapy results in a body of scientifically recognized knowledge. Analyses and recommendations for new therapies therefore often emerge following delays of several years.

It is therefore expected that analysis of additional publications in the coming years will shed more light on emerging and re-emerging techniques such as pit picking, endoscopic surgery and the use of lasers. More precise recurrence rates that incorporate longer follow-ups and new RCTs are to be expected.

The quality of studies has improved remarkably within the last decades, and is expected to increase further. Prospective randomized studies currently constitute 30% of the body of published articles.

CONCLUSION

In conclusion, both surgical interest and scientific activity are increasing in pilonidal sinus disease, and the Mediterranean region-especially Turkey-is contributing the lion´s share to this body of evidence. As there is an increased interest in new treatment methods, new surgical approaches and respective evidence are eagerly awaited.

Ethics Committee Approval: This article does not contain any studies with human participants, human samples or live vertebrates. Therefore, no informed consent was needed or obtained prior to preparation of the current manuscript.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (3): 284-290

Türkiye 21. yüzyıl pilonidal sinüs hastalığı araştırmalarında liderdir

Dietrich Doll[1], Verena Stauffer[2], Maja Diekmann[1], Pieter Van Wyk[3], Markus M Luedi[4]

[1] St. Marienhospital, Prokto Cerrahi Anabilim Dalı, Vechta, Almanya
[2] Lindenhofgruppe, Acil Tıp Anabilim Dalı, Bern, İsviçre
[3] Karolinska Üniversitesi Hastanesi, Travma ve Akut Bakım Bölümü, Stockholm, İsveç
[4] Bern Üniversitesi Hastanesi, Bern Üniversitesi Anesteziyoloji Anabilim Dalı, Bern, İsviçre

ÖZET

Giriş ve Amaç: Pilonidal sinüs hastalığı (PSD), son 188 yıldır tanınan bir patolojidir. Bu yaygın hastalığa bilimsel ilginin zaman içinde artmış mı yoksa azalmış mı olduğunu araştırdık. Araştırmamız, 1833-2018 yılları arası dünya literatürünün analizini içeriyordu.

Gereç ve Yöntem: Pilonidal sinüs hastalığı ile ilgili, ülkeye, yayın yılına ve dahil edilen veya açıklanan hasta sayısına göre değerlendirilmiş tüm yayınları tanımlamak için bir PubMed araştırması yapılmıştır.

Bulgular: İncelenen hasta sayısı artmakta olup, 1970 yılından bu yana her dekadda 10.000'den fazla hasta yayınlanmıştır ve 2010 yılında toplam hasta sayısı n= 40.000'i aşmıştır. Türkiye, Akdeniz bölgesindeki hastaların %39'unu, dünya genelindeyse hastaların %18'ini bildirerek bilimsel araştırmalara öncülük etmektedir. İtalya Akdeniz hastalarının %26'sını ve küresel toplamın %12'sini bildirmektedir. Flep çalışmaları artarken, birincil açık tedavi çalışmaları ise 1940'taki %40'lık değerden günümüzdeki %10'ların altındaki düzeylere düşmüştür. Bugün yapılan çalışmaların yüzde yirmisi birincil medyan yaklaşımları bildirmekte ve randomize kontrollü çalışmaların sayısı artmaktadır.

Sonuç: Türk cerrahları şu anda pilonidal sinüs literatüründeki aslan payını yayınlamaktadır.

Anahtar Kelimeler: Kıl, pilonidal sinüs, cerrahi, nüks oranı, yayınlar, çalışma büyüklüğü

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Unusual infectious agents detected in appendectomy specimens: A retrospective analysis of 42 cases

Kemal Barış Sarıcı[1], Sami Akbulut[1], Mehmet Özcan[2], Khaled Demyati[3], Emine Şamdancı[2], Burak Işık[1]

[1] Department of Surgery, Inonu University Faculty of Medicine, Malatya, Turkey
[2] Department of Pathology, Inonu University Faculty of Medicine, Malatya, Turkey
[3] Department of Surgery, An-Najah National University, Nablus, Palestinian Territories

ABSTRACT

Objective: The aim of this study was to evaluate the clinical and histopathological features of 42 patients with unusual infectious agents detected in their appendectomy specimens.

Material and Methods: Between January 1999 and November 2018, 2.754 patients underwent emergency or incidental appendectomy in our clinic, and their pathology reports were retrospectively reviewed. Unusual infectious agents or eosinophilic infiltration of the appendix were reported in the initial pathological examinations of 57 patients. The pathological slides of these patients were re-examined by histopathologists. The examinations revealed that 15 of these patients had no microscopic findings suggestive of parasitic infections. The remaining 42 patients with unusual appendiceal infectious agents were included into the study.

Results: A total of 42 patients (25 females and 17 males) aged 18 to 75 years were included into this study. While 32 of these patients (76%) underwent emergency appendectomy with a presumed diagnosis of acute appendicitis (AAp), the remaining 10 patients underwent incidental appendectomy for various reasons. Twenty-two patients (52.4%) had histopathological changes consistent with AAp while 20 patients had no evidence of AAp. Histopathological examination revealed infection with Enterobius vermicularis in 38 of the patients, Taenia species in 2, and Ascaris lumbricoides and *Actinomyces* species in 1 patient each. A total of 24 patients were treated for infections with mebendazole (n= 20), albendazole (n= 1), niclosamide (n= 2), and amoxicillin (n= 1).

Conclusion: Unusual infectious agents should be considered as factors potentially triggering AAp, especially in patients living in endemic areas. The appendiceal stump should be inspected for parasite residues.

Keywords: Acute appendicitis, enterobiasis, taeniasis, actinomycosis, ascariasis

INTRODUCTION

Acute appendicitis (AAp) is one of the most common causes for admission to emergency units due to abdominal pain, and appendectomy is one of the most frequently carried out surgical procedures worldwide. The pathogenesis of AAp is believed to reflect an initial insult to the mucosa, resulting from luminal obstruction, followed by bacterial infection that progressively spreads from the mucosa into the wall of the appendix. It has been previously shown that multiple parasitic diseases can cause AAp in many parts of the world, in particular in underdeveloped countries due to socio-cultural issues and poor hygienic conditions (1-10). The ability of parasites to cause AAp has been debated in the past (3,4,11). Parasites found in the appendix can cause symptoms of AAp, but parasitic infections are rarely the cause of AAp. Herein, we aimed to evaluate the clinical and histopathological features of 42 patients whose appendectomy specimens were compatible with unusual microbial pathogens.

MATERIAL and METHODS

The primary aim of this study was to share the demographic and histopathological features of patients with unusual microbial pathogens or eosinophilic infiltration in appendectomy specimens. In order to achieve this goal, the pathological reports of patients who underwent appendectomy with a preliminary diagnosis of AAp in the Department of Surgery İnönü University, Faculty of Medicine between January

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Corresponding Author
Sami Akbulut
E-mail: akbulutsami@gmail.com

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1999 and November 2018 were reviewed retrospectively. In the same period, pathological reports of patients who underwent incidental appendectomy for any reason were also reviewed. As a result, pathological reports of 2.754 patients who underwent appendectomy were examined in detail. The pathology slides of 57 patients whose initial pathological examinations had been reported as unusual microbial pathogens or eosinophilic infiltration were re-examined by two histopathologists. The examinations revealed that 15 of these patients had no evidence of any direct or indirect evidence of parasitic infections. Histopathological findings of the remaining 42 patients were consistent with unusual microbial pathogens. The following parameters were examined in this study: age (years), sex (male, female), indication of appendectomy (presumed diagnosis of AAp, incidental appendectomy), appendix width (mm), appendix length (mm), histopathological features (AAp, appendix vermiformis, perforated AAp), and unusual histopathological findings (enterobius vermicularis, actinomyces spp., taenia spp.). Ethical approval of the study was obtained from Inonu University institutional review board for non-interventional studies (approval no: 2019/3-3).

RESULTS

A total of 2.754 patients underwent emergency or incidental appendectomy at our clinic. Of these, 42 patients (1.52%) had unusual infectious pathogens detected in their appendectomy specimens. Of the 42 patients, aged between 18 and 75 years, 25 were females and 17 were males. The age of the men ranged from 18 to 75 years (mean ± SD: 34.2 ± 16.5, median: 27 years), while the age of the women ranged from 18 to 73 years (mean ± SD: 32.7 ± 14.0, median: 30 years). The lengths of appendectomy specimens ranged from 10 to 90 mm (mean ± SD: 59 ± 20.7, median: 60 mm), while their diameter ranged from 4 to 30 mm (mean ± SD: 7.18 ± 4.8, median: 6 mm).

While 32 patients underwent emergency appendectomy with a presumed diagnosis of AAp, the remaining 10 patients underwent incidental appendectomy for various reasons. Histopathologically, 22 patients had inflammatory cell infiltration consistent with AAp in the appendectomy specimens, while 20 patients had no evidence of AAp in their appendectomy specimen. AAp was detected in 21 (65.6%) patients who underwent emergency appendectomy, whereas AAp was detected in only 1 (10%) of the patients who underwent incidental appendectomy. Macroscopically, 38 patients had no perforation in the appendectomy specimen, while the remaining 4 patients had perforation in the specimens. Histopathological examination of the appendectomy specimen revealed Enterobius vermicularis (pinworm), in 38 patients (Figure 1); Taenia saginata (tapeworm), in 2 patients (Figure 2); Ascaris lumbricoides (roundworm), in one patient; and Actinomyces spp. in one patient (Figure 3a-b). The main surgical indications in patients who underwent incidental appendectomy were living donor hepatectomy (n= 5), ovarian cyst rupture (n= 2), laparoscopic cholecystectomy (n= 1), peptic ulcer perforation (n= 1), and Amyand's hernia (n= 1).

Twenty patients with pinworm infection were given a single dose of mebendazole (100 mg), and the same dose was repeated one week later. Patients with Actinomyces spp. were given oral amoxicillin treatment for four months. Patients with tapeworm infection were administered a single dose (2000 mg) of niclosamide. Patients with roundworms were given a single dose of albendazole (400 mg), and the same dose was repeated three weeks later. Postoperative anthelminthic treatment was not recommended in the remaining patients in line with our clinical approach. None of the patients who did or did not receive postoperative anthelminthic treatment develop any new signs or symptoms indicating parasitic infection during the follow-up period.

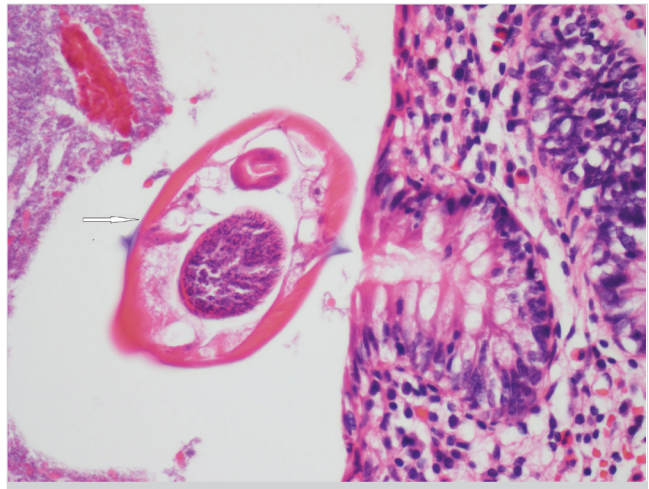

Figure 1. Enterobius vermicularis in the lumen of the appendix vermicularis (arrow) (HEx10).

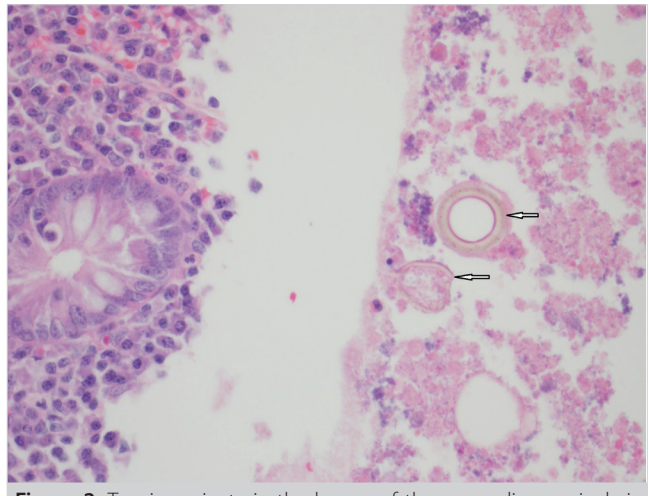

Figure 2. Taenia saginata in the lumen of the appendix vermicularis (arrows) (HEx10).

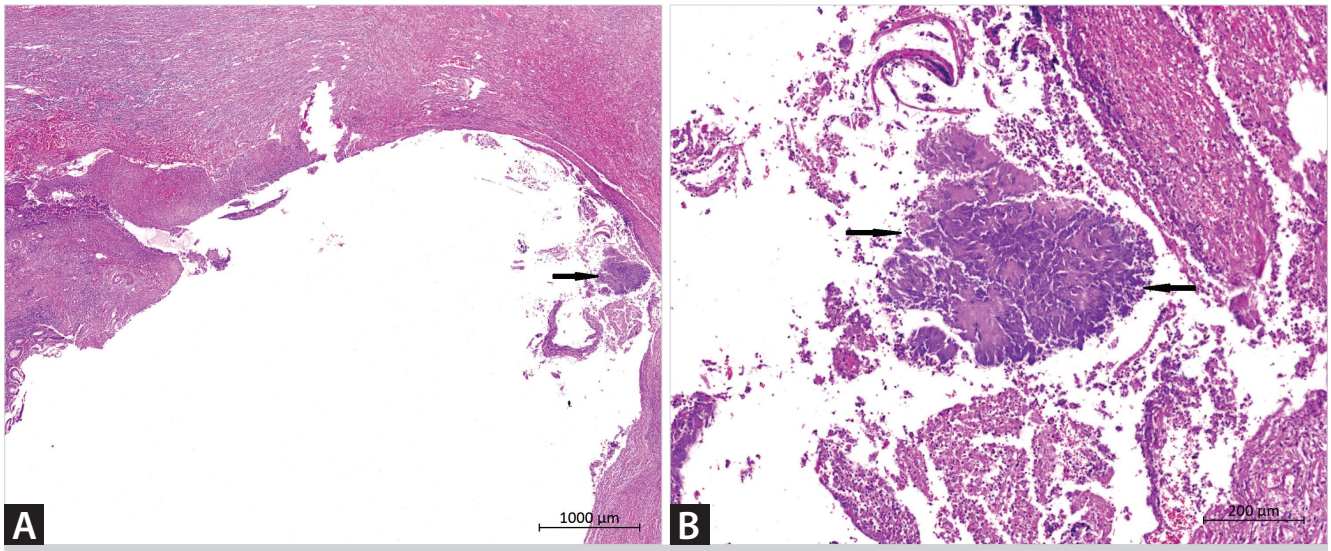

Figure 3. Actinomyces colony (a, b) in the lumen of the appendix vermicularis (arrows) (HEx10).

DISCUSSION

AAp is one of the most common acute surgical emergencies, with an incidence of approximately 100 per 100.000 people (1,2). The incidence varies with different age groups and in different countries, and is lower in populations where a high-fiber diet is consumed (1,12). The pathogenesis of AAp is believed to reflect an initial insult to the mucosa, resulting from luminal obstruction, followed by bacterial infection that progressively spreads from the mucosa into the appendix wall. This luminal obstruction can be caused by fecalith, lymphoid hyperplasia, tumor, or parasites such as pinworms (most commonly), roundworms, tapeworms, or entamoeba histolytica. Inflammation of the appendiceal wall leads to ischemia, necrosis, and eventually perforation, which can result in a localized abscess, plastron, or generalized peritonitis (13).

