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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.

As a surgical journal, the Turkish Journal of Surgery covers all specialties, and its target audience includes scholars, practitioners, specialists and students from all specialties of surgery.

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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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The Turkish Journal of Surgery requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

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- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- 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.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7: 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

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.

Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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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All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s) and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. The Journal reserves the right to reject work believed to have not been conducted in a high ethical standard, even when formal approval has been obtained.

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.

Animal Research

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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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Only references cited in the text should be included in the reference list. The reference list must be numbered according to the order of mention of the references in the text. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." The reference styles for different types of publications are presented in the following examples.

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.

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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/ncidodlElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

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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LETTER TO THE EDITOR

FROM THE EDITOR'S DESK

Dear Authors of Turkish Journal of Surgery,

As you all know, the first half of 2020 was an historical era of the human history, regarding the Coronavirus pandemic. We are all affected by the medical, social, economical and psychological etc. effects of this disease. The long-term impact is still unclear. It is undoubtedly the biggest global pandemic of our generations with more than 7 millions of patients and above 400.000 deaths. The healthcare workers were (and are still) among the most affected professionals in this pandemic.

On behalf of my editorial team I would like to present our deepest and most sincere condolences for all the losses and we are wishing a speed recovery for those who are still under therapy.

Coronavirus outbreak affected also the patients who are waiting for a treatment for other medical causes. It is a very challenging situation for the colleagues to perform the best treatment in this particular time. We are operating the patients with verified or suspected Coronavirus infection, or have to schedule elective /semi-elective operations in seronegative patients. Since it is a very acute problem, we do not still have enough data in order to guide our daily decisions. Throughout the pages of this present June 2020 issue of Turkish Journal of Surgery you may find four articles that address this problem (1-4). We are glad to publish these reviews and studies regarding digestive and breast surgeries in Coronavirus era and hope that they ease the decision-making in your practical work.

The June 2020 issue contains also numerous high-quality studies of different disciplines. We are persuaded that you will find these articles interesting and useful for your daily work. I would like to point out the study of Schellenberg et al. about the frostbite injuries (5). It is an interesting and a very large study based on the data of National Trauma Databank. I hope that you may benefit from the experience of the authors, who are among the prominent surgeons in trauma surgery.

Finally you were certainly informed that the 22nd Turkish National Surgery Congress had to be postponed because of the measures against Coronavirus pandemic. The Turkish Surgical Society has recently announced that the meeting will take place from October 7th to 11th, 2020 in the same Congress Center in Antalya. Please note these dates. Again we look forward to see you all in 22nd Turkish National Surgery Congress to benefit from your contributions.

We wish you a pleasant reading.

Kindest regards,

Kaya SARIBEYOĞLU
Professor of Surgery
Turkish Journal of Surgery
Editor

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REVIEW
Turk J Surg 2020; 36 (2): 121-131

Surgical management of digestive system cancers during the coronavirus disease 2019 pandemic: review of general suggestions

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ABSTRACT

Since December 2019, the world has been battling the COVID-19 pandemic, and health workers are at the forefront of the fight. Surgeons also fulfill their duty; however, elective cases had to be postponed in order to use resources appropriately in the fight against coronavirus. Although benign elective surgical procedures can be postponed to a distant time during this pandemic, surgical interventions for urgent and life-threatening situations are mandatory to perform but the main uncertainty among surgeons is about cancer patients. In this paper, we aimed to present a suggestion to the surgeon about how to manage digestive system cancers during pandemic in the light of the published articles and guidelines.

Keywords: COVID-19, coronavirus, pandemic, digestive system, cancer, malign

INTRODUCTION

"There are no incurable diseases - only the lack of will. There are no worthless herbs - only the lack of knowledge."

When Ibn-i Sina said this sentence many centuries ago, perhaps he did not know that he would give such hope to physicians of the future struggling with a pandemic for which an optimal treatment method is not discovered yet. While in a health crisis that concerns the whole world and threatens people from all walks of life, healthcare professionals continue to work at the frontline, adhering to their oaths. Surgeons also continue to work properly everywhere in the task given to them in this difficult process. In many places with intensive patient burden, most surgeons perform medical duties in the emergency room, inpatient or intensive care units reserved only for COVID-19 patients. However, although benign elective surgical procedures can be delayed and postponed to a distant time during this pandemic, surgical interventions for urgent and life-threatening situations are mandatory to perform. Although there is no dilemma in terms of management to these emergency cases, the main uncertainty among surgeons is about cancer patients.

It appears that there are three major problems for the management of cancer patients during the pandemic. The first of these is the patient bed, ventilator and intensive care capacity of the hospital where the surgeon works. Due to the increasing number of COVID-19 patients, the need to keep these patients isolated and ventilator and intensive care needs due to respiratory problems, most of these resources are used for patients with COVID-19. For this reason, a surgeon has to consider how long the patient will stay in the preoperative and postoperative period, whether there will be a need for a ventilator and how long he/she can stay in the intensive care unit before operating the cancer patient. Moreover, in this process, there is legal uncertainty against the risk of the patient becoming infected with COVID-19 in the hospital.

Secondly, first data from the Far East have shown us that mortality rate is high in malignant patients infected with COVID-19. When malignant patients undergoing

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surgery have been infected with coronavirus, mortality rates are even higher (1). Therefore, the surgeon will have to choose between the risk of progression of the disease if he/she waits and the risk of infection in the process of making an operation decision to a cancer patient.

The third problem is the risks posed by the operation itself to the surgeon. The operations of cancer patients are relatively long, and the surgeon is in direct contact with the patient's body fluids during this period. Also, it is not yet clear whether the COVID-19 virus is transported by fumes from the electrocautery used, or by gases leaking from the patient in minimally invasive surgery. For this reason, the surgeon will be obliged to know the risk of COVID-19 of the patient he/she will operate and, if positive, take all precautions to protect itself and its team. Therefore, the surgeon should be able to provide these measures or have optimal conditions before operating the cancer patient.

Cancer is a progressive disease, and how long this pandemic process will last is uncertain. For this reason, oncologic surgeons are obliged to know which disease or patients should not be risked, and which patients should be operated at risk, and to make a decision by reporting this risk to the patient and the family. In this context, digestive system cancers constitute one of the most risky groups. In this paper, we aimed to present a suggestion to the surgeon by reviewing the articles on the subject so far and the suggestions of different associations and guidelines. Since this process is an ongoing condition and new information continues to appear, the surgeon should not forget that he / she should constantly renew him/herself.

MATERIAL and METHODS

Evaluation of the current suggestions was carried out in two separate areas. First, the articles published since the beginning of pandemic up to date (01/12/2019-15/04/2020) about the subject have been passed through an elimination process. For that purpose, the widely used Pubmed database was referred. In the search area, the variables written for the purpose (Coronavirus 19/COVID 19/ Surgery/Cancer etc.) and the results were evaluated one by one and articles related to surgery of the digestive system and cancer were reviewed. In search combinations, the option that gave the widest result on the subject was chosen (COVID 19 Surgery/368 results). From these, 20 articles were identified on the management of digestive system cancers during the pandemic (10 in English, 10 in Chinese). Articles written in English were evaluated entirely, and articles written in other languages (all Chinese) were evaluated after translation. The articles were categorized according to the organs they were interested in and the results were presented separately. Secondly, the suggestions of the associations and organizations known worldwide and have many international members were presented. Article categories and guides are shown in Table 1.

Table 1. Search results, article categories and guides presented

Search results	
COVID 19: 4272 (chosen) COVID: 3831 Coronavirus: 3100 Coronavirus 19: 2212 nCoV: 485 nCoV 19: 343	**COVID 19 Surgery: 368 (chosen)** COVID 19 Cancer: 273 COVID 19 Gastrointestinal: 81 COVID 19 Digestive: 72 COVID 19 Malignancy: 41
Article categories (n= 20) (English) • General Digestive System: 3 • Esophagogastric: 1 • Hepatopancreaticobiliary: 0 (transplantation excluded) • Colorectal: 6	(Chinese) • General Digestive System: 3 • Esophagogastric: 1 • Hepatopancreaticobiliary: 2 (transplantation excluded) • Colorectal: 4
Guidelines • American College of Surgeons COVID-19 Guidelines for Triage of Colorectal Cancer Patients • Society for Surgical Oncology Resource for Management Options of Colorectal Cancer During COVID-19 • Society for Surgical Oncology Resource for Management Options of GI and HPB Cancers During COVID-19 • Society of American Gastrointestinal and Endoscopic Surgeons Recommendations Regarding Surgical Management of Gastric Cancer Patients During the Response to the COVID-19 Crisis • Society of American Gastrointestinal and Endoscopic Surgeons - AHPBA Recommendations Regarding Surgical Management of HPB Cancer Patients During the Response to the COVID-19 Crisis • Society of American Gastrointestinal and Endoscopic Surgeons Recommendations Regarding Surgical Management of Colorectal Cancer Patients During the Response to the COVID-19 Crisis	

Before proceeding to get the results, it is important to remind that the working conditions will not be the same for every surgeon in the pandemic process so that the decision must be made according to the patient and these conditions during the process. The surgeon must be alert that the information may change constantly in the ongoing process.

EARLY SUGGESTIONS and RESULTS of FIELD STUDIES

1. Management of Esophagogastric Cancer Patients

Based on the Eastern literature, progression time from localized to locally advanced esophagogastric cancer disease is 34-44 months (2). In esophageal tumors, this period may be shorter, and the patient may become symptomatic even in the early period. However, since postoperative complication risks are high and patients become vulnerable to respiratory and septic complications, it should be kept in mind that operating these patients during the pandemic also has risks. Therefore, the decision must be made individually according to the patient.

Li et al. have made suggestions about the management of patients with esophageal cancer during the pandemic period (2). Accordingly, in stage I patients, surgical treatment or endoscopic resection can be selected according to the patient's condition. Pre-operative neoadjuvant therapy is recommended in stage II and III patients. Stage IV patients are directed to the oncology and radiotherapy department. For patients who complete pre-operative neoadjuvant therapy, depending on the limited or elective surgery system of the hospital, if the patient is unable to perform surgery on time, additional chemotherapy may be added 1 or 2 times, or preoperative nutritional support is provided to heal and closely monitor the underlying disease.

In their extensive study, Ma et al. remind that 6-month waiting period in early stomach cancer does not change the prognosis, and in stage II and III disease, this period is 3 months (3). Therefore, Ma et al. advocates that operation can be postponed in patients with early gastric cancer, and in local advanced diseases, appropriate time can be gained with neoadjuvant therapy. Similarly, Chen et al. have stated that appropriate patients should be directed to neoadjuvant therapy based on NCCN guideline suggestions (4).

Likewise, the French group recommends postponing operations in a way to prioritize neoadjuvant therapy in esophageal and gastric tumors and suggests discussing the risks with the patient planned to undergo surgery (5).

2. Management of Hepatopancreaticobiliary Cancer Patients

As stated in the article of Wu et al. in hepatocellular carcinoma, the tumor volume duplication time is on average 85.7 days (6). This period may be shortened in hepatocellular cancers that initially have a small tumor volume or carcinoma due to Hepatitis C. According to Wu et al., most hepatobiliary system tumors will not turn into non-resectable tumors after the appropriate operation postpone. Although this delay time is not clear, these tumors can progress aggressively. Even if the tumor is found to progress rapidly after 1 to 2 months and is no longer suitable for surgery, this indicates that the tumor has an extremely high degree of malignancy and possibly the first surgical effect will not be satisfactory. Furthermore, for patients with cholangiocarcinoma with jaundice, one may consider catheterization and drainage to reduce jaundice and improve nutrition. In addition to surgery, interventional treatment methods is an important option for malignant tumors of the hepatobiliary system and can be selected in suitable patients (6). Radiofrequency ablation (RFA) or chemoembolization in hepatocellular cancer; RFA for colorectal liver metastases are some options.

Advice of the French group is to postpone the planned operation time for early liver tumors. They suggest minor hepatic resections if the patient has low postoperative risks but if major hepatic resection is needed or patient has high postoperative risks, operation time might be postponed (5).

Morbidity after pancreatic surgery could be high and this is mostly an aggressive tumor. The French group suggests operation only for low risk patients and only if resources are avaible for patient (5). For high risk group, they offer neoadjuvant chemotheraphy. Gou et al. have reported four patients with pancreatic disease treated during the pandemic, and all were infected with COVID-19, one died, one was still in hospital and two were discharged, and mentioned the importance of preventing nosocomial infections during this process (7).

3. Management of Colorectal Cancer Patients

Yu et al. have reported their experience on the method of operation in colorectal cancer patients during the pandemic process (8). According to the opinions of the authors, in laparoscopic surgery, the surgeon›s contact with the abdominal cavity will decrease and the aerosol emission overcome by electrical equipment will also decrease. Moreover, compared with total laparoscopic surgery, laparoscopic surgery with an auxiliary incision can reduce the operation time and thus the exposure time. Based on these ideas, Yu et al. recommends laparoscopy-assisted radical surgery for colorectal cancer patients during the pandemic but they highlight that the aerosols need to be strictly managed. They also underline that NOSES and TaTME procedures should be carried out cautiously and protective stomas should be carried out reasonably. There are very few publications on transmission of COVID-19 in open and minimally invasive surgery, and their level of evidence is low. There are points where laparoscopic and open surgery provide advantages and disadvantages to each other and there is no consensus in this regard. However, the only point provided by consensus is that risk reduction modifications must be provided, whether open

or minimal surgery (9). In this regard, the recommendations of the Turkish Surgical Society and Turkish Society of Colon and Rectum Diseases can be reviewed (10,11).

Hu et al. have reported their views on the management of precancerous, early, locally advanced, obstructive, metastatic and neoadjuvant colorectal cancer patients during the pandemic process (12). Accordingly, they recommend symptom and colonoscopy follow-up once a month during the pandemic for polyps that are dysplastic and are not suitable for endoscopic resection. It is stated that treatment can be postponed in patients with early colorectal cancer after screening and evaluation, but surgical treatment, especially endoscopic resection, can be applied depending on the patient's intent to treat. In locally-advanced disease, it was emphasized that neoadjuvant therapy can be applied in both colon and rectum tumors, and time can be saved in this process. Chen et al. and the French group have made similar suggestions in their articles (4,5). A similar algorithm has been proposed for metastatic disease. However, the authors emphasize that the patient should be followed up with symptoms, tumor markers and imaging during the treatment and the necessity of surgery in case of progression. The necessity of surgery in obstructive colorectal cancer is unquestionable. The removal of the main tumor with ostomy or the application of a stent should be decided according to the patient. After all, Angelos et al. recommend traditional open method rather than laparoscopy for emergency colorectal surgery for their concern about airborne transmission of the virus (13). For patients who have completed neoadjuvant therapy and who need to make an appointment for radical surgery, it is recommended that patients be properly delayed during surgery and chemotherapy is performed during the waiting period. Generally, surgery is recommended to be performed 8 to 12 weeks after neoadjuvant chemoradiotherapy and can be extended up to 12 weeks for now.

Luo et al. have had several additional suggestions for colorectal surgery during the pandemic process (14). In this process, they have argued that respiratory department and infectious department should also be included in the multidisciplinary team. Because of the cross infection risk during the colonoscopy examination, they suggest giving priority to urgent and life-threatening cases.

Suggestions also appear in the same direction on the western side of the world (15). Pellino et al. remind us that 3-10 years survival is lower if treatment is started after more than 90 days from diagnosis for colorectal cancer (16). The ideal time of resection of colon cancer has been estimated to be between 3 and 6 weeks from diagnosis and the authors suggest that alternative treatment to radical surgery in very early-stage cancer or in very advanced disease should be discussed. In another study by them, they hypothesize that laparoscopic surgery may be the approach of choice, and they find open and transanal approach hazardous because of aerosolized biological fluids (17). In fact, it is still not clear whether the virus can be found in the leaked CO_2 used for minimal invasive surgery.

De Felice et al. recommend short-course radiotheraphy but delayed surgery after 5-13 weeks for locally-advanced rectal tumors (18). They have concluded that it has same results in terms of sphincter preservation and negative margins compared to immediate surgery but higher pathological complete response rates. With this plan, they state that the patient's hospital stay will be minimized.

4. Management of Oncological Emergencies

In fact, there is no difference between the management of oncological emergencies and management of other emergencies, except for a slight nuance differences. It is possible to encounter emergencies such as obstruction, perforation, bleeding and infection, as well as cancer related conditions such as nutritional disorders and jaundice during the pandemic. It is not possible to delay the operation in life-threatening situations. Therefore, the operation should be carried out by explaining the possible risks to the patients and their relatives. Recommendations of Gok et al. can be used for the management of emergency patients (19).

Except for these emergencies, patients with esophagogastric cancer may have emergencies such as bleeding and fistula. Conservative symptomatic treatment can be chosen in patients with mild bleeding and small fistula with minor systemic symptoms. In severe bleeding, interventional radiology, endoscopy or emergency surgery can be preferred. Patients with severe systemic infection caused by fistula should also be treated with drainage and medical theraphy (2). Patients with hepatopancreaticobiliary cancer with jaundice and malnutrition, catheterization and drainage can be considered, if their operations will be postponed (6). The patient with colorectal bleeding can be approached in a similar way. Colorectal cancer patients with obstruction, perforation and massive bleeding should be operated immediately (20).

SUGGESTIONS of ASSOCIATIONS and ORGANIZATIONS

Before understanding the recommendations of the guides, it is necessary to review the classification of healthcare institutions according to COVID-19 patient density. This classification is presented in Table 2. Some of the world's leading associations and organizations have prepared some organ-based guidelines for the management of cancer patients in the pandemic process. Although these guidelines are similar to the study results, we think that they will give the physician an organized idea (Table 3-8).

Table 2. COVID-19 phases of hospital or healthcare systems

Phase		Description
0	**Unaffected**	No COVID-19 patients, hospital works properly.
1	**Semi-Urgent**	Few COVID-19 patients, hospital resources not exhausted, institution still has ICU ventilator capacity and COVID-19 trajectory not in rapid escalation phase.
2	**Urgent**	Many COVID-19 patients, ICU and ventilator capacity limited, OR supplies limited.
3	**Emergent**	Hospital resources are all routed to COVID-19 patients, no ventilator or ICU capacity, OR supplies exhausted.

Table 3. American College of Surgeons COVID-19 Guidelines for Triage of Colorectal Cancer Patients (https://www.facs.org/covid-19/clinical-guidance/elective-case/colorectal-cancer)

Phase I	Phase II	Phase III
Cases that need to be operated as soon as feasible (recognizing status of each hospital likely to evolve over next week or two): • Nearly obstructing colon • Nearly obstructing rectal cancer • Cancers requiring frequent transfusions • Asymptomatic colon cancers • Rectal cancers after neoadjuvant chemoradiation with no response to therapy • Cancers with concern about local perforation and sepsis • Early stage rectal cancers where adjuvant therapy not appropriate **Diagnoses that could be deferred 3 months** • Malignant polyps, either with or without prior endoscopic resection • Prophylactic indications for hereditary conditions • Large, benign appearing asymptomatic polyps • Small, asymptomatic colon carcinoids • Small, asymptomatic rectal carcinoids **Alternative treatment approaches to delay surgery that can be considered:** • Locally advanced resectable colon cancer - Neoadjuvant chemotherapy for 2-3 months followed by surgery • Rectal cancer cases with clear and early evidence of downstaging from neoadjuvant chemoradiation - Where additional wait time is safe - Where additional chemotherapy can be administered • Locally advanced rectal cancers or recurrent rectal cancers requiring exenterative surgery - Where additional chemotherapy can be administered • Oligometastatic disease where effective systemic therapy is available	**Cases that need to be operated as soon as feasible (recognizing status of hospital likely to progress over next few days):** • Nearly obstructing colon cancer where stenting is not an option • Nearly obstructing rectal cancer (should be diverted) • Cancers with high (inpatient) transfusion requirements • Cancers with pending evidence of local perforation and sepsis **Cases that should be deferred:** • All colorectal procedures typically scheduled as routine **Alternative treatment approaches:** • Transfer patients to hospital with capacity • Consider neoadjuvant therapy for colon and rectal cancer • Consider more local endoluminal therapies for early colon and rectal cancers when safe	**Cases that need to be operated as soon as feasible (status of hospital likely to progress in hours)** • Perforated, obstructed, or actively bleeding (inpatient transfusion dependent) cancers • Cases with sepsis **All other cases deferred** **Alternate treatment recommended** • Transfer patients to hospital with capacity • Diverting stomas • Chemotherapy • Radiation

Table 4. Society for Surgical Oncology Resource for Management Options of Colorectal Cancer During COVID-19 (https://www.surgonc.org/wp-content/uploads/2020/04/Colorectal-Resource-during-COVID-19-4.6.20.pdf)

Phase I	Phase II	Phase III
Conditions for which operations to be deferred • Benign colorectal polyps • Malignant colorectal polyps (focus of cancer within polyps) • Prophylactic procedures for hereditary (e.g. familial adenomatous polyposis) or inflammatory (e.g. inflammatory bowel disease) conditions **Conditions for which operations may be considered** • Emergency cases (as defined) • Non-metastatic colon cancer- curative intent surgery - Asymptomatic - Near-obstructing - Requiring frequent transfusions - Evidence of impending perforation • Non-metastatic rectal cancer - Early stage rectal cancer not appropriate for neoadjuvant/adjuvant therapy - Rectal cancers after neoadjuvant therapy with no response to therapy • Resectable oligometastatic disease - Exhausted effective systemic therapy	**Conditions for which operations to be deferred** • All procedures for asymptomatic or minimally-symptomatic cancers **Conditions for which operations may be considered** • Emergency cases (as defined) • Significantly symptomatic cancers (e.g. severe pain) • Near-obstructing colon and rectal cancers - Consider diversion alone for rectal or complex colon cancers • Bleeding colorectal cancers with high transfusion requirements	**Conditions for which operations to be deferred** • All procedures unless imminently life-threatening (death within hours without intervention) **Conditions for which operations may be considered** • Emergency cases (as defined) with no feasible alternative approach

ALTERNATIVE CONSIDERATIONS AND APPROACHES TO DELAY SURGERY (ALL PHASES)

- Locally-advanced resectable colon cancer
  - Consider neoadjuvant chemotherapy
- Locally-advanced resectable rectal cancer
  - Strong consideration of total neoadjuvant therapy (TNT)
  - For radiation component, strongly consider short course 5 x 5 Gy regimen (vs. long course chemoradiation)
  - With evidence of downstaging, delay surgery post-neoadjuvant therapy up to 12-16 weeks
  - Consider additional systemic chemotherapy if prolonged delay
- Bleeding from cancer
  - Consider radiation treatment, embolization where appropriate
- Near-obstructing cancers
  - Consider stenting where possible
  - Consider chemotherapy, radiation where possible
- Resectable oligometastatic disease
  - Continue effective systemic therapy
  - Consider non-surgical ablative/embolic approaches where appropriate
- Where possible, consider transfer of urgent patients to other facilities with capacity

Table 5. Society for Surgical Oncology Resource for Management Options of GI and HPB Cancers During COVID-19 (https://www.surgonc.org/wp-content/uploads/2020/04/GI-and-HPB-Resource-during-COVID-19-4.6.20.pdf)

Gastric and Esophageal Cancer

- cT1a lesions amenable to endoscopic resection may preferentially undergo endoscopic management where resources are available.
- cT1b cancers should be resected.
- cT2 or higher and node positive tumors should be treated with neoadjuvant systemic therapy.
- Staging laparoscopy with peritoneal washings is often utilized for patients being considered for neoadjuvant treatment. Given the recent concerns of laparoscopic surgery in COVID-19 patients and the additional use of resources, consideration may be given to proceeding straight to neoadjuvant treatment in COVID-19 positive patients, and if staging laparoscopy is decided to be performed, efforts to minimize PPE utilized and staff involved / exposed in the procedure should be made using appropriate pneumoperitoneum risk reduction strategies.
- Patients finishing neoadjuvant chemotherapy may stay on chemotherapy if responding to and tolerating treatment, and resources do not support proceeding to resection. If patients are not responding to systemic treatment, resection and/or referral may be considered.
- Patients with gastric outlet obstruction or hemorrhage may be treated with endoscopic measures to allow for enteral nutrition/ control of bleeding and proceed to surgery if these measures fail.
- Surgery may be considered for short-term deferral in less biologically aggressive cancers, such as GIST, unless symptomatic or bleeding.