AAp is pathologically classified in various studies as catarrhal, suppurative, gangrenous, and perforated, according to the degree of inflammation of the various layers of the appendix vermiformis wall. Catarrhal or focal appendicitis is characterized by the initial stage of the inflammation consisting of neutrophils, while edema and inflammation are limited to the mucosal and submucosal areas. In suppurative AAp, inflammation is characterized by marked edema with or without pus involving all the wall layers. In gangrenous AAp, inflammation is seen in all layers, and there are dilated and congested blood vessels in the serosa with necrosis of appendiceal walls. Perforated AAp is characterized by perforation in the serosa and muscularis propria due to inflammation (11,13).

The ability of parasites to cause AAp has been debated (3,4,11). Parasites found in the appendix can cause clinical symptoms of AAp, but parasitic infection is rarely the cause of true AAp. In the majority of parasitic cases, there is no histological evidence of acute inflammation and a significant proportion of the patients infected with pinworm are asymptomatic (5-7). There is a wide spectrum of pathologic findings, ranging from nonspecific changes to perforated AAp (3,11). With careful pathological examination, helminths and their ova may be identified in appendectomy specimens (3).

Numerous parasitic osrganisms can cause AAp and initiate the clinical symptoms of AAp (3,8,9,11). The most common parasites causing AAp are pinworm, tapeworm, roundworm, and the schistosoma species (8,9). The incidence of parasites in patients who undergo appendectomy due to AAp is between 0.35% and 12.5% in different parts of the world, which is known to vary according to the different age groups (children or adults) and geographical regions (2-10). A subset of studies published in Turkey has shown that the prevalence of appendiceal parasites in patients who underwent appendectomy due to AAp ranged from 0.7% to 3.15% (3,9,11,14-16).

Enterobiasis, are the most common helminths that affect humans and have a worldwide distribution, including even developed countries (17). This small parasite is predominantly found in pediatric populations, with approximately 4% to 28% of children infected (18). Enterobiasis infection is usually asymptomatic; however, children with high parasitic burdens have impairments in physical, intellectual, and cognitive development (18). Pinworms inhabit the cecum and are able to crawl into the lumen of the appendix, leading to clinical manifestations resembling AAp. Zouari et al. (7) have reported that 50% of pediatric patients with negative appendectomy had pinworm infection. This study suggests that enterobiasis should be considered in children with suspected AAp, and recommends that all appendectomy specimens be examined histopathologically, regardless of whether the specimens are macroscopically normal or

not (7). Although the prevalence of enterobiasis in appendectomy specimens ranges from 0.2% to 41.8%, it has been shown to be around 1-2% (3,4,9,11,16). In the present study, pinworm was detected in the appendectomy specimens of 1.16% of the patients, which is comparable to the literature.

Taeniasis is characterized by the presence of tapeworms in the lumen of the intestine. Eggs are released when tapeworms shed gravid proglottids into the intestine, which are then shed into stools. Patients with tapeworm infection are usually asymptomatic and often only present after passing a proglottid segment in stool (19). The prevalence of tapeworm in appendectomy specimens ranges from 0.039% to 0.45%, and according to a large literature analysis, tapeworm has been detected in 0.001% of patients with AAp (5,9,16). In the present study, tapeworm was detected in appendectomy specimens of 0.072% of the patients.

Ascariasis is one of the most common helminthic diseases and is seen in the intestines of individuals in tropical and semi-tropical countries (9,20). Ascariasis-associated AAp is a form of wandering ascariasis. Ascariasis can be found in the normal appendix but may also be associated with appendicitis. In a study from India, 11 children have been found to have appendiceal roundworms during surgery for different intestinal complications caused by roundworms, 8 of whom (72.7%) had roundworms inside their vermiform appendix but not did not suffer from AAp, whereas the remaining three patients (27.2%) were found to have Ascariasis-associated AAp. The characteristic finding in the ascaris-infested vermiform appendix is that the worm is positioned with its head at the base and its tail at the tip of the appendix (20). In the present study, roundworm was detected in appendectomy specimens of 0.036% of the patients.

Actinomycosis is a rare chronic infectious bacterial disease caused by Actinomyces subtypes. Actinomycosis species are gram-positive bacteria, which are normal commensals of the oral cavity, gastrointestinal tract, and urogenital tract, but they become pathogenic in the presence of necrotic tissue. The cervicofacial, thoracic, and abdominopelvic regions are the most common sites involved in this type of disease. In abdominal actinomycosis, the most commonly involved site is the ileocecal region, including the appendix (21-23). It has been reported that the prevalence of appendiceal Actinomyces in patients undergoing appendectomy due to AAp ranges from 0.02% to 0.06% (21,22). In the present study, Actinomyces species were detected in a single appendectomy specimen (0.036% of the patients).

It is not yet clear whether appendectomy is sufficient in patients with parasites detected in their appendectomy specimen, or whether postoperative medical treatment should be given. While the prevalence of intestinal parasitic infections is high, the morbidity and mortality caused by these infections is much lower than expected. They are usually considered an unimportant problem, especially in asymptomatic patients. However, intestinal parasitic infections associated with clinical disease are also well documented. Ascariasis can result in fatal intestinal obstruction, hookworm infections can cause iron deficiency anemia, trichuria causes chronic dysentery and is also associated with rectal prolapse, Amebiasis can result in dysentery and extraintestinal complications, and finally giardiasis is associated with acute diarrhea, steatorrhea, and lactose intolerance.

These complications imply that every patient with parasites detected in the appendectomy specimen should receive medical treatment in the postoperative period. A comprehensive literature review published by Akbulut et al. (9) in 2011 showed that most patients with parasitic, tuberculosis, or actinomyces in appendectomy specimens received medical treatment postoperatively. Based on their experience from review studies, Akbulut et al. (9) stated that patients must receive anthelmintic treatment because appendectomy treats only the consequence and not the cause of the disease. Considering the previous experience in our clinic (3), patients with appendiceal parasitic disease usually receive routine postoperative anthelmintic treatment. However, our clinical approach has changed in recent years. We do not recommend routine postoperative treatment for adult patients who have no other clinical signs or symptoms indicating parasitic disease. We do; however, routinely administer postoperative medical treatment for patients with Actinomyces and tuberculosis infections characterized by chronic granulomatous inflammation.

In summary, parasitic infections should be considered as an underlying factor causing AAp, especially in patients living in underdeveloped countries, poor hygiene conditions, and in close-living areas. Parasitic infections can cause inflammation of the appendix or can imitate AAp clinically. It is recommended that all appendectomy specimens be examined histopathologically, regardless of whether the specimens are macroscopically normal. It is still unclear whether appendectomy is sufficient in these patients or whether postoperative medical treatment should be given.

Ethics Committee Approval: Ethics committee approval was received for this study from İnönü University Health Science Non-interventional Clinical Research Ethical Committee (05.02.2019/2019 3-3).

Peer-review: Externally peer-reviewed.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Apendektomi spesimeninde tespit edilen sıra dışı enfeksiyon ajanları: 42 olgunun retrospektif analizi

Kemal Barış Sarıcı[1], Sami Akbulut[1], Mehmet Özcan[2], Khaled Demyati[3], Emine Şamdancı[2], Burak Işık[1]

[1] İnönü Üniversitesi Tıp Fakültesi, Cerrahi Anabilim Dalı, Malatya, Türkiye
[2] İnönü Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Malatya, Turkey
[3] An-Najah National Üniversitesi, Cerrahi Anabilim Dalı, Nablus, Filisitin Bölgesi

ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, apendektomi spesimeninde sıra dışı enfeksiyon ajanları tespit edilen 42 hastanın klinik ve histopatolojik özelliklerini değerlendirmektir.

Gereç ve Yöntem: Ocak 1999 ve Kasım 2018 arasında kliniğimizde acil veya insidental apendektomi yapılan 2.754 hastanın patoloji raporları retrospektif olarak incelendi. Elli yedi hastanın ilk patolojik değerlendirmesinde sıra dışı enfeksiyon ajanları veya eozinofilik infiltrasyonun rapor edildiği bulundu. Bu hastaların patoloji preparatları histopatologlar tarafından yeniden incelendi. Yeniden değerlendirme sonucunda hastaların 15'inde sıra dışı enfeksiyon ajanlarını düşündüren herhangi bir mikroskobik bulgu tespit edilmedi. Sıra dışı apendiceal enfeksiyon ajanları saptanan 42 hasta çalışmaya dahil edildi.

Bulgular: Yaşları 18 ila 75 yıl arasında değişen toplam 42 hasta (25 kadın ve 17 erkek) bu çalışmaya dahil edildi. Bu hastaların 32 (%76)'sine akut apandisit ön tanısıyla acil apendektomi yapılırken geriye kalan 10 hastaya çeşitli sebeplerden dolayı insidental apendektomi yapıldı. Yirmi iki hastada (%52,4) akut apandisit ile uyumlu histopatolojik değişiklikler bulunurken 20 hastada akut apandisit bulgusu yoktu. Histopatolojik incelemede 38 hastada Enterobius vermicularis, ikisinde Taenia türü, birinde Ascaris türü ve bir hastada *Actinomyces* türü saptandı. Toplam 24 hastaya mebendazol (n= 20), albendazol (n= 1), niklosamid (n= 2) ve amoksisilin (n= 1) tedavisi verildi.

Sonuç: Özellikle endemik bölgelerde yaşayan hastalarda akut apandisiti tetikleyen faktörler arasında sıra dışı enfeksiyon ajanları düşünülmelidir ve apendiks güdüğü parazit kalıntıları açısından incelenmelidir.

Anahtar Kelimeler: Akut apandisit, enterobiyazis, tenyazis, aktinomikozis, askariyazis

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Radioguided occult lesion localization for minimally-invasive parathyroidectomy without quick PTH monitoring and frozen section: impact of the learning curve

Lütfi Soylu[1], Oğuz Uğur Aydın[2], Seyfettin Ilgan[3], Serdar Özbaş[1], Banu Bilezikçi[4], Alptekin Gürsoy[5], Savaş Koçak[1]

[1] Department of Endocrine Surgery, Ankara Guven Hospital, Ankara, Turkey
[2] Department of Endocrine Surgery, Ankara Medicana International Hospital, Ankara, Turkey
[3] Department of Nuclear Medicine, Ankara Guven Hospital, Ankara, Turkey
[4] Department of Pathology, Ankara Guven Hospital, Ankara, Turkey
[5] Department of Endocrinology, Ankara Guven Hospital, Ankara, Turkey

ABSTRACT

Objective: Minimally-invasive parathyroidectomy (MIP) is a surgical procedure that reduces the duration of operation, hospital costs, and hypocalcemia, and shortens the length of hospital stay. This study addressed the important procedural details of the radioguided occult lesion localization (ROLL)-MIP technique and evaluated the consequences of the learning curve from a series of patients.

Material and Methods: A total of 80 patients who underwent ROLL-MIP for a single parathyroid adenoma were included into this retrospective study. In order to analyze the effect of the learning curve, these subjects were then divided into 2 groups per time period and the operative times were compared. Group A consisted of 22 previously reported patients who served as the control group. Group B consisted of 58 consecutive patients.

Results: Serum calcium and parathyroid hormone (PTH) levels were normalized in all of the patients within 2 days and remained normal during the follow-up period (31 ± 18.5 months). None of the patients who underwent ROLL-guided parathyroidectomy suffered temporary or permanent recurrent laryngeal nerve injuries. Mean operation time (time from incision to excision of the adenoma) was 23 ± 6 min in Group A and 18 ± 7 min in Group B. Mean operative times were significantly shorter in group B.

Conclusion: The success of MIP administered with the ROLL technique in a single adenomatous patient was quite high. This method seems especially valuable in patients with atypically located or small adenomas.

Keywords: Parathyroid adenoma, minimally-invasive parathyroidectomy, radioguided occult lesion localization

INTRODUCTION

Primary hyperparathyroidism (pHPT) is a generalized disorder of calcium, phosphate, and bone metabolism caused by an increased secretion of the parathyroid hormone, with a prevalence of 1-3% in western countries. The most common clinical presentation of pHPT is asymptomatic hypercalcemia (1-4). It is explained by a single parathyroid adenoma in most of the cases (80%-85%), followed by hyperplasia, double adenomas, and parathyroid carcinoma.

Surgery continues to remain the mainstay of treatment for patients with symptomatic pHPT (nephrolithiasis, symptomatic hypercalcemia). Indications for surgery during the monitoring of asymptomatic patients include an increase in serum calcium ≥ 1 mg/dL above the upper normal limit, a decreased glomerular filtration rate (< 60 mL/min), a reduction in bone density and/or the occurrence of fragility fracture, the occurrence of nephrolithiasis or nephrocalcinosis on the imaging study, and an age of < 50 years (5).

The unilateral focused surgical approach, known as minimally-invasive parathyroidectomy (MIP), is becoming more widespread, because it results in reduced operative time, lower hospital costs, a shorter hospital stay, and fewer events of transient hypocalcemia with cure rates equal to that of formal bilateral neck exploration.

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Corresponding Author
Lütfi Soylu
E-mail: lutfisoylu@hotmail.com

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Radioguided occult lesion localization (ROLL) is a new localization technique originally described for nonpalpable breast lesions (6). Recently, it has been reported that the use of ROLL for MIP in patients with pHPT due to a single parathyroid adenoma in the neck is technically safe and effective (7). It has also been shown that the ROLL technique does not impair the postoperative histopathological examination of the parathyroid glands.

Implementation of new procedures, including the ROLL-MIP, must be done in a responsible way to ensure that the procedures are performed correctly. This study addressed the important procedural details of the ROLL-MIP technique and evaluated the consequences of the learning curve from a series of patients.

MATERIAL and METHODS

A total of 80 patients who underwent ROLL-MIP for a single parathyroid adenoma were studied in this retrospective study. The study was conducted in accordance with the ethical standards set by the Declaration of Helsinki. Informed consent was obtained from all individual participants included into the study.

All diagnostic imaging studies and US-guided interventions were conducted by the same team member and all patients were operated on by the same surgical team headed by one of our senior endocrine surgeons.

All patients underwent a localization study consisting of dual-phase MIBI scintigraphy and high-resolution US. The parathyroid adenoma was localized preoperatively by scintigraphy and/or US. Diagnosis was confirmed by measuring the PTH in the needle aspirate of the suspicious lesions if scintigraphy and US were inconclusive or discordant. Since the recognition of an adenoma on a US is a prerequisite for ROLL, patients were excluded from the study when their cause of pHPT was neither correlated nor localized sonographically. Exclusion criteria were suspicion of multiple gland disease, multiple endocrine neoplasm syndrome, and thyroid disease requiring thyroidectomy. Surgical success was defined as the excision of the preoperatively identified lesions and normalization of the PTH and serum calcium levels.

Statistical Analysis

Analysis of the data was done using the IBM SPSS 25.0 statistical package program. Descriptive statistical methods (frequency, percentage, median, min-max) were used when the study data were evaluated. Normal distribution of the data was assessed using the Kolmogorov-Smirnow and Shapiro-Wilk tests, and the data were not normal. In the study, the Mann-Whitney U test was used for comparisons between the groups. Likelihood (P) values smaller than ✔ = 0.05 were significant and there was a difference between the groups, with large values being insignificant and no differences between the groups.

Patients

The study group consisted of all of the surgical candidates presenting at the Department of Endocrine Surgery of Güven Hospital with pHPT due to a single adenoma between September 2011 and November 2017. In order to analyze the effect of the learning curve, these subjects were then divided into 2 groups per time period, and the operative times were compared. Group A consisted of the first 22 previously reported patients, who served as the control group. Group B consisted of 58 consecutive patients enrolled between January 2014 and November 2017.