Hepato-pancreato-biliary Cancer

Phase I	Phase II	Phase III
Cases to be operated as soon as feasible • Symptomatic and asymptomatic duodenal adenocarcinoma • Symptomatic and asymptomatic ampullary adenocarcinoma • Symptomatic and asymptomatic extra-hepatic cholangiocarcinoma • Symptomatic and asymptomatic intra-hepatic cholangiocarcinoma • Symptomatic and asymptomatic gallbladder adenocarcinoma • Pancreatic adenocarcinoma patients completing the projected course neoadjuvant therapy where more therapy may be detrimental to their health status • Pancreatic neuroendocrine carcinomas (small/large cell) completing the projected course neoadjuvant therapy where more therapy may be detrimental to their health status • Metastatic colorectal cancer to the liver completing the projected course neoadjuvant therapy where more therapy may be detrimental to their liver • Symptomatic low grade tumors **Cases to consider alternative therapies to safely delay surgery to a more stable time** • Consider neoadjuvant chemotherapy for large intra-hepatic cholangiocarcinoma that will require a major liver resection • Consider ablation, regional therapy procedures, or neoadjuvant therapy for hepatocellular carcinoma • Consider neoadjuvant therapy for all newly diagnosed pancreatic adenocarcinoma patients and extending planned neoadjuvant to total upfront therapy if patient tolerating regimen • Consider adding radiation to neoadjuvant chemotherapy protocols to delay surgery if warranted for biology by multi-disciplinary tumor boards • Staging/margin operations in incidentally detected gallbladder cancers on final pathology • Consider somatostatin analogues or regional therapy in newly identified liver metastasis in well-differentiated neuroendocrine in previously resected **Cases that should be deferred** • Asymptomatic pancreatic or duodenal well-differentiated neuroendocrine tumors • Asymptomatic duodenal and ampullary adenomas with or without high grade dysplasia • Asymptomatic GIST • Asymptomatic high risk IPMN or MCN pancreatic cysts • Hepatic adenomas, gallbladder confined polyps/masses, or indeterminant low- grade appearing neoplasms • Choledochal cysts • Metastatic renal cell cancer to pancreas or liver	**Cases to be operated as soon as feasible** • Peri-ampullary tumors causing gastric outlet obstruction where endoscopic stenting is not a good option • Bleeding tumors that cannot safely be managed with interventional radiology, endoscopy, or radiation • Hormonally active neuroendocrine tumors, like insulinomas, that post a major health threat untreated • If extended delay would potentially make an advanced tumor become unresectable and all other forms of therapy have been maxed out • Management of surgical complications if interventional approach not feasible **Cases that should be deferred** • Same cases from Phase 1 • All asymptomatic tumors from Phase 1 **Alternative treatment approaches recommend** • All delayed approaches suggested in Phase 1 • Consider neoadjuvant chemotherapy in tumors that you otherwise would not give chemotherapy upfront if could do so safely • Consider adding radiation to tumors that you otherwise would not give radiation to if could do so safely • SBRT to liver metastasis • Consider regional liver therapy for extended indications to bridge to a later surgery • Consider neoadjuvant hormone therapy where appropriate • Observation in low grade tumors	**Cases to be operated as soon as feasible** • Management of surgical complication if interventional approach not feasible • Bleeding tumors that cannot safely be managed with interventional radiology, endoscopy, or radiation • Any tumor with acute perforation that can be salvaged operatively **Cases that should be deferred** • All HPB tumors **Alternative treatment approaches recommend** • Same as above

Table 6. Society of American Gastrointestinal and Endoscopic Surgeons Recommendations Regarding Surgical Management of Gastric Cancer Patients During the Response to the COVID-19 Crisis (https://www.sages.org/sages-recommendations-surgical-management-gastric-cancer-covid-19-crisis/)

Gastric Cancer
T1a cancers - these patients may be candidates for EMR or ESD and referring them for a same-day procedure. These may be considered in Phase I depending on hospital resources. If not, then weekly "check-ins" to reassess the stage are reasonable to find the best "window". In Phase II - III, these should be deferred. Also note, there are concerns for aerosolization with endoscopic procedures (EMR/ESD) and thus we recommend delaying these procedures and ensuring patient is COVID-19 negative.
T1b and T2 cancers - these patients need surgery, however, a 4-6 week window to time the operation when hospital resources are optimal (relatively-speaking) is reasonable. Minimally invasive options are preferable as they will likely decrease the length of stay in the hospital.
T3 or higher cancers, or those who are clinically node positive - these are patients in whom neoadjuvant chemotherapy is recommended, allowing physicians a 3-4 month window to plan surgery (likely after the crisis phase has passed).
Staging Diagnostic Laparoscopy - although patients with this stage of gastric cancer typically have staging with diagnostic laparoscopy prior to the initiation of chemotherapy to rule out occult metastatic disease, if hospital resources and space are critical at the time and the patient is at higher risk due to age or comorbidities, then consideration for proceeding straight to chemotherapy is reasonable. Plan for diagnostic laparoscopy after chemotherapy is completed and prior to operation.
Obstructing and Bleeding Gastric Cancers - for gastroesophageal junction cancers, immediate initiation of chemotherapy and radiation therapy may obviate the need for a stent for gastric outlet obstructions. If the obstruction is complete and the patient requires admission to a hospital, then proceed with gastrectomy. However, for near-complete obstructions, chemotherapy may improve the ability to eat within 2-3 days. Avoid stents as they make as they could make subsequent procedures more challenging.
For a bleeding lesion, non-surgical approaches (IR and or endoscopy) should be attempted first. When not able to control otherwise, a surgical resection may be indicated.
Patients who have completed Neoadjuvant treatment and are Waiting for Surgery - these patients are difficult to manage, although from last chemotherapy to operation there is a window of 3-6 weeks during which surgery can be planned without losing the opportunity for potential cure. For some patients, consider speaking with the medical oncologist about adding an additional 1-2 cycles of chemotherapy to bridge the patient through the worst of the pandemic crisis and plan surgery there after.

Table 7. Society of American Gastrointestinal and Endoscopic Surgeons - AHPBA Recommendations Regarding Surgical Management of HPB Cancer Patients During the Response to the COVID-19 Crisis (https://www.sages.org/sages-ahpba-recommendations-surgical-management-of-hpb-cancer-covid-19/)

Organ	Clinical Situation	Phase I	Phase II	Phase III
Liver	HCC Very early stage (0)/Early Stage (A)/< 3 cm * For later stages consider TACE, Medical therapy, supportive care as appropriate	Consider ablation/resection/transplant as appropriate	Consider TACE, ablation, or observation (ie delay of definitive tx)	
	Colorectal mets	Consider chemotherapy vs. resection	Chemotherapy	
Biliary	Intrahepatic cholangiocarcinoma	Consider chemotherapy vs. resection	Consider chemotherapy, embolic therapy	
	Hilar cholangiocarcinoma	Stenting as indicated. Resection, transplantation as indicated	Stenting as indicated. Consider chemotherapy, chemoradiation, and/or transfer	
Pancreatic and extra-hepatic biliary	Resectable	Resection or consider chemotherapy	Neoadjuvant chemotherapy	
	Borderline	Neoadjuvant chemotherapy		
	Pancreatic IPMN, cysts, low-mod grade neuroendocrine neoplasms	All: observation (i.e. delay surgical management) Neuroendocrine: if metastatic or progressing, consider targeted therapy		

Table 8. Society of American Gastrointestinal and Endoscopic Surgeons Recommendations Regarding Surgical Management of Colorectal Cancer Patients During the Response to the COVID-19 Crisis (https://www.sages.org/recommendations-surgical-management-colorectal-cancer-covid-19/)

Clinical Situation	Phase I	Phase II	Phase III
Large or suspicious polyps Hereditary syndromes Dysplasia/Carcinoma in situ in biopsy specimens, Incomplete, questionable margins on polypectomy	For COVID-19 Phase I - III Hospitals surgery would be delayed until the pandemic abates and resources return		
Early cancer in resected polyp	Consider deferring surgery vs. resection	Defer Surgery	
Asymptomatic Cancer T1-2 N0	Resect	Resect vs. deferring surgery	Defer surgery
Asymptomatic Cancer Colon T3-4, N0 and Tx N+	Resect	Resect vs. deferring surgery	Consider chemotherapy vs. transfer
Rectal T3-4, N0 and Tx N+	Induction chemotherapy versus chemoradiation versus radiation, consider extended chemotherapy, also consider delaying surgery up to 12-16 weeks following completion of radiation		
Symptomatic cancers defined as bleeding requiring transfusion, obstructing or near-obstructing, impending perforation	Resect	Resect, consider stent vs. stoma	Stoma vs. stent, consider transfer

CONCLUSIONS and RECOMMENDATIONS to TURKISH SURGEONS DEALING with GASTROINTESTINAL CANCERS

1. To help prevent the spread of the virus, control of staff mobility and measures to reduce the number of accepted patients to the hospital, available service and intensive care capacity and number of ventilators should be the largest determinant of the surgeon's ability to perform oncologic surgeries. An isolated unit, operating room and team can be created for oncologic patients to continue operations, if possible.

2. The level of exposure of the hospital with COVID-19 and the upcoming action plan should be known and the operation plan of oncological patients should be decided accordingly.

3. All patients with malignancy should be informed according to the recommendations of the guides and the treatment plan should be decided together with the patient and the patient's family. In accordance with the guidelines, the operation of suitable patients should be postponed as much as possible, and the age and comorbidities of the patient and the postoperative risk of the surgery should be taken into consideration in patients to undergo surgery. Again, appropriate cases could be directed to secondary therapies in line with the guidelines. In this group of patients, a multidisciplinary oncology team must make the decision. Patients whose operation is postponed or directed to secondary treatment should be called for routine control.

4. An informed consent form must be obtained from all malignant patients who will be operated and hospitalized regarding COVID-19 infection and its predicted risks.

5. There are very few studies on viral transmission in open or minimally invasive surgery, and the evidence levels of these studies are low. Laparoscopic surgery seems to be advantageous both in terms of low risk to the patient and early postoperative discharge time. However, the risk of transmission by gases that spread from the abdomen to the operating room environment and put the instruments and items in the operating room and other personnel at risk is not clear yet. Open surgery is advantageous because it reduces the duration of surgery and minimizes the risk of transmission to non-operating personnel. However, the risk of direct contact with body fluids and the transmission of fume from the energy devices used is not yet clear. Until otherwise indicated, all surgeons must take precautions for COVID-19 spread related to the surgical method to be performed in the operating room (endoscopic/minimally invasive/open).

6. In these difficult times, every surgeon should remember that there is always another surgeon who will help himself or herself in every subject and condition, and should not hesitate to seek help. We are all in this together.

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DERLEME-ÖZET
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2019 koronavirüs hastalığı sırasında sindirim sistemi kanserlerinin cerrahi yönetimi: genel önerilerin gözden geçirilmesi

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ÖZET

Aralık 2019 tarihinden bu yana dünya COVID-19 salgınıyla mücadele etmekte ve sağlık çalışanları mücadelenin ön saflarında yer almaktadır. Cerrahlar da bu süreçte görevlerini yerine getirmektedir, ancak koronavirüsle mücadelede kaynakları uygun bir şekilde kullanmak için elektif olguların ertelenmesi gerekmektedir. Benign elektif cerrahi işlemler, pandemi sırasında uzak bir zamana ertelenebilmesine rağmen, acil ve hayatı tehdit eden durumlara yönelik cerrahi müdahalelerin yapılması zorunlu olmakla birlikte, cerrahlar arasındaki esas belirsizlik kanser hastaları ile ilgilidir. Bu yazıda, pandemi sırasında sindirim sistemi kanserlerine nasıl yaklaşılması gerektiği, ilgili makaleler ve kılavuzlar ışığında gözden geçirilerek, cerraha bir öneri sunmak amaçlanmıştır.

Anahtar Kelimeler: COVID-19, koronavirüs, pandemi, sindirim sistemi, kanser, malign

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REVIEW
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Recommendations for bariatric and metabolic surgical operations during the COVID-19 pandemic in Turkey

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ABSTRACT

The world has been struggling with the COVID-19 virus since December 2019. Turkey has also been battling with the virus since March 2019. While struggling with this unknown virus, we have postponed our new bariatric surgeries like most elective surgery. However, curfew and quarantine period (increase in food intake and decreased physical activity) increases risks for morbidity and mortality because of obesity and diabetes. When the pandemic decreases and disappears, many obesity patients will seek treatment for obesity and the workload of surgeons will increase. Before bariatric and metabolic surgery operations, which is the most effective treatment of obesity and related comorbidities, necessary precautions must be determined and implemented to protect patients and healthcare workers before and during surgery. In this review, it was aimed to determine the pre-peri and post-operative periods of bariatric surgical requirements. This review has been written on behalf of the Turkish Society for Metabolic and Bariatric Surgery as an initiative in order to answer some questions about bariatric and metabolic surgery during the COVID-19 pandemic.

Keywords: Bariatric and metabolic surgery, COVID-19, coronavirus

Introduction

Obesity is a public health problem affecting the whole world, lowers the quality of life and is associated with many comorbid diseases such as diabetes, hypertension, hyperlipidemia, obstructive sleep apnea syndrome and degenerative joint diseases. Bariatric surgery is the most effective treatment method that provides intensive weight loss and lowers comorbidities associated with over-weight (1). During the COVID-19 epidemic, which was announced by the World Health Organization as a pandemic in March 2020, new bariatric surgeries, like most elective surgeries, were postponed all over the world because of intraoperative risks for viral contagion among patients and healthcare workers.

However, the curfew and quarantine period (increase in food intake and decreased physical activity) increase risks for morbidity and mortality because of obesity and diabetes. On the other hand, obesity itself increases the risk of various diseases, including type II diabetes, hypertension, dyslipidemia, non-alcoholic fatty liver disease, cardiovascular and cerebrovascular diseases, various type of cancers, osteoarthritis, and nowadays the COVID-19 infection. All of the mentioned diseases also reduce quality of life, increase psychosocial dysfunction and obesity-related morbidity and mortality. Despite COVID-19, obesity and related comorbidities have reduced life expectancy by 5-20 years (2). In addition to the well-known indications for bariatric surgery, Diabetes Surgery Summit (DSS) guidelines recommend the consideration of metabolic surgery for appropriate candidates, including patients who has un-controlled type II diabetes with class I obesity (3).

Due to the increasing number of COVID-19 patients, patient beds, ventilators and intensive care units have been reserved for these patients. At the same time, when the pandemic decreases and disappears, many obesity patients will seek treatment for obesity, and the workload of surgeons will increase. However, the

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clinical presentation and outcomes of surgical patients during the COVID-19 outbreak have not been clearly characterized (4). Before starting operations, some questions such as 'which operation is the most effective treatment of obesity and related comorbidities, what kind of precautions must be determined and implemented to protect patients and healthcare workers before and during surgery' should be answered. According to the severity of the diseases that require bariatric and metabolic surgery, clinicians and health care authority should ensure that these operations are not further delayed because of increased morbidity and mortality (5).

This review has been written on behalf of the Turkish Society for Metabolic and Bariatric Surgery as an initiative in order to answer some questions about bariatric and metabolic surgery during COVID-19 pandemic.

Pre-operative Patient Preparation

Due to comorbidities and risks of morbidity, we should be more careful in preparing obesity patients for bariatric operation during the outbreak, who have undergone a more detailed pre-operative preparation process than other surgical patients before the pandemic. The patients who undergo surgery are required to meet the following criteria: BMI (body mass index) between 35-40 kg/m^2 with obesity-related co-morbidities or BMI ≥ 40 kg/m^2 with or without obesity related co-morbidities and BMI 30 to 34.9 kg/m^2 with metabolic syndrome or diabetes that is uncontrolled with medical therapy.

Before all preparations, the patient's detailed medical history in terms of covid-19 disease should be taken and evaluated by the pulmonologist in terms of COVID-19 with the help of blood tests and thoracic computerized tomography images (Figure 1). While non-serious symptoms can emerge in nearly half of the patients infected with COVID-19, the other half can show primary symptoms such as fatigue, dry cough, myalgia and dyspnea (6). The most common laboratory findings are leukopenia and lymphopenia. Lactate dehydrogenase and creatinine kinase elevation may also be seen. Half of the patients may have abnormal liver function tests like alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation. Although normal serum procalcitonin levels are seen in the majority of patients, C-reactive protein (CRP) levels have been found above the normal range. D-Dimer has been determined high in one third of the patients (7,8). If available, surgical patients should be tested pre-operatively for COVID-19.

If surgery is considered, screening and precaution measures should be taken strictly just like during the pandemic. Safety of the patients and healthcare professionals is a top priority in all clinical practices. The number of operations should be limited.

Preoperative evaluation should be made by a multidisciplinary team consisting of endocrinologists, dieticians, psychologists, pulmonologists, cardiologists, anesthesiologists and the surgeon. An informed consent form must be obtained from all bariatric and metabolic surgery candidates regarding operation in the COVID-19 pandemic and its predicted risks, as recommended other gastrointestinal operations (9). Additionally, a COVID informed patient program could be planned to inform the patients about potential complications and avoiding strategies in the post-operative period (10).

A detailed past medical and surgical history should be taken, and anthropometric measurements should be made. Laboratory workup should include a comprehensive metabolic panel, complete blood count and CRP, iron, vitamins, and folate, hemoglobin A1C, and a coagulation panel.

An abdominal ultrasonography should be performed for the screening of cholelithiasis and intra-abdominal mass (adrenal gland, liver, etc.). Esophagogastroduodenoscopy can be applied if the patient has upper digestive symptoms. The American Society of Metabolic and Bariatric Surgery advises the use of endoscopy only for patients with significant gastrointestinal symptoms (11,12).

The patient should also complete screening for cardiac diseases such as ischemic heart disease, systemic and pulmonary hypertension, right or left ventricular failure signs etc.

Psychologic and behavioral evaluation, nutritional evaluation, medical clearance, and anesthesiology evaluation are mandatory during the pre-operative work-up of the patient undergoing weight loss surgery.

If the surgery is delayed, glycemic control should be carefully optimized in patients awaiting metabolic surgery for type II diabetes. In addition, dietary or pharmacological interventions for weight control in patients who face prolonged waiting times for bariatric surgery might become necessary (5).

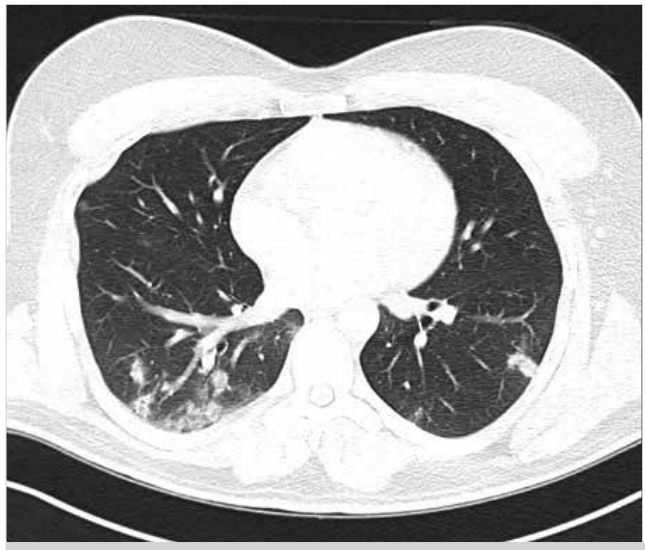

Figure 1. Thorax tomography image of a patient diagnosed with COVID-19.

DSS recommendations for the management of surgical candidates for bariatric and metabolic surgery during and after COVID-19 pandemic suggests categorization for elective surgery into urgent, semi-urgent, or non-urgent. Urgent elective surgery is required within 30 days for patients, whose conditions might deteriorate quickly. Semi-urgent elective surgery defined as if it delayed beyond 3 months, the patients could suffer from severe pain or dysfunction. Non-urgent elective surgery is planned for patient conditions that are unlikely to cause harm if treated within 1 year (5) (Table 1).

Peri-operative Period (Operating Room)

The operating room is one of the places where attention should be intensified to protect both patients and healthcare professionals during the COVID-19 outbreak. It is even more important to be protected from COVID-19 when performing elective surgeries that are relatively less urgent, such as obesity surgery. All staff must be trained to use personnel protection equipment (PPE) including masks (level 2 or 3 filtering face piece (FFP) depending on the aerosol-generating risk level), eye protection, double non-sterile gloves, gowns, suites, caps, and socks (13) (Figure 2). The number of staff in the operating room should be kept as low as possible, and staff's travel between operating rooms should be prevented unless it is necessary and all doors must be kept closed (14).

During patient transport, in order to minimize the possibility of encountering the virus, a shortest possible route should be defined in advance and kept away from other patients and people in general within the hospital.

Although negative pressure operation rooms minimize the risk of infection spread, operating rooms generally have positive pressure air circulation (15). High frequency of air exchanges (25 cycles/h) effectively reduces viral load within the operation room (16).

All equipment required for surgery should be available in the operating room, thus minimizing staff entry and exit during surgery. Use of non-disposable materials should be avoided, unless essential. The operation team should arrive in the room on time and should not leave the operating room unless the operation ends to prevent unnecessary entry and exit.

There is little evidence of relative risks of Minimal Invasive Surgery (MIS) compared to the conventional open approach. The risk and benefit of laparoscopic surgery remain favorable for patients and should be preferred to open surgery (5). However, since obesity surgery is usually performed laparoscopically, protective measures must be taken due to the possibility of viral contamination during surgery.

Although some studies have claimed that laparoscopy can lead to aerosolization of blood-borne viruses, there is no evidenced base proof support that COVID-19 has spread in this way and laparoscopic procedures should not be performed (17,18). Nevertheless, it should be kept in mind that the coronavirus may have similar aerosolization properties, and the use of devices that can filter the emitted CO_2 for aerosolized particles in laparoscopic procedures is useful. If possible, it would be safer to perform intubation and extubation in a negative pressure room.

Table 1. Categories of access to bariatric and metabolic surgery*

Urgent access: surgery within 30 days
Patient's condition is associated with one of the following:
• Conditions with potential to deteriorate quickly
• Severe symptoms or dysfunction
• Examples include severe dysphagia or vomiting from anastomotic stenosis, symptomatic internal hernia, severe nutritional deficiencies, or acute band-related complications
Expedited access: surgery within 90 days
Patient's conditions are not likely to deteriorate quickly but are associated with one of the following:
• Substantial risk of morbidity or mortality
• Reasonable risk of harm or reduced efficacy of treatment if surgery is delayed beyond 90 days
• Complex medical regimens or insulin requirement
• Weight loss, metabolic improvement, or both, are required to allow other time-sensitive treatments (e.g., organ transplants or orthopaedic surgery)
Standard access: surgery after 90 days
• Patient's conditions are unlikely to deteriorate within 6 months
• Only mild dysfunction or symptoms
• Delaying surgical treatment beyond 90 days is unlikely to significantly reduce effectiveness of surgery

* Retrieved from source 5.

Figure 2. Personnel protective equipment.

During the laparoscopic surgery, the incisions made for the ports should be as large as the instruments can pass and are small enough not to allow gas leakage. If the first trocar is placed by open Hasson technique, the purse string suture should be made around the first trocar in order to prevent gas leak. Intra-abdominal CO_2 insufflation pressure must be kept to a minimum level. Ultrafiltration (smoke evacuation system or filtration) should be used if it is available. Filtration system should be used to safely discharge intra-abdominal gas.

Post-operative Period

In order to reduce hospital and patient contamination in the postoperative period, the primary priority should be keeping patients' hospital stay short. Enhanced recovery after surgery (ERAS) protocol can also be applied for this purpose (19). The number of visitors should be kept to a minimum during the time of hospital stay. It should be ensured that the nurses and staff who continue the treatment of the patient are trained on contamination and have taken all necessary precautions.

Conclusion

In the period when the whole world has been struggling with the COVID-19 pandemic and the speed of outbreak spread is the fastest, bariatric surgeries are unfortunately postponed. However, in case of long-term delay of these surgeries, the possibility of morbidities regarding morbid obesity and related diseases and their negative effects on the country's economy should not be ignored. Therefore, with the onset of the normalization process, bariatric surgery will also be started with correct patient selection and appropriate pre-intra and postoperative preparations. An informed consent form must be obtained from all obesity patients regarding COVID-19 infection and its predicted risks. The most important issue here is that the entire team that will contact the patient before, during and after the surgery is trained and takes all necessary measures to reduce contamination.

This review has been written on behalf of the Turkish Society for Metabolic and Bariatric Surgery in order to answer some questions about bariatric and metabolic surgery during COVID-19 pandemic.

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DERLEME-ÖZET
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Türkiye'de COVID-19 pandemisi sürecinde bariatrik ve metabolik cerrahi operasyonlar için öneriler

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Türk Metabolik ve Bariatrik Cerrahi Derneği Yönetim Kurulu Girişimi Adına

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ÖZET

Dünya Aralık 2019'dan beri COVID-19 virüsü ile mücadele ediyor. Türkiye de Mart 2019'dan beri mücadele ediyor. Bu bilinmeyen virüsle mücadele ederken, diğer elektif cerrahi operasyonlar gibi yeni bariatrik ameliyatlarımızı da erteledik. Bununla birlikte, sokağa çıkma yasağı ve karantina süresi (gıda alımındaki artış ve fiziksel aktivitenin azalması) obezite ve diyabet nedeniyle morbidite ve mortalite risklerini arttırmaktadır. Pandemi azaldığında ve kaybolduğunda birçok obezite hastası, obezite için tedavi arayışına girecek ve cerrahların iş yükü artacaktır. Obezite ve ilgili komorbiditelerin en etkili tedavisi olan bariatrik ve metabolik cerrahi operasyonlarına başlamadan önce, ameliyat öncesi ve sırasında hastaları ve sağlık çalışanlarını korumak için gerekli önlemler belirlenmeli ve uygulanmalıdır. Bu derlemede, bariatrik cerrahi gerekliliklerinin ameliyat öncesi ve sonrası dönemlerinin belirlenmesi amaçlanmıştır. Bu derleme, COVID-19 salgını sırasında bariatrik ve metabolik cerrahi ile ilgili bazı soruları cevaplamak amacıyla, Türk Bariatrik ve Metabolik Cerrahi Derneği insiyatifinde yazılmıştır.

Anahtar Kelimeler: Bariatrik ve metabolik cerrahi, COVID-19, koronavirüs

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ORIGINAL ARTICLE
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The attitude of Turkish general surgeons during the COVID-19 pandemic: results of "general surgery COVID-19 pandemic attitude survey"

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ABSTRACT

Objective: The whole world is dealing with the COVID-19 pandemic, and healthcare professionals are the most affected group. The aim of this study was to evaluate the knowledge of general surgeons about COVID-19 and understand the attitude and current situation of our colleagues.

Material and Methods: This descriptive study comprised general surgeons working in different parts of Turkey. A survey with 23 questions was prepared to determine the demographic characteristics of the participants, workplace characteristics, change in daily work practices and their attitudes in the pandemic process.

Results: A total of 332 forms were evaluated. Survey results show that the majority of surgeons have changed their daily surgical practices. Many surgeons take part in the treatment of COVID-19. While most benign cases are delayed, the managemet of malignant cases differs. There are also differences in the evaluation of patients preoperatively and the type of operation. Personal protective measures are followed. While the rate of infected surgeons is low, the majority of surgeons have concerns about infection.

Conclusion: Turkish surgeons have managed to get a quick reaction from the start of the pandemic. However, there are still differences in preoperative patient evaluation and operation selection and precautions during the operation. Surgeons also should be informed about the management of malignant patients.

Keywords: COVID-19, coronavirus, pandemic, surgery, survey

INTRODUCTION

There is an intense fight worldwide against the 2019-nCoV virus which has a high risk of transmission, and mortality rates increases especially in a significant group of patients. This war will have many social and economic impacts on the world, but the greatest impact at present is the impact on the healthcare system that directly interferes with healthcare providers at the forefront of the war. In this situation, which seems to have spread throughout the country and increases its density especially in metropols, hospitals had to postpone the treatment of other non-emergency diseases and devoted most of their resources to the treatment of COVID-19 patients at different levels. Similarly, different areas of expertise had to take part in this common war to meet the need or had to change their daily routines.

During the pandemic, general surgeons either take part in the primary treatment of COVID-19 patients, or undertake the surgical treatment of COVID-19 suspected or positive patients in their daily routines (1). For this reason, changes in the approach or daily practice of general surgeons raised several questions. Answering these questions will enable us to have an idea about the role of general surgeons in the pandemic process, the situation of surgical education, changes in daily surgical practice, how surgeons approach the patient and how they protect themselves and especially their pyscological well-being. The answers to these questions are very important in terms of understanding our situation as Turkish General Surgeons and giving way to the measures we will take.

In order to achieve this goal, a survey containing 23 questions was prepared and the results were evaluated. Our aim was to evaluate not only the knowledge of

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general surgeons about COVID-19 but to understand the attitude and current situation of our colleagues.

MATERIAL and METHODS

This descriptive study comprised general surgery specialists and residents working in different parts of Turkey. This study was approved by the Ministry of Health, General Directorate of Health Services. A survey with 23 questions was prepared to determine the demographic characteristics of the participants, the workplace characteristics, the change in daily work practices and their attitudes in the pandemic process. Google forms (Google Inc, California, USA) were used in the preparation of the survey. The researchers following the guidelines including the suggestions about management of surgical practices during pandemic and the World Health Organization (WHO) suggestions were involved in the preparation of the survey. After the survey had been prepared, a link was sent to the members to participate in the survey using the Turkish Surgical Society mailing list and this link was also tried to be reached to more surgeons through various social media platforms. Access to the survey was provided between 13-17 April 2020. Results were evaluated after the survey had expired and results were expressed as mean ± standard deviation and numbers with percentages (%).

RESULTS

At the end of the survey period, the total number of participants reached 336 in five days. Three forms were not included in the evaluation due to missing information, and one form with a participant from North Cyprus was excluded to avoid creating bias. A total of 332 forms were evaluated. Considering the total number of general surgeons in Turkey, with this sample size, the confidence interval (margin of error) was 5.2%, at 95% confidence level, which was a reliable rate. The distribution of the participants across the country is shown in Figure 1. While most of the participation was from metropolitan cities, it is understood that participation from all regions of the country can be achieved.

The types of hospitals where the participants work and the rates of their density by the COVID-19 pandemic are presented in Figure 2. COVID-19 density classification of hospitals is divided into four cat-

Figure 1. Distribution of the participants across Turkey.

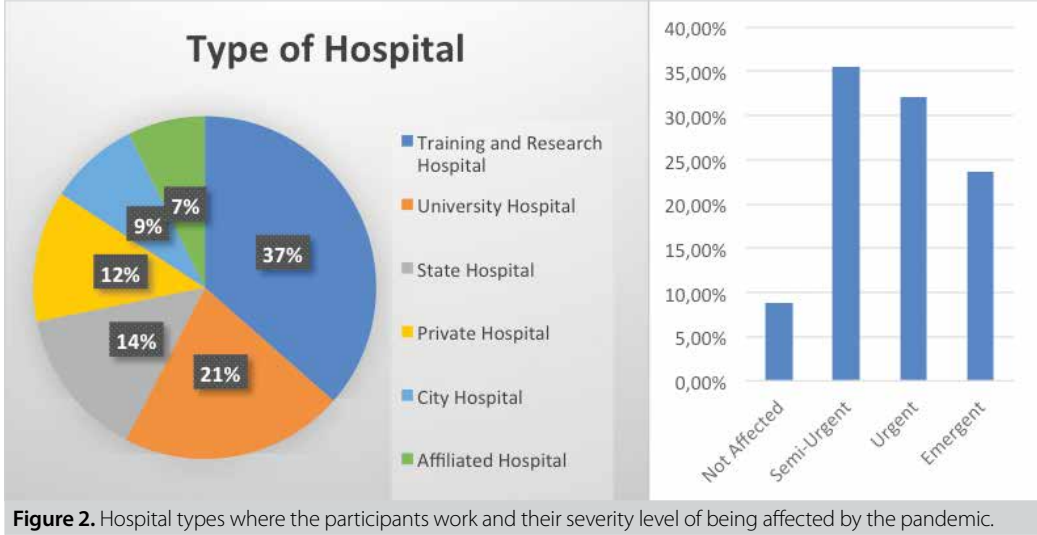

Figure 2. Hospital types where the participants work and their severity level of being affected by the pandemic.

egories; 1. Unaffected: No COVID-19 patients, hospital works properly. 2. Semi-Urgent: Few COVID-19 patients, hospital resources not exhausted, institution still has intensive care unit (ICU) ventilator capacity and COVID-19 trajectory not in rapid escalation phase. 3. Urgent: Many COVID-19 patients, ICU and ventilator capacity limited, operation room (OR) supplies limited, and 4. Emergent: Hospital resources are all routed to COVID 19 patients, no ventilator or ICU capacity, OR supplies exhausted. Accordingly, while the majority of the participants (35.5%) were found to have been working in semi-urgent hospitals, the rate of those working in emergent hospitals is 23.6%. Twenty-nine surgeons (8.8%) stated that they are still working in hospitals that have never been affected.

While questioning the daily routines of surgeons, 74.2% of surgeons reported that they stopped daily training, council and meeting activities during the pandemic process. The rest continued their meetings either by reducing the number of participants or by video conference method. The rate of those who did not change their daily activities was 4.6%. These rates can be seen in Figure 3.

Figure 4 shows the changes in surgeons' daily operation practice during the pandemic process. According to this, the majority of the participants (61.8%) stated that they only operated emergency and cancer cases. The number of surgeons who did not change operation routine was only 5 (1.5%). Other surgeons, either only perform emergency surgeries (20.9%) or have stopped their daily practice completely (15.8%). When asked to the surgeons who stopped the daily operation practices completely, the majority (29.5%) stated that they were working in other areas (polyclinic, service, intensive care) where COVID-19 patients were treated. The second major majority (26.9%) stated that they did not perform cases because they experienced anxiety due to COVID-19. Other answers with decreasing rates were the flexible work program, lack of resources or beds due to COVID-19 and other reasons.

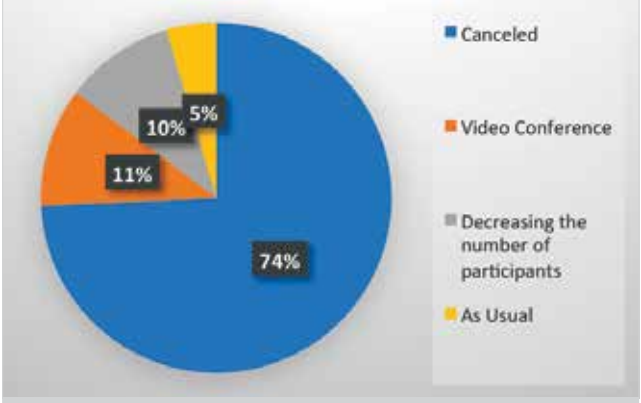

Figure 3. Changes in daily training, council and meeting activities during the pandemic process.

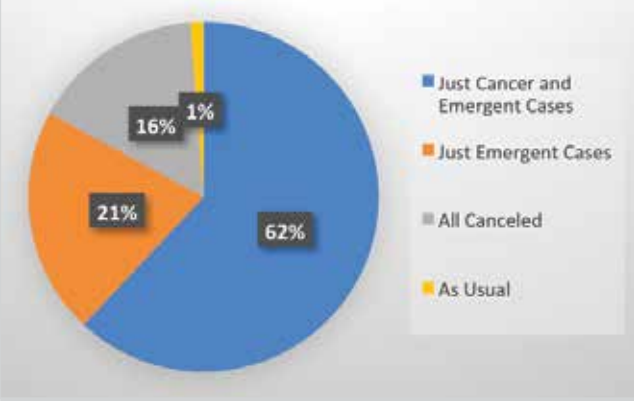

Figure 4. Changes in surgeons' daily operation practice during the pandemic process.

Then, the attitude of COVID-19 was questioned in surgeons who continued the operation, and 34.2% of surgeons stated that they considered all patients positive in the preoperative period and took precautions accordingly. The rate of making only symptomatic evaluation was 31.2%, the rate of preoperative thorax computed tomography request was 20.5%, and the rate of PCR request was 7.3%. Seven percent of the surgeons stated that they did not perform any evaluation and that they took action if any problems developed during the process. Almost half (46.4%) of the surgeons did not receive a consent form for COVID-19 from the patient prior to surgery. Suspected or positive patient contact and operation rates of surgeons are shown in Figure 5. Surgeons' management of benign and malignant patients in this process is presented in Figure 6. 22.7% (n= 69) of the general surgeons had COVID-19 test or imaging for themselves. One percent (n= 3) of the participants had COVID-19 positivity and treatment.

Almost half (51.8%) of the surgeons did not have a separate operating room reserved for COVID-19 patients. Surgeons' attitudes to using personal protection equipment in non-operating room and operating room routines are shown in Figure 7.

Four operation methods (open, laparoscopic, robotic and endoscopic) were presented in the survey and the method consid-

Figure 5. Suspected or positive patient contact and operation rates.

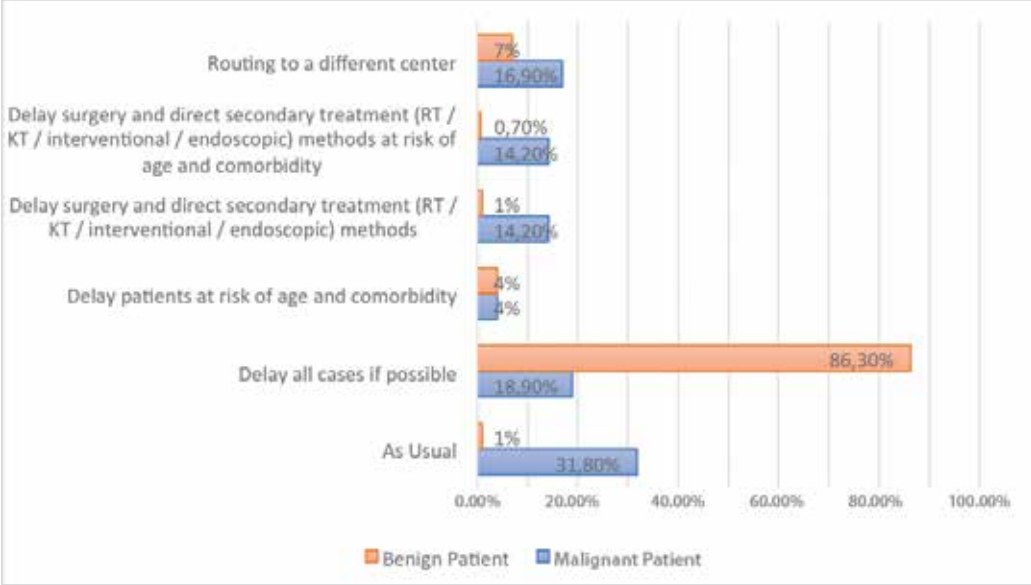

Figure 6. Surgical management choices of benign and malignant patients.

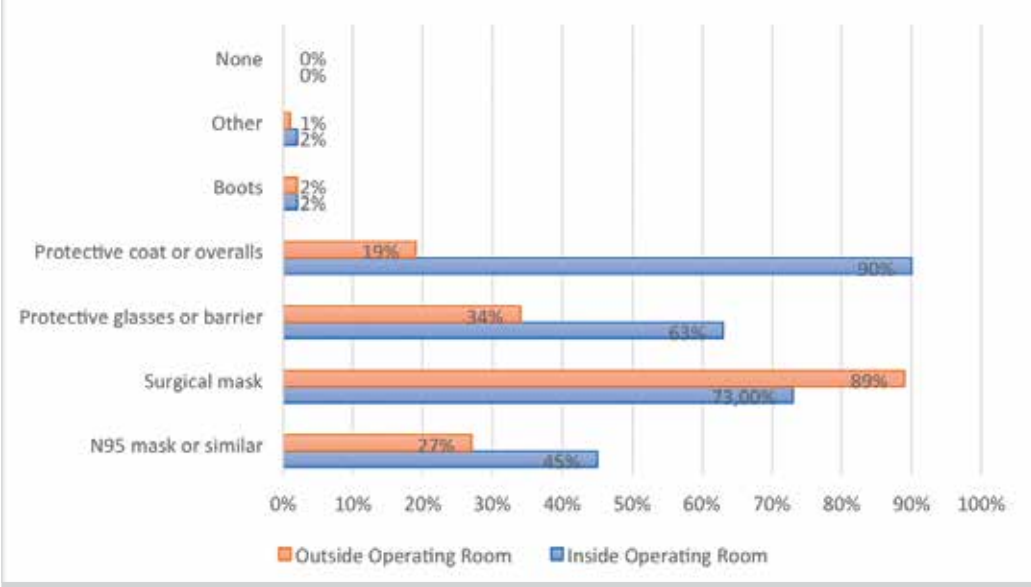

Figure 7. Surgeons' attitudes to using personal protection equipment.

ered to be the most risky in terms of COVID-19 transmission was asked. The method that received the most response with 41.9% rate was upper endoscopic surgery, which was followed by laparoscopic, open and robotic methods, respectively. When asked for the method that is considered to be the lowest risk in terms of COVID-19 transmission, open surgery was the method with the highest response with 56% answer rate, which was followed by robotic, laparoscopic and upper endoscopic surgery, respectively. The rate of those who took measures in open surgery to minimize the risk of COVID-19 transmission was 29.7%, while in minimally invasive surgery this rate was 41.2%.

From a social perspective, it was observed that 76.4% of the participants still stayed with their families at home during the pandemic process, 18.7% lived alone, and 4.9% resided in hotels or guesthouses. Half of the participants were concerned about being infected with COVID-19, 76% were afraid to carry COVID-19 infection to their relatives. The rate of those who stated that they did not experience these concerns was 20.4%.

DISCUSSION

Until April 5, 2020 in Italy, 10% of the infected individuals were healthcare workers, and a total of 105 healthcare workers died due to COVID-19 (2). In a community that directly encounters

patients infected with COVID-19, it is quite challenging to prevent this spread, and the only effort that can be taken is strict measures. In the United States, at the beginning of the pandemic (February-2020), 43 of 121 healthcare professionals who had contact with only one infected patient developed symptoms within 14 days, and three showed PCR positivity (3). Until April 9, 2020, COVID-19 positivity was reported in 9282 healthcare professionals in the United States (4). This situation shows that health professionals must protect themselves first, in order to achieve victory in the fight against the pandemic. There are precautions to be taken regarding health professionals (5). The Turkish Surgical Society has also conducted a study on the precautions surgeons should take during this process (6).

This survey was conducted to assess the attitudes of surgeons in Turkey during the early period of COVID-19 pandemic. The aim of this study was to determine the current situation and to shed light on the future measures. Survey questions were also prepared for this purpose by the researchers who followed the relevant guidelines.

Vast majority of the survey participants are from the metropolitan areas, however, there are participants from all regions of the country and it is seen that this diversity is also provided in hospital types that were responded. 91.8% of these hospitals were affected at different levels from COVID-19. It is seen that surgeons have changed their daily surgical practices and postpone elective cases. Most of the Turkish surgeons have arranged their working routines only to operate emergency and cancer cases and suspended training or meeting activities during the pandemic process. It is also seen that most surgeons work in other places of concern for the treatment of COVID-19 patients. We think that this is a successful early reflex across the country.

In the preoperative period, it is seen that Turkish surgeons evaluate their patient in terms of COVID-19 either with symptomatic evaluation, thorax imaging or a PCR test. We think that symptomatic evaluation should be done to all patients, and all emergency cases should be treated as a positive case, and in elective cancer cases, thorax tomography, which is already part of metastase screening, should be evaluated (7). In non-urgent suspected patients, PCR testing may be required before surgery. The proportion of surgeons who did not make any evaluation (6.8%) likely belongs to surgeons working in unaffected hospitals. However, considering the spread of the disease, we think that these surgeons also should take precautions. Our survey showed that the number of surgeons with a suspicious or positive patient contact is not low at all. However, almost half of the participants do not receive informed consent from patients regarding COVID-19. Patients can become infected with COVID-19 during their hospital stay for the operation. Surgery, especially in cancer patients, increases the mortality rate due to COVID-19 (8). There is legal uncertainty about these issues, and it is essential to obtain a consent form from patients for this information. Our survey study shows that surgeons should be informed about this issue.

Vast majority of Turkish surgeons has postponed benign elective cases but there is difference in approach to malignant elective cases. There are many guidelines on this subject (9-14). Currently, it is observed that one third of Turkish surgeons perform malignant patient management as before the pandemic. This may cause problems in hospital resource management or increase the risk of patients during the pandemic. The management of these patients should be done in accordance with the guidelines and therefore, surgeons should be informed. We are in preparation of a review on this topic.

It is seen that Turkish surgeons use the necessary personal protection equipment in their internal and external OR routines. It is also seen that the use of boots is very low in the operating room. Surgeons must be informed about this. Almost half of the participants stated that they did not have a separate operating theatre for COVID-19 patients. The possibilities of each hospital are different, but we think that a regulation should be made for the creation of these operating theaters in the cities.

There are very few studies on viral transmission in open or minimally invasive surgery, and the evidence levels of these studies are low. Our review mentioned above showed that laparoscopic surgery seems to be advantageous both in terms of low risk to the patient and early postoperative discharge time. However, the risk of transmission by gases that spread from the abdomen to the operating room environment and the risk of putting the instruments and items in the operating room and other personnel at risk are not clear yet. Open surgery is advantageous because it reduces the duration of surgery and minimizes the risk of transmission to non-operating personnel. However, the risk of direct contact with body fluids and the transmission of fume from the energy devices used is not yet clear. Turkish surgeons think open surgery is safe and upper endoscopic and laparoscopic surgery is risky in the pandemic process. The surgeons' attitudes towards robotic surgery are interesting. Although it is not very different with laparoscopic surgery, robotic surgery is considered to be safe. The perception on this issue is unknown. Whether the operation is minimally invasive or not, all surgeons must take risk-reducing measures. It is seen that the rate of taking these measures in Turkish surgeons is low. Surgeons should be informed in terms of these measures to protect themselves and their team.

Like every human being in the world, Turkish surgeons are concerned about getting ill or infecting their relatives. For this reason, it was observed that approximately 24% of the participants changed their social life conditions. This is a relatively high rate and the need for psychological support of physicians should be considered in this process and at the end of the process. It

is promising that the number of infected workers is quite low among our colleagues. However, this should not cause us to relax. Pandemic is an ongoing process, and it should be kept in mind that strict rules are still valid.

CONCLUSION

Turkish surgeons have managed to get a quick reaction from the start of the pandemic. However, there are still differences in preoperative patient evaluation and operation selection and precautions during the operation. Surgeons should also be informed about the management of malignant patients.

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Peer-review: Externally peer-reviewed.

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SURVEY. General Surgery COVID-19 Pandemic Attitude Survey

1- Name of the city you work in
Write the name of the city you are currently working in

2- Type of the institution you work in?
Mark only one item.
-University Hospital
-Affiliated Hospital
-Training and Research Hospital
-State Hospital
-City Hospital
-Private Hospital

3- Which of the following definitions does the hospital you work in comply with during the current pandemic process?
Mark only one item.
-Unaffected: No COVID-19 patient
-Semi-Urgent: Few COVID-19 patients, hospital resources not exhausted, institution still has ICU ventilator capacity and COVID-19 trajectory not in rapid escalation phase.
-Urgent: Many COVID-19 patients, ICU and ventilator capacity limited, OR supplies limited
- Emergent: Crisis situation in which all resources and intensive care beds are directed to COVID-19 patients

4- How did you arrange your daily training / council and meetings during the pandemic?
Mark only one item.
-As usual
-We reduced the number of participants
-We continued as video conference
-We canceled them

5- What is the change in your daily surgical practice during the pandemic process?
Mark only one item.
-I continue my daily practice as before the pandemic (ignoring the number of cases)
-I canceled benign cases. I only operate cancer and emergency cases
-I canceled benign and cancer cases. I only operate emergency cases
-I completely canceled my daily practice

6- If you canceled your daily practice completely, what is the main reason?
Mark only one item.
-I am on administrative leave due to age or comorbidity
-I am on administrative leave due to the flexible work program
-I do not perform operations due to the lack of personal protective equipment.
-I do not perform operations due to the lack of intensive care.
-I do not perform operations due to my concerns about COVID-19
-I do not perform operations because I am currently working in other services where patients with COVID-19 are treated.
-Other:

7- If you continue to perform operations during the pandemic, how do you evaluate the patients in terms of COVID-19 in the preoperative period? (Except for emergency cases)
Mark only one item.
-Routine test for everyone (PCR / antibody test) and wait for the result
-Routine thorax CT for everyone and wait for the result
-I just evaluate the symptoms (fever, cough, dyspnea)
-I do not perform additional evaluation but intervene if it is symptomatic in the process
-I accept everyone as positive and take precautions accordingly.

8- Do you get a separate consent form related to COVID-19 from the patient you will operate?
Mark only one item.
-Yes
-No

SURVEY. General Surgery COVID-19 Pandemic Attitude Survey (continue)

9- Have you operated COVID-19 suspected or positive patients?
Mark only one item.
-I have not
-Operate suspected patient
-Operate positive patient
-I do not know

10- Have you ever got in contact with COVID-19 suspect or positive patient?
Mark only one item.
-I have not
-Contact with suspected patient
-Contact with positive patient
-I do not know

11- What is your operation management to malignant patients during the pandemic process?
Mark only one item.
-I perform the same management as before the pandemic process
-I delay all patients, if possible
-I postpone patients at risk of age and comorbidity
-I refer to secondary treatment (RT / CT / interventional / endoscopic) options and postpone surgery
- I refer patients at risk of age and comorbidity to secondary treatment (RT / CT / interventional / endoscopic) options and postpone surgery
-I redirect patients to a different center

12- What is your operation management to benign patients during the pandemic process?
Mark only one item.
-I perform the same management as before the pandemic process
-I delay all patients if possible
-I postpone patients at risk of age and comorbidity
-I refer to secondary treatment interventional / endoscopic) options and postpone surgery
-I refer patients at risk of age and comorbidity to secondary treatment (interventional / endoscopic) options and postpone surgery
-I redirect patients to a different center

13-Personal protective equipments you use out of the operating room
More than one box can be checked.
-I use N95 or similar masks
-I use surgical mask.
-I use protective glasses or barrier.
-I use protective gowns or overalls.
-I use protective boots
-I don't use any protective equipment.
-Other:

14- Do you have a separate operating room for COVID-19 suspected or positive patients?
Mark only one item.
-Yes
-No

15-Personal protective equipments you use inside the operating room
More than one box can be checked.
-I use N95 or similar masks
-I use surgical mask.
-I use protective glasses or barrier.
-I use protective gowns or overalls.
-I use protective boots
-I don't use any protective equipment.
-Other:

SURVEY. General Surgery COVID-19 Pandemic Attitude Survey (continue)

16- Which of the following operation methods do you think has the highest risk for the surgeon in terms of COVID-19 infection transmission?

Mark only one item.

-Open Surgery

-Laparoscopic Surgery

-Upper Endoscopic Surgery

-Robotic Surgery

17- Which of the following operation methods do you think has the least risk for the surgeon in terms of COVID-19 infection transmission?

Mark only one item.

-Open Surgery

-Laparoskopic surgery

-Upper Endoscopic Surgery

-Robotic Surgery

18-Do you take additional measures (low pressure / filter) for risk reduction of COVID-19 transmission while performing minimally invasive surgery (Laparoscopic / Robotic) during the pandemic?

Mark only one item.

-Yes

-No

19- Do you take additional measures for risk reduction of COVID-19 transmission while performing open surgery during the pandemic?

Mark only one item.

-Yes

-No

20- Have you had COVID-19 test or imaging?

Mark only one item.

-Yes

-No

21- Have you received COVID-19 treatment?

Mark only one item.

-Yes

-No

22-Where do you live during the pandemic?

Mark only one item.

-With my family at home

-Alone at home

-Hotel / Guesthouse

-Other

23- Which of the following emotions do you experience during the pandemic?

Multiple boxes can be checked

-I am concerned about getting infected with COVID-19

-I am concerned to carry COVID-19 infection to my relatives.

-I am not concerned about getting COVID-19 infection or carrying it to someone else with the precautions I have taken.

ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (2): 137-146

COVID-19 salgını sırasında Türk genel cerrahlarının tutumu: "Genel cerrahi COVID-19 pandemi tutum araştırması" sonuçları

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ÖZET

Giriş ve Amaç: Tüm dünya COVID-19 salgını ile mücadele etmektedir ve sağlık profesyonelleri bu mücadeleden en çok etkilenen gruptur. Bu çalışmanın amacı, genel cerrahların COVID-19 hakkındaki bilgilerini değerlendirmek ve çalışma arkadaşlarımızın tutumunu ve mevcut durumunu anlamaktır.

Gereç ve Yöntem: Tanımlayıcı tipteki bu çalışma, Türkiye'nin farklı bölgelerinde çalışan genel cerrahlardan oluşmaktadır. Katılımcıların demografik özelliklerini, iş yeri özelliklerini, günlük çalışma uygulamalarındaki değişimi ve pandemik süreçteki tutumlarını belirlemek için 23 sorudan oluşan bir anket hazırlanmıştır.

Bulgular: Toplam 332 form değerlendirildi. Anket sonuçları cerrahların çoğunun günlük cerrahi uygulamalarını değiştirdiğini göstermektedir. Birçok cerrah COVID-19'un tedavisine aktif katılmaktadır. Çoğu benign olgu ertelenirken, malign olguların yönetimi ise farklılık göstermektedir. Ameliyat öncesi hastaların ve ameliyat tipinin değerlendirilmesinde de farklılıklar vardır. Kişisel koruyucu önlemlere uyulduğu görülmektedir. Enfekte cerrahların oranı düşük olmakla birlikte, cerrahların çoğunun enfeksiyona yakalanma konusunda endişeleri mevcuttur.

Sonuç: Türk cerrahlar pandeminin başlangıcından itibaren hızlı bir tepki almayı başardılar. Bununla birlikte, ameliyat öncesi hasta değerlendirmesi ve operasyon seçimi ile operasyon sırasında alınacak önlemler arasında hala farklılıklar bulunmaktadır. Cerrahlar malign hastaların yönetimi hakkında da bilgilendirilmelidir.