Group A included 3 males and 19 females, with an average age of 56 ± 14 years (35-85 years) at the time of primary diagnosis. Four out of the 22 patients had previously undergone thyroid/parathyroid surgery. Group B included 19 males and 39 females, with an average age of 50 ± 14 years (22-87 years) at the time of primary diagnosis. Of the patients in both groups, 10 had previously undergone thyroid/parathyroid surgery (4 in Group A, 6 in Group B). Demographic data, preoperative and postoperative serum calcium and PTH levels, localization of the adenoma, and operative time (time from incision to excision of the adenoma) were available for all patients (Table I). Final diagnosis was confirmed histopathologically.

Imaging studies and ROLL technique

We have previously described our imaging techniques and interventions for ROLL MIP. Briefly, the diagnosed single parathyroid adenomas were injected with 3.7-5.55 MBq (0.1-0.15 mCi) of Tc-99m labeled macro-aggregated albumin (MAA) on the morning of surgery, using a tuberculin syringe equipped with a 22-G standard needle under US guidance. The total injected volume was 0.1-0.15 mL, depending on the size of the adenoma.

Surgery

All patients were operated on under general anesthesia. Surgery was focused on the preoperatively located and injected index gland. Parathyroid adenomas were searched for and localized over the skin with a gamma probe equipped with an 11-mm angled probe (Europrobe 3; EuroMedical Instrument, Paris, France) to decide the best incision level (Figure 1). Midline incisions were made in a skin fold at an appropriate level according to gamma probe measurements. The incisions were slightly weighted toward the expected side of the adenoma. Excised lesions were counted ex-vivo with the gamma probe to make sure that the preoperatively detected and injected lesion had been found (Figure 2,3). Frozen sections and intraoperative quick PTH monitoring were not routinely used. Time from incision to excision of the adenoma (operative time) was recorded. Postoperative follow-up consisted of the evaluation of serum calcium and PTH levels sampled at 6-8 h after surgery. The patients were discharged on calcium and vitamin D supplementation for 2 weeks, with a control visit after 1 week.

Table 1. Group demographics and comparisons

	Group A (n= 22)	Group B (n= 58)	p
Sex			
Female	19 (86.4%)	37 (63.8%)	0.090[a]
Male	3 (13.6%)	21 (36.2%)	
Age* (years)	57 (35-85)	46 (22-87)	0.091[b]
Operative time* (min)	23 (13-35)	16 (8-45)	**0.000**[b]
Adenoma Location			
LI	7 (31.8%)	25 (43.1%)	
LS	6 (27.3%)	5 (8.6%)	**0.000**[a]
RI	2 (9.1%)	25 (43.1%)	
RS	7 (31.8%)	3 (5.2%)	
Size on US* (mm × mm)	73 (21-248)	150 (21-1320)	**0.000**[b]
Previous cervical exploration			
-	18 (81.8%)	52 (89.7%)	
TT	2 (9.1%)	5 (8.6%)	--
BST	--	1 (1.7%)	
BST + CTx	1 (4.5%)	--	
UE	1 (4.5%)	--	

a: Chi-Square Test, b: Mann-Whitney U Test, *: Median (Min-Max).

Figure 1. Lack of background activity makes the detection of the injected adenomas with gamma probe over the skin easier during the ROLL-MIP technique. This facilitates the selection of the best incision level before surgery.

Figure 2. Ex-vivo counting of the excised parathyroid adenoma after removal. The count ratio from the excised adenoma to the lesion bed is always high enough to determine an effective removal of the lesions. Reflux of the injected radiopharmaceutical may cause recognizable residual activity in the lesion bed, especially in small adenomas. This should not alert the surgeon to incomplete surgical excision if completeness of the adenoma is visually confirmed.

RESULTS

Localization of the adenoma was determined based on the PTH levels in the needle washout in 26 patients, by concordant US and scintigraphy results in 41 patients, and by only US results in 13 patients. The size of the successfully biopsied or injected lesions ranged from 7 × 3 mm to 40 × 33 mm in diameter. Parathyroid adenomas were found in inferior parathyroid locations in 59 (73.75%) patients (32 left inferior, 27 right inferior) and in superior parathyroid locations in 21 (26.25%) patients (11 left superior, 10 right superior). US-guided interventions were made without local anesthesia and were well-tolerated without complications in 78 patients. In the remaining 2 patients, who had a phobia of needle procedures, the injections were made after general anesthesia in the operating room.

Radioguided Surgery

All of the injected lesions were successfully located over the skin with the gamma probe. Despite previous cervical explorations in 10 patients, the gamma probe safely guided the surgeon to the preoperatively injected lesions. Mean operation time (time from incision to excision of the adenoma) was 23 ± 7 min in Group A and 18 ± 7 min in Group B. Mean operative times were significantly shorter in group B.

Serum calcium and PTH levels normalized in all of the patients within 2 days and remained normal during the follow-up peri-

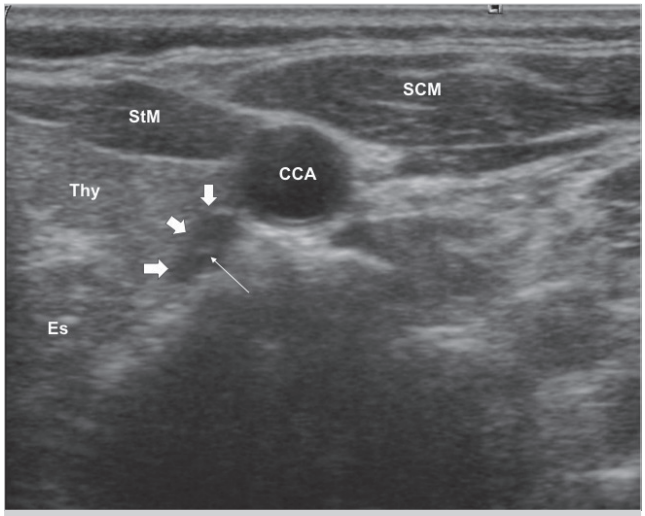

Figure 3. The axial slice of the left thyroid lobe shows a markedly hypoechoic solid lesion, which is typical with extra thyroidal parathyroid adenoma (thick arrows). Thin arrow shows the hyperechoic needle tip at the center of the lesion during injection.

CCA: Left common carotid artery, StM: Strap muscles, SCM: Sternocleidomastoid muscle, Thy: Left thyroid lobe, Es: Esophagus.

od (31 ± 18.5 months). None of the patients who underwent ROLL-guided parathyroidectomy suffered temporary or permanent recurrent laryngeal nerve injuries. No wound infection, seroma formation, or hematomas occurred in our patients.

DISCUSSION

pHPT is a complex endocrinopathy involving calcium metabolism and a potent hormone made by the parathyroid glands. Diagnosis is confirmed by inappropriately elevated parathyroid hormone levels accompanied by high-normal or elevated serum calcium. Although classic presentation of pHPT involves the presence of renal stones, bone loss, and gastrointestinal complaints, the screening of serum calcium levels during routine medical examinations has changed the clinical spectrum to include patients with minimally objective symptoms who are referred to as "asymptomatic".

Over the past decade, there has been a shift towards MIP; a focused operation whereby only 1 parathyroid is removed. Compared to the conventional neck exploration, in which all 4 glands are investigated intra-operatively, MIP is associated with a shorter operating time, lower complication rates, smaller incision size, shorter hospital stay, and greater patient satisfaction (8-11).

Imaging is critical in order to enable successful MIP. Aside from its ability to localize the pathological gland(s), accurate imaging provides valuable anatomical information for the surgeon.

Preoperative localization studies have been regarded as necessary but their use is still controversial (12). Some authors suggest that these studies may reduce surgical time, technical failures, complication rates (13) by improving pHPT operation by MIP (14), and radioguided surgery (15,16). Several imaging techniques, such as neck ultrasound (US) (17,18), computerized tomography (CT) (19), and dual-phase Tc-99m MIBI scan with single-photon emission CT (SPECT)/CT are currently available (20) although neck US and MIBI scans are generally used as the first tools in the diagnostic approach of pHPT (21).

ROLL-MIP seems to have several advantages over standard radioguided MIP with an intravenous injection of Tc-99m MIBI: 1) It is independent from the uptake potential of the diseased parathyroid glands and could be used in patients with negative MIBI scintigraphy, 2) It requires very small activity compared with the systemic injection of Tc-99m MIBI (0.1-0.15 mCi vs. 15-20 mCi), 3) The ROLL technique does not cause background activity and potentially gives the best lesion-to-background count ratios, 4) Contrary to the intravenous injection method, the lack of background activity makes the detection of injected adenomas with a gamma probe over the skin easier and facilitates the selection of the incision level as well, and 5) the technique warrants the excision of the preoperatively located adenoma since direct inoculation of Tc-99m labeled particles does not cause false-positive results like an intravenous injection of Tc-99m MIBI.

In our series, all of the preoperatively depicted parathyroid adenomas were found in a timely manner (23 ± 7 min in Group A, 18 ± 7 min in Group B) for the entire study group, including inpatients that had undergone previous neck explorations. In this study, we observed the effect of the learning curve over the duration of the operation, which generally showed a decrease in the duration of the operation as experience increased.

In general, MIP shortens operative and anesthesia time (22-24). In the literature, mean operation time of MIP ranges from 15 to 56 min (25,26). It also shortens hospitalization time (19). In this study, duration of the surgery was short 19.4 ± 7.2 (8-45 min) in the whole group and the patients were not hospitalized for longer than 1 day.

None of the patients had a permanent rise in their PTH and serum calcium levels or required a reoperation due to insufficient resection. In our study, we reached a 100% success rate without requiring additional tests like intraoperative quick PTH monitoring and frozen section.

In summary, the success of the ROLL-MIP technique without rapid PTH measurement and frozen section was quite high in patients with single adenoma. Repeated application of the ROLL-MIP technique resulted in a significant decrease in operative time, as expected. The technique seems to be particularly valuable in patients with atypically located or small adenomas.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Ankara Guven Hospital (18.03.2020)

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Hızlı PTH ölçümü ve frozen inceleme olmadan occult lezyonlarda radyolojik kılavuzlu minimal invaziv paratiroidektomi: öğrenme eğrisinin etkisi

Lütfi Soylu[1], Oğuz Uğur Aydın[2], Seyfettin Ilgan[3], Serdar Özbaş[1], Banu Bilezikçi[4], Alptekin Gürsoy[5], Savaş Koçak[1]

[1] Ankara Güven Hastanesi, Endokrin Cerrahi Bölümü, Ankara, Türkiye
[2] Medicana International Ankara Hastanesi, Endokrin Cerrahi Bölümü, Ankara, Türkiye
[3] Ankara Güven Hastanesi, Nükleer Tıp Bölümü, Ankara, Türkiye
[4] Ankara Güven Hastanesi, Patoloji Bölümü, Ankara, Türkiye
[5] Ankara Güven Hastanesi, Endokrinoloji Bölümü, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Minimal invaziv paratiroidektomi (MIP); operasyon süresini, hastane maliyetlerini ve hipokalsemiyi azaltan ve hastanede kalış süresini kısaltan cerrahi bir işlemdir. Bu çalışma, radyoaktif madde ile küçük lezyon lokalizasyonunun (ROLL)-MIP tekniğinin önemli prosedürel detaylarını ele almakta ve bir dizi hastadan gelen öğrenme eğrisinin sonuçlarını değerlendirmektedir.

Gereç ve Yöntem: Bu retrospektif çalışmada tek paratiroid adenomu için ROLL-MIP uygulanan toplam 80 hasta incelendi. Öğrenme eğrisinin etkisini analiz etmek için hastalar operasyon zamanlarına göre 2 gruba ayrıldı ve operasyon zamanları karşılaştırıldı. Grup A, daha önce kontrol grubu olarak görev yapan 22 hastadan oluşuyordu. B grubu ardışık 58 hastadan oluşuyordu.

Bulgular: Serum kalsiyum ve paratiroid hormonu (PTH) düzeyleri tüm hastalarda 2 gün içerisinde normalize edildi ve takiplerinde (31 ± 18.5 ay) normal kaldı. ROLL eşliğinde paratiroidektomi yapılan hiçbir hastada geçici veya kalıcı rekürren laringeal sinir yaralanması olmadı. Ortalama ameliyat süresi (insizyondan adenomun eksizyonuna kadar geçen süre) Grup A'da 23 ± 6 dakika ve Grup B'de 18 ± 7 dakika idi. Ortalama ameliyat süresi grup B'de anlamlı olarak kısaydı.

Sonuç: Tek adenomalı hastalarda ROLL tekniği ile uygulanan MIP başarısı oldukça yüksekti. Bu yöntem özellikle atipik yerleşimli veya küçük adenomlu hastalarda değerli gibi görünmektedir.

Anahtar Kelimeler: Paratiroid adenomu, minimal invaziv paratiroidektomi, radyoaktif madde yardımlı occult lezyon

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ORIGINAL ARTICLE
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Robotic nipple sparing mastectomy through a single incision: Advantages of starting with posterior dissection

Cihan Uras[1,2,3], Akif Enes Arıkan[1,2,3], Halil Kara[2,3,4], Onur Dülgeroğlu[2,4,5], Yakup Avşar[6]

[1] Acibadem Mehmet Ali Aydinlar University, School of Medicine, Department of General Surgery, Istanbul, Turkey
[2] Acibadem Mehmet Ali Aydinlar University, Research Institute of Senology, Istanbul, Turkey
[3] Acibadem Maslak Hospital, Department of General Surgery, Division of Breast Health and Diseases, Istanbul, Turkey
[4] Acibadem Mehmet Ali Aydinlar University, Vocational School of Health Sciences, Istanbul, Turkey
[5] Acibadem Atakent Hospital, Department of General Surgery, Division of Breast Health and Diseases, Istanbul, Turkey
[6] Private Avşar Clinic, Istanbul, Turkey

ABSTRACT

Objective: Loss of breast, which is an important body marking of women, causes a huge decrease in quality of life (QoL) after treatment. In order to overcome this morbidity and increase QoL, nipple sparing mastectomy (NSM) has been developed. Even though the demand for better cosmetic results has yielded endoscopic nipple sparing mastectomy, limitations like unsuitable optical window and limited manual control of rigid-tip instruments, and struggling to keep dissection space have led robotic nipple sparing mastectomy (rNSM) to be developed.

Material and Methods: Records of three patients who underwent to rNSM for invasive breast carcinoma with DaVinci Xi (Intuitive Surgical, Sunnyvale, CA) in affiliated hospitals of Acıbadem Mehmet Ali Aydınlar University, Research Institute of Senology in 2018 were investigated retrospectively. In all breasts (n= 4), dissection was started from the posterior side of breast.

Results: In the unit, 738 breast cancer patients underwent surgery between 2018 and 2019 with an NSM ratio of 31.4% (n= 232). Of these patients, three underwent rNSM with DaVinci Xi robotic system. The operation was performed on the left breast in one patient, right in one, and bilateral in one patient. Only in patient #2, who was a neoadjuvant chemotherapy recipient, seroma was observed six weeks after surgery (3 weeks after removal of drains) and spontaneously resolved in 4 weeks. No other complication was seen in all patients. In the follow-up period of median 21 months, no loco-regional recurrence or distant metastasis was seen.

Conclusion: A single incision robotic mastectomy can be performed easily and safely when the dissection starts from the pre-pectoral plane rather than the subcutaneous plane.