Anahtar Kelimeler: COVID-19, koronavirüs, pandemi, cerrahi, anket

DOİ: 10.5578/turkjsurg.4809

ORIGINAL ARTICLE
Turk J Surg 2020; 36 (2): 147-163

Turkish national consensus on breast cancer management during temporary state of emergency due to COVID-19 outbreak

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ABSTRACT

Objective: Cancer care is excessively influenced by the COVID-19 outbreak for various reasons. One of the major concerns is the tendency for delayed surgical treatment of breast cancer patients. The outbreak has urged clinicians to find alternative treatments until surgery is deemed to be feasible and safe. Here in this paper, we report the results of a consensus procedure which aimed to provide an expert opinion-led guideline for breast cancer management during the COVID-19 outbreak in Turkey.

Material and Methods: We used the Delphi method with a 9-scale Likert scale on two rounds of voting from 51 experienced surgeons and medical oncologists who had the necessary skills and experience in breast cancer management. Voting was done electronically in which a questionnaire-formatted form was used.

Results: Overall, 46 statements on 28 different case scenarios were voted. In the first round, 37 statements reached a consensus as either endorsement or rejection, nine were put into voting in the second round since they did not reach the necessary decision threshold. At the end of two rounds, for 14 cases scenarios, a statement was endorsed as a recommendation for each. Thirty-two statements for the remaining 14 were rejected.

Conclusion: There was a general consensus for administering neoadjuvant systemic therapy in patients with node-negative, small-size triple negative, HER2-positive and luminal A-like tumors until conditions are improved for due surgical treatment. Panelists also reached a consensus to extend the systemic treatment for patients with HER2-positive and luminal B-like tumors who had clinical complete response after neoadjuvant systemic therapy.

Keywords: COVID-19, breast cancer, breast surgery, consensus

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INTRODUCTION

We are going through an exceptional period in which the Coronavirus Disease-2019 (COVID-19) outbreak has dramatically affected all aspects of human life worldwide including Turkey (1). As the number of COVID-19 cases is increasing, its burden on health care system becomes more demanding. In many parts of the world, routine health care for non-COVID 19 disorders are either being restricted or interrupted due to COVID-19 patient overload (2). Daily practice involving surgical treatment is also influenced by this unprecedented situation as well. Recently, many surgical societies have released statements recommending that elective surgeries other than those for cancer should be cancelled or postponed due to current restrictions on standard health care provision (3,4). However, none of these recommendations provide guidance for circumstances in which surgery would not be feasible even in the context of cancer treatment. Operation room schedules for cancer patients

are becoming more tightened as the demand for specific care of COVID-19 patients is increasing. With the escalation of the outbreak, surgical wards are also increasingly being reserved for COVID-19 patients when necessary. Therefore, imbalanced bed allocations for those patients further decreases the chance of timely surgery (5-7). Another concern is the likelihood of viral transmission even during day-case procedures in cancer who have a high risk for COVID-19-related mortality due to impaired immune function (8,9).

Management of breast cancer (BC) patients whose surgery is inadvertently delayed due to the restrictions is also an ongoing matter of uncertainty (10,11). Valid alternatives include starting or extending systemic treatments comprising of chemotherapy (CT), endocrine treatment (ET) and/or HER2-blokade with or without radiotherapy (RT). Nevertheless, CT may predispose patients to severe infection or contribute to the higher mortality risk in patients who have already acquired COVID-19 during their treatment course (12,13). Thus, due to the aforementioned factors, current COVID-19 outbreak may potentially influence the outcome of BC patients by jeopardizing standard practice. Therefore, BC specialists urgently need a guideline on how to manage those BC patients in whom surgery is deferred until the outbreak subsides.

Categorically, there are two groups of BC patients anticipated to be managed separately under the current pandemic circumstances: those who are already eligible for up-front surgery and those who recently completed their neoadjuvant systemic treatment (NST) and are waiting to be scheduled for surgery as their next step of treatment.

In order to provide guidance for BC specialists in routine daily practice for BC management during outbreaks such as COVID-19, we designed a consensus procedure with the Delphi method. The consensus design consists of statements on different case scenarios provided to panel members for their voting on a 9-point Likert scale. In all cases, patients were assumed to be otherwise healthy, COVID-19-free, physically fit and without any comorbidity that may interfere with the treatment. We asked the panelists to vote for their preferred management among the given options considering that a surgical approach is not a suitable option until the outbreak subsides.

MATERIAL and METHODS

Delphi method with Likert scale was used for the current consensus procedure (14). Consensus development committee (CDC) consisted of four breast surgeons (AS, GKC, SOG, BMG) and four medical oncologists (IC, GB, BOU, YE). As the first step, CDC generated the statements, decided the voting system, number of rounds, turn-around time for each round, quorum requirement, voting score thresholds for endorsement and rejection as well as panelist nomination criteria.

Nine-point Likert scale was used for each voting: selecting 1, 2, 3 meant "I disagree", 7, 8, 9 "I agree" and 4, 5, 6 "abstained" for each statement (Supplement). If the panel could not reach a consensus on any statement at the first round, a second round of voting was held. For each round, the panelists were given 72 hours to return their voting results. "Quorum" was regarded to be attained if overall voting (attendance) rate for any statement was minimum 51%. As decision thresholds, "endorsed as a recommendation" was regarded if minimum 75% of the panelists voted for "1, 2, 3: agree", whereas "rejected as a recommendation" was regarded if minimum 25% of the panelists voted for "7, 8, 9: disagree".

For any decision to be reached, voting on statements had to pass through 2 steps. First, quorum had to be attained and second, at least one of the endorsement or rejection thresholds had to be crossed at any of the rounds. If voting on a statement did not attain the quorum or pass the threshold for any of decision, the result was regarded as "consensus not reached" for that particular statement. If the quorum was attained but votes did not cross the thresholds, then a second round of voting was held for that particular statement. During the second round, the same requirements for decision was sought. If any of the decision thresholds was attained at any round, consensus procedure was regarded to be completed for that particular statement. On the other hand, if any decision was not reached for a particular statement at the end of the second round, the result was regarded as "consensus not reached" accordingly.

Requirements of being a member of the consensus panel for voting included: having at least 10 years of BC surgical or oncological treatment experience, dealing with BC patients during minimum %50 of his/her daily clinic time, working at a tertiary reference hospital with comprehensive BC treatment facilities for minimum 5 years and attending regular multidisciplinary tumor boards at least every week for minimum 5 years. All correspondences with the panelists were done by e-mail.

No statistical analysis was used. Results of each voting at rounds were given as descriptive variable (n= %).

RESULTS

Totally, 46 statements on 28 different case scenarios were drafted and sent to the panelists for voting. Seventy-six physicians were nominated as panelists according to the eligibility criteria. Forty-eight of them were breast surgeons and 28 were medical oncologists. Informed consent was obtained from all individual panelists.

The first round of voting started on March 25th, 2020 and finished on March 27th, 2020. At this round, fifty-one panelists returned with their voting, and therefore, the quorum (67%) was attained. Of those who voted, 40 were breast surgeons and 11 were medical oncologists. According to the voting results of the first round, five statements were endorsed as recommendation for 5 case

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey

Condition: In patients who are physically fit and without any co-morbidity, under exceptional circumstances like the COVID-19 outbreak in which routine surgical management of breast cancer is suspended for a temporary period of time.

Abbreviations (HR: Hormone receptor, NST: Neoadjuvant systemic treatment, RT: Radiation treatment)

Definition (Relevant regimen: Single or combined systemic treatments previously recommended for similar subgroup of patients in neoadjuvant and/or adjuvant settings)

In newly admitted patients with invasive breast cancer diagnosis:

1. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 3, triple negative (HER2-negative/HR-negative) tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

2. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 3, triple negative (HER2-negative/HR-negative) tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

3. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-negative tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

4. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-negative tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

5. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-positive tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

6. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-positive tumor, giving NST (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: Comment (if applicable, please state your preferred regimen): _____

7. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 1, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: _____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

8. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 1, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

9. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

10. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

11. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

12. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new premenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant chemotherapy alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

13. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

14. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a new postmenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant chemotherapy alone (4-6 months) with any relevant regimen is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

In patients with triple negative tumor who had complete clinical response following neoadjuvant chemotherapy:

15. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with triple negative tumor who had "complete" clinical response after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

16. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with triple negative tumor who had "complete" clinical response after NST, giving loco-regional RT without any further systemic treatment is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

17. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with triple negative tumor who had "complete" clinical response after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

18. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with triple negative tumor who had "complete" clinical response after NST, giving loco-regional RT without any further systemic treatment is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

In patients with triple negative tumor who had partial clinical response following neoadjuvant chemotherapy:

19. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with triple negative tumor who had "partial" clinical response after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

20. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with triple negative tumor who had "partial" clinical response after NST, giving loco-regional RT without any further systemic treatment is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

21. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with triple negative tumor who had "partial" clinical response after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

22. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with triple negative tumor who had "partial" clinical response after NST, giving loco-regional RT without any further systemic treatment is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: _____

_____

In patients with HER2-positive/HR-negative tumor who had complete clinical response following neoadjuvant chemotherapy:

23. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-negative tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

24. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-negative tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

25. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-negative tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

26. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-negative tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

In patients with HER2-positive/HR-negative tumor who had partial clinical response following neoadjuvant chemotherapy:

27. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-negative tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

28. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-negative tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

29. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-negative tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: Comment (if applicable, please state your preferred regimen): _____

_____

30. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-negative tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

In patients with HER2-positive/HR-positive tumor who had complete clinical response following neoadjuvant chemotherapy:

31. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-positive tumor who had "complete" clinical response after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

32. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-positive tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

33. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-positive tumor who had "complete" clinical response after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

34. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-positive tumor who had "complete" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

In patients with HER2-positive/HR-positive tumor who had partial clinical response following neoadjuvant chemotherapy:

35. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-positive tumor who had "partial" clinical response after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

36. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with HER2-positive/HR-positive tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

37. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-positive tumor who had "partial" clinical response after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

38. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with HER2-positive/HR-positive tumor who had "partial" clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

In patients with luminal B-like (HER2-negative) tumor with complete clinical response following neoadjuvant chemotherapy:

39. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with luminal B-like (HER2-negative) tumor who had "complete" clinical response after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

40. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with luminal B-like (HER2-negative) tumor who had "complete" clinical response after NST, giving extended chemotherapy with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

41. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had "complete" clinical response after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

42. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had "complete" clinical response after NST, giving extended chemotherapy only with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9

Strongly Disagree Strongly agree

Comment: (if applicable, please state your preferred regimen): _____

_____

SUPPLEMENT. National Consensus on Breast Cancer Management During Temporary State of Emergency Due to COVID-19 Outbreak in Turkey (continue)

In patients with luminal B-like (HER2-negative) tumor with partial clinical response following neoadjuvant chemotherapy:

43. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal l patient with luminal B-like (HER2-negative) tumor who had "partial" clinical response after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: (if applicable, please state your preferred regimen): _____

44. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a premenopausal patient with luminal B-like (HER2-negative) tumor who had "partial" clinical response after NST, giving extended chemotherapy only with any relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: (if applicable, please state your preferred regimen): _____

45. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had "partial" clinical response after NST, giving endocrine treatment only with relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: (if applicable, please state your preferred regimen): _____

46. Under exceptional circumstances like the COVID-19 outbreak in which routine surgical management is unlikely; For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had "partial" clinical response after NST, giving extended chemotherapy with relevant regimen (with or without RT) is suitable.

1 2 3 4 5 6 7 8 9
Strongly Disagree Strongly agree
Comment: (if applicable, please state your preferred regimen): _____

scenarios (one for each). Overall, thirty-two statements were rejected, and the remaining nine received votes which did not exceed any required threshold for a decision.

After considering comments obtained from the first round, the remaining inconclusive statements (Statement no: 2, 5, 6, 7, 25, 31, 33, 39 and 41) for 9 case scenarios were sent to the panelists for re-voting at a second round. The new round started on April 5th, 2020 and finished on April 7th, 2020. At this round, 45 panelists voted, and therefore the quorum (59%) was attained. Of those who voted at this round, 35 were breast surgeons and 10 were medical oncologists. All statements at the second round were endorsed as recommendation by the panel. Therefore, overall 14 statements were endorsed as recommendation for 14 case scenarios (one for each). Whereas, the panel did not endorse any statement for the remaining 14 case scenarios as recommendation after two rounds of consensus.

Briefly, the panel endorsed statements for replacing surgery with minimum one alternative treatment in patients with node-negative triple negative, HER2-positive and luminal A-like tumors. The panel endorsed giving NST with relevant regimen accordingly for 4-6 months to all patients with node-negative, stage I, triple negative and HER2-positive [both hormone receptor (HR) positive and negative] tumors until the surgical procedure was deemed to be feasible in situations where there was no clear indication for NST. The panel also endorsed giving neoadjuvant ET for 4-6 months until due surgery to all patients with low-risk luminal A-like (node-negative, early stage, high HR-positivity, low grade, low Ki67) tumor as well as to postmenopausal patients with limited node-positive luminal A-like tumor.

For patients with HER2-positive/HR-negative tumor who had clinical complete response (cCR) after NST, the panelists overwhelmingly agreed on giving antiHER2 treatment (with or without RT) for a temporary period in postmenopausal patients if surgery was not feasible. Furthermore, provided with the same circumstances, for those patients with HER2-positive/HR-positive tumors who had cCR after NST, the panelists endorsed giving both antiHER2 and ET (with or without RT) in all patients.

Finally, for patients with luminal B-like (HER2-negative/HR-low positive) tumor who had cCR after NST, panelists endorsed the alternative treatment with ET only (with or without RT) in all patients if surgery could not be performed (Table 1).

Table 1. Statements and voting results accordingly

***Condition*: In patients who are physically fit and without any co-morbidity and under exceptional circumstances like the COVID-19 outbreak in which routine surgical management of breast cancer is suspended for a temporary period of time.**

Recommendation	Voting counts			Result
In newly admitted patients with invasive breast cancer diagnosis:	**Disagree**	**Abstain**	**Agree**	
1. For a new premenopausal patient with stage T1N0M0, grade 3, triple negative (HER2-negative/HR-negative) tumor, giving NST (4-6 months) with any relevant regimen* is suitable.	14%	10%	76%	Endorsed
2. For a new postmenopausal patient with stage T1N0M0, grade 3, triple negative (HER2-negative/HR-negative) tumor, giving NST (4-6 months) with any relevant regimen is suitable.	4%	3%	93%	Endorsed
3. For a new premenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-negative tumor, giving NST (4-6 months) with any relevant regimen is suitable.	10%	14%	76%	Endorsed
4. For a new postmenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-negative tumor, giving NST (4-6 months) with any relevant regimen is suitable.	10%	15%	75%	Endorsed
5. For a new premenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-positive tumor, giving NST (4-6 months) with any relevant regimen is suitable.	2%	9%	89%	Endorsed
6. For a new postmenopausal patient with stage T1N0M0, grade 3, HER2-positive/HR-positive tumor, giving NST (4-6 months) with any relevant regimen is suitable.	1%	0%	99%	Endorsed
7. For a new premenopausal patient with stage T1N0M0, grade 1, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	4%	9%	87%	Endorsed
8. For a new postmenopausal patient with stage T1N0M0, grade 1, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	10%	4%	86%	Endorsed
9. For a new premenopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	27%	18%	55%	Rejected
10. For a new postmenopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	10%	12%	78%	Endorsed
11. For a new premenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	50%	23%	27%	Rejected
12. For a new premenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant chemotherapy alone (4-6 months) with any relevant regimen is suitable.	25%	26%	49%	Rejected
13. For a new postmenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.	29%	32%	39%	Rejected
14. For a new postmenopausal patient with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving neoadjuvant chemotherapy alone (4-6 months) with any relevant regimen is suitable.	25%	18%	57%	Rejected

Table 1. Statements and voting results accordingly (continue)

***Condition:* In patients who are physically fit and without any co-morbidity and under exceptional circumstances like the COVID-19 outbreak in which routine surgical management of breast cancer is suspended for a temporary period of time.**

Recommendation	Voting counts			Result
After completion of NST in triple negative tumor:	**Disagree**	**Abstain**	**Agree**	
15. For a premenopausal patient with triple negative tumor who had cCR after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.	53%	16%	31%	Rejected
16. For a premenopausal patient with triple negative tumor who had cCR after NST, giving loco-regional RT without any further systemic treatment is suitable.	57%	19%	24%	Rejected
17. For a postmenopausal patient with triple negative tumor who had cCR after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.	49%	24%	27%	Rejected
18. For a postmenopausal patient with triple negative tumor who had cCR after NST, giving loco-regional RT without any further systemic treatment is suitable.	47%	20%	33%	Rejected
19. For a premenopausal patient with triple negative tumor who had cPR after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.	49%	27%	24%	Rejected
20. For a premenopausal patient with triple negative tumor who had cPR after NST, giving loco-regional RT without any further systemic treatment is suitable.	82%	10%	8%	Rejected
21. For a postmenopausal patient with triple negative tumor who had cPR after NST, giving extended systemic treatment with any relevant regimen (with or without RT) is suitable.	53%	20%	27%	Rejected
22. For a postmenopausal patient with triple negative tumor who had cPR after NST, giving loco-regional RT without any further systemic treatment is suitable.	67%	21%	12%	Rejected
After completion of NST in HER2-positive/HR-negative tumor:	**Disagree**	**Abstain**	**Agree**	
23. For a premenopausal patient with HER2-positive/HR-negative tumor who had cCR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	25%	20%	55%	Rejected
24. For a premenopausal patient with HER2-positive/HR-negative tumor who had cCR after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.	33%	20%	47%	Rejected
25. For a postmenopausal patient with HER2-positive/HR-negative tumor who had cCR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	11%	2%	87%	Endorsed
26. For a postmenopausal patient with HER2-positive/HR-negative tumor who had cCR after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.	33%	26%	41%	Rejected
27. For a premenopausal patient with HER2-positive/HR-negative tumor who had cPR clinical response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	53%	22%	25%	Rejected
28. For a premenopausal patient with HER2-positive/HR-negative tumor who had cPR after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.	43%	30%	27%	Rejected
29. For a postmenopausal patient with HER2-positive/HR-negative tumor who had cPR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	39%	24%	37%	Rejected

Table 1. Statements and voting results accordingly (continue)

***Condition:* In patients who are physically fit and without any co-morbidity and under exceptional circumstances like the COVID-19 outbreak in which routine surgical management of breast cancer is suspended for a temporary period of time.**

Recommendation	Voting counts			Result
	Disagree	**Abstain**	**Agree**	
30. For a postmenopausal patient with HER2-positive/HR-negative tumor who had cPR after NST, continuing with anti-HER2 treatment and extended chemotherapy with any relevant regimen (with or without RT) is suitable.	31%	40%	29%	Rejected
After completion of NST in HER2-positive/HR-positive tumor:	**Disagree**	**Abstain**	**Agree**	
31. For a premenopausal patient with HER2-positive/HR-positive tumor who had cCR after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.	9%	7%	84%	Endorsed
32. For a premenopausal patient with HER2-positive/HR-positive tumor who had cCR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	45%	30%	25%	Rejected
33. For a postmenopausal patient with HER2-positive/HR-positive tumor who had cCR after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.	9%	2%	89%	Endorsed
34. For a postmenopausal patient with HER2-positive/HR-positive tumor who had cCR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	55%	16%	29%	Rejected
35. For a premenopausal patient with HER2-positive/HR-positive tumor who had cPR after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.	49%	12%	39%	Rejected
36. For a premenopausal patient with HER2-positive/HR-positive tumor who had cPR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	63%	6%	31%	Rejected
37. For a postmenopausal patient with HER2-positive/HR-positive tumor who had cPR after NST, continuing with anti-HER2 and endocrine treatments with any relevant regimen (with or without RT) is suitable.	41%	10%	49%	Rejected
38. For a postmenopausal patient with HER2-positive/HR-positive tumor who had cPR after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with or without RT) is suitable.	61%	15%	24%	Rejected
After completion of NST in luminal B-like (HER2-negative) tumor:	**Disagree**	**Abstain**	**Agree**	
39. For a premenopausal patient with luminal B-like (HER2-negative) tumor who had cCR after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.	11%	11%	78%	Endorsed
40. For a premenopausal patient with luminal B-like (HER2-negative) tumor who had cCR after NST, giving extended chemotherapy with any relevant regimen (with or without RT) is suitable.	53%	23%	24%	Rejected
41. For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had cCR after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.	9%	4%	87%	Endorsed
42. For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had cCR after NST, giving extended chemotherapy only with any relevant regimen (with or without RT) is suitable.	59%	17%	24%	Rejected

Table 1. Statements and voting results accordingly (continue)

***Condition:* In patients who are physically fit and without any co-morbidity and under exceptional circumstances like the COVID-19 outbreak in which routine surgical management of breast cancer is suspended for a temporary period of time.**

Recommendation	Voting counts			Result
	Disagree	Abstain	Agree	
43. For a premenopausal patient with luminal B-like (HER2-negative) tumor who had cPR after NST, giving endocrine treatment only with any relevant regimen (with or without RT) is suitable.	49%	16%	37%	Rejected
44. For a premenopausal patient with luminal B-like (HER2-negative) tumor who had cPR after NST, giving extended chemotherapy only with any relevant regimen (with or without RT) is suitable.	55%	14%	31%	Rejected
45. For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had cPR after NST, giving endocrine treatment only with relevant regimen (with or without RT) is suitable.	25%	30%	45%	Rejected
46. For a postmenopausal patient with luminal B-like (HER2-negative) tumor who had cPR after NST, giving extended chemotherapy with relevant regimen (with or without RT) is suitable.	50%	28%	22%	Rejected

HR: Hormone receptor, NST: Neoadjuvant systemic treatment, cCR: Clinical complete response, cPR: Clinical partial response, RT: Radiation treatment.
* Relevant regimen: Single or combined systemic treatments previously recommended for similar subgroup of patients in neoadjuvant and/or adjuvant settings.

DISCUSSION

Current national/regional consensus has provided that NST may be given to most of those node-negative early stage BC patients, regardless of age, if up-front surgical therapy is not feasible. All recommendations were based on the assumption that a surgical procedure would not be performed temporarily due to restrictions under the COVID-19 pandemic conditions. Options included CT for patients with triple negative tumor, combination of anti-HER2 treatment and CT for those with HER2-positive tumor and ET for those with luminal A-like tumor. Moreover, there was an agreement among the panelists to administer neoadjuvant ET to patients with luminal A-like tumor with limited nodal involvement. All options were recommended temporarily for a period of 4 to 6 months until the outbreak subsided.

The panel also endorsed extension of systemic treatments in certain subgroups of patients who received and responded well to NST. Continuation of anti-HER2 treatment for postmenopausal patients with HER2-positive/HR-negative tumor, add-on ET with continued antiHER2 treatment for all patients with HER2-positive/HR-positive tumor and ET alone for all patients with luminal B-like tumor were regarded as acceptable alternatives to surgery under the COVID-19 outbreak circumstances, provided that there was cCR to the given NST.

Severity of the symptoms related to COVID-19 infection depends mainly on the immune condition of the host. There is clinical data suggesting that surgery may exacerbate infectious complications in critically ill patients due to impaired immune functions or augmented cytokine response, limiting surgical procedures in recently diagnosed patients (15). Although, cancer inherently creates an immune compromised environment and CT may render a patient more vulnerable to infection due to a temporary decrease in lymphocyte and neutrophil counts, decision of administering systemic therapy requires a personalized approach with a detailed risk-to-benefit evaluation (16). Until this date, there was no recommendation to forgo curative CT for patients who are otherwise in good health without any comorbid conditions that may place the patient at high risk for COVID-19-related complications. Despite statements issued by numerous oncology societies and health authorities, clear-cut recommendations cannot be made given the lack of high-quality evidence-based guidelines valid for circumstances such as the COVID-19 outbreak that we currently face (17,18). Therefore, we planned to perform a consensus which would provide guidance on the management of BC patients when standard surgical practice options are suspended.

We used the Delphi method with Likert scale to implement the procedure electronically in order to expedite data retrieval. Although the Delphi method has been previously described as a practical, easy and user-friendly technique, there exists some limitations such as relative inaccuracy of the drafted statements and inability to integrate panelists' comments into the procedure. Furthermore, grading with 9-point in Likert scale was also criticized as it may be found confusing by the panelists (19-21).

We designated panelists through strict criteria in order to maintain a high profile of experts for the consensus. Only those breast surgeons and medical oncologists who have a special interest in breast oncology with better knowledge, skills, judgements

and a wider range of experience were nominated as panelists. Experts were chosen from different regions of Turkey to ensure nation-wide coverage. We invited only surgeons and medical oncologists since RT was included as an optional choice in the queries to prevent confusion among panelists. Despite the seemingly high proportion of surgeons among the panelists, the actual number of both group of physicians in Turkey reflects a similar distribution (1 to 5). One of the limitations of the consensus was the low voting rates at both rounds. Although, quorum was attained at both rounds, attendance rates were not satisfactorily high. However, the clinical experience of each panelist who attended the consensus was above satisfactory.

We chose case scenarios which we believed to have reflected the real world. Case scenarios included patients in whom surgery was regarded to be the standard-of-care treatment according to evidence-based guidelines. We identified early stage patients who were normally candidates for up-front surgery or those with early or locally-advanced disease who completed their NST to be considered for this consensus. We stratified cases according to their menopausal state, molecular cancer subtype and level of response to NST, where appropriate.

Due to the common instructions of the Delphi method, some recommendations were rejected although absolute majority revealed otherwise, which was because the votes exceeded a priori decided threshold for rejection (25%) (22). Ten statements were rejected because the number of votes exceeded the rejection threshold even though the majority held a decision favoring the endorsement but did not reach the threshold for it (75%). Although we limited the scenarios in strict condition of which surgery could not be performed, in half of the scenarios, the panel did not provide a non-surgical alternative. Therefore, there are certain conditions which remained uncertain for a given patient. For these cases, the absolute voting percentage result would provide clinicians guidance on management in less than ideal conditions. For these scenarios, crude results with agreement exceeding half of the votes may assist clinicians to make informed decisions. Therefore, even so, some would prefer to consider absolute majority when choosing a management modality for patients with those scenarios. For example, despite rejection by a quarter of the voters, the continuation of HER2 blockade in premenopausal patients with HER2-positive/HR-negative tumor who had cCR after NST would be the preferred treatment approach as absolute majority with 55% of the votes favored this type of option.

There are also some statements, which at the first round seemed to be rejected. However, when considering the comments written and provided by the majority of the panelists, an alternative non-surgical treatment would be supported if the statement was re-written accordingly. This was observed in patients with node-positive luminal A-like tumor for whom panelists made comments favoring neoadjuvant CT. In addition, for patients with node-negative luminal B-like tumor, the majority expressed their concern for a single type of treatment instead of up-front surgery. Comments revealed that a combination of ET and CT should be preferred. Therefore, although all given statements seemed to be rejected, the panel agreed to provide a non-surgical option for these particular patients (Table 2).

However, after the voting of two rounds, there were scenarios left with no alternative option to replace surgery. All recommendations for patients with triple negative tumor, regardless of menopausal status, after NST were rejected. The panel rejected both options including extended CT or no systemic treatment with or without RT for these patients. Furthermore, for all patients with HER2-positive tumor, regardless of the menopausal status, who did not have cCR after NST, the panelists rejected all non-surgical recommendations including continuation of HER2 blockade with or without extended CT. Again, for all patients with luminal B-like tumor with clinical partial response (cPR) to NST, panelists did not endorse any of the non-surgical alternative treatment options limited to ET or extended CT alone. However, due to the missing treatment alternatives for cases with HER2-positive/HR-positive as well as with luminal B-like tumors who had cPR after NST, voting might have resulted inconclusive. For both pre and postmenopausal patients, we missed to integrate combination treatments in the statements, such as extended CT along with both antiHER2 blockade and ET for patients with HER2-positive/HR-positive tumor and combination of extended CT and ET for those with luminal-B like tumor. However, the panelist comments on these scenarios were not significant enough to raise a necessity for any revision accordingly.

Although our consensus results provided some guidance for daily practice during the outbreak, it should be highlighted that the results discussed here are not supported by high-level evidence, but should be acknowledged within the context of expert opinion. We did not name any specific agents regarding CT, ET and HER2 blockade as options to be voted. Therefore, the final decision on how to manage those patents is left at the physicians' discretion in daily practice. Furthermore, we did not ask the panelists' opinion on RT choices for any of the given scenarios. Nevertheless, recently an international guideline was published for RT in breast cancer patients during the COVID-19 outbreak (23). Therefore, recommendations regarding RT should be individualized for each scenario discussed in this consensus report. A multidisciplinary approach is crucial to determine practical and relevant solutions for each given patient.

Conceptually, the results yielded by the current consensus can be considered to have validity as the intended inferences or interpretations remain generally consistent with an inherent

Table 2. Recommendation box (Summary of the endorsed statements)

"Below recommendations are endorsed only under the temporary conditions where surgical treatment is not feasible due to extraordinary circumstances and are valid until due surgical treatment is available."

Strong endorsement (*with over-threshold agreement ≥ 75%*)

- For a new patient (regardless of menopausal stage) with stage T1N0M0, grade 3, triple negative tumor (HER2-negative/HR-negative), giving NST (4-6 months) with any relevant regimen* is suitable.
- For a new patient (regardless of menopausal stage) with stage T1N0M0, grade 3, HER2-positive (regardless of HR expression level) tumor, giving NST (4-6 months) with any relevant regimen (including anti HER2 treatment) is suitable.
- For a new patient (regardless of menopausal stage) with stage T1N0M0, grade 1, luminal A-like (HER2-negative/HR-highly positive/ Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.
- For a new postmenopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/Ki67 < 15%) tumor, giving neoadjuvant endocrine treatment alone (4-6 months) with any relevant regimen is suitable.
- For a postmenopausal patient with HER2-positive/HR-negative tumor who had clinical complete response after NST, continuing with anti-HER2 treatment alone with any relevant regimen (with/without RT) is suitable.
- For a patient (regardless of menopausal stage) with HER2-positive/HR-positive tumor who had clinical complete response after NST, continuing with combined anti-HER2 and endocrine treatments (with/without RT) with any relevant regimen is suitable.
- For a patient (regardless of menopausal stage) with luminal B-like (HER2-negative/HR-low positive) tumor who had clinical complete response after NST, continuing with endocrine treatment only (with/without RT) with any relevant regimen is suitable.

Endorsed (*after statement revision with panelists' comments*)

- For a new pre-menopausal patient with stage T1-2N1M0, grade 2, luminal A-like (HER2-negative/HR-highly positive/ Ki67 < 15%) tumor, giving neoadjuvant chemotherapy alone (4-6 months) with any relevant regimen is suitable.
- For a new patient (regardless of menopausal stage) with stage T1N0M0, grade 2, luminal B-like (HER2-negative/HR-low positive/Ki67 > 15%) tumor, giving combined neoadjuvant chemotherapy and endocrine treatment (4-6 months) with any relevant regimen is suitable.

Weak endorsement (*only by absolute majority >50% with rejection rate ≥ 25%*)

- For a pre-menopausal patient with HER2-positive/HR-negative tumor who had clinical complete response after NST, continuing with anti-HER2 treatment alone (with/without RT) with any relevant regimen is suitable.

HR: Hormone receptor, NST: Neoadjuvant systemic treatment, RT: Radiation treatment.
* Relevant regimen: Single or combined systemic treatments previously recommended for similar subgroup of patients in neoadjuvant or adjuvant settings.

logical perspective. We think that the results of this consensus would provide guidance for clinicians dealing with BC patients under compelling conditions such as the COVID-19 outbreak, when surgery is not deemed to be feasible. It should be noted that the results discussed herein should not be used to refute surgery in an appropriate clinical setting under normal conditions where no potential contraindication exists.

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ORİJİNAL ÇALIŞMA-ÖZET
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COVID-19 salgınına bağlı olağanüstü durumlarda meme kanseri yönetiminde Türkiye ulusal konsensüsü

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ÖZET

Giriş ve Amaç: Kanser tedavisi çeşitli nedenlerden ötürü COVID-19 salgınından büyük ölçüde etkilenmiştir. Bu noktada en büyük endişelerden biri meme kanseri hastalarının cerrahi tedavilerinin gecikmesine eğilimdir. Salgın klinisyenleri cerrahinin uygun ve güvenli olduğu düşünülene kadar alternatif tedaviler bulmaya yönlendirmektedir. Bu çalışmada, Türkiye'de COVID-19 salgını sırasında meme kanseri tedavisi için uzman görüşü temelli bir rehber sunmayı amaçlayan konsensüs prosedürünün sonuçlarını bildiriyoruz.

Gereç ve Yöntem: Meme kanseri tedavisinde gerekli bilgi ve tecrübeye sahip 51 cerrah ve tıbbi onkoloğun iki turda oyladığı dokuz ölçekli Likert Skalalı Delphi metodunu kullandık. Oylama elektronik ortamda anket formatlı form ile gerçekleştirildi.

Bulgular: Yirmi sekiz farklı olgu senaryosuna ait toplamda 46 öneri oylandı. İlk turda 37 öneri üzerinde onay veya ret şeklinde konsensüs sağlandı. Dokuz öneri konsensüs için yeterli karar eşiğini geçemediğinden ikinci tura aktarıldı. İki turun sonunda 14 olgu senaryosu için bir öneri kabul edilerek onaylandı. Geriye kalan 14 olgu senaryosuna ait 32 öneri ise reddedildi.

Sonuç: Gereken cerrahi tedavi için uygun şartlar sağlanıncaya kadar nod negatif küçük çaplı üçlü negatif, HER-2 pozitif ve Luminal-A tümörlerde neoadjuvan sistemik tedavinin uygulanması konusunda genel konsensüs sağlandı. Panelistler ayrıca neoadjuvan sistemik tedavi sonrası klinik tam yanıt veren HER-2 pozitif ve Luminal B tümörlerde de sistemik tedavinin uzatılması konusunda konsensüse ulaştı.

Anahtar Kelimeler: COVID-19, meme kanseri, meme cerrahisi, konsensüs

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ORIGINAL ARTICLE
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The role of selective venous sampling in patients with non-localized primary hyperparathyroidism

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ABSTRACT

Objective: The aim of this observational clinical study was to evaluate the success of angiographic selective venous sampling (ASVS) in locating parathyroid adenoma in patients with primary hyperparathyroidism (PHPT), in whom the other imaging modalities have failed, and and to evaluate its possible contribution to the applicability of minimal invasive surgery.

Material and Methods: Fifty-five patients who were admitted to our hospital's General Surgery department between January 2012 and January 2015 for PHPT in whom ultrasound and sestamibi scintigraphy have failed to localize the diseased gland were included to the study. Patients were divided into two groups: those who underwent ASVS and those who did not. The outcomes of patients were reviewed retrospectively.

Results: Among 55 patients, 20 underwent ASVS. ASVS successfully lateralized the diseased gland in 17 (85%) patients, and minimally invasive parathyroidectomy could be performed in 14 (70%) patients. The cut-off value of parathormon gradient was considered 10% for lateralization and the accuracy of ASVS in lateralization was 94.1%. In 11 (59%) patients, the superior-inferior discrimination could be achieved in addition to lateralization.

Conclusion: ASVS has a high sensitivity in locating the diseased gland in patients with PHPT in whom ultrasound and sestamibi scan have failed, and thereby, rendering the performance of minimally invasive surgery possible. Further studies may reveal the role of ASVS in providing useful information about not only lateralization but also the superior-inferior discrimination.

Keywords: Primary hyperparathyridism, parathyroid adenoma, selective venous sampling

INTRODUCTION

Primary hyperparathyroidism (PHPT) results from the over-secretion of parathormone (PTH) from one or more autonomous parathyroid glands. Once the diagnosis of PHPT is biochemically confirmed, it is determined whether the patient is a candidate for surgery. If a patient is scheduled for PHPT surgery, abnormal parathyroid gland(s) should be localized. Parathyroid glands may be present in an extensive region including the neck and the thorax due to their embryological development.

Preoperative localization of parathyroid glands is crucial as it significantly affects surgical intervention. The most commonly used methods for parathyroid localization include ultrasonography (USG) and Technetium Pertechnetate (Tc 99m) sestamibi scintigraphy. Either method alone can localize abnormal glands with 80% success rate. Where USG and sestamibi are not successful, computerized tomography (CT) and magnetic resonance imaging (MRI) may be used. Single Photon Emission Computed Tomography (SPECT) and also MRI are particularly useful in identifying glands in the thorax. With recent advances in radiology and nuclear medicine, new modalities such as 4 dimension (4D)-CT or ^{11}C Methionine Positron Emission Tomography (PET) and Choline PET have higher rates of adenoma localization (1,2). But unfortunately, these modalities are available in only a few institutions for now.

In cases where preoperative localization studies fail to define an abnormal gland or if reoperation is required, angiographic selective venous sampling (ASVS) may

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help identify the lateralization of hyperfunctioning parathyroid glands. This method is invasive and should be used for very limited number of patients. An accuracy rate between 33-79% has been reported in the literature for this method (3).

The conventional surgical approach used in PHPT is bilateral neck exploration (BNE) under general anesthesia (BNE). In experienced hands, success levels reaching 95% have been reported with BNE (4-6). However, with the developments in preoperative parathyroid localization methods and intraoperative PTH monitorization, minimally invasive parathyroidectomy (MIP) also yields similar or even better results (7).

The primary aim of the present study was to investigate the effectiveness of preoperative ASVS in the localization of adenoma in necessary cases when imaging studies were not useful. The secondary aim of the study was to go further than right-left lateralization and enable superior-inferior localization with ASVS as well. A further aim of the study was to seek an answer to the following question in the literature: "What should be the PTH gradient cut-off value in ASVS?"

MATERIAL and METHODS

The records of patients who were operated in our surgical department between January 2012 and January 2015 due to hyperparathyroidism were examined retrospectively. A total of 55 patients for whom imaging methods such as USG or sestamibi scintigraphy as well as MRI or CT of the neck and thorax did not lead to localization and who were scheduled for surgery by the Multidisciplinary Endocrine Council were included in the study. Due to inavailability of 4D-CT or PET (neither ^{11}C Methionine nor Choline) and intraoperative PTH monitorization in the institution, ASVS is planned as third line study for localization. A written informed consent for ASVS and for the surgical procedure were received from all patients.

The patients were divided into two groups: The group that received ASVS (study group) and others who did not (control group). Prior to the study, ethics approval was obtained from the local ethics committee (Nr: 2014.13.11, Date: October 10th, 2014). The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and the manuscript was prepared in accordance with STROBE guidelines for case control studies.

Patients

The first group comprised 20 patients in whom USG and sestamibi scintigraphy and also MRI or CT of the neck and thorax did not reveal localization and who underwent ASVS, while the second group comprised 35 patients in whom USG and sestamibi scintigraphy or other non-invasive imaging studies did not reveal localization. Patients' age, gender, complaints, preoperative calcium, PTH, albumin, phosphorus, vitamin D levels, preoperative USG, sestamibi, other imaging studies, ASVS results, operation type and duration, pre-operative PTH results, parathyroid adenoma localization found in the operation, frozen section results, final pathology results, mass size, and calcium and PTH results on postoperative day 1, week 3, month 3 and month 6 were identified. Prior to the operation, consent was obtained from all patients about the details of the invasive procedure they would undergo at the interventional radiology department and the radiation they would be exposed to.

Exclusion Criteria

Those whose primary focus localization could be found with USG and sestamibi, those with secondary hyperparathyroidism, those with tertiary hyperparathyroidism due to chronic renal disease, and ASVS contraindicated patients (ischemic heart disease in the last 6 months, contrast medium allergy, continuous antithrombotic treatment, etc.) were excluded from the study (Figure 1).

Angiographic Selective Venous Sampling Technique

All venous sampling was carried out in the angiogram unit with fluoroscopy (Allura Xper FD 20/20; Philips Medical Systems, Best, The Netherlands) under local anesthesia. Venous access was obtained via the right femoral vein. An Introducer (6 F Introducer; Cordis Corporation, Bridgewater, NJ, U.S.A.) was inserted in the right femoral vein with the Seldinger technique. Venous samples were obtained from right and left internal jugular veins, right and left brachiocephalic veins and from the superior vena cava with a vertebral catheter (5 F Vertebral Catheter; Cordis Corporation, Bridgewater, NJ, U.S.A.). Peripheral venous samples were obtained from the right femoral vein. Blood samples were numbered and sent to the biochemistry lab for PTH levels to be examined.

Surgical Technique

All patients with non-localized PHPT were operated on by experienced endocrine surgeons at the department of general surgery. All operations took place under general anesthesia. Patients in whom localisation was achieved with ASVS underwent MIP, while those in whom localisation could not be achieved with ASVS underwent bilateral neck exploration (BNE).

In BNE, midline was opened in the avascular plane and the thyroid gland was visualized after opening the platysma through standard Kocher incision. Four-gland exploration was done after the ligation of the middle thyroid vein on both sides by retracting the strap muscles laterally and the thyroid gland medially. Suspicious parathyroid gland(s) were excised and sent for frozen section.

In MIP, the skin was incised approximately 1.5 cm by keeping the sternocleidomastoid muscle lateral to the operative site. The operative site was entered between the strap and sternocleidomastoid muscles. Parathyroidectomy was completed by protecting recurrent nerves and vascular structures, and the material excised was sent for frozen section.

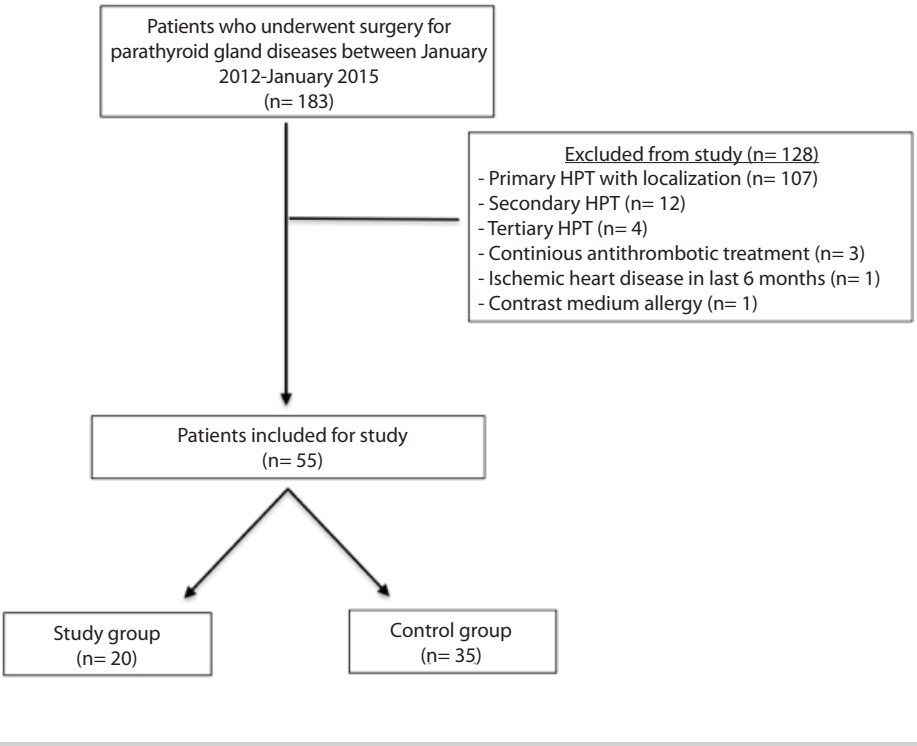

Figure 1. Study flow-chart.

Histopathological Examination

Specimens from all patients were buried in paraffin blocks and routinely examined after confirming that the material was parathyroid tissue with perioperative frozen section. The specimens were evaluated histopathologically through staining with hematoxylin eosine (H&E).

Statistical Evaluation

Data were evaluated via the Statistical Package for the Social Sciences (SPSS 17 for Windows; SPSS Inc, Chicago, IL, U.S.A.). The parametric definitions included mean ± standard deviation or median (interval). Categorical comparisons utilized chi-square, while comparisons of continuous variables utilized the Student t-test for parametric data and the Mann-Whitney U test for nonparametric data. In the study group, pre and postoperative laboratory values were evaluated for the effectiveness of treatment by using the Wilcoxon test. $p< 0.05$ was considered statistically significant.

RESULTS

Median age was 54 (25-79) in the study group and 57 (35-84) in the control group (p= 0.260). Females constituted 90% of the study group and 85.7% of the control group (p= 0.641). Duration of surgery in the study group was 45.5 ± 21.2 minutes and in the control group 58.4 ± 28.7 minutes (p= 0.084). Study and control group patients both presented with fatigue, weakness and widespread pain. The two groups did not vary significantly. Likewise, no significant difference existed between the groups regarding reoperative corrected calcium values, preoperative PTH values, preoperative phosphorus values, or preoperative vitamin D levels (Table 1).

In the study group, 14 patients out of 20 (70%) received MIP. Of the remaining 6 that did not, 4 (20%) of them were the patients with total thyroidectomy indication owing to concomitant thyroid pathology, and the remaining 2 underwent BNE with Kocher incision as their parathyroid adenoma could not be located.

Intraoperative gamma probe was used in 25% of the study group and 25.7% of the control group. No significant difference existed between the two groups regarding the size of the removed parathyroid gland. While preoperative, perioperative and postoperative parathormone levels were examined in the study group, only preoperative and postoperative parathormone values were examined in the control group. Therefore, only preoperative and postoperative parathormone values were compared in order to measure the decline in parathormone levels. This comparison revealed a decrease above 50% in the parathormone levels in 85% of the study group (n= 17) and 91.5% of the control group (n= 32) on postoperative day 1 (Table 2).

Perioperative samples from 75% of the patients in the study group and 60% in the control group were sent for frozen. Frozen section was not preferred for patients who did not receive minimal invasive surgery. In 19 (96%) of the study group patients, pathological results revealed adenoma and in 1 (4%) parathyroid

Table 1. Preoperative tests of the study and control groups

Parameter	Study group (n= 20)	Control group (n= 35)	p
Laboratory (mean ± SD)*			
Calcium† (mg/dL)	11.4 ± 0.8	11.6 ± 0.7	0.341
PTH (pg/mL)	169.7 ± 30.7	289.6 ± 57.2	0.132
Phosphorus (mg/dL)	2.6 ± 0.5	2.5 ± 0.7	0.730
Albumin† (g/dL)	3.9 ± 0.5	4.3 ± 0.4	0.001
25 hydroxy vitamin D (ng/mL)	27.0 ± 2.6	19.9 ± 11.6	0.051
Preferred imaging (n)**			
USG + sestamibi	20	33	0.348
Additional CT	4	10	
Additional MRI	13	23	

* Laboratory values were compared using the Student t test.
† As albumin values differed significantly between the groups, calcium values were given after being corrected.
** The distribution of imaging methods between the groups was calculated using the Chi-Square test.
PTH: Parathormone, USG: Ultrasonography, CT: Computerized tomography, MRI: Magnetic resonance imaging.

Table 2. Comparison of operation data from the study and control groups

Parameter	Study group (n= 20)	Control group (n= 35)	p
Operation type (n, Four-gland/Minimally invasive)*	6/14	15/20	0.836
Minimally invasive parathyroidectomy (%)	70	57.1	0.055
Intraoperative gamma probe use (%)	25	25.7	0.953
Size of mass (cm, mean ± SD)	1.7 ± 0.3	1.9 ± 0.1	0.521
Frozen section use (%)	75	60	0.254
Drop level from preoperative to postoperative day 1† (mean ± SD)			
Calcium (mg/dL)	2.5 ± 0.2	2.4 ± 0.1	0.519
PTH (pg/mL)	131.6 ± 35.8	244.4 ± 58.4	0.179
Mean drop PTH from preoperative to postoperative day 1 (%)	76.9 ± 24.6	87.8 ± 14.9	0.056
Histopathology (adenoma/hyperplasia)	19/1**	33/2**	0.986

* An additional operation was performed on 4 study group and 12 control group patients.
† Wilcoxon test was used to compare paired preoperative and postoperative calcium and parathormone levels. The Student t test was used to compare the remaining parameters given in the table.
** Hyperplasia was evident in 1 study group patient and 2 control group patients. These patients received 3,5 parathyroidectomy.

hyperplasia. The 12-month follow-up of the latter patient showed improved PTH and Ca levels and also improved clinical symptoms. A mismatch was observed between pathological findings and clinical view of this patient. In the control group, pathological findings indicated parathyroid adenoma in 33 (94.2%) patients and parathyroid hyperplasia in 2 (5.8%) patients.

Postoperative follow-up of patients included calcium and PTH levels on postoperative day 1, week 3, months 3 and 6. Postoperative changes in PTH and calcium levels in the study and control groups are shown in Table 3. Calcium values in both groups were in the normal bracket while one patient from each group still had higher than normal PTH values at month 3. No significant difference was found between the two groups regarding the postoperative calcium and parathormone levels (Table 3).

Among the 20 patients in the study group, venous sampling brought accurate parathyroid localization in 17 (85%) (Table 4). In the remaining 3, localization was not possible with venous sampling. The first one of these 3 patients had previously undergone right lower parathyroid surgery but still had persistent hyperparathyroidism. The failure in this patient was attributed to disrupted vascular pattern due to previous surgery. The second patient had a negative MIBI, and in the USG a lesion appearing to be separate from the thyroid gland on the left inferior posterior, with central vascularization, and giving the impression of a lymph node. Minimally invasive exploration was applied on the left and the tissue was suspected to be parathyroid adenoma. Frozen examination revealed parathyroid tissue and the operation was ended. The third patient had multinodular goiter together with hyperparathyroidism. The exploration revealed widespread thyroid nodules

Table 3. Comparison of the parameters of 6-month period after the operation in study and control groups

Parameter	Study group (n= 20)	Control group (n= 35)	p
Postoperative day 1 (mean ± SD)			
Calcium* (mg/dL)	8.8 ± 0.2	9.2 ± 0.1	0.042
PTH (pg/mL)	38.8 ± 8.6	44.2 ± 21.6	0.855
Postoperative week 3 (mean ± SD)			
Calcium (mg/dL)	9.4 ± 1.2	9.1 ± 1.1	0.342
PTH (pg/mL)	50.6 ± 8.8	75.7 ± 21.1	0.296
Postoperative month 3 (mean ± SD)			
Calcium (mg/dL)	9.1 ± 1.1	11.3 ± 1.8	0.356
PTH (pg/mL)	56.8 ± 13.7	59.5 ± 8.8	0.874
Postoperative month 6 (mean ± SD)			
Calcium (mg/dL)	9.1 ± 0.5	9.2 ± 0.3	0.817
PTH (pg/mL)	12.4 ± 0.1	44.6 ± 15.6	0.533

* All calcium values in the table have been corrected.
The Student t test was used to compare the parameters given in the table.
PTH: Parathormone.

Table 4. Diagnostic success of selective venous sampling in the study group

Selective venous sampling	Diagnosis %	n/N
Direction towards right or left (all cases)	85%	17/20*
Direction towards right or left (cases where left-right difference is > 10%)	94.1%	16/17
Direction towards lower or upper parathyroid gland on the same side**	59%	10/17

* Right-left difference was below 10% in two cases. In one case, double adenoma was identified in right and left upper parathyroids. In the case with left lower parathyroid adenoma, the difference was 22.7% in favor of right.
** Sampling was performed from both jugular veins for upper parathyroid glands, and from both brachyocephalic veins for lower parathyroid glands.

and four-gland exploration was undertaken. The right lower nodule which was suspected to be intrathyroidal parathyroid was sent for frozen and the suspicion was confirmed. The failure of venous sampling in this patient may have been due to concomitant thyroid nodules and/or the intrathyroidal parathyroid gland. Therefore, localization with venous sampling was not possible in only 1 (5%) patient with parathyroid adenoma alone.

It was determined that the PTH gradient cut-off value for study group patients who received ASVS could be taken as 10% because the accuracy rate of lateralization in this case is 94.1%. According to the results of our study, superior-inferior distinction as well as left-right lateralization was achieved in 59% of the patients (Table 4).

DISCUSSION

Recent developments in surgical methods, imaging techniques and changing patient expectations have led to the popularity of minimally invasive surgical procedures. As for the treatment of many other diseases, minimally invasive surgical techniques have been defined for parathyroidectomy in order to treat primary hyperparathyroidism. The most important advantages of MIP mentioned in the literature include small incision size, short operation duration and fast recovery. Owing to these advantages, MIP has come to be the most commonly used surgical procedure in PHPT with single gland involvement (8,9).