Keywords: Breast, robotic surgical procedure, minimally invasive surgical procedures

INTRODUCTION

In early periods, radical mastectomy (i.e. extended removal of the breast and neighboring tissues) was considered as the ultimate treatment (1). However, advancements in medical oncology and surgical technique (such as proven safety and efficiency with the protection of pectoral muscles and even the skin with or without nipple areolar complex in appropriate cases, tools with increased precision) have provided surgeons and patients with a better cosmetic outcome (2). Loss of breast, which is an important body marking of women, causes a huge decrease in quality of life (QoL) after treatment (2). In order to overcome this morbidity and increase QoL, nipple sparing mastectomy (NSM) has been developed (2). After proven oncological safety, patients and surgeons demanded better cosmetic results which yielded endoscopic nipple sparing mastectomy (eNSM) (2, 3). Even though eNSM was facilitated by many authors with oncological safety, limitations like unsuitable optical window due to two-dimensional endoscopic in-line camera and limitations in manual control of rigid-tip instruments by the natural curvature of the breast, and struggling to keep dissection space, robotic nipple sparing mastectomy (rNSM) was developed in Milan, in August of 2015 (4).

The search from the Web of Science (WOS) database for "robotic" and "mastectomy" words yielded 58 results; however, only 25 of them were related to robotic nipple sparing mastectomy (4-28).

In the literature, eight studies have investigated rNSM through single incision for therapeutic or prophylactic purposes (5, 6, 9, 21, 22, 26-28). The current study is

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Corresponding Author
Akif Enes Arıkan
E-mail: enesarikan@yahoo.com

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the first report of rNSM from Turkey and showed a different approach from the literature.

MATERIAL and METHODS

Records of three patients who underwent to rNSM for invasive breast carcinoma with DaVinci Xi (Intuitive Surgical, Sunnyvale, CA) (robot) in Acıbadem Maslak Hospital (an affiliation of Acıbadem Mehmet Ali Aydınlar University, Research Institute of Senology) in 2018 were investigated retrospectively. Demographics and operative and histopathology information of the patients were recorded. All patients had given informed consent for rNSM prior to surgery independent from this study.

This study was approved by Acıbadem Mehmet Ali Aydınlar University, Clinical Research Evaluation Ethical Board on 27.06.2019 with number of 2019-11/24.

Patient Positioning

All surgical procedures were performed under general anesthesia. Patient lied flat supine, contralateral arm to operation side was adducted, a soft pad was placed under the ipsilateral scapula, and ipsilateral arm was positioned over the head covered with sterile covering (Figure 1). The table was positioned in 5º tilted to the contralateral side.

Set-up of the Robotic System

The robot was positioned at the opposite side of the patient, middle of the robot's shoulder positioned to the nipple line, and arms crossed over the torso of the patient. Target markings of the robot was aligned with the incision and the nipple. Three ports of the robot were introduced through a single access system (SAS) in triangular setting to prevent collision and sustain better approximation (Figure 2). A monopolar cautery attached scissor was placed on the right arm and a bipolar cautery attached fenestrated forceps was placed on the left arm of the robot. A 30º camera (Intuitive Surgical®, Denzlingen, Germany) was introduced through the port in the top center. Following that, the other two instruments were introduced to the pouch under camera vision.

While the surgeon was sitting in the console, the assistant surgeon was waiting next to the patient to watch over the robot arms and trans-illumination (visual observation) through the breast skin to prevent injuries.

Surgical Technique

A 5-cm lateral peripheral incision starting from the middle portion of the breast to the cranial direction, positioned on the anterior axillary line in parallel to the curvature of the breast, was performed (Figure 3, 4). Sentinel lymph node biopsy (SLNB)

Figure 1. Position of the patient on the operation table.

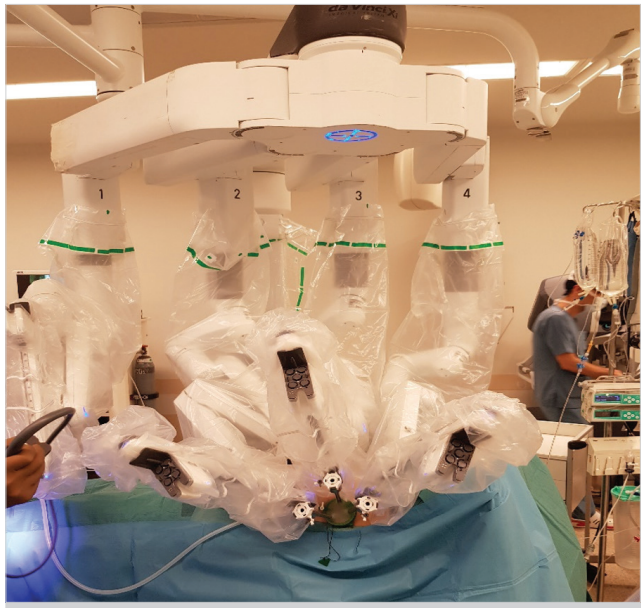

Figure 2. Docking of the Da Vinci Xi Robotic System.

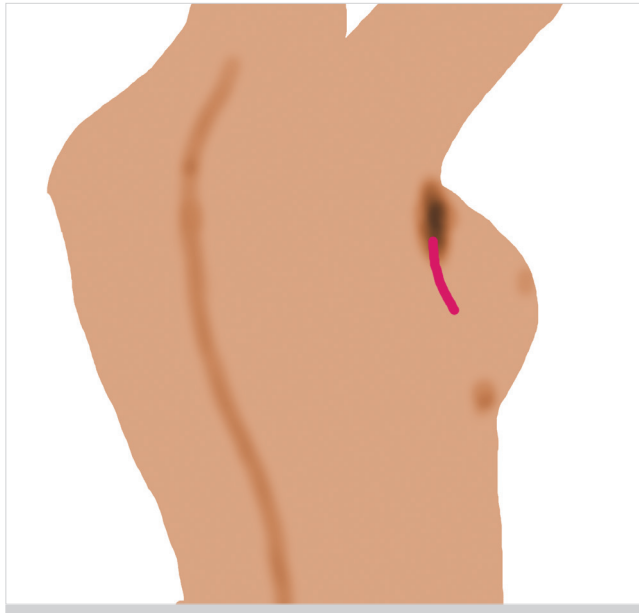

Figure 3. Location of the incision.

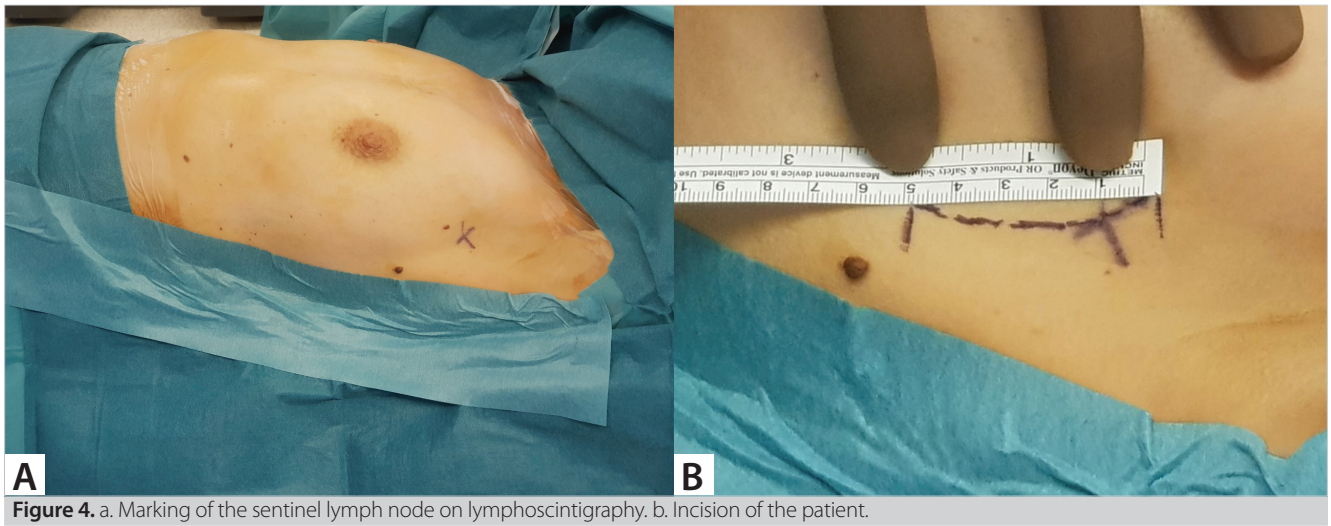

Figure 4. a. Marking of the sentinel lymph node on lymphoscintigraphy. b. Incision of the patient.

was performed through this incision with conventional open technique via radioisotope method. The incision was planned to allow axillary lymph node dissection (ALND) through the same incision after removal of the breast tissue, in case SLNB resulted positive.

After SLNB, a pouch, 3-cm in length, was dissected between the fascia and anterior side of the pectoralis muscle with Bouvie cautery to introduce SAS. After that, GelPOINT Mini (Applied Medical, Rancho Santa Margarita, CA) was positioned as SAS to the pouch, and the posterior cavity was insufflated with CO2 gas at a pressure of 6 mmHg (Figure 5).

Posterior side of the breast was dissected with electrocautery attached scissor, while the breast tissue was handled with fenestrated forceps (Figure 6). Extension of the dissection was observed externally by the assistant surgeon next to the patient. Caution for the preservation of the perforating branch from the 2nd intercostal artery was sustained to reduce risk for loss of nipple areolar complex (NAC).

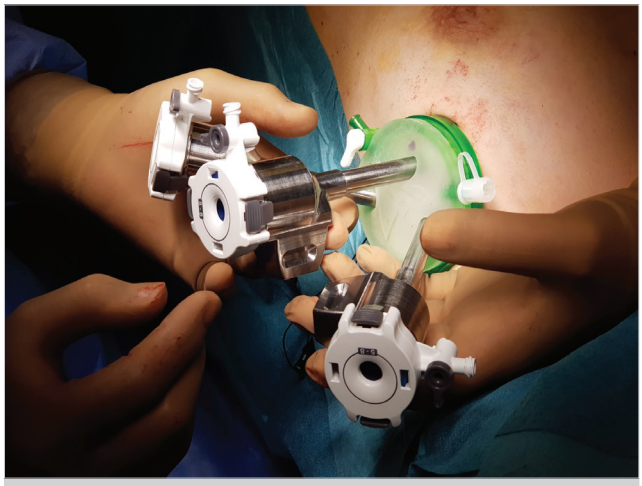

Figure 5. Positioning of the air sealing system and robotic ports.

After having completed the posterior dissection, the robotic system was undocked and SAS removed. In order not to cause ischemia, 500 mcg of adrenaline was diluted in 1000 mL 0.9% NaCl solution as tumescent solution (TS). Two-hundred milliliters of TS was injected to the subdermal layer of the breast skin by liposuction cannula to sustain hydro-dissection between the skin and breast tissue with additional effect of vasoconstriction to lower bleeding. After that, an anterior pouch between the skin and breast tissue for SAS was created with scissor under direct vision and SAS was placed similarly. The anterior cavity was insufflated with CO_2 gas at a pressure of 6 mmHg (Figure 7), and dissection was performed with scissor and fenestrated forceps. Retro-nipple breast tissue was cored-out and sent to frozen section assessment for malignant cells. If malignancy was detected in the frozen section, then NAC was removed.

After completion of NSM, an implant (either silicone-gel or expender according to the necessity of radiotherapy depending on the result of SLNB) was placed by a plastic, reconstructive and esthetic surgeon through the same incision.

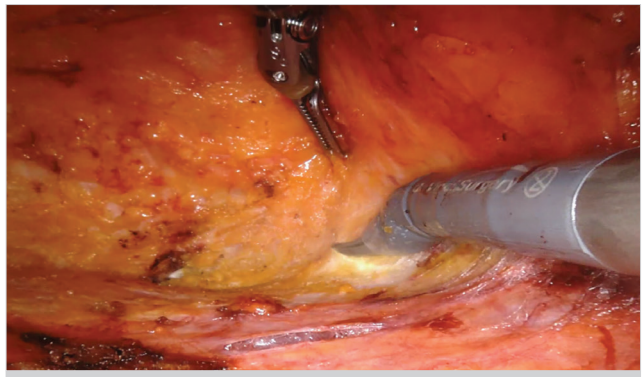

Figure 6. View of the posterior dissection by the Da Vinci Xi robotic System.

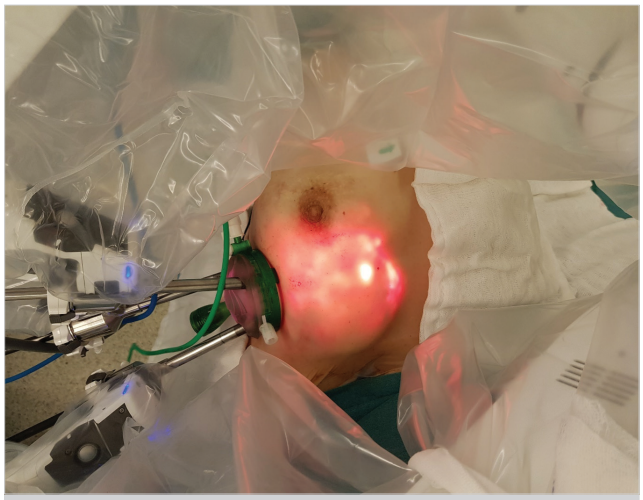

Figure 7. iInsufflated breast and view of transillumination during surgery.

RESULTS

In the Breast Unit, 738 breast cancer patients underwent surgery between 2018 and 2019 with an NSM ratio of 31.4% (n= 232). Of these patients, three underwent robotic nipple sparing mastectomy with the DaVinci Xi robotic system. All patients were females.

All three patients were operated on for breast carcinoma. Patient #2 received neoadjuvant chemotherapy. The operation was performed on the left breast in one patient, right in one, and bilateral in one patient (patient #1). All patients underwent SLNB (patient #1 underwent SLNB only on the malignant side); however, ALND was not performed in any of the patients. Median age was 43 (38-47) years, median docking time (anterior and posterior in total) was 12 (10-15) minutes, median anterior dissection time was 86 (60-108) minutes, and median posterior dissection time was 32 (30-39) minutes. Median length of the rNSM was 134 (105-161) minutes. In the pathology report, all margins were clear and far from the tumor, and the retro-nipple tissue was free from tumor. None of the patients were converted to another technique, no complications observed, and no subcutaneous shaving needed. All patients were admitted on the morning of the operation day and stayed two nights after surgery. In the pathology report, the average tumor size was 25.7 ± 9 mm, margins were negative, estrogen receptor positivity was 67 ± 58%, and Ki-67 score was 49±44%. In all patients, progesterone receptor was negative and human epidermal growth factor receptor 2 (Her-2) was negative in two patients. Only in patient #2 (who received neoadjuvant chemotherapy due to axillary lymph node involvement), seroma was observed six weeks after surgery (3 weeks after the removal of drains) and spontaneously resolved in 4 weeks. No other complication was seen in all patients. In the follow-up period of median 21 (range: 19-24) months, no loco-regional recurrence nor distant metastasis was seen. Data of each patient is given in Table 1 and Table 2.

Table 1. Data of all patients

Patient number	Age (years)	Side of Cancer	Sentinel Lymph Node Status	Axillary Lymph Node Dissection	Anterior Docking Time (minutes)	Posterior Docking Time (minutes)	Anterior Dissection Time (minutes)	Posterior Dissection Time (minutes)	Implant Type	SLNB Time (Minutes)	Length of rNSM (Minutes)	Follow-up period (month)
1L	38	Left	1i(mol+)/7	NP	9	6	108	32	RMP 350 mL	6	161	21
1R	38		NP	NP	8	6	100	31	RMP 350 mL		145	
2*	47	Left	0/2	NP	6	4	72	39	RMP 200 mL	5	126	18
3	47	Right	0/2	NP	6	4	60	30	RMP 300 mL	5	105	16

* Neoadjuvant treatment, 1L: patient #1 left breast, 1R: patient #1 right breast, SLNB: Sentinel lymph node biopsy, rNSM: Robotic nipple sparing mastectomy, i(mol+): isolated tumor cells with one-step nucleic acid amplification , RMP: round medium plus profile, NP: Not performed,

Table 2. Pathology results of all patients

Patient	Type of cancer	Tumor Size (millimeters)	Nuclear Grade	Histological Grade	ER (%)	PR (%)	Her-2	Ki-67 (%)	cTNM	pTNM
1	IDC	17	3	3	0	0	0	80	cT1cN0M0	pT1cN0(mol+)
2	DCIS	25	3*		100*	0	NP	NP	cTisN1M0*	ypTisN0
3	IDC	35	2	2	100	0	0	18	cT1cN0M0	pT1bN1a

*Prior to neoadjuvant chemotherapy, IDC: Invasive ductal carcinoma, DCIS: Ductal carcinoma in situ, ER: Estrogen receptor, PR: Progesterone receptor, NP: Not performed, cTNM: Clinical TNM classification, pTNM: pathological TNM classification.

DISCUSSION

The search from the Web of Science (WOS) database for "robotic" and "mastectomy" words yielded 58 results; however, only 25 were related with robotic nipple sparing mastectomy (4-28). Of these 25 articles, six were congress abstracts (4, 11-15), five were letters to the editor (16-20), six were case reports(5-10), and eight were original articles. Of these 14 articles (case reports and original articles), when institute of the first or majority of the authors was assumed as the origin of country, eight (57%) were originated from Asia (seven from Far East) and six (43%) were from Europe (one (7%) was co-authored from the USA).

The center where the operations were performed has a volume of 1688 breast cancer surgeries, in which 35% (n= 590) was NSM in a period of 4 years.

In the current literature, eight studies investigated rNSM through a single incision for therapeutic or prophylactic purposes. In all of these articles, authors (three different first authors: Lai H, Park H, and Toesca A) preferred to start the dissection from the subcutaneous side of the breast. Toesca, A et al. (21) and Lai, H et al. (22) have mentioned that it is needed to pull up the breast to create sufficient working space during the dissection of the breast tissue from the pectoralis major muscle, and even they insufflated the cavity with CO_2 gas at a 8 mmHg pressure. In addition, Park, H (6) has presented a gasless technique and used a special retractor (Modified Chung's retractor) to create space.

In NSM, it is important to preserve the integrity of the skin and pectoralis muscle. Skin integrity is required to prevent necrosis, and pectoralis muscle integrity is required to preserve the retropectoral positioned implant. It is known that direct contact of the implant with the skin will result with erosion of the skin and exposure of the implant to the atmosphere with time. There are other precautions such as the use of acellular dermal matrix; however, cost and seroma formation increase (29).

In the present study, dissection was first performed between the breast tissue and pectoralis major muscle. By this way, breast tissue is not separated from the skin and insufflated CO_2 stays only on the posterior of the breast, and thus, even a 6-mm Hg pressure is enough to create space for dissection. Since the breast tissue is still attached to the skin, posterior dissection can be performed more precisely without injuring the pectoralis major muscle and bleeding. A stable breast tissue eases direct visualization of the second intercostal artery, which is an important blood supply to NAC, during dissection. Anterior dissection is performed after completion of the posterior dissection. Due to lower CO_2 pressure, breast gland will hang down from the skin with its own weight, and anterior dissection can be easily performed by scissor with aid of fenestrated forceps. In addition to not rising the breast tissue, complications related to air pressure, such as pneumothorax, subcutaneous emphysema, and hypercarbia can be prevented with lower CO_2 pressure (6). Extend of the dissection is observed by the assistant via palpation and trans-illumination.

While performing NSM with conventional retractors, surgeons cannot easily visualize upper quadrants through infra-mammarian fold incision. Endoscopic mastectomy, with/without insufflation, can be performed with rigid tools; however, visibility and access decrease during dissection beyond the dome of the breast, but with DaVinci Xi robotic system, these restrictions can be avoided (21, 23, 28).

Seroma was the only complication encountered in the current study, and similarly, Toesca et al. (28) have reported seroma as the most common complication. Even though patient number was small, the only complication was observed in the patient who received systemic treatment as first-line. Although we are aware that this cannot be concluded from the current study, when experience from NSM is adjoined and when first line treatment is systemic treatment, then complication increases after NSM, contrary to the literature (30).

Lai et al. (26) have utilized a higher and oblique incision located in the axilla, Toesca et al. (21) have performed the incision in the axilla on the mid axillary line, and Park et al. (6) have performed a vertical incision on the anterior axillary line but did not mention the exact position. Sarfati et al. (23) have performed the incision on the projection of the bra and proposed it could be hidden easily by the patient; however, the surgery was not performed with single incision. In this study, a 5-cm lateral peripheral incision starting from the middle portion of the breast to the cranial direction, which is positioned on the anterior axillary line in parallel to curvature of the breast, was performed. Since the incision stays on the outer border of the breast, it is hidden

and with this position, it is both easy to access upper and lower quadrants in addition to medial portion of the breast and SLNB can still be performed.

CONCLUSION

A single incision robotic mastectomy can be performed easily and safely when the dissection starts from the pre-pectoral plane rather than the subcutaneous plane. It is important to hide the scar to improve QoL of the patient either by positioning it more laterally or on the natural curves, but it must not harden surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from Clinical Research Evaluation Ethical Board (2019-11/24).

Peer-review: Externally peer-reviewed.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (3): 303-309

Tek kesiden robotik meme başı koruyucu mastektomi: Arka taraf diseksiyonu ile başlamanın avantajı

Cihan Uras[1,2,3], Akif Enes Arıkan[1,2,3], Halil Kara[2,3,4], Onur Dülgeroğlu[2,4,5], Yakup Avşar[6]

[1] Acıbadem Mehmet Ali Aydınlar Üniversitesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye
[2] Acıbadem Mehmet Ali Aydınlar Üniversitesi, Senoloji Araştırma Enstitüsü, İstanbul, Türkiye
[3] Acıbadem Mehmet Ali Aydınlar Üniversitesi, Genel Cerrahi Kliniği, Meme Sağlığı ve Hastalıkları Bölümü, İstanbul, Türkiye
[4] Acıbadem Mehmet Ali Aydınlar Üniversitesi, Sağlık Bilimleri Yüksekokulu, İstanbul, Türkiye
[5] Acıbadem Atakent Hastanesi, Genel Cerrahi Kliniği, Meme Sağlığı ve Hastalıkları Bölümü, İstanbul, Türkiye
[6] Özel Avşar Kliniği, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Kadın için önemli bir vücut belirleyicisi olan memenin kaybı, hastanın yaşam kalitesinde (YK) büyük bir bozulmaya yol açmaktadır. Bu morbiditenin ortadan kaldırılması ve YK'nın artırılması için meme başı koruyucu mastektomi (MBKM) geliştirilmiştir. Daha iyi kozmetik sonuçlar endoskopik MBKM'yi gündeme getirse de görüş alanındaki ve sert uçlu aletlerin kontrolündeki kısıtlılık, diseksiyon boşluğunu sağlamadaki zorluk robotik meme başı koruyucu mastektomiyi (rMBKM) doğurmuştur.

Gereç ve Yöntem: İnvaziv meme kanseri için DaVinci Xi (Intuitive Surgical, Sunnyvale, CA) ile 2018'de Acıbadem Mehmet Ali Aydınlar Üniversitesi, Senoloji Araştırma Enstitüsü afiliye hastanelerinde rMBKM yapılan üç hastanın kayıtları retrospektif olarak incelendi. Tüm memelerde (n= 4) diseksiyona posteriordan başlanmıştı.

Bulgular: Birimde 2018-2019 yılları arasında 738 meme kanseri hastası ameliyat edilmiş olup MBKM oranı %31,4 (n= 232) idi. Bu hastalardan üçüne DaVinci Xi robotik sistemi ile rMBKM yapılmıştı. Ameliyatlar bir hastada sol, bir hastada sağ, bir hastada ise çift taraflı yapılmıştı. Sadece 2 numaralı, neoadjuvan kemoterapi alan, hastada ameliyattan altı (drenler çekildikten üç) hafta sonra seroma gözlendi ve dört haftada düzeldi. Tüm hastalar için başka komplikasyon gözlenmedi. Ortanca 21 aylık takip süresinde lokorejyonel nüks veya metastaz görülmedi.

Sonuç: Tek kesiden robotik mastektomi subkutan plandan ziyade pre-pektoral plandan başlanarak kolay ve güvenli olarak gerçekleştirilebilir.

Anahtar Kelimeler: Meme, robotik cerrahi, minimal invaziv cerrahi

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ORIGINAL ARTICLE
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Fasciocutaneous elliptical rotation flap for pilonidal sinus disease and its outcomes

Emre Gündoğdu[1]

[1] Liv Hospital Ankara, General Surgery, Ankara, Turkey

ABSTRACT

Objective: Sacrococcygeal pilonidal sinus is a common disease especially in the Caucasians of the Middle East. It has been reported in the incidence of 12-26 in a 100.000 population. Previously thought to be due to etiological reasons of congenital origin, it is now widely accepted as an acquired disease. The optimal treatment for pilonidal sinus disease still has no consensus. The elliptical rotation flap was first described by Nessar in the surgery of pilonidal sinus and reported successful results, but it has weak points. The purpose of this study was to share the findings of the fasciocutaneous elliptic rotation flap technique retrospectively.

Material and Methods: One hundred and eighty-six patients (149 were males and 37 were females) operated for pilonidal disease with fasciocutaneous elliptic rotation flap between 2013 and 2018 were included into this study. Data of the patients including operation time, wound issues (infection, seroma, wound separation), time required to return to daily activities, complete healing time and recurrence rates were recorded retrospectively.

Results: The patients' complete healing time was 13 ± 3 days and mean follow-up was 19 (6-37) months. Mean operative time was 43 ± 13 minutes. Mean time of drain removal was 2.20 ± 1.18 days. There were no flap necrosis or ischemia. Postoperative infection developed in two patients (1%). Seroma developed in 7 (3.8%) patients. Partial wound dehiscence occurred in 5 (3.2%) patients. None of the cases developed hematoma or complete dehiscence. No recurrence was observed in postoperative follow-ups.

Conclusion: Fasciocutaneous elliptical rotation flap is a method that has follow-up results similar to both the elliptical rotation flap technique and its modification and can be safely preferred in the treatment of pilonidal sinus with its other advantages.

Keywords: Pilonidal sinus disease, elliptical rotation flap, limberg flap, rotation flap

INTRODUCTION

Pilonidal sinus disease (PSD) was first described by Herbert Mayo in 1883 as a cyst containing hair at the natal cleft (1). Previously, this disease was believed to occur only in the sacrococcygeal region; however, it has been shown that PSD can form in the anal canal, and in the vulvar, umbilical, interdigital and scalp regions (2,3). Sacrococcygeal PSD is common especially in Caucasians of the Middle East (4). PSD can appear as an abscess, a chronic sinus which causes persistent discharge, or a silent cyst in the acute or chronic process (5). PSD has been reported with an incidence of 12-26 in 100.000 populations (6,7). Studies have shown that PSD is 3-7 times higher in males than females (4,8,9). The disease often occurs around the ages of 15-35 and peaks between the ages of 17-27, and it's rare after 45 years-old (10).

Etiology

Having been previously considered to be due to etiological reasons of congenital origin (11), PSD is now widely accepted as a disease acquired as a result of presence of hair in the gluteal sulcus (8). According to congenital theory, PSD is thought to be formed either by residual epithelium in the skin and spinal canal or by the introduction of hair follicles into the cavity formed as a consequence of the mal fusion of the dermal layers in the early embryologic period (6). On the other hand, according to the acquired theory, free hairs are gathered at the deep natal cleft, and a follicle penetrates the dermis by the friction power. Later on, a foreign-body reaction happens, and sinus formation takes place at this stage (12). This condition has many predisposing factors, including deep and narrow natal clefts, moist sulcus with chronic skin maceration, fissures or scar tissue at the natal cleft, regional trauma associated with long sitting times, poor hygiene, obesity and hairy body type, and an increased number of free hair follicles (4,8,13).

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Corresponding Author
Emre Gündoğdu
E-mail: dremregundogdu@gmail.com

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Treatment

The optimal treatment for PSD still has no consensus (5), but ideal treatment should not be technically difficult and be easy to apply, require short hospitalization and provide early return to work and daily routine, ensure better cosmetic results and low cost, and achieve low morbidity and low recurrence.

Non-operative methods such as laser epilation, phenol or fibrin glue injection are used alone or as an adjunct to operative methods in the treatment of PSD. Operative techniques are very diverse; simple excision primary suturing, excision and laying open or marsupialization, Karydakis flap, Bascom technique, Z-plasty, V-Y advancement flap, Limberg flap and its modifications, elliptical rotation flap (ERF) and its modification, gluteus maximus fasciocutaneous flap, vacuum-assisted closure are the most common methods widely used in clinic treatment (14).

Removal of the diseased tissue from the post sacral fascia is similar in all operative techniques, but the main argument is how to close the created defect. In addition to the complete removal of the diseased tissue, the deep intergluteal sulcus, which plays a role in the etiology of the disease, should be elevated and flattened and thus, the accumulation of hair follicles, maceration and fissure formation in this area should be prevented. Moreover, it should be aimed to apply the option of a surgical treatment that does not leave as much scar tissue in midline as possible and does not cause tissue tension in this area (15).

Aim

Elliptical rotation flap (ERF) was first described by Nessar in the surgery of pilonidal sinus and reported successful results (14). In this described technique, the flap was prepared cutaneously and the root of the flap pedicle was 1 cm wide. Later on, Dizen et al. and Yoldaş et al. (16,17) modified this technique, using an oblique incision, instead of a vertical incision, to prevent scar tissue formation in the midline and to place the lower edge of the flap 1-2 cm laterally to the natal cleft and to flatten the intergluteal sulcus.

The purpose of this study was to share the findings of the fasciocutaneous elliptic rotation flap (FERF) technique retrospectively, in which we could lateralize the flap edge without disrupting flap viability that would provide less tissue loss.

MATERIAL and METHODS

One hundred and eighty-six patients operated for PSD with FERF between 2013 and 2018 were included into this study. All patients had chronic pilonidal sinus. Those who had previously been treated with non-operative techniques or those with recurrent disease were excluded from the study. In addition, patients with a disease that negatively affected wound healing (diabetes mellitus, immune deficiencies, etc.) or those who used immunosuppressive therapy for any reason were also excluded. Informed consent was obtained from the patients by explaining all operative surgical options. Data of the patients were recorded retrospectively. The study protocol was approved by the Committee on Institutional Ethics of Liv Hospital.

Surgical Technique

Patients were taken to surgery on the day of their hospitalization. They were operated under spinal or general anesthesia in line with the decision taken by the patient and the anesthesiologist. In the operating room, the surgical area was shaved, and 1 gr of cefazolin was given prophylactically to all patients during anesthesia induction. The patient's hip was placed in the Jack-knife position and was lateralized with the help of adhesive tapes on both sides to make the surgical field more visible (Figure 1a). Gluteal and sacral regions were prepared with the help of iodine solution. All diseased tissue was excised till the post sacral region with a simple elliptical incision made to include all pit and lateral fistula openings in the intergluteal region (Figure 1b). After excision, traction bands in the hip were released, and a drawing was made with a marker pen for the reconstruction with flap. An elliptical flap was drawn at the same length and width as the length of the excised area, regardless of which side it was prepared. The distance between the lateral lower end of the elliptic flap and the lower end of the excision area was set by leaving a distance as long as the length of the widest part of the excision area, contrary to the 1 cm distance described by Nessar et al. (Figure 1c). Again, contrary to Nessar et al., the flap was not prepared cutaneously but fasciocutaneously, including the fascia of the gluteus maximus muscle (Figure 1d). After the flap was completely released, it was transposed into the post sacral area (Figure 1e). After meticulous hemostasis, a hemovac drain was inserted to the surgical area. The subcutaneous tissue was then approached by 2-0 vicryl sutures. The skin was closed with intermittent matrix sutures with 2/0 prolene, and care was taken not to leave the nodes on the flap (Figure 1f).