Minimally invasive parathyroidectomy requires the localization of the hyperfunctioning parathyroid gland. Where localization is not possible, MIP cannot be used. High resolution USG is superior to MR and CT in resolution. Normal size parathyroid glands are often not visible in USG. Various authors have reported USG sensitivity levels ranging between 55-83% in detecting parathyroid adenoma. USG sensitivity is especially limited, below 29%, in the mediastinum (10). The capability of USG in identifying parathyroid adenoma is reported by various authors to be between 40-98% (10).

Sestamibi scintigraphies are used in combination with ultrasound. Where both confirm adenoma, sensitivity reaches 96% (11,12). Where USG and sestamibi are not successful, MRI is often preferred. It may be particularly effective in suspected cases of ectopic mediastinal gland (6,13).

Bilateral neck exploration is often the preferred procedure in patients of primary hyperparathyrioidism where scintigraphy and USG fail to localize the gland. Experienced hands can locate 98% of pathological gland(s) with bilateral neck exploration (6,14). However, operation times are much longer than in MIP. In our study, mean operation time for neck exploration and MIP were 73.4 and

37.5 minutes, respectively. Morbidity rates among patients who undergo neck exploration are also higher than those who undergo MIP. According to the literature, the rate of recurrent nerve injury reported is 2%, also bleeding and hematoma rates are below 0.5% in BNE (15,16). All these rates are all lower in MIP. Another disadvantage of bilateral neck exploration is the poor cosmetic result that occurs. This negatively affects patients, 70% of whom are females. The majority of patients therefore prefer MIP solely for cosmetic reasons. To sum up, MIP is clearly more advantageous than bilateral neck exploration. The only issue for MIP; if the adenoma is not found at previously localized area, BNE is required according to the current consensus guidelines (6).

There is no consensus in the literature about the optimal approach to be preferred in cases where sestamibi, USG and MRI are inadequate in localizing the adenoma. Conventional imaging methods may fail to localize parathyroid glands when hyperactive parathyroid glands are small, there are multiple hyperfunctioning glands, or additional thyroid pathologies are present (17).

The goal in parathyroid surgery is to remove the hyperfunctioning gland at first trial. If the glands cannot be localized at this time, future operations have lower success chance and higher complication rates. In our study, two patients required reoperation. The first patient had retrosternal adenoma in the superior mediastinum which could not be located through neck exploration. In this patient, hypercalcemia did not improve despite undergoing 3.5 parathyroidectomy with total thyroidectomy in the first operation. Although preoperative scintigraphy, USG and MRI of the neck could not locate the adenoma, postoperative MRI of the thorax showed a retrosternal hyperfunctioning gland which was consequently removed in a second operation. In the second patient, ASVS showed findings of a right lower parathyroid adenoma, which was excised through MIP. Even though pathology results were compliant with parathyroid adenoma, the patient's persistent hypercalcemia continued. In this patient's second operation, a second right lower parathyroid adenoma was identified, excised and sent for frozen. This patient was diagnosed as having double adenoma.

It is obvious that new methods are available for localizing parathyroid adenoma. However, these new methods such as 4D-CT or PET with 11C Methionine or Choline are not widely used yet in many countries such as our country. Where conventional methods are not successful, ASVS may still help localize parathyroid adenoma in the neck (6).

Angiographic selective venous sampling has generally been used to localize parathyroid glands postoperatively that can not be localized through neck exploration. However, it is harder to interpret ASVS results following neck operations that disrupt vascular drainage. In our study, ASVS was performed on a patient who was previously operated on due to thyroid cancer and subsequently developed unlocalized primary hyperparathyroidism. In this patient, ASVS helped accurate localization and MIS was used to excise the parathyroid adenoma. Even though ASVS has lower success rates among patients with previous neck surgery, it affected the choice of surgical strategy for this particular patient and ensured that the operation and complication risks were smaller.

Complications such as contrast medium oversensitivity reaction (renal deficiency, anaphylactic reaction, etc.), bleeding, infection, pseudoaneurysm, and arteriovenous fistulae are very rare after ASVS, and risks are minor and less frequent compared to bilateral neck exploration. In our study, we did not witness any complications due to ASVS.

ASVS is not an initial method, but a minimally invasive technique to be preferred when non-invasive investigations fail to locate (6). It is a diagnostic method that should definitely be considered in the identification of unlocalized adenoma owing to its potential to prevent repeated surgical operations and make surgery minimally invasive, even though it is an invasive technique itself. In this study, parathyroid adenoma could not be clearly localized with scintigraphy and USG in any of the 55 patients. The 20 patients in the study group received ASVS for localization. The technique was successful in 17 (85%) patients and 14 of them underwent MIS. Venous sampling was not adequate for localization in the remaining 3 patients. The first patient had undergone right lower parathyroid surgery previously, but had persistent hyperparathyrodism. The failure in this patient was probably due to vascular pattern disruption after previous surgery. The second patient had a lesion with negative MIBI which gave the impression of a lymph node in USG. The lesion, which was defined as a lymph node in exploration, was later identified as parathyroid adenoma. The third patient had concomitant multinodular goitre with hyperparathyroidism, and this patient's hyperfunctioning parathyroid gland was intrathyroidal. The failure of venous sampling in this patient may have been due to accompanying thyroid nodules and/or the intrathyroidal parathyroid gland. ASVS did not lead to localization in only 1 (5%) patient with a single parathyroid adenoma. Our study aimed to achieve localization with ASVS prior to initial surgery in patients whose parathyroid adenoma could not be localized preoperatively. ASVS has been used by numerous authors in the literature prior to the perioperative removal of adenoma, and later when identifying whether or not quick PTH levels drop in the samples from the jugular vein. Such uses of ASVS aim to evaluate the sufficiency of perioperative parathyroidectomy rather than to achieve parathyroid localization. However, our study used ASVS alone as a localization technique in the preoperative stage. Barczynski et al. report venous sampling to increase the chance of localizing parathyroid adenoma with USG from 33.3% to 65.4% in patients with negative sestamibi (18). When parathyroid adenoma gets localized with ASVS and a re-examination with preoperative USG confirms the adenoma, the localization may be marked for a more accurate and appropriate incision.

Perioperative frozen section was preferred for 75% of the study group patients and 60% of the control group patients. Frozen

section was not preferred for patients who did not undergo MIP. Pathology results in the study group revealed adenoma in 19 (96%) and parathyroid hyperplasia in 1 (5%). In the control group, pathology results revealed parathyroid adenoma in 33 (94.3%) and parathyroid hyperplasia in 2 (5.7%). While the literature reports that parathyroid hyperplasia plays a role in the etiology of approximately 15-20% of primary hyperparathyroidism patients, the rate of parathyroid hyperplasia was smaller in our study. The two groups did not vary significantly regarding the size of parathyroid glands removed (p= 0.521). As no significant difference was found in parathyroid gland size where ASVS achieved localization, no relationship could be found between SVS and parathyroid size.

No consensus has been reached on a single technical method in previous ASVS studies and, more importantly, no cut-off values have been reported. In one of the rare studies on this topic, Maceri et al. have reported 100% success rate in jugular venous sampling when PTH gradient > 200%, and 88% success rate when PTH gradient was between 20-200% (19).

Another important goal of our study was to determine cut-off values for localization in ASVS. Out of the 17 patients in this study in whom localization was successful, 16 (94.1%) had PTH gradient > 10%. More comprehensive studies are needed on this topic. In our study, we accepted that the cut-off value needed to be 10%.

Angiographic selective venous sampling has most commonly been used in the literature for either right or left lateralization. However, considering the principles and concept of minimally invasive focus surgery, merely right-left lateralization is not adequate. Another goal of our study was to test the effectiveness of ASVS in determining superior-inferior localization as well as right-left lateralization. We obtained accurate superior-inferior localization in 10 (59%) of the 17 patients in whom accurate lateralization could be achieved. In this study, we attempted to make inferior and superior distinction as well as right and left localization by increasing the number of ASVS samples. Lower and upper parathyroid adenoma distinction was successful in 10 (62.5%) of the 16 patients whose ASVS localization was also successful. We are of the opinion that these success rates will increase with more selective vascular cannulation thanks to the advances in angiography. Without a doubt, precise localization will enable minimally invasive surgery in the true meaning of the word.

Small number of cases is the major limitation of our study. However, the number of these patients represents the minority of the patients with PHPT who had surgery between 2012 and 2015 in our institution. Another limitation is the lack of radiologist who is focused on endocrine ultrasound, which might also be a factor to increase the rate of accurate diagnosis for PHPT. Our institution could be considered as a large volume center for parathyroid surgery based on the case numbers per year; however, the lack of modern diagnostic modalities such as 4D-CT or PET-CT (choline or 11C methionine) and intraoperative PTH assay kits during the period of this study is the third limitation. Despite all these limitations, this study emphasizes the role of ASVS which is still a third line diagnostic tool in latest international guidelines.

CONCLUSION

ASVS is a limited but reliable method for localizing previously unlocalized parathyroid adenoma. It should be used as third line localization study after US/sestamibi and CT/MRI. It eliminates the need for neck exploration and enables patients to undergo MIP, which has fewer complications and similar success rates. In addition to right-left lateralization, ASVS can also reveal superior-inferior localization. Future randomized controlled trials are needed into this topic.

Ethics Committee Approval: Prior to the study, ethics approval was obtained from the local ethics committee (Nr: 2014.13.11, Date: October 10th, 2014).

Informed Consent: Informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Yeri belirlenemeyen primer hiperparatiroidi hastalarında selektif venöz örneklemenin yeri

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ÖZET

Giriş ve Amaç: Gözlemsel klinik çalışmamızın amacı primer hiperparatiroidi (PHPT)'li hastalarda diğer görüntüleme yöntemleri ile lokalize edilemeyen paratiroid adenomunun saptanmasında anjiyografik selektif venöz örnekleme (ASVÖ) tekniğinin lokalizasyon başarısını tespit etmek ve minimal invaziv cerrahi uygulanabilirliğine katkısını değerlendirmektir.

Gereç ve Yöntem: Hastanemiz Genel Cerrahi Kliniğine Ocak 2012-Ocak 2015 tarihleri arasında başvuran, ultrasonografi veya sestamibi sintigrafi ile yeri lokalize edilemeyen 55 hasta çalışmaya dahil edildi. Hastalar ASVÖ yapılanlar ve yapılmayanlar olarak ikiye ayrıldı. Hastaların sonuçları retrospektif olarak incelendi.

Bulgular: Elli beş hastanın 20'si ASVÖ grubunda yer almıştır. Bu hastaların 17 (%85)'sinde venöz örnekleme ile doğru paratiroid lokalizasyonu yapılabilmiş ve bu hastaların 14 (%70)'üne minimal invaziv paratiroidektomi uygulanmıştır. Lateralizasyon için parathormon gradiyent eşik değeri %10 olarak kabul edilmiş ve hastalarda lateralizasyonun doğruluk oranı %94,1 olarak bulunmuştur. Hastaların %59'unda sağ sol lateralizasyonuna ek olarak süperior-inferior ayırımı da başarılmıştır.

Sonuç: ASVÖ görüntüleme yöntemleri ile lokalize edilemeyen PHPT'li hastalarda duyarlılığı yüksek bir yöntemdir ve bu sayede hastalara minimal invaziv cerrahi yapılabilir. Daha geniş çalışmalar sayesinde sadece sağ-sol lokalizasyonu dışında süperior-inferior lokalizasyonu hakkında da bilgi verebilecek bir yöntemdir.

Anahtar Kelimeler: Primer hiperparatiroidizm, paratiroid adenom, selektif venöz örnekleme

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ORIGINAL ARTICLE
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Esophagoduodenoscopy or colonoscopy: which should be done first?

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ABSTRACT

Objective: Esophagoduodenoscopy and colonoscopy can be done as bidirectional endoscopy in the same session. The aim of this study was to compare anesthetic requirements and hemodynamic effects in esophagoduodenoscopy or colonoscopy done first for bidirectional endoscopy.

Material and Methods: Eighty patients, aged 18-70 years with an American Society of Anesthesiologists Classification (ASA) as I-III, were included randomly into this study. The patients were allocated into two groups: Group C: first colonoscopy followed by esophagoduodenoscopy. Group E: first esophagoduodenoscopy followed by colonoscopy. All patients received standard anesthesia with 1 µg/kg fentanyl and 1 mg/kg propofol. Demographical variables, Heart rate SpO_2, Ramsey Sedation Score were recorded every 10 minutes. Total propofol consumption, retching during esophagoduodenoscopy and time to reach cecum were also recorded. Endoscopist and patient satisfaction were questioned.

Results: Retching during esophagoduodenoscopy was not statistically significantly different in both groups. Total procedure duration and esophagoduodenoscopy duration were statistically significant longer in Group E. Complication frequency was higher in Group E. Endoscopist and patient satisfaction were lower in Group E. There was no difference in time to reach the cecum and the recovering period. Additional propofol dose was increased in Group E.

Conclusion: Regarding shorter procedural duration, lower consumption amount of propofol and fewer complications, it could be a better choice to start bidirectional procedure with colonoscopy first.

Keywords: Colonoscopy, gastroscopy, anesthesia, patient satisfaction.

INTRODUCTION

Bidirectional endoscopy (BE) consists of esophagoduodenoscopy (EDS) and colonoscopy, which are done at the same session on the same day. BE is an important tool to diagnose nonspecific symptoms as iron deficiency, positive fecal occult blood test, suspected gastrointestinal system (GIS) malignancy, stomachache, abdominal distention and weight loss (1,2). Completing the procedure in the same session shortens not only hospital stay, but also reduces risks related to anesthesia (3). Usually, it is the endoscopist's choice from which side to start, EDS or colonoscopy. There is still no agreement between the endoscopists on whether to begin bidirectional endoscopy from EDS or colonoscopy first (4-6).

Nowadays, sedation is preferred for endoscopic procedures (7). Propofol application watched by an anesthesiologist for sedation provides a fast onset time and fast recovery in comparison to other anesthetic drugs (8).

The aim of this study was to determine whether EDS or colonoscopy should be done first, and as a result, to determine the optimal order for BE.

MATERIAL and METHODS

This study was a prospective, randomized and controlled study, which started after receiving local ethics committee approval (28.05.2013/197) and obtaining patient's informed consent in our Endoscopy Unit, and it was completed in a 6-month period.

Eighty patients scheduled for BE aged 18-70, with an American Society of Anesthesiologists Classification (ASA) as I-III, were included in this study.

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Patients with active GIS bleeding, severe cardiac and respiratory failure, propofol or fentanyl allergy, alcohol or drug addiction, neuropsychiatric disease, suspicious of difficult airway and patients, who could not complete the screening because of inadequate colon cleaning or obstruction because of colon cancer were excluded.

The patients were allocated randomly in two groups via the closed envelope technique. Group C patients underwent the colonoscopy procedure first, then the EDS procedure. Group G patients underwent EDS procedure first and afterwards, the colonoscopy procedure. All endoscopic interventions were done by the same two endoscopists.

For endoscopic procedures (Olympus® EVIS EXERA Video Gastroscope GIF-160; Olympus Switzerland AG, Volketswil 8604, Switzerland) endoscope and Olympus® CF Q160L/I/S; Olympus Switzerland AG, Volketswil 8604, Switzerland) colonoscopes were used. Insufflation was done with room air. Prior to each procedure, disinfection and drying were carried out after mechanical cleaning of the gastroscope and colonoscopes on separate washing machines. Endoscopists wore protective equipment such as aprons and gloves before the procedure. They changed their aprons and gloves when they passed from gastroscopy to colonoscopy and from colonoscopy to gastroscopy.

Patients were advised to starve for a 12-hour period, to take laxatives the day before endoscopy appointment and to administer enema for gut cleaning. Patients were also warned not to take alcohol or any sedative drugs.

Patient's informed consent was obtained when the patient was admitted on the day of endoscopy. All procedures were performed in the endoscopy unit. All patients were inserted an intravenous (IV) catheter sized 22 Gauge and transfused 0.9% NaCl. Then they were prepared for the endoscopy procedure in a lateral decubitus position and monitored with electrocardiography, noninvasive blood pressure measuring and pulse oximetry. Oxygen supply was provided by a nasal cannula with a flow of 3-4 L/minute oxygen. Initial heart rate (HR) and saturation (SpO_2) were recorded. All patients received premedication with 1 mg midazolam (Dormicum®; DEVA pharm, Istanbul, Turkey) intravenously. The oropharyngeal was topically anesthetized with 3 puffs of lidocaine 10% (Xylocain® 10% spray; AstraZeneca, Istanbul, Turkey) spray. Deep sedation was provided by the same two anesthetists with 1 mcg/kg fentanyl citrate (Fentanyl® amp; Abott laboratories, North Chicago, USA) and 1 mg/kg propofol 1% (Propofol® 1%; Fresenius, Graz, Austria). Sedation depth was achieved to be Ramsey Sedation Score (RSS, Appendix 1). Additional propofol doses of 0.5 mg/kg were given when RSS was under 3 and recorded. RSS scores were also recorded during the procedure.

Demographic variables as age, sex, weight, height, and ASA score were recorded. HR, SpO_2 and RSS were recorded every 10 minutes. Retching during EDS, identification of a tumor or polyp, success in reaching the cecum, and if successful in reaching the cecum, time to reach the cecum were recorded.

Appendix 1. Ramsey Sedation Score (RSS)

Definition	Score
Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

Total procedure duration was the time from beginning of anesthesia induction until end of BE procedure. Total procedure duration, EDS and colonoscopy durations, additional preparation time including time from the end of a procedure until the beginning of the next procedure were recorded. Complications related to the interventions or to anesthetic management were recorded all over the procedure duration and recovery period. Recovery period was defined as time from beginning of anesthesia induction to recovery to Aldrete score 9 (Appendix 2). Endoscopist's and patient's satisfaction were evaluated with a visual analog scale (VAS) score (1: very bad, 10: very good). When patients received an Aldrete score of 9, they were transported to the recovery room and observed for one hour before discharge.

Statistical Analysis

Statistical analyses were made with NCSS (Number Cruncher Statistical System, 2007, Statistical Software, Utah, USA) package program. Descriptive statistics for mean ± standard deviation, repeated analysis of variants for repeated measurements of multiple groups, Newman Keuls multiple comparison test for subgroup comparisons, Student t-test fort two group comparisons, Chi-Square and Fisher Exact test for qualitative data comparisons were used for statistical analyzes. Results were accepted as statistically significant when $p< 0.05$.

RESULTS

Totally 80 patients of ASA I-III, aged between 18-70 years, scheduled for BE were included in this study (Appendix 3). There was no statistically significant difference in demographical data between the groups. Frequency of retching at the oropharyngeal placement of the endoscope was not statistically significant different between the groups. Colonoscopy duration was not statistically significant different between the groups ($p= 0.131$). EDS was prolonged in Group G (3.22 ± 1.31 for group C and 4.1 ± 1.85 min for group G, $p= 0.016$), and the total procedure time

Appendix 2. Aldrete Recovery Score		
	Definition	**Score**
Activity	Able to move 4 extremities voluntarily or on command	2
	Able to move 2 extremities voluntarily or on command	1
	Able to move 0 extremities voluntarily or on command	0
Respiration	Able to deep breath and cough freely	2
	Dyspnea or limited breathing	1
	Apnea	0
Circulation	Blood Pressure ± 20% of Preanesthetic level	2
	Blood Pressure ± 20-50% of Preanesthetic level	1
	Blood Pressure ± 50% of Preanesthetic level	0
Consciousness	Fully Awake	2
	Arousable on calling	1
	Not responding	0
O_2 saturation	Maintains > 92% on room air	2
	Needs O_2 inhalation to maintain O_2 saturation > 90%	1
	Saturation < 90% even with supplemental oxygen	0

was prolonged in Group G, as well (15.21 ± 3.15 for group C and 16.64 ± 2.53 group G, p= 0.028). Complications occurred in 6 patients in Group G (p= 0.011). One patient suffered an allergic reaction treated with antihistamines, one patient had bradycardia (HR < 50 beats per minute for 30 seconds) treated with 0.5 mg atropine, four patients had hypersalivation and one patient was desaturated (SpO_2 < 90%) because of hypersalivation. No complication was observed in Group C (Table 1).

HR was statistically significantly lower at the start and at the 20th minute in Group G (p= 0.036, p= 0.001) when compared to Group C. In Group C, changes in HR were statistically significantly different between the start, 5th minute, 10th minute and 20th minute values (p< 0.001). In Group G, changes in HR were statistically significantly different between the start, 5th minute, 10th minute and 20th minute values (p< 0.001). HR at 5th minute and 10th minute were not statistically significantly different between the groups (Figure 1).

RSS at 5th minute was statistically significantly lower in Group G compared to Group C (p< 0.001). RSS score at 10th minute was statistically significantly higher in Group G (p< 0.001). RSS at 20th minute were not statistically significantly different. In Group C, RSS at the start, 5th minute, 10th minute and 20th minute values were statistically significantly different (p< 0.001). In Group G, RSS at the start, 5th minute, 10th minute and 20thminute values were statistically significantly different (p< 0.001) (Figure 2).

Endoscopist's satisfaction was significantly lower in Group G compared to Group C (p= 0.049). Patient's satisfaction significantly decreased lower in Group G compared to Group C (p< 0.001) (Figure 3).

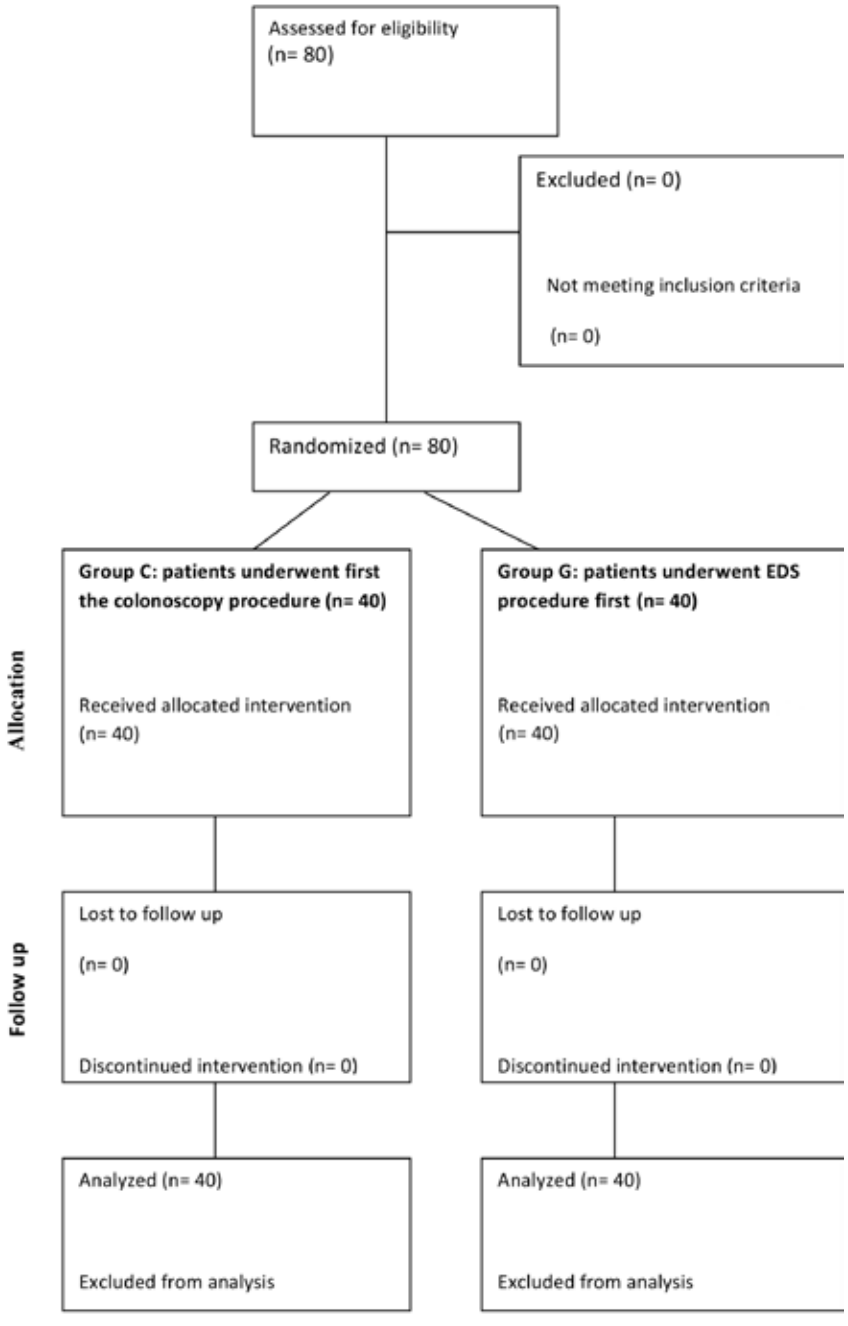
Recovery time was not statistically significantly different between the groups (p= 0.318). Additional propofol dose was statistically higher in Group G compared to Group C (2.2 ± 0.69 for group C and 2.58 ± 0.68 for group G, p= 0.016) (Table 2).

Total consumption of propofol was not statistically significantly different between the groups. However, Group G received a higher amount of propofol dosage than Group C (145.88 ± 25.39 for group C and 154.63 ± 28.85 for group G, p= 0.154). All procedures were successful in reaching the cecum. Time to reach the cecum was not statistically different between the two groups (Table 3).

DISCUSSION

BE includes lower and upper GIS endoscopy (colonoscopy and upper endoscopy) proceeded the same day and the same session. Although there is insufficient data regarding indications and frequency of application of BE, iron deficiency anemia, fecal occult blood, dyspepsia and/or pain are the most important indications (1,2).

BE reduces patient's and the physician's loss of time and additionally reduces adverse effects due to sedation (3). In the retrospective study performed by Urquhart et al. (3) the patients who underwent lower and upper GIS endoscopy between 2000 and 2004 for four years in United States of America (USA) were analyzed, and it was determined that a total of 591,074 patients had lower and upper endoscopy and the procedure was performed on the same day and at the same session in 66,265 of them. Thus, the frequency of application of BE in the USA was determined to be 11.2%. Fifty-two point one of the patients



Appendix 3. CONSORT flow diagram.

were females (52.1%), and mean age of the patients was 60.8 years. In our study, mean age of the patients was 48.7 years, and 48.8% (n= 39/80) of the patients were females.