Follow Up

Patients were discharged on the first post-operative day with antibiotics and painkillers. If the drainage was below 20 ml, the drain was removed during patient discharge, otherwise it was waited until the drainage decreased below 20 ml in the outpatient clinic follow-up to remove the drain. In order to prevent sweating, wetting and maceration in the intergluteal sulcus, patients were advised to do wound dressings every day for a week and place a rolled gauze in the newly created intergluteal area during wound dressing. The patients were invited to outpatient clinic controls on postoperative 2^{nd}, 7^{th} and 12^{th} days for wound assessment and stitch removal. Following the first month after surgery, the patients were advised to have a laser epilation covering the back, waist and hip areas if possible or a monthly epilation with depilatory creams if not. Data of the patients including operation time, wound issues (infection, seroma, wound

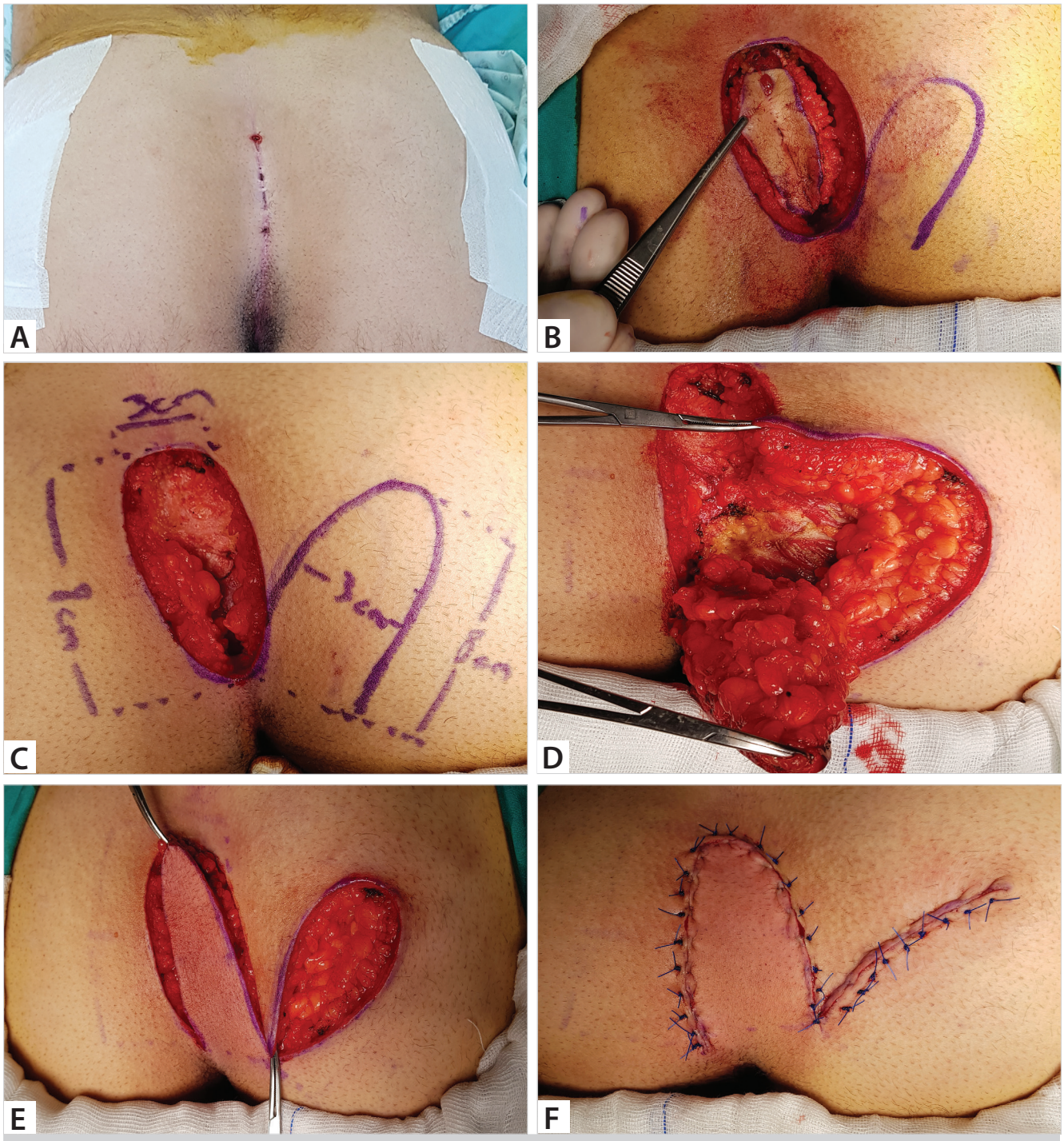

Figure 1. Fasciocutaneous elliptical rotation flap technique; a. Lateralization of the hip with the help of adhesive tapes, b. Simple elliptical excision, c. Flap preparation, d. Flap elevation, e. Transposition of the flap, f. Final view of the surgical area.

separation), time required to return to daily activities, complete healing time, and recurrence rates were recorded.

Statistical Analyses

Data were expressed as percentage, mean ± standard error of the mean, or as median and interquartile range. All data were analyzed using the Statistical Package for Social Sciences 21 (SPSS Inc., Chicago, IL, USA) for Mac.

RESULTS

Of the 186 patients who were operated on for PSD and underwent FERF, 149 (80.1%) were males and 37 (19.9%) were females. Mean

Table 1. Characteristics of the patients and the results of the fasciocutaneous elliptical rotation flap technique

	FERF (n= 186)
Age	23.6 ± 4.4 years
Sex	
Male	149 (80.1%)
Female	37 (19.9%)
BMI	24.2 ± 9.7 kg/m^2
Previous abscess attack	119 (63.9%)
Type of anesthesia	
Spinal	147 (79%)
General	39 (21%)
Operation time	43 ± 13 min.
Drain removal time	2.20 ± 1.18 days
Complications	
Seroma	7 (3.8%)
Hematoma	N/A
Dermal ischemia	1 (0.5%)
Infection	2 (1%)
Complete wound dehiscence	N/A
Partial wound dehiscence	5 (3.2%)
Complete healing time	13 ± 3 days
Recurrence	N/A
Follow up time	19 (6-37) months

FERF: Fasciocutaneous elliptic rotation flap, BMI: Body mass index.

age of the patients was 23.6 ± 4.4. Mean body mass index (BMI) of the patients was 24.2 ± 9.7 kg/m^2, and 119 (63.9%) of the patients described a previous abscess attack. Complete healing time of the patients was 13 ± 3 days. One hundred and forty-seven (79%) patients underwent spinal anesthesia and 39 (21%) were operated under general anesthesia, and mean operative time was 43 ± 13 minutes. Mean time of the patients' drain removal was 2.20 ± 1.18 days. Mean follow-up time was 19 (6-37) months. There were no flap necrosis or ischemia, but we encountered dermal ischemia at the corner where the flap was removed in one patient, and the flap was reconstructed. In two patients (1%) who developed postoperative infections, the wound was treated by removing several skin sutures and using antibiotics. Seroma developed in 7 (3.8%) patients. Partial wound dehiscence occurred in 5 (3.2%) patients, 4 of whom developed seroma and 1 developed dermal ischemia in the flap corner. None of the cases experienced hematoma or complete dehiscence. No recurrence was observed in postoperative follow-ups. Characteristics of the patients and results of the FERF technique are summarized in Table-1.

DISCUSSION

There are many operative and non-operative options for the treatment of PSD, but discussions about the optimal treatment is still ongoing. Although cosmetic results, length of hospital stay, and the amount of postoperative pain are important in ideal treatment, we are of the opinion that the surgical method should improve patient comfort as quickly as possible, provide early return to daily routines, should not require long-term wound care, re-surgery and intervention, and cause recurrence. Since the complications of the disease themselves and their treatments often require patients and caregivers to go to the office or hospital for wound care, it causes individuals to lose time from work or school (5).

Primary excision and lay open procedure, which have been commonly used before, have a very long complete healing period, and yet they have substantial levels of recurrence (18). Primary closure of the wound is a simple method, but due to the continuing natal cleft, it has a high rate of recurrence (19). Nowadays, it is widely agreed that off-midline (rather than midline) skin closure should become the preferred treatment after wide excision of the sinuses. The evidence of this concept has been shown by several randomized controlled studies and a subsequent meta-analysis (15).

Due to the negative consequences of midline closure techniques, Karydakis and Bascom have published their techniques that provide off-midline closure and noted significant improvements in morbidity and recurrence rates (8,13).

Rotation flap techniques have been successfully tried in patients in the following process, as procedures that flatten the intergluteal sulcus depth, bring the suture line to an area other than the midline, and reduce tissue tension seem advantageous. Today, the most commonly used plasty methods are Limberg flap, V-Y plasty, and Z plasty (5).

The Z-plasty method was first introduced by Monro and MacDermot for PSD treatment (20). This treatment has the disadvantage that some of the scar tissue persists in the midline, which is the leading cause of recurrence. With the Z-plasty technique, Lamke et al. have noticed a 16% recurrence rate (21).

The V-Y advancement flap can cover the defects up to 10 cm in size. In some studies, it has been shown that this technique provides good healing and minimal wound complication and good recurrence rates (22). Furthermore, Berkem et al. have reported better results with off-midline V-Y plasty rather than midline related V-Y plasty (23).

Limberg flap and its modifications are the most commonly known and accepted methods for PSD treatment with flap technique (12). Cihan et al. have reported that reconstruction with the Limberg flap gives better results than primary closure, and the modified Limberg flap (MLF) technique corrects the weaknesses of the standard limber flap and gives even better results (24).

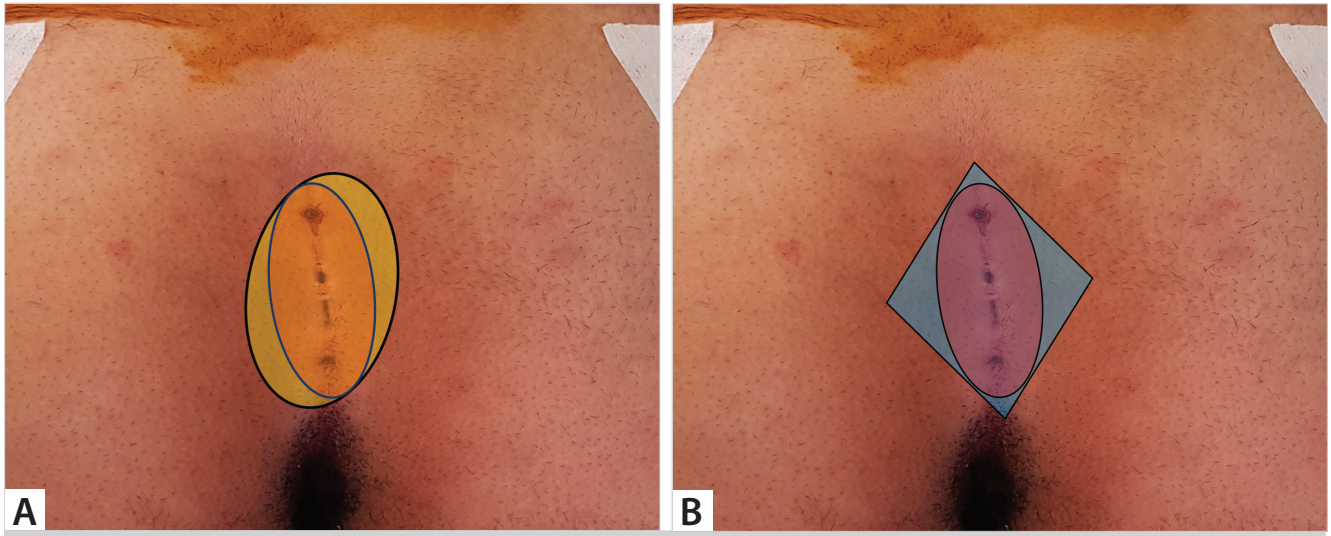

Figure 2. Comparison of the resection areas required by the types of surgery to excise the same sized pilonidal sinus; a. Modified elliptical rotation flap technique (Yellow area) vs. Fasciocutaneous elliptical rotation flap technique (Red area), b. Limberg flap technique (Blue area) vs. Fasciocutaneous elliptical rotation flap technique (Red area).

In order to correct the acute angling end points in other flap techniques, which are the causes of tissue ischemia, dehiscence and infection, Nessar et al. have described the ERF technique with 0% recurrence and short hospital stay (14). ERF technique contains cutaneous flap with 1 cm pivot point in its lower corner, which has caused concerns about flap blood supply (25). Dizen et al. have modified this technique for its weak point, which has an end point in the natal cleft that causes maceration and prolonged wound healing with an oblique elliptical excision and an opposite-sided flap, and they have also reported 0% recurrence again (16). Later on, Yoldaş et al. have compared MERF with MLF and reported no significant difference between the groups by means of flap ischemia, dehiscence, infection, pain and quality of life; however, MERF has proven shorter operative time and improved cosmetic outcomes. In addition, Yoldaş et al. have not reported any recurrence in the MERF group (17).

Fasciocutaneous flaps have been used for many decades in reconstructive surgery. Fasciocutaneous flaps consisting of skin, fat, and deep fascia have been successfully used to close off a variety of limb, trunk, and head and neck defects. These flaps provide many advantages: they restore blood flow, increase healing rate, and help restore function faster (26). In this study, we preferred a fasciocutaneous flap for the reconstruction of the excision area to remove the limitations of the ERF in the treatment of PSD. In addition, we aimed to contribute to the flap blood supply by leaving the root width of the flap as wide as the distance of the excision area, and also to reach the promising results of the ERF technique. As a result of our study, we obtained a 0% recurrence rate similar to previous studies and did not experience flap ischemia or necrosis in any of our patients. We think that the advantage of our technique compared to the MERF technique is that it requires less resection area (Figure 2a), especially in complicated cases containing bilateral lateral fistula openings, and allows flap preparation from any side if desired. We believe that the superiority of our FERF technique over MLF technique also requires a smaller surface area (Figure 2b) compared to the rhomboid excision area of the elliptical excision area and thus, has better cosmetic results and faster recovery.

CONCLUSION

In conclusion, it is to our belief that fasciocutaneous elliptical rotation flap is a method that has follow-up results similar to both the ERF technique and its modification and can be safely preferred in the treatment of pilonidal sinus with its other advantages.

Ethics Committee Approval: Ethic committee approval was received for this study Committee on Instutional Ethics of Liv Hospital (2020-006)

Peer-review: Externally peer-reviewed.