Currently, most endoscopic procedures are performed with sedation. Use of sedation improves success of the procedure, and patient's and physician's comfort, as well (7,8). Additionally, it lowers stress hormone levels (9). For this purpose, benzodiazepines, meperidine and propofol are commonly used. Due to the advantages such as rapid onset of action and providing short-term anesthesia, propofol is the most commonly preferred anesthetic agent for endoscopic procedures in recent years (7,8). In a study performed in our clinic and comparing the use of propofol-fentanyl, propofol-alfentanyl during colonoscopy, the need for additional propofol dose has been found lower and re-

Table 1. Demographical data, procedure duration, complications

		Group C (n= 40)		Group G (n= 40)		p
Age		48.78 ± 9.53		48.68 ± 12.22		0.968*
Sex	Female n (%)	21	(52.50%)	18	(45.00%)	0.502**
	Male n (%)	19	(47.50%)	22	(55.00%)	
BMI (m^2/kg)		26.98 ± 3.76		26.86 ± 4.23		0.898*
Procedure duration (minutes)		15.21 ± 3.15		16.64 ± 2.53		**0.028***
Colonoscopy duration (minutes)		9.8 ± 2.85		10.68 ± 2.22		0.131*
Esophagoduodenoscopy (minutes)		3.22 ± 1.31		4.1 ± 1.85		**0.016***
Retching	Yes	14	35.00%	13	32.50%	0.813**
	No	26	65.00%	27	67.50%	
Complication	Yes	40	100.00%	34	85.00%	**0.011****
	No	0	0.00%	6	15.00%	

* Student t-test; ** Chi-square test, p< 0.05 statistically significant different, values are mean ± SD.
BMI: Body mass index.

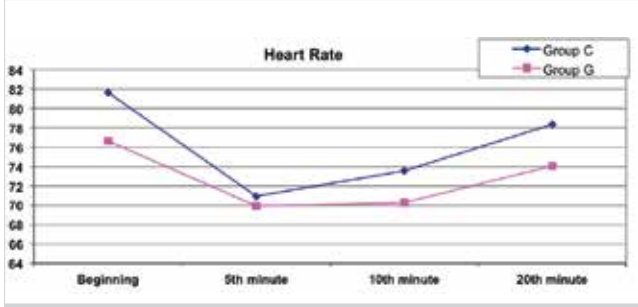


Figure 1. Heart rate (beats per minute).

Figure 2. Ramsey sedation score.

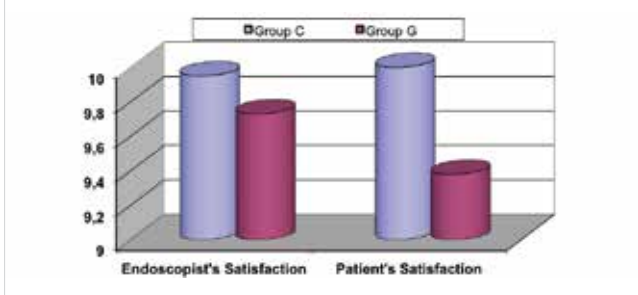


Figure 3. Endoscopist's and patient's satisfaction.

covery more rapid in the propofol-fentanyl group (9,10). Therefore, we also preferred to administer propofol-fentanyl combination for sedation in our study.

In our study, we used RSS for the evaluation of the sedation level. It could also be benefited from Bispectral Index Score (BIS) to measure the depth of sedation and reduce the use of sedative drug. There are studies comparing the use of RSS and BIS (11,12). In these studies, it has been emphasized that BIS is a suitable monitorization tool for the patients under sedation and over-sedation and complications related to over-sedation could be prevented by BIS (11,12). However, there are studies indicating that measurements of RSS and BIS are consistent, the amount of sedative drug use does not change (11,12). Not using BIS can be considered the weakness of our study. Which of the examinations (gastroscopy and colonoscopy) will be performed first in BE usually depends on the preference and experience of the endoscopist. While some endoscopists believe that performing gastroscopy first makes the colonoscopy procedure more difficult due to gas insufflation, some endoscopists think that performing colonoscopy first makes the gastroscopy procedure more difficult due to increased bowel motility and the external pressure of the colon on the stomach. However, in recent years, this condition has also been the subject of studies despite in limited number, and it was studied on procedure priority regarding many issues such as procedural success, procedure duration, complications and consumption of sedative agents used (4-6).

In the retrospective study performed by Oner et al. (13), time to reach the cecum has been compared between the patients undergoing colonoscopy alone and the patients undergoing gastroscopy first followed by colonoscopy. The study included two-year data. One thousand six hundred and seventy-two patients underwent colonoscopy alone and three hundred and

Table 2. Additional propofol dose and recovery time			
	Group C (n= 40)	**Group G (n= 40)**	**p**
Additional propofol dose	2.2 ± 0.69	2.58 ± 0.68	0.016
Recovery time (minutes)	1.04 ± 0.63	1.19 ± 0.71	0.318
p< 0.05 statistically significantly different, values are mean ± SD.			

Table 3. Total propofol consumption and time to reach cecum			
	Group C (n= 40)	**Group G (n= 40)**	**p**
Total propofol amount	145.88 ± 25.39	154.63 ± 28.85	0.154
Time to reach cecum (min)	6.91 ± 2.15	7.69 ± 2.09	0.108
p< 0.05 statistically significantly different, values are mean ± SD.			

nineteen patients underwent BE. No difference was seen between the two groups regarding the time to reach the cecum. However, endoscopy performance and patient's comfort were found to be better and the need for analgesia was found to be lower in the patients undergoing BE. The authors concluded that performing gastroscopy did not affect the colonoscopy performance negatively and it could be performed in the same session.

Hsieh et al. (4) have searched the answer for the question "which one of gastroscopy and colonoscopy should be performed first in bidirectional endoscopy?" and compared 87 patients undergoing colonoscopy first and 89 patients undergoing gastroscopy first regarding procedure duration, recovery period, patient tolerance, adverse effects and consumption of propofol needed for sedation. Procedure duration, recovery period, adverse effects and patient tolerance have been found similar in both groups, but consumption of propofol and patient movement during procedure have been found higher in the group undergoing colonoscopy first. Total propofol consumed is 135 mg in the group undergoing colonoscopy first and 124 mg in the group undergoing gastroscopy first. This is the most important study focusing on the consumption of sedative agent, and especially, consumption of propofol in BE.

The results of our study indicate that while the number of administration of additional propofol dose was higher in the group undergoing gastroscopy first, no difference was found between the groups regarding consumption of propofol. Total dose of propofol is 145 mg in the group undergoing colonoscopy first and 154 mg in the group undergoing gastroscopy first in our study. No difference was found between the groups regarding recovery period. This condition can be explained by similar total propofol consumptions. RSS showed an increase in both groups beginning from the 5th minute. RSS values measured in the 5th minutes were lower in the group undergoing gastroscopy first than the group undergoing colonoscopy first. This condition can be explained by gastroscopy duration lasting approximately 3-4 minutes, position change during colonoscopy procedure in the 5th minutes and increase in awakening with the beginning of colonoscopy procedure. Similarly, RSS values of the group undergoing colonoscopy first showed a decrease in the 10th minute. This condition can be explained by gastroscopy duration lasting 9-10 minutes, position change during colonoscopy procedure in the 10th minute and increase in awakening with the beginning of gastroscopy procedure.

Cho et al. (5) have suggested beginning the procedure first with gastroscopy by stating that beginning the procedure first with gastroscopy followed by colonoscopy reduced the stress level of the patient in BE performed by them in 80 patients without sedation. However, they determined no significant differences regarding procedural success. Choi et al. (6) have performed a new large-scale study focusing on endoscopy performance by stating that the number of patients of the study performed by Cho et al.(5) was insufficient and endoscopy performance was not evaluated sufficiently in the study performed by Hsieh et al. (4) They analyzed 1100 patients undergoing BE regarding colonoscopy performance. They determined no significant differences between performing gastroscopy or colonoscopy first regarding the time to reach the cecum, cecal intubation and the adenoma detection rates. The time to reach the cecum was found to be 6.3 minutes and 6.4 minutes, respectively. Cecal intubation became more difficult in female patients over the age of 55, patients with insufficient bowel cleansing and patients with previous surgery. They stated that procedure priority did not affect procedural success, but performing colonoscopy first followed by gastroscopy disturbed patient comfort. Furthermore, they performed the procedure without sedation in 554 patients. They emphasized that administration of sedation did not change procedural success either but improved patient comfort. In our study, it was observed that gastroscopy duration and total procedure duration were longer in the group undergoing gastroscopy first followed by colonoscopy. However, no significant difference was determined regarding colonoscopy duration. No difference was determined between

the groups regarding the time to reach the cecum. The time to reach the cecum was found to be 6.9 minutes in the colonoscopy first group followed by gastroscopy and 7.6 minutes in the group undergoing gastroscopy first followed by colonoscopy. The time to reach the cecum in our study was found to be similar to Choi's study.

In the study performed by Carter et al. (14) on 163 patients undergoing bidirectional endoscopy with conscious sedation using i.v meperidine and midazolam, procedure priority of gastroscopy and colonoscopy has been investigated. They have determined no significant difference between two procedures regarding procedure duration, procedural success, the time to reach the cecum, recovery period, need for additional midazolam, pain scores and patient satisfaction. In our study, while endoscopist and patient satisfaction scores were higher in both groups, patient satisfaction and physician satisfaction were found to be better in the group undergoing colonoscopy first.

In the studies performed, adverse effects have not been evaluated. In our study, while no adverse effect was observed in the patient group undergoing colonoscopy first, adverse effect was observed in 6 patients of the group undergoing gastroscopy first. These adverse effects were allergic reaction in 1 patient, bradycardia in 1 patient and desaturation occurring due to increased secretion after gastroscopy in 4 patients. No difference was determined between the groups regarding observation of nausea during gastroscopy.

In our study, performing procedures at the same session may cause concerns about contamination, especially when the colonoscopy is implemented before gastroscopy group. Endoscopic infections can be divided into two types: endogenous and exogenous infections. Endogenous infections are most common in endoscopic procedures. This is related to factors such as the patient's immunosuppression or abscess existence. Exogenous infections are less common and can be prevented by endoscope cleaning, disinfection and drying according to a strict protocol. In bidirectional endoscopy, there is no data showing the relationship of the procedure sequence with the infection. We also paid attention to the cleaning of the endoscope in accordance with the recommendation of the guidelines (15,16). In addition, endoscopists changed their aprons and gloves from gastroscopy to colonoscopy and from colonoscopy to gastroscopy. Although there was one of the follow-up parameters absent in our study protocol, no process related infection was reported. However, this subject can guide future studies.

CONCLUSION

In conclusion, performing colonoscopy first followed by gastroscopy in BE can be preferred since gastroscopy and procedure have a short duration and complication rates and additional propofol doses are lower. However, large-scale studies are required to reply the question, "which one of gastroscopy and colonoscopy should be performed first in bidirectional endoscopy?" regarding anesthesia and procedural success.

Ethics Committee Approval: Local ethics committee approval (28.05.2013/197) was obtained for this study.

Informed Consent: Informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.S., Ö.B., H.Ş.T; Design – P.S., C.T.I.; Supervision – S.O., M.M.; Resource – P.S., Ö.B.; Materials – P.S., H.Ş.T.; Data Collection and/or Pro-cessing – C.T.I., P.S.; Analysis and Interpretation – C.T.I., S.O.; Literature Review – S.O., M.M.; Writing Manuscript – H.Ş.T., Ö.B.; Critical Reviews – M.M., S.O.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (2): 172-179

Özofagoduedonoskopi veya kolonoskopi: ilk ne yapılmalı?

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ÖZET

Giriş ve Amaç: Özofagoduedonoskopi ve kolonoskopi aynı seansta iki yönlü endoskopi olarak yapılabilir. Bu çalışmanın amacı, iki yönlü endoskopi için ilk kez yapılan özofagoduedonoskopi veya kolonoskopide anestezi gereksinimlerinin ve hemodinamik etkilerinin karşılaştırılmasıdır.

Gereç ve Yöntem: On sekiz-70 yaş arası, "American Society of Anesthesiologists (ASA)" sınıflaması I-III 80 hasta randomize olarak çalışmaya dahil edildi. Hastalar iki gruba ayrıldı; Grup C: İlk kolonoskopi, ardından özofagoduedonoskopi. Grup E: ilk özofagoduedonoskopiyi takiben kolonoskopi yapıldı. Tüm hastalara 1 µg/kg fentanil ve 1 mg/kg propofol ile standart anestezi uygulandı. Olguların her 10 dakikada bir kalp atım hızı SpO_2, Ramsey Sedasyon Skoru kaydedildi. Toplam propofol tüketimi, özofagoduedonoskopi sırasında öğürme ve çekuma ulaşma zamanı da kaydedildi. Endoskopist ve hasta memnuniyeti sorgulandı.

Bulgular: Özofagoduedonoskopi sırasında öğürme, her iki grupta istatistiksel olarak anlamlı farklı değildi. Grup E'de toplam işlem süresi ve özofagoduedonoskopi süresi istatistiksel olarak anlamlı uzun bulundu. Grup E'de komplikasyon sıklığı arttı. Endoskopist ve hasta memnuniyeti Grup E'de daha düşüktü. Çekuma ulaşma ve derlenmeye kadar geçen sürede fark yoktu. Ek Propofol tüketimi Grup E'de artmıştı.

Sonuç: Prosedür süresinin kısalması, propofol tüketiminin daha az olması ve komplikasyonların azalması sebebiyle, çift yönlü endoskopide işleme kolonoskopi ile başlamak daha iyi bir seçenek olabilir.

Anahtar Kelimeler: Kolonoskopi, gastroskopi, anestezi, hasta memnuniyeti

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ORIGINAL ARTICLE
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Most cited 100 articles from Turkey on abdominal wall hernias: a bibliometric study

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ABSTRACT

Objective: The aim of the present study was to search the most-cited articles from Turkey on abdominal wall hernias and analyze their characteristics with several parameters.

Material and Methods: In March 2019, a search was conducted through all databases in the Web of Science (WoS) to determine the most-cited articles on abdominal wall hernias. Each article was evaluated in regard to host journal, year of publication, the complete list of authors, the type of article, main subject of the study, institution of the study group. Citation counts in Google Scholar (GSch) were also obtained.

Results: Mean number of citations of the top 100 articles in herniology was 30.50. Articles were published in 38 journals; Hernia is the leading host. No correlation was observed between the journal impact factors and the number of the citations. Two thirds of the articles were clinical studies. Article types had no significant effect on the citation counts. Inguinal hernia was the most frequent topic by taking place in 58 papers. Articles related to incisional hernias had a higher mean number of citations in comparison with other topics. Ankara University School of Medicine had most cited articles, the highest number of total citations, and the highest citation per articles. Ankara Numune Training and Research Hospital and Istanbul University School of Medicine had the highest number of the articles in the list.

Conclusion: Citation counts of hernia related articles from Turkey are relatively low. Hernia is the leading journal for Turkish studies. Inguinal hernia is the most frequent topic whereas papers about incisional hernias receive more citations than others.

Keywords: Hernia, abdominal wall, bibliometric, citation

INTRODUCTION

The number of publications from Turkey displays an obvious growth as biomedical publishing advances globally (1). However, recently Onat has performed a citation analysis and stated that Turkey's contribution to the medicine by scientific articles is not enough compared with the potential of the country (2). Citation (a reference to subsequent studies) in another paper is one of the criteria to value an article. Citation analysis of the publications in a specific subject is performed by bibliometric methodology. The earliest example was published in the *Journal of the American Medical Association* as one of the most-cited articles in the same journal in 1985 (3). In 2002, a study on 100 citation classics in general surgery journals was published (4). Mayir et al. have searched the most cited articles from Turkey in the general surgery field and revealed that hydatid disease, pilonidal sinus, breast diseases, and inguinal hernia were the most frequent subjects (5). Scientific papers on abdominal wall hernias also show a steady rise worldwide (6). Hernia repairs, especially those for inguinal hernias, can be performed in every institution, and the surgeons find opportunity to prepare scientific papers more easily in comparison with major operations in surgical practice.

The present study was done with the purpose of listing the most-cited articles from Turkey in the field of abdominal wall hernia and analyzing their characteristics with several parameters.

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MATERIAL and METHODS

Database Search

In March 2019, a search was conducted through all databases in the Web of Science (WoS) to determine the most-cited articles on abdominal wall hernias from Turkey. The keywords for the topic line of the search were "inguinal hernia," "ventral hernia," "incisional hernia," "umbilical hernia," "paraumbilical hernia," and "femoral hernia." Additionally, combinations of "hernia and emergency," "hernia and mesh" were added. The keywords were searched in the titles, abstracts, and keywords given.

Data Recording

The study adhered to the Helsinki Declaration developed by the World Medical Association for medical research involving human material and data. After the top-cited 100 articles were determined and ranked by the number of citations, all full texts were reached. Each article was evaluated in regard to journal name, main field of the journal (surgery, general medicine, others), year of publication, the complete list of authors, number of authors, the type of article (clinical study; review/systematic review/meta-analysis/literature search; case report/case series; laboratory study/animal experiment/cadaver dissection), main subject of the study (inguinal, incisional, umbilical, femoral, etc; emergency; mesh and other materials—if the study focused on the characteristics or properties of prosthetic materials, or if several meshes were compared in repairing certain hernia types), institution of the study group. Citation counts in Google Scholar (GSch) were also obtained. The data were recorded in Office Excel 2016 (Microsoft, Redmond, WA).

Statistical Analysis

Data were exported to SPSS v.21 (IBM, Chicago, IL) for statistical analysis. A one-way ANOVA test was used to determine the differences between mean values. A correlation coefficient (r) was calculated to determine whether recorded parameters correlated with the citation counts of the listed articles. A p value less than 0.05 was accepted as significant.

RESULTS

The top 100 list of hernia related papers from Turkey is given in Table 1. The total number of citations of the top 100 articles in herniology was 3.050 in WoS (range: 12-145), and 5.672 in GSch (range: 16-272). Mean number of citations was 30.50 in WoS, and 56.72 in GSch.

The publication year was evaluated in 3 consecutive decades (Table 2). No article published before 1995 or earlier took place in the list. The most productive decade was 2000-2009, with 72 papers. The year with the highest number of articles in the list was 2006 (14 papers). The most recent paper in the list was published in 2014. No effect of the publication decade was observed on citation counts (Table 3).

One hundred top cited articles were published in 38 different journals: 80 papers in surgical journals and 20 papers in others (anesthesia, biomaterials, etc.). Hernia was the most frequent host journal with 23 articles (Table 4). Articles published in surgical journals had more citations than the ones in the journals from other disciplines (WoS: 32.85 vs. 21.10; p= 0.030, and GSch: 60.70 vs. 40.80; p= 0.57). No correlation was observed between the journal impact factors and the number of the citations. The number of the authors differed 1 to 11 with a mean number of 5.66; only 3 papers were written by one single author, and 2 by two authors. There was no correlation between the number of the authors and the citation counts. Interestingly, four papers had no authors from general surgery at all; two by anesthesiologists, one by radiologists, and another one by neurologists and urologist.

Two thirds of the articles were clinical studies. The types of the articles had no significant effect on citation counts (Table 5). Amongst the clinical studies, retrospective series had more citation counts than prospective studies (WoS: 44.38 vs. 27.76; p= 0.007, and GSch: 85.43 vs. 51.47; p= 0.011).

Inguinal hernia was the most frequent topic by taking place in 58 papers, incisional hernia was the second with 16 studies (Table 6). Twenty-one articles studied mesh materials. Six studies which investigated hernia repairs in emergency conditions had the highest mean citation number (WoS: 95.50; GSch: 177.50). Articles related to incisional hernias had a higher mean number of citations in comparison to ones about inguinal hernias (WoS: 38.73 vs. 28.12; p= 0.080).

The top 100 articles originated from 43 institutions. There were 29 university hospitals, 10 teaching hospitals other than medical schools, 3 private hospitals and 1 rural public hospital. From another view, there were 39 publications from Ankara, 22 from Istanbul, 11 from Izmir and 28 from other cities. Ankara University School of Medicine had the most-cited article, the highest number of total citations, and the highest citation counts per articles. Ankara Numune Training and Research Hospital and Istanbul University School of Medicine had the highest number of the articles in the list (Table 7). On the other hand, no differences in citation counts were determined in comparison of university hospitals and other training hospitals.

DISCUSSION

Bibliometric analyses for citation counts in medical publishing have revealed that the most-cited articles were published between 1990 and 2010 (7-12). The most productive decade in the present study was 2000-2009. Even the most scientific articles need time to get citations by subsequent publications. Citation count lists are dynamic, and rankings may change by time, and we can see a rapid rise in the citation counts of papers produced in the last decade. Similarly, some articles that are not yet in the

Table 1. Top 100 list of papers with the highest citation counts

	Authors	Reference	WoS citations	GSch citations
1	Yerdel MA, Akin EB, Dolalan S, Turkcapar AG, Pehlivan M, Gecim IE, Kuterdem E.	Effect of single-dose prophylactic ampicillin and sulbactam on wound infection after tension-free inguinal hernia repair with polypropylene mesh: the randomized, double-blind, prospective trial. Ann Surg. 2001 Jan;233(1):26-33.	145	272
2	Kulah B, Kulacoglu IH, Oruc MT, Duzgun AP, Moran M, Ozmen MM, Coskun F.	Presentation and outcome of incarcerated external hernias in adults. Am J Surg. 2001 Feb;181(2):101-4.	104	203
3	Cingi A, Cakir T, Sever A, Aktan AO.	Enterostomy site hernias: a clinical and computerized tomographic evaluation. Dis Colon Rectum. 2006 Oct;49(10):1559-63.	91	141
4	Barbaros U, Asoglu O, Seven R, Erbil Y, Dinccag A, Deveci U, Ozarmagan S, Mercan S.	The comparison of laparoscopic and open ventral hernia repairs: a prospective randomized study. Hernia. 2007 Feb;11(1):51-6.	88	166
5	Kulah B, Duzgun AP, Moran M, Kulacoglu IH, Ozmen MM, Coskun F.	Emergency hernia repairs in elderly patients. Am J Surg. 2001 Nov;182(5):455-9.	83	152
6	Ozgün H, Kurt MN, Kurt I, Cevikel MH.	Comparison of local, spinal, and general anaesthesia for inguinal herniorrhaphy. Eur J Surg. 2002;168(8-9):455-9.	67	127
7	Bilsel Y, Abci I.	The search for ideal hernia repair; mesh materials and types. Int J Surg. 2012;10(6):317-21.	65	112
8	Geçim IE, Koçak S, Ersoz S, Bumin C, Aribal D.	Recurrence after incisional hernia repair: results and risk factors. Surg Today. 1996;26(8):607-9.	65	104
9	Gurer A, Ozdogan M, Ozlem N, Yildirim A, Kulacoglu H, Aydin R.	Uncommon content in groin hernia sac. Hernia. 2006 Apr;10(2):152-5.	64	167
10	Kurt N, Oncel M, Ozkan Z, Bingul S.	Risk and outcome of bowel resection in patients with incarcerated groin hernias: retrospective study. World J Surg. 2003 Jun;27(6):741-3.	62	140
11	Uslu HY, Erkek AB, Cakmak A, Kepenekci I, Sozener U, Kocaay FA, Turkcapar AG, Kuterdem E.	Trocar site hernia after laparoscopic cholecystectomy. J Laparoendosc Adv Surg Tech A. 2007 Oct;17(5):600-3.	58	86
12	Basoglu M, Yildirgan MI, Yilmaz I, Balik A, Celebi F, Atamanalp SS, Polat KY, Oren D.	Late complications of incisional hernias following prosthetic mesh repair. Acta Chir Belg. 2004 Aug;104(4):425-8.	55	104
13	Alptekin H, Yilmaz H, Acar F, Kafali ME, Sahin M.	Incisional hernia rate may increase after single-port cholecystectomy. J Laparoendosc Adv Surg Tech A. 2012 Oct;22(8):731-7.	53	78
14	Sen H, Sizlan A, Yanarateş O, Senol MG, Inangil G, Sücüllü I, Ozkan S, Dağli G.	The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol. 2009 Sep;26(9):772-6.	52	88
15	Avtan L, Avci C, Bulut T, Fourtanier G.	Mesh infections after laparoscopic inguinal hernia repair. Surg Laparosc Endosc. 1997 Jun;7(3):192-5.	50	90
16	Demirer S, Kepenekci I, Evirgen O, Birsen O, Tuzuner A, Karahuseyinoglu S, Ozban M, Kuterdem E.	The effect of polypropylene mesh on ilioinguinal nerve in open mesh repair of groin hernia. J Surg Res. 2006 Apr;131(2):175-81.	46	71
17	Demir U, Mihmanli M, Coskun H, Dilege E, Kalyoncu A, Altinli E, Gunduz B, Yilmaz B.	Comparison of prosthetic materials in incisional hernia repair. Surg Today. 2005;35(3):223-7.	46	73

Table 1. Top 100 list of papers with the highest citation counts (continue)