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

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (3): 310-316

Pilonidal sinüs hastalığında fasyokutan eliptik rotasyon flebi ve sonuçları

Emre Gündoğdu[1]

[1] Liv Hospital Ankara, Genel Cerrahi, Ankara, Türkiye

ÖZET

Giriş ve Amaç: Sakrokoksigeal pilonidal sinus hastalığı özellikle Orta Doğu Kafkasyalılarında yaygın bir hastalıktır. Yüz bin popülasyonda 12-26 insidansında rapor edilmiştir. Daha önceleri konjenital orijinli etiyolojik nedenlerden kaynaklandığı düşünülmekteyken, günümüzde edinilmiş bir hastalık olduğu kabul edilmektedir. Pilonidal sinüs hastalığının ideal tedavisiyle ilgili hala bir fikir birliği yoktur. Eliptik rotasyon flebi ilk olarak Nessar tarafından pilonidal sinüs cerrahisinde tanımlanmış ve başarılı sonuçlar bildirmiştir, ancak bazı zayıf noktaları vardır. Bu çalışmanın amacı fasiokütanöz eliptik rotasyon flep tekniğini ve bulgularını retrospektif olarak paylaşmaktır.

Gereç ve Yöntem: 2013-2018 yılları arasında pilonidal hastalık nedeniyle opere edilen ve fasiokütanöz eliptik rotasyon flebi uygulanan 186 hasta (149'u erkek, 37'si kadın) çalışmaya dahil edildi. Ameliyat süresi, yara problemleri (infeksiyon, seroma, yara ayrışması), günlük aktivitelere dönmeleri için gereken süre, tam iyileşme süresi ve nüks oranları da dahil olmak üzere hastaların verileri retrospektif olarak kaydedildi.

Bulgular: Hastaların tam iyileşme sürelerinin ortalaması 13 ± 3 gün, ortalama takip süresi 19 (6-37) aydı. Ortalama ameliyat süresi 43 ± 13 dakikaydı. Dren çekilme süresi ortalama 2,20 ± 1,18 gündü. Hastaların hiçbirisinde flep nekrozu veya iskemi gelişmedi. İki hastada (%1) ameliyat sonrası infeksiyon gelişti. Yedi hastada (%3,8) seroma gelişti. Beş hastada (%3,2) kısmi yara ayrımı meydana geldi. Olguların hiçbirinde hematom veya tam yara ayrışması gelişmedi. Postoperatif takiplerde nüks görülmedi.

Sonuç: Fasiokütanöz eliptik rotasyon flebi, hem eliptik rotasyon flebi tekniğine hem de onun modifikasyonuna benzer takip sonuçlarına sahip bir yöntemdir ve pilonidal sinüs tedavisinde beraberinde getirdiği diğer avantajlar ile güvenle tercih edilebilir bir yöntemdir.

Anahtar Kelimeler: Pilonidal sinus disease, elliptical rotation flap, limberg flap, rotation flap

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CASE REPORT
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A rare cause of acute abdomen: isolated necrosis of the cecum

Kemal Eyvaz[1], Hasan Ediz Sıkar[2], Mehmet Gökçeimam[2], Hasan Fehmi Küçük[2], Necmi Kurt[2]

[1] Deparment of General Surgery, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[2] Deparment of General Surgery, University of Health Sciences, Kartal Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: We aimed to present a 76-year-old female patient with cecal necrosis, which is a rare cause of acute abdomen in elderly women and a variant of ischemic colitis.

Material and Methods: The patient was admitted to hospital with abdominal pain, anorexia and nausea. Physical examination, laboratory parameters and abdominal computed tomography revealed acute abdomen. We operated the patient with below umbilical midline incision. Although the pain localized to the right lower quadrant made us consider acute appendicitis as first diagnosis, other pathologies were also kept in mind for differential diagnosis.

Results: Non-occlusive cecal necrosis was determined, and terminal ileum and cecum resection and Meckel's diverticulum excision were performed. Arterial pulsation was palpated, and no sign of thrombus was found.

Conclusion: Isolated necrosis of the cecum may be due to multiple reasons. Especially in elderly female patients with predisposing factors like hypotension, sepsis, shock, drug use, vasculitis, and hypercoagulability, cecum necrosis should be kept in mind.

Keywords: Isolated necrosis of cecum, acute abdomen, ischemic colitis

INTRODUCTION

Although acute intestinal ischemia is the most commonly seen ischemia in elderly patients, isolated necrosis of the cecum is a rare entity frequently encountered with diseases including chronic heart disease, systemic sepsis, hypovolemic shock, fungal infections, and rheumatoid fever (1,2). Ischemic colitis is a known form of non-occlusive mesenteric ischemia resulting in a decrease in the blood flow of the colon. It may develop, in some cases, in the event of a systemic hypotension, with the use of drugs causing hypotension, and following a decrease in the heart pump and aortic and open heart surgeries. In some cases, ischemic colitis may occur spontaneously without any evidence supportive of a decrease in the mesenteric blood flow (3). Isolated necrosis of the cecum may also develop due to the congenital insufficiency of the anatomic structure of the cecum (4). Isolated necrosis of the cecum may occur following hypotension secondary to dialysis and trauma (5). This study aimed to present a case preliminarily diagnosed with and taken into operation for acute appendicitis, and then operated on for cecum and partial ileum resection due to isolated necrosis of the cecum.

CASE REPORT

A 76-year-old female patient presented to our emergency clinic with complaints of nausea and localized abdominal pain in the right lower quadrant that had started 12 h prior. Physical examination of the patient revealed deep tenderness, defense and rebound at McBurney's point on the right lower quadrant of the abdomen. Test and examination results were as follows: leucocyte: 16.200/mm^3, blood pressure: 125/80 mmHg, pulse: 84/min, fever: 37.7°C, and there was no feature on direct abdominal graphy in the upright position. Abdominal computed tomography (CT) showed thickening on the cecum wall. It was learned from the patient's history that she had received treatment for tuberculosis 20 years ago, had undergone total

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Corresponding Author
Kemal Eyvaz
E-mail: drkemal07@gmail.com

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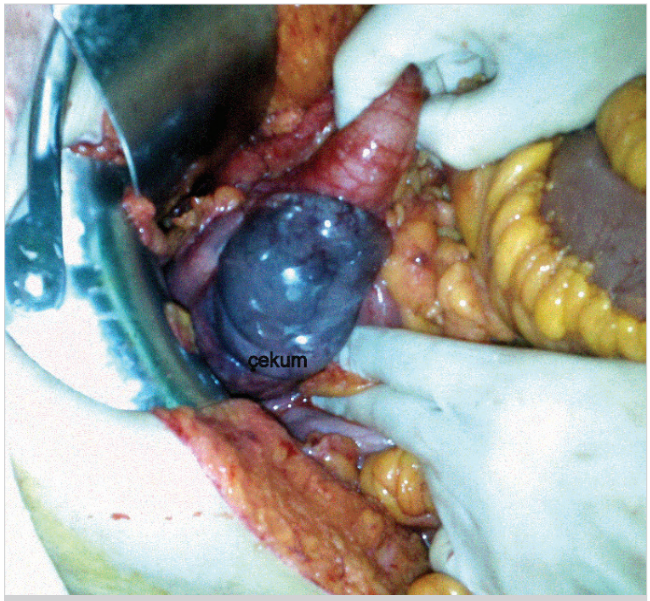

Figure 1. Necrosis in the cecum is viewed during the operation.

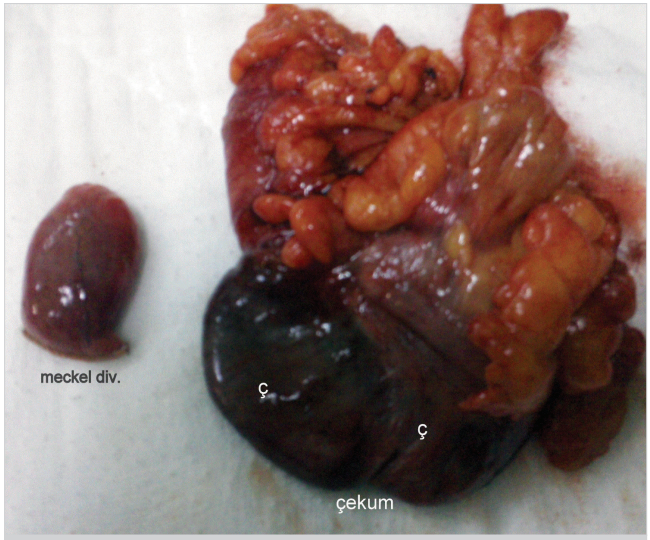

Figure 2. After the operation, the Cecum and Meckel diverticulum excision materials with terminal ileum resection are viewed.

thyroidectomy for multinodular goiter 10 years prior, and had started suffering from hypertension in recent years. With the data at hand, the patient was taken to surgery with a preliminary diagnosis of acute abdomen, primarily acute appendicitis. Since there was thickening of the cecum wall on tomography, a sub-umblical median incision was performed because another pathology could manifest itself, and it was observed that cecum necrosis was present (Figure 1). It was seen that the appendix was normal and also, there was Meckel's diverticulum, 5 cm in length and 65-70 cm proximal to the ileocecal valve. Cecum and 10 cm distal ileum resections were performed on the patient (Figure 2). End-to-side anastomosis was performed between the

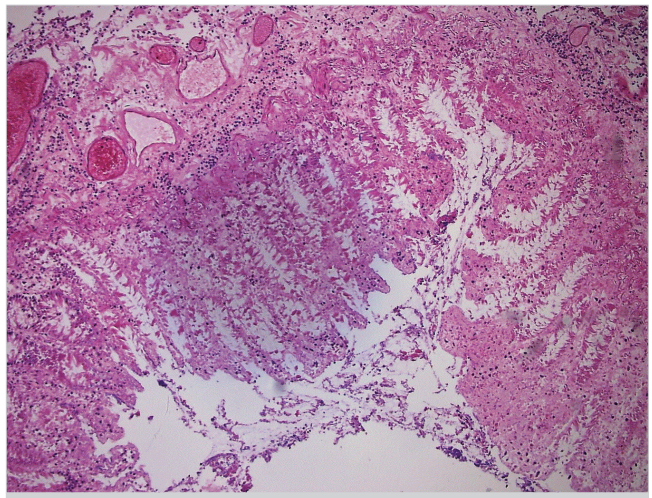

Figure 3. Ischemic areas are viewed as a result of the pathological examination of the removed material.

ileum and the ascending colon. Excision of the Meckel's diverticulum was done at the same session. The section excised was sent to pathology. Pathological examination resulted in the diagnosis of ischemic colitis (Figure 3).

DISCUSSION

Intestinal ischemia is particularly important in elderly patients. It is investigated in two groups as occlusive and non-occlusive (6). Occlusive (obstruction) conditions are investigated as obstructions related to the obstruction of major arteries, venous obstructions, obstructions due to small arterial disease, and mechanical intestinal obstructions. Obstruction of major arteries occur due to embolism, thrombus, and vein ligation. Small artery obstructions develop in patients with diabetes mellitus, vasculitis or those having received radiotherapy. Intestinal ischemia can occur due to distal tumors and the effect of sigmoid volvulus. Rarely, it can also develop as a result of the obstruction of venous flow due to hypercoagulability, pancreatitis, and portal hypertension (6).

In non-occlusive ischemic colitis, the most important factor is shock. It is believed that in case of a shock, mesenteric vasoconstriction occurs in order to provide sufficient blood flow to vital organs like the brain, kidneys, heart, and liver and disrupts feeding in the splanchnic area and result in intestinal ischemia. Isolated necrosis of the cecum is a form of acute intestinal ischemia.

Isolated necrosis of the cecum is a rarely seen surgical acute abdomen manifesting itself with complaints such as abdominal pain, nausea, and diarrhea. Physical examination may detect tenderness in the lower right abdominal region on palpation, and sometimes local or general rebound and distention signs may be found. In laboratory test, leucocyte elevation can be generally determined as 10.000-20.000/mm^3. Due to the fact that it is mostly seen in the elderly population, it is understood

from the literature that abdominal computed tomography is requested considering cecum carcinoma and that these elderly patients are taken into surgery with a preliminary diagnosis of acute appendicitis or cecum tumor (3,7,8).

Methods such as ultrasonography, abdominal tomography, colonoscopy, colon graphy, occult blood in stool, direct abdominal graphy on standing position, electrocardiography, and chest X-ray can be used in diagnosis. Schuler et al. have preliminarily diagnosed two elderly patients aged 71 and 85 out of five cases with cecum carcinoma using abdominal CT and colonography and taken them to surgery, and their pathology results have yielded cecum necrosis (3). Thickening of the cecum wall on computed tomography is significant. In the evaluation of the aforementioned two cases, thickening of the cecum wall and a 3-4-cm filling defect on colonography were observed, and thus the cases were taken to surgery.

Fungal infections are one of the factors causing isolated necrosis of the cecum. Phycomycosis (mucormycosis) primarily involves the stomach and then the colon, cecum and terminal ileum respectively (1,9). Calle and Klasky have published 14 cases in the literature (9). In almost all cases, uncontrollable diabetes mellitus, lymphoma, malnutrition, cirrhosis, gastroenteritis, antibiotic and steroid use, anemia, uremia, radiation therapy, and wounds with large tissue damage as in large burns that disrupts the immune system have been established. Treatment of this type of cases has unfortunately been fatal (9).

Although ischemic colitis leading to isolated necrosis of the cecum can involve all parts of the colon, it mostly involves the left colon (10). Especially blood build-up of the splenic flexura located between the inferior and superior mesenteric arteries is less in this region. Again, the cecum can be insufficiently fed due to the fact that the anterior and posterior cecal arteries feeding the cecum stem out of the colic branch of the ileocolic artery without forming vascular arc and collateral circulation (4). It is known that ischemic colitis develops due to non-occlusive mesenteric ischemia. While the causes of the development of ischemic colitis cannot be found in some, it can occur secondary to systemic hypotension in the event of a shock, hypovolemia, and systemic sepsis (3). Mesenteric ischemia can occur with vasoconstriction that develops as a result of digital and catecholamine drug use (4). Isolated necrosis of the cecum may also be seen with chronic heart disease, cardiopulmonary surgery, systemic chemotherapy, and cholesterol embolization (11).

Majority of the patients with isolated necrosis of the cecum published in the literature until today are females and the average age is above 68 (3,12,13). We would like to emphasize that our case was a 76-year-old female patient. Isolated necrosis of the cecum should be kept in mind in elderly female patients with right lower quadrant abdominal pain and in those considered to have acute abdomen. Again, in elderly female patients suffering from right lower quadrant abdominal pain, acute appendicitis, cecum diverticulitis, and cecum perforation should also be kept in mind apart from isolated necrosis of the cecum. Although abdominal CT gives sufficient information for the diagnosis of acute appendicitis, complicated diverticulitis, and cecum tumor, the thickening of the cecum wall in patients with cecum necrosis might resemble cecum tumor by clustering the terminal ileum and omentum on itself (3,4). Apart from those recommending colonoscopy for the diagnosis of especially isolated necrosis of the cecum in ischemic colitis, there are those that do not recommend it due to the fact that colonoscopy may lead to transmural pressure increase and perforation by increasing intraintestinal pressure (12,14). It has been reported in some cases with isolated necrosis of the cecum that colonography was performed considering the possibility of a cecum tumor and were taken to surgery with the diagnosis of cecum tumor seeing irregularities in the cecum on colonography (3).

In our case, a preliminary diagnosis of acute appendicitis was made with tests including physical examination, direct abdominal graphy on a standing position, abdominal CT, and laboratory tests; however, the possibility of another pathology was kept in mind. It is seen in the literature that most of the cases with isolated necrosis of the cecum have been taken to surgery without further tests for acute appendicitis. Surgical treatments of the cases with isolated necrosis of the cecum right hemicolectomy, cecum resection, and partial cecum resection (3,7,8).

To conclude, isolated necrosis of the cecum is a rare variant of ischemic colitis. Isolated necrosis of the cecum should be kept in mind in elderly female patients with lower quadrant pain if leucocyte is elevated, physical examination points to acute appendicitis, and thickening of the cecum wall has been detected on CT.

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

Peer-review: Externally peer-reviewed.

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OLGU SUNUMU-ÖZET
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Akut batının nadir bir nedeni: izole çekum nekrozu

Kemal Eyvaz[1], Hasan Ediz Sıkar[2], Mehmet Gökçeimam[2], Hasan Fehmi Küçük[2], Necmi Kurt[2]

[1] Sağlık Bilimleri Üniversitesi Antalya Eğitim ve Araştırma Hastanesi, Genel Cerrahi Anabilim Dalı, Antalya, Türkiye
[2] Sağlık Bilimleri Üniversitesi Kartal Eğitim ve Araştırma Hastanesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye

ÖZET

Giriş ve Amaç: Akut batın tablosuna neden olan ve iskemik kolitin bir varyantı olup nadir görülen izole çekum nekrozlu 76 yaşındaki hastamızı literatür eşliğinde sunup yaşlı kadın hastalarda izole çekum nekrozunun akut batına sebep olabileceğine dikkat çekmek istedik.

Gereç ve Yöntem: Karın ağrısı, bulantı ve iştahsızlık nedeniyle başvuran hasta yapılan fizik muayenesi, laboratuvar tetkikleri ve görüntüleme yöntemleri sonucunda akut batın tanısı ile göbek altı median insiyonla ameliyata alınmıştır. Ağrının sağ alt kadrana lokalize olması ilk etapta akut apandisiti düşündürmüş olmakla birlikte benzer tabloya sebep olabilecek diğer patolojiler de akılda tutulmuştur.

Bulgular: Laparatomide non-oklüziv izole çekum nekrozu saptanmış olup terminal ileum + çekum rezeksiyonu ameliyatı yapılmış, ayrıca mevcut olan Meckel divertikülü eksize edilmiştir. Çekuma giden damarlar palpe edilmiş ve herhangi bir trombüs bulgusuna rastlanmamıştır. Arteriyel pulsasyon alınmıştır.

Sonuç: İzole çekum nekrozu multipl nedenlerden dolayı olabilir. Özellikle yaşlı bayan hastalarda hipotansiyon, sepsis, şok, ilaç kullanımı, vaskülit, hiperkoagülabilite gibi predispozan risk faktörleri olduğu durumlarda çekum nekrozunun olabileceğini düşünmek gerekir.

Anahtar Kelimeler: Çekum nekrozu, akut batın, iskemik kolit

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CASE REPORT
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Ectopic adrenal gland tissue in the inguinal hernia sac occuring in an adult

İsmail Zihni[1], Oktay Karaköse[1], Serkan Yılmaz[2], Kazım Çağlar Özçelik[1], Hüseyin Pülat[1], Derya Demir[3]

[1] Department of General Surgery, Suleyman Demirel University, School of Medicine, Isparta, Turkey
[2] Clinic of General Surgery, Manisa State Hospital, Manisa, Turkey
[3] Clinic of Pathology, Manisa State Hospital, Manisa, Turkey

ABSTRACT

Ectopic adrenal tissue is a benign lesion generally determined incidentally during a surgical intervention applied for another reason. This tissue may be present along the path of the testicles and groin discovered during surgery. While the condition has been mainly reported in the pediatric population, it is very rarely reported in adults. The aim of this study was to present an adult patient with ectopic adrenal tissue which was determined incidentally within an indirect inguinal hernia sac.

Keywords: Adrenal glands, ectopic tissue, hernia sac, adult

INTRODUCTION

The observation of adrenal tissue ectopically in other localizations was first described by Morgagni in 1740 (1). Currently, majority of the cases of ectopic adrenal tissue are known to be encountered in the retroperitoneal area, the kidney parenchyma, the celiac plexus, thorax, liver capsule, lungs brain and less often in the spermatic cord, testis and the surrounding tissues (2). In the literature, it has been noted that the majority, primarily in the pediatric age group, are determined incidentally during surgery (1,3). In contrast to the literature, the case presented here is 35 years old. In this age, ectopic adrenal tissue is very rarely seen in the location of an inguinal hernia sac.

CASE REPORT

A 35-year-old male presented with complaints of pain and swelling in the right inguinal area. From anamnesis, it was learned that the complaints had been ongoing for approximately 5 years and the pain and swelling increased when undertaking strenuous labor. There was nothing remarkable in the patient history, and physical examination determined a right-sided inguinal hernia. The decision was taken to operate on the patient, who was informed on the surgical technique and a written informed consent form was received. With this diagnosis, the patient was admitted for surgery, and in the exploratory operation, it was seen that there was an indirect inguinal hernia and within the hernia sac, a yellow-colored mass of approximately 5 mm. The hernia was excised together with the sac, and Lichtenstein herniorrhaphy was applied. No complications developed and the patient was discharged on postoperative day 1. The histopathologic examination of the mass was reported as ectopic adrenal tissue (Figure 1).

DISCUSSION

The observation of accessory adrenal tissue around the gonads distant to its own original location is related to the embryogenesis of the gland. The adrenal cortex and medulla originate from separate embryological tissues. While the cortex originates from the coelomic mesodermal epithelium, at between 7-8 weeks of embryogenesis, ectodermal cells of the neural cleft separate from the celiac plexus and advance into the primordial cortex. Thus, the medulla section of the adrenal

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Corresponding Author
İsmail Zihni
E-mail: ismailzihni@gmail.com

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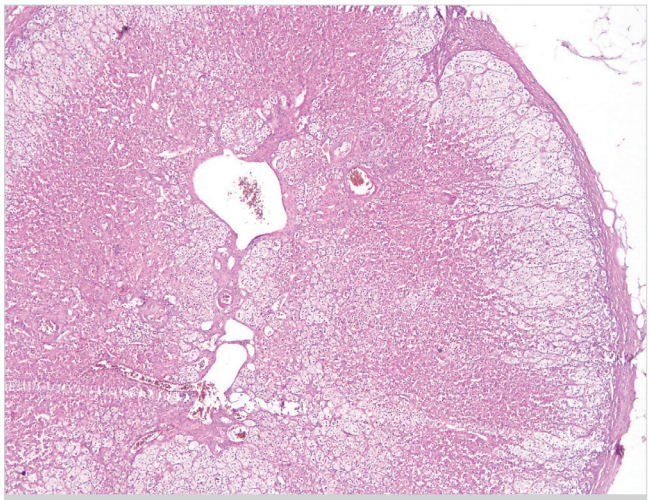

Figure 1. Ectopic adrenal cortex. (H&E, x100).

gland develops. Aberrant adrenal glands or accessory adrenals form between this 7th and 8th week. They develop in the form of multiple primordial or separately secondary to the main gland. If they are close to the main gland, they include the medulla (1,4). Therefore, the majority of ectopic adrenal tissues seen in the spermatic cord or the epididymis are formed from the cortex section only. Consistent with these studies, in histopathologic examination, only the cortex layer of the ectopic adrenal tissue was in the specimen (Figure 1).

Extra-adrenal tissue is seen at a rate of 3% in children in inguinal region operations and at 7.5-15% in the testis region of newborns. In inguinal region operations, extra-adrenal tissue is more often encountered together with undescended testis than in inguinal hernia (5,6).

Ectopic adrenal tissue within an inguinal hernia sac, as in the current case, is rarely seen in adults. The reason for this is that over time, ectopic adrenal tissue becomes atrophied (1). In their search in the English literature, Mendez et al. (3) have found 117 reported cases in infants and children and only 25 cases in adults. Adrenal ectopia at this site is encountered mainly in males (3,5,7) and very rarely in females where the ectopic tissue lies in a paraovarian location (8).

Ectopic adrenal tissue is known to be benign. In majority, nodules are 1-5 mm in diameter, round and yellow in color. The ectopic adrenal tissue can potentially undergo hyperplasia and neoplasia. In some studies, it has been reported that these nodules can transform to the pheochromocytoma, Leydig cell tumor or adrenal adenoma. Therefore, surgical resection is advisable whenever incidentally found (1,7,9). Furthermore, it has been reported in the literature that compensatory hypertrophy and re-function may be seen after adrenalectomy performed for Cushing (2).

CONCLUSION

Ectopic adrenal tissue is usually found during inguinal surgery in pediatric patients. Since it may undergo progressive atrophy over time, it is rarely encountered in the adult age group. If yellow millimetric nodules are detected during inguinal surgery, ectopic adrenal tissue should be considered in differential diagnosis, and it should be excised for histopathologic analysis since it is accepted as one of possible cause of malignancy.

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

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OLGU SUNUMU-ÖZET
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Yetişkin bir hastada inguinal herni kesesinde görülen ektopik adrenal bez dokusu

İsmail Zihni[1], Oktay Karaköse[1], Serkan Yılmaz[2], Kazım Çağlar Özçelik[1], Hüseyin Pülat[1], Derya Demir[3]

[1] Süleyman Demirel Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Isparta, Türkiye
[2] Manisa Devlet Hastanesi, Genel Cerrahi Kliniği, Manisa, Türkiye
[3] Manisa Devlet Hastanesi, Patoloji Kliniği, Manisa, Türkiye

ÖZET

Ektopik adrenal doku genellikle başka bir amaçla yapılan cerrahi girişimlerde tesadüfen saptanan benign bir lezyondur. Bu lezyon kasık cerrahisi sırasında, testislerin iniş yolu boyunca fark edilebilir. Bu durum genellikle çocuk hastalarda görülmekle birlikte; çok nadir olarak yetişkinlerde bildirilmektedir. Biz bu çalışmamızda; yetişkin bir hastada, indirekt inguinal fıtık kesesi içinde tesadüfen saptanan, ektopik adrenal doku olgusunu sunduk.

Anahtar Kelimeler: Adrenal bez, ektopik doku, fıtık kesesi, yetişkin

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SURGICAL TECHNIQUE
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Prevention of inadvertent injury to the aberrant hepatic artery arising from SMA during laparoscopic pancreaticoduodenectomy

Mehmet Fatih Can[1], Mustafa Kerem[2], Kürşat Dikmen[2]

[1] Lokman Hekim University, School of Medicine, General Surgery, Ankara, Turkey
[2] Gazi University School of Medicine, General Surgery, Ankara, Turkey

ABSTRACT

Laparoscopic pancreatoduodenectomy is a challenging surgical procedure. Presence of aberrant hepatic artery arising from the superior mesenteric artery increases the complexity througout dissection. Herein we propose some important points and tricks that help surgeon avoid an inadverdent injury to aberrant hepatic artery during laparoscopic pancreatoduodenectomy.

Keywords: Pancreatoduodenectomy, laparoscopy, hepatic artery, injury

Dissection during laparoscopic pancreaticoduodenectomy (LPD) is a complex surgical intervention and requires a comprehensive understanding of anatomical relations and vascular variations around the duodenum and hepatoduodenal ligament. While the process carries a risk of inadvertent injury to the adjacent vasculature throughout the procedure, safe dissection along the superior mesenteric artery (SMA) is extremely vital since nearly one fifth of the patients have aberrant hepatic artery (HA) coming off of the superior mesenteric artery (1). If exists, the replaced or accessory hepatic artery typically courses just right and inferior to the portal vein. With accompanying video, this paper aims to share the technique we adopt to avoid injury to the aberrant hepatic artery during LPD.

We believe adherence to some technical rules will significantly reduce the risk of an accidental arterial injury during the procedure:

1. Preoperative radiological evaluation: Vascular anatomy and variations of the hepatic artery should be assessed preoperatively with high quality computed tomography imaging. Both arterial and portal phase images should be obtained. The three commonest variations of HA coming off of the SMA are accessory right HA, replaced right HA and replaced common hepatic artery (Figure 1). It should

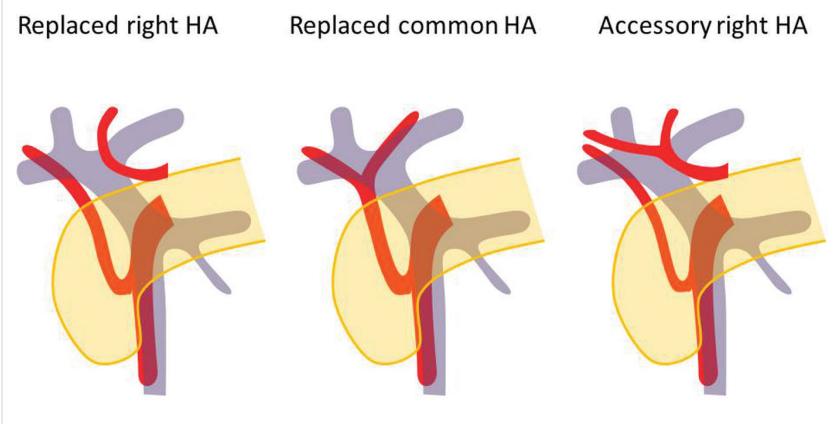

Figure 1. Three commonly encountered types of aberrant hepatic artery arising from the superior mesenteric artery.

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Corresponding Author
Mehmet Fatih Can
E-mail: mfcanmd@gmail.com

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also be noted that the aberrant vessel may have a short or long course beneath the portal vein (PV).

2. The landmark #1 to identify aberrant HA: The first jejunal branch of the superior mesenteric vein (SMV) is a reliable landmark to identify the area where SMA is encountered during the uncinate process dissection (Video). However, an aberrant HA often origins from a point closer to the root of SMA. Radiological assessment with MPR images aids in determining the level at which the aberrant artery comes off.

3. Traction and counter-traction: Adequate retraction with proper triangulation of the organs and tissues is of paramount importance during advanced laparoscopic surgery. However, over traction on portal vein may also cause axial displacement of the vein; which, in turn, can disrupt surgeon's orientation to the portal vein/aberrant HA relationship (Video: asterisk shows tip of the sealing device while dissecting on incorrect area). Anatomical vascular neighborhoods should be checked by releasing all retractors if suspicion arises.

4. The landmark #2 to identify aberrant HA: It is easier to identify an aberrant HA during dissection of the hepatoduodenal ligament (HDL) than when uncinate process is being dissected (video). The artery can be found just beneath the common bile duct (CBD) immediately after the gastroduodenal artery is ligated and divided. It is now our practice to complete HDL dissection and secure HA, PV, CBD and accessory/replaced HA (if any) by placing a tape around each. This should preferentially precede dissection over the inferior edge of the pancreas, infrapancreatic tunnel creation and uncinate process dissection. Transection of the neck of the pancreas should not be delayed. Nevertheless, it is essential to know that earlier identification of an aberrant HA distally may not guarantee to prevention of the the artery during uncinate process dissection.

5. Nearby structures mistaken for aberrant HA: A thick lymphatic vessel or a long lymph node may be mistaken for an accessory or replaced HA, especially when the uncinate process dissection has fairly advanced (Video). Looking for arterial pulsation helps discriminate between an artery and a lymphatic vessel. Continuity of the structure should also be viewed before placement of a sealing device at this region.

Ethics Committee Approval: Not Relevant.

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CERRAHİ TEKNİK-ÖZET
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Laparoskopik pankreatikoduodenektomi sırasında SMA kökenli aberran hepatik arter yaralanmasının önlenmesi

Mehmet Fatih Can[1], Mustafa Kerem[2], Kürşat Dikmen[2]

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

ÖZET

Laparoskopik pankreatoduodenektomi oldukça zorlu bir cerrahi işlemdir. Süperior mezenterik arter kaynaklı aberran hepatik arter varlığı diseksiyonu daha da kompleks hale getirmektedir. Bu yazıda, laparoskopik pankreatoduodenektomi ameliyatı sırasında cerrahın aberran hepatik arteri yaralamasını önlemeye yardımcı olacak bazı önemli nokta ve püf noktaları önerilmiştir.

Anahtar Kelimeler: Pankreatoduodenektomi, laparoskopi, hepatik arter, yaralanma

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