	Authors	Reference	WoS citations	GSch citations
18	Berberoğlu M, Uz A, Ozmen MM, Bozkurt MC, Erkuran C, Taner S, Tekin A, Tekdemir I.	Corona mortis: an anatomic study in seven cadavers and an endoscopic study in 28 patients.Surg Endosc. 2001 Jan;15(1):72-5.	42	85
19	Atila K, Guler S, Inal A, Sokmen S, Karademir S, Bora S.	Prosthetic repair of acutely incarcerated groin hernias: a prospective clinical observational cohort study. Langenbecks Arch Surg. 2010 Jun;395(5):563-8.	39	71
20	Derici H, Unalp HR, Bozdag AD, Nazli O, Tansug T, Kamer E.	Factors affecting morbidity and mortality in incarcerated abdominal wall hernias. Hernia. 2007 Aug;11(4):341-6.	38	74
21	Alimoglu O, Kaya B, Okan I, Dasiran F, Guzey D, Bas G, Sahin M.	Femoral hernia: a review of 83 cases. Hernia. 2006 Mar;10(1):70-3.	36	100
22	Aydede H, Erhan Y, Sakarya A, Kara E, Ilkgül O, Can M.	Effect of mesh and its localisation on testicular flow and spermatogenesis in patients with groin hernia. Acta Chir Belg. 2003 Nov-Dec;103(6):607-10.	36	59
23	Gönüllü NN, Cubukçu A, Alponat A.	Comparison of local and general anesthesia in tension-free (Lichtenstein) hernioplasty: a prospective randomized trial. Hernia. 2002 Mar;6(1):29-32.	35	91
24	Kulacoglu H.	Current options in inguinal hernia repair in adult patients. Hippokratia. 2011 Jul;15(3):223-31.	34	94
25	Kayaoglu HA, Ozkan N, Hazinedaroglu SM, Ersoy OF, Erkek AB, Koseoglu RD.	Comparison of adhesive properties of five different prosthetic materials used in hernioplasty. J Invest Surg. 2005 Mar-Apr;18(2):89-95.	34	52
26	Gürleyik E, Gürleyik G, Cetinkaya F, Unalmiser S.	The inflammatory response to open tension-free inguinal hernioplasty versus conventional repairs. Am J Surg. 1998 Mar;175(3):179-82.	34	47
27	Surgit O.	Single-incision Laparoscopic surgery for total extraperitoneal repair of inguinal hernias in 23 patients. Surg Laparosc Endosc Percutan Tech. 2010 Apr;20(2):114-8.	31	44
28	Cingi A, Solmaz A, Attaallah W, Aslan A, Aktan AO.	Enterostomy closure site hernias: a clinical and ultrasonographic evaluation. Hernia. 2008 Aug;12(4):401-5.	31	42
29	Andaç N, Baltacioğlu F, Tüney D, Cimşit NC, Ekinci G, Biren T.	Inguinoscrotal bladder herniation: is CT a useful tool in diagnosis? Clin Imaging. 2002 Sep-Oct;26(5):347-8.	31	67
30	Uzunköy A, Coskun A, Akinci OF, Kocyigit A.	Systemic stress responses after laparoscopic or open hernia repair. Eur J Surg. 2000 Jun;166(6):467-71.	31	53
31	Oruç MT, Akbulut Z, Ozozan O, Coşkun F.	Urological findings in inguinal hernias: a case report and review of the literature. Hernia. 2004 Feb;8(1):76-9.	29	83
32	Kapan S, Kapan M, Goksoy E, Karabicak I, Oktar H.	Comparison of PTFE, pericardium bovine and fascia lata for repair of incisional hernia in rat model, experimental study. Hernia. 2003 Mar;7(1):39-43.	29	74
33	Dogru O, Girgin M, Bulbuller N, Cetinkaya Z, Aygen E, Camci C.	Comparison of Kugel and Lichtenstein operations for inguinal hernia repair: results of a prospective randomized study. World J Surg. 2006 Mar;30(3):346-50.	28	61
34	Saygun O, Agalar C, Aydinuraz K, Agalar F, Daphan C, Saygun M, Ceken S, Akkus A, Denkbas EB.	Gold and gold-palladium coated polypropylene grafts in a S. epidermidis wound infection model. J Surg Res. 2006 Mar;131(1):73-9.	28	47

Table 1. Top 100 list of papers with the highest citation counts (continue)

	Authors	Reference	WoS citations	GSch citations
35	Colak T, Akca T, Kanik A, Aydin S.	Randomized clinical trial comparing laparoscopic totally extraperitoneal approach with open mesh repair in inguinal hernia. Surg Laparosc Endosc Percutan Tech. 2003 Jun;13(3):191-5.	28	56
36	Türkçapar AG, Yerdel MA, Aydinuraz K, Bayar S, Kuterdem E.	Repair of midline incisional hernias using polypropylene grafts. Surg Today. 1998;28(1):59-63.	28	58
37	Cakmak A, Cirpanli Y, Bilensoy E, Yorganci K, Caliş S, Saribaş Z, Kaynaroğlu V.	Antibacterial activity of triclosan chitosan coated graft on hernia graft infection model. Int J Pharm. 2009 Nov 3;381(2):214-9.	27	47
38	Polat C, Dervisoglu A, Senyurek G, Bilgin M, Erzurumlu K, Ozkan K.	Umbilical hernia repair with the prolene hernia system. Am J Surg. 2005 Jul;190(1):61-4.	27	49
39	Karahasanoglu T, Onur E, Baca B, Hamzaoglu I, Pekmezci S, Boler DE, Kilic N, Altug T.	Spiral tacks may contribute to intra-abdominal adhesion formation. Surg Today. 2004;34(10):860-4.	27	38
40	Akbulut G, Serteser M, Yücel A, Değirmenci B, Yilmaz S, Polat C, San O, Dilek ON.	Can laparoscopic hernia repair alter function and volume of testis? Randomized clinical trial. Surg Laparosc Endosc Percutan Tech. 2003 Dec;13(6):377-81.	27	45
41	Demirer S, Geçim IE, Aydinuraz K, Ataoğlu H, Yerdel MA, Kuterdem E.	Affinity of Staphylococcus epidermidis to various prosthetic graft materials. J Surg Res. 2001 Jul;99(1):70-4.	27	35
42	Derici H, Unalp HR, Nazli O, Kamer E, Coskun M, Tansug T, Bozdag AD.	Prosthetic repair of incarcerated inguinal hernias: is it a reliable method? Langenbecks Arch Surg. 2010 Jun;395(5):575-9.	26	54
43	Celik A, Kutun S, Kockar C, Mengi N, Ulucanlar H, Cetin A.	Colonoscopic removal of inguinal hernia mesh: report of a case and literature review. J Laparoendosc Adv Surg Tech A. 2005 Aug;15(4):408-10.	26	38
44	Anadol ZA, Ersoy E, Taneri F, Tekin E.	Outcome and cost comparison of laparoscopic transabdominal preperitoneal hernia repair versus Open Lichtenstein technique. J Laparoendosc Adv Surg Tech A. 2004 Jun;14(3):159-63.	26	48
45	Alimoglu O, Akcakaya A, Sahin M, Unlu Y, Ozkan OV, Sanli E, Eryilmaz R.	Prevention of adhesion formations following repair of abdominal wall defects with prosthetic materials (an experimental study). Hepatogastroenterology. 2003 May-Jun;50(51):725-8.	26	37
46	Altuntas I, Tarhan O, Delibas N.	Seprafilm reduces adhesions to polypropylene mesh and increases peritoneal hydroxyproline. Am Surg. 2002 Sep;68(9):759-61.	25	37
47	Gultekin FA, Kurukahvecioglu O, Karamercan A, Ege B, Ersoy E, Tatlicioglu E.	A prospective comparison of local and spinal anesthesia for inguinal hernia repair. Hernia. 2007 Apr;11(2):207.	24	61
48	Dilek ON, Yucel A, Akbulut G, Degirmenci B.	Are there adverse effects of herniorrhaphy techniques on testicular perfusion? Evaluation by color Doppler ultrasonography. Urol Int. 2005;75(2):167-9.	24	38
49	Besim H, Yalçin Y, Hamamcí O, Arslan K, Soníşik M, Korkmaz A, Erdoğan S.	Prevention of intraabdominal adhesions produced by polypropylene mesh. Eur Surg Res. 2002 May-Jun;34(3):239-43.	24	41
50	Gönüllü NN, Dülger M, Utkan NZ, Cantürk NZ, Alponat A.	Prevention of postherniorrhaphy urinary retention with prazosin. Am Surg. 1999 Jan;65(1):55-8.	24	49

Table 1. Top 100 list of papers with the highest citation counts (continue)

	Authors	Reference	WoS citations	GSch citations
51	Aydinuraz K, Ağalar C, Ağalar F, Ceken S, Duruyürek N, Vural T.	In vitro S. epidermidis and S. aureus adherence to composite and lightweight polypropylene grafts. J Surg Res. 2009 Nov;157(1):e79-86.	23	39
52	Ersin S, Aydin U, Makay O, Icoz G, Tamsel S, Sozbilen M, Killi R.	Is testicular perfusion influenced during laparoscopic inguinal hernia surgery? Surg Endosc. 2006 Apr;20(4):685-9.	23	31
53	Dilege E, Coskun H, Gunduz B, Sakiz D, Mihmanli M.	Prevention of adhesion to prosthetic mesh in incisional ventral hernias: comparison of different barriers in an experimental model. Eur Surg Res. 2006;38(3):358-64.	23	28
54	Carilli S, Alper A, Emre A.	Inguinal cord lipomas. Hernia. 2004 Aug;8(3):252-4.	22	51
55	Vatansev C, Belviranli M, Aksoy F, Tuncer S, Sahin M, Karahan O.	The effects of different hernia repair methods on postoperative pain medication and CRP levels. Surg Laparosc Endosc Percutan Tech. 2002 Aug;12(4):243-6.	22	38
56	Yavuz N, Ipek T, As A, Kapan M, Eyuboglu E, Erguney S.	Laparoscopic repair of ventral and incisional hernias: our experience in 150 patients. J Laparoendosc Adv Surg Tech A. 2005 Dec;15(6):601-5.	21	45
57	Baykal A, Yorganci K, Sokmensuer C, Hamaloglu E, Renda N, Sayek I.	An experimental study of the adhesive potential of different meshes. Eur J Surg. 2000 Jun;166(6):490-4.	21	28
58	Koç M, Tez M, Yoldaş O, Dizen H, Göçmen E.	Cooling for the reduction of postoperative pain: prospective randomized study. Hernia. 2006 Apr;10(2):184-6.	20	47
59	Cihan A, Ozdemir H, Uçan BH, Acun Z, Comert M, Tascilar O, Cesur A, Cakmak GK, Gundogdu S.	Fade or fate. Seroma in laparoscopic inguinal hernia repair. Surg Endosc. 2006 Feb;20(2):325-8.	20	33
60	Ozdogan M, Yildiz F, Gurer A, Orhun S, Kulacoglu H, Aydin R.	Changes in collagen and elastic fiber contents of the skin, rectus sheath, transversalis fascia and peritoneum in primary inguinal hernia patients. Bratisl Lek Listy. 2006;107(6-7):235-8.	20	41
61	Gokalp A, Inal M, Maralcan G, Baskonus I.	A prospective randomized study of Lichtenstein open tension-free versus laparoscopic totally extraperitoneal techniques for inguinal hernia repair. Acta Chir Belg. 2003 Oct;103(5):502-6.	20	44
62	Polat C, Kahraman A, Yilmaz S, Koken T, Serteser M, Akbulut G, Arikan Y, Dilek ON, Gokce O.	A comparison of the oxidative stress response and antioxidant capacity of open and laparoscopic hernia repairs. J Laparoendosc Adv Surg Tech A. 2003 Jun;13(3):167-73.	20	27
63	Salman AE, Yetişir F, Yürekli B, Aksoy M, Yildirim M, Kiliç M.	The efficacy of the semi-blind approach of transversus abdominis plane block on postoperative analgesia in patients undergoing inguinal hernia repair: a prospective randomized double-blind study. Local Reg Anesth. 2013 Jan 18;6:1-7.	19	27
64	Anadol AZ, Akin M, Kurukahvecioglu O, Tezel E, Ersoy E.	A prospective comparative study of the efficacy of conventional Lichtenstein versus self-adhesive mesh repair for inguinal hernia. Surg Today. 2011 Nov;41(11):1498-503.	19	29
65	Karakayali F, Oksuz E, Turk E, Pekmez M, Karabulut Z, Yilmaz T, Moray G, Haberal M.	Effectiveness of multiple neurectomies to prevent chronic groin pain after tension-free hernia repair. Int Surg. 2010 Jan-Mar;95(1):40-8.	19	32
66	Kamer E, Unalp HR, Derici H, Tansug T, Onal MA.	Laparoscopic cholecystectomy accompanied by simultaneous umbilical hernia repair: a retrospective study. J Postgrad Med. 2007 Jul-Sep;53(3):176-80.	19	35

Table 1. Top 100 list of papers with the highest citation counts (continue)

	Authors	Reference	WoS citations	GSch citations
67	Eryilmaz R, Sahin M, Tekelioglu MH.	Which repair in umbilical hernia of adults: primary or mesh? Int Surg. 2006 Sep-Oct;91(5):258-61.	19	40
68	Terzi C.	Antimicrobial prophylaxis in clean surgery with special focus on inguinal hernia repair with mesh. J Hosp Infect. 2006 Apr;62(4):427-36.	19	46
69	Abci I, Bilgi S, Altan A.	Role of TIMP-2 in fascia transversalis on development of inguinal hernias. J Invest Surg. 2005 May-Jun;18(3):123-8.	19	37
70	Ozden I, Emre A, Bilge O, Tekant Y, Acarli K, Alper A, Aryogul O.	Elective repair of abdominal wall hernias in decompensated cirrhosis. Hepatogastroenterology. 1998;45(23):1516-1518.	19	38
71	Günal O, Ozer S, Gürleyik E, Bahçebaşi T.	Does the approach to the groin make a difference in hernia repair? Hernia. 2007 Oct;11(5):429-34.	18	45
72	Yelimlieş B, Alponat A, Cubukçu A, Kuru M, Oz S, Erçin C, Gönüllü N.	Carboxymethylcellulose coated on visceral face of polypropylene mesh prevents adhesion without impairing wound healing in incisional hernia model in rats. Hernia. 2003 Sep;7(3):130-3.	18	37
73	Kama NA, Coskun T, Yavuz H, Doganay M, Reis E, Akat AZ.	Autologous skin graft, human dura mater and polypropylene mesh for the repair of ventral abdominal hernias: an experimental study. Eur J Surg. 1999 Nov;165(11):1080-5.	18	29
74	Yilmazlar T, Kizil A, Zorluoglu A, Ozgüç H.	The value of herniography in football players with obscure groin pain. Acta Chir Belg. 1996 Jun;96(3):115-8.	18	30
75	Ergul Z, Akinci M, Ugurlu C, Kulacoglu H, Yilmaz KB.	Prophylactic antibiotic use in elective inguinal hernioplasty in a trauma center. Hernia. 2012 Apr;16(2):145-51.	17	31
76	Kulacoglu H, Yazicioglu D, Ozyaylali I.	Prosthetic repair of umbilical hernias in adults with local anesthesia in a day-case setting: a comprehensive report from a specialized hernia center. Hernia. 2012 Apr;16(2):163-70.	17	24
77	Sucullu I, Filiz AI, Sen B, Ozdemir Y, Yucel E, Sinan H, Sen H, Dandin O, Kurt Y, Gulec B, Ozyurt M.	The effects of inguinal hernia repair on testicular function in young adults: a prospective randomized study. Hernia. 2010 Apr;14(2):165-9.	17	30
78	Malazgirt Z, Topgul K, Sokmen S, Ersin S, Turkcapar AG, Gok H, Gonullu N, Paksoy M, Ertem M.	Spigelian hernias: a prospective analysis of baseline parameters and surgical outcome of 34 consecutive patients. Hernia. 2006 Aug;10(4):326-30.	17	33
79	Terzi C, Kiliç D, Unek T, Hoşgörler F, Füzün M, Ergör G.	Single-dose oral ciprofloxacin compared with single-dose intravenous cefazolin for prophylaxis in inguinal hernia repair: a controlled randomized clinical study. J Hosp Infect. 2005 Aug;60(4):340-7.	17	33
80	Kuzu MA, Hazinedaroğlu S, Dolalan S, Ozkan N, Yalçin S, Erkek AB, Mahmoudi H, Tüzüner A, Elhan AH, Kuterdem E.	Prevention of surgical site infection after open prosthetic inguinal hernia repair: efficacy of parenteral versus oral prophylaxis with amoxicillin-clavulanic acid in a randomized clinical trial. World J Surg. 2005 Jun;29(6):794-9.	17	24
81	Akcaboy EY, Akcaboy ZN, Gogus N.	Ambulatory inguinal herniorrhaphy: paravertebral block versus spinal anesthesia. Minerva Anestesiol. 2009 Dec;75(12):684-91.	16	32
82	Erhan Y, Erhan E, Aydede H, Mercan M, Tok D.	Chronic pain after Lichtenstein and preperitoneal (posterior) hernia repair. Can J Surg. 2008 Oct;51(5):383-7.	16	40

Table 1. Top 100 list of papers with the highest citation counts (continue)

	Authors	Reference	WoS citations	GSch citations
83	Astarcioğlu H, Sökmen S, Atila K, Karademir S.	Incarcerated inferior lumbar (Petit's) hernia. Hernia. 2003 Sep;7(3):158-60.	16	37
84	Onal A, Sökmen S, Atila K.	Spigelian hernia associated with strangulation of the small bowel and appendix. Hernia. 2003 Sep;7(3):156-7.	16	20
85	Ozmen MM, Aslar AK, Terzi MC, Albayrak L, Berberoğlu M.	Prevention of adhesions by bioresorbable tissue barrier following laparoscopic intraabdominal mesh insertion. Surg Laparosc Endosc Percutan Tech. 2002 Oct;12(5):342-6.	16	22
86	Demirci A, Efe EM, Türker G, Gurbet A, Kaya FN, Anil A, Cimen I.	[Iliohypogastric/ilioinguinal nerve block in inguinal hernia repair for postoperative pain management: comparison of the anatomical landmark and ultrasound guided techniques]. Rev Bras Anestesiol. 2014 Sep-Oct;64(5):350-6.	15	30
87	Akyol C, Kocaay F, Orozakunov E, Genc V, Kepenekci Bayram I, Cakmak A, Baskan S, Kuterdem E.	Outcome of the patients with chronic mesh infection following open inguinal hernia repair. J Korean Surg Soc. 2013 May;84(5):287-91. doi:10.4174/jkss.2013.84.5.287.	15	27
88	Caliskan K, Nursal TZ, Caliskan E, Parlakgumus A, Yildirim S, Noyan T.	A method for the reduction of chronic pain after tension-free repair of inguinal hernia: ilioohypogastric neurectomy and subcutaneous transposition of the spermatic cord. Hernia. 2010 Feb;14(1):51-5.	15	27
89	Kurukahvecioglu O, Ege B, Yazicioglu O, Tezel E, Ersoy E.	Polytetrafluoroethylene prosthesis migration into the bladder after laparoscopic hernia repair: a case report. Surg Laparosc Endosc Percutan Tech. 2007 Oct;17(5):474-6.	15	34
90	Bademkiran F, Tataroglu C, Ozdedeli K, Altay B, Aydogdu I, Uludag B, Ertekin C.	Electrophysiological evaluation of the genitofemoral nerve in patients with inguinal hernia. Muscle Nerve. 2005 Nov;32(5):600-4.	15	21
91	Ipek T, Eyuboglu E, Aydingoz O.	Laparoscopic management of inferior lumbar hernia (Petit triangle hernia). Hernia. 2005 May;9(2):184-7.	15	30
92	Yilmaz I, Karakaş DO, Sucullu I, Ozdemir Y, Yucel E.	A rare cause of mechanical bowel obstruction: mesh migration. Hernia. 2013 Apr;17(2):267-9.	14	25
93	Seker D, Kulacoglu H.	Long-term complications of mesh repairs for abdominal-wall hernias. J Long Term Eff Med Implants. 2011;21(3):205-18.	14	36
94	Dilege E, Deveci U, Erbil Y, Dinççağ A, Seven R, Ozarmagan S, Mercan S, Barbaros U.	N-butyl cyanoacrylate versus conventional suturing for fixation of meshes in an incisional hernia model. J Invest Surg. 2010 Oct;23(5):262-6.	14	24
95	Piskin T, Aydin C, Barut B, Dirican A, Kayaalp C.	Preoperative progressive pneumoperitoneum for giant inguinal hernias. Ann Saudi Med. 2010 Jul-Aug;30(4):317-20.	14	29
96	Ozkan D, Akkaya T, Cömert A, Balkc N, Ozdemir E, Gümüs H, Ergül Z, Kaya O.	Paravertebral block in inguinal hernia surgeries: two segments or 4 segments? Reg Anesth Pain Med. 2009 Jul-Aug;34(4):312-5.	14	29
97	Kulacoglu H, Ozdogan M, Gurer A, Ersoy EP, Onder Devay A, Duygulu Devay S, Gulbahar O, Gogkus S.	Prospective comparison of local, spinal, and general types of anaesthesia regarding oxidative stress following Lichtenstein hernia repair. Bratisl Lek Listy. 2007;108(8):335-9.	14	32
98	Hengirmen S, Cete M, Soran A, Aksoy F, Sencer H, Olcay E.	Comparison of meshes for the repair of experimental abdominal wall defects. J Invest Surg. 1998 Sep-Oct;11(5):315-25.	14	33
99	Ramadan SU, Gokharman D, Tuncbilek I, Ozer H, Kosar P, Kacar M, Temel S, Kosar U.	Does the presence of a mesh have an effect on the testicular blood flow after surgical repair of indirect inguinal hernia? J Clin Ultrasound. 2009 Feb;37(2):78-81.	13	16
100	Yavuz N, Ersoy YE, Demirkesen O, Tortum OB, Erguney S.	Laparoscopic incisional lumbar hernia repair. Hernia. 2009 Jun;13(3):281-6.	12	27

WoS: Web of Science, GSch : Google Scholar,

Table 2. Number of articles regarding journal type and decade of publication

Decade	Surgery	Others	Total
1990-1999	8	1	9
2000-2009	58	14	72
2010-2019	14	5	19
Total	80	20	100

Table 3. Mean citations counts of top 100 papers regarding decade of publication

Decade	No of papers	WoS citations	GSch citations
1990-1999	9	30.00 (270)	53.1 (478)
2000-2009	72	32.26 (2.323)	60.69 (4.370)
2010-2019	19	24.05 (457)	43.37 (824)
p		0.35	0.27

The figures in parenthesis are total numbers within the decade.

Table 4. Leading journals in the "Top 100 List" in herniology

Journal name	No of papers
Hernia	23
Journal of Laparoendoscopic Advanced Surgical Techiques and Videoscopy	6
Surgical Laparoscopy Endoscopy & Percutaneous Techniques	6
Journal of Surgical Research	5
Surgery Today	5
Acta Chirurgica Belgica	4
American Journal of Surgery	4
European Journal of Surgery	4
Journal of Investigative Surgery	4
World Journal of Surgery	3
Surgical Endoscopy	3

Table 5. Citation counts regarding type of article

Study type	No of papers	WoS citations	GSch citations
Clinical study	66	33.05	62.27
Review	4	33.00	72.00
Case report or case series	10	20.90	39.70
Laboratory studies, animal experiments, cadaver study	20	26.40	43.85
p		0.310	0.156

Table 6. Topics of the article	
Inguinal hernia	58
Incisional hernia	16
Umbilical hernia	5
Femoral hernia	1
Spigelian hernia	2
Lumbar hernia	2
Emergency repairs	6
Mesh	21
Fixing material	2
Infection	11
Some articles focused on multiple topics.	

Table 7. Most influential authors with more than 200 citations in total in the "Top 100 List" in herniology

Institution	Total number of citations	Total number of articles	Citation per article	Highest citation count for an article
Ankara University School of Medicine	401	8	50.13	145
Ankara Numune Teaching Hospital	366	10	36.60	104
İstanbul University School of Medicine	366	10	36.60	91
Ankara Atatürk Teaching Hospital	117	4	29.25	64
9 Eylül Üniversity	107	5	21.40	39
Gazi University School of Medicine	84	4	21.00	26
İzmir Atatürk Teaching Hospital	83	3	27.67	38
Dışkapı Yıldırım Beyazıt Teaching Hospital	79	4	19.75	34
Kocaeli University School of Medicine	77	3	25.67	35

top 100 list can also enter the list in, and there may be changes in the ranking of some papers already on the list. Also, the citation and publication numbers of the authors in top 100 lists may not thoroughly reflect their overall productivity in those fields.

van Noorden et al. have reported that 43.8% of all scientific publications have collected no citations at all, and 1.84% of all stay in the citation band of 100-999 citations (13). Amongst articles in herniology from Turkey, only two papers have passed the 100 citations threshold, and other 13 papers have collected more than 50 citations. Mean number of citations in WoS is only 30. In 2002, Paladugu et al. have reported that the mean citation number of the 100 citation classics in general surgery journals is 405 (4). There was no article on abdominal wall hernias in that top 100 list. A very recent bibliometric study in general surgery has found a median number of 490 citations within the 5 journals with the highest impact factor (14). On the other hand, Mayir et al. have reported that 7.7% of the most cited articles in general surgery from Turkey was on inguinal hernias (5). Onat has detected 6 papers from general surgery field in a list of 271 articles for Turkey's contribution to medicine, and only one of those was related to the abdominal wall hernias (2). That paper was produced by the Surgical Department of Ankara University School of Medicine (15). Its citation count had been 76 that time and was found to reach 145 in the present search.

The top 100 articles in the herniology field were produced by 43 institutions. Five of the 10 most productive institutions were complied with Nayir et al.'s list for general surgery publications from Turkey (5). Moreover, the most productive city was Ankara in both studies, and non-academic teaching hospitals exhibited as great success as university hospitals did. This difference probably originated from the nature of the hernia surgery, which is suitable for almost all surgical facilities. On the contrary, vast majority of the publications on more complex surgical procedures like transplantation is produced by university hospitals (16). Onat's study on citation counts of Turkish papers from all disciplines revealed a different picture, 90% of the medical publications in that list were produced by university hospitals (2). A

bibliometric study for orthopedic publications originating from Turkey concordantly revealed that only one out of the most productive 10 institutions was non-academic teaching hospital (17); it was Ankara Numune Training and Research Hospital, which is also in the second rank in the present study.

The 100 top-cited papers were published in 38 journals. This figure ranges between 10 and 46 in previous publications on citation analyses in different fields (7-9,18,19). Top 100 papers in general surgery was published in only 10 surgical journals (4). In the present study, 80 articles were published in surgical journals, and these articles collected more citations than those in the journals from other disciplines. As a specific journal in its field, Hernia journal receives a large number of submissions related to abdominal wall hernias. It is clearly the top journal in the present study. Unfortunately, no single article published in a journal from Turkey entered the top 100 list.

Journal impact factor is a reflection of the average number of citations to recent articles published in journals. A positive correlation between the journal impact factor and the citation counts is an expected finding. Accordingly, some studies have shown that journal impact factors are strong predictors for citation counts (7,11,12,19,20). However, no correlation was detected between the journal impact factors and the number of the citations in the present study.

Clinical studies are the most frequent article types in the previous bibliometric analyses for citation counts (10,11,18). Unlike, in a bibliometric study on hepatocellular carcinoma articles revealed that review articles collected higher mean number of citations than that for other types (18). In the present study, clinical studies and review articles received more citations than case reports and laboratory studies; however, the difference was not significant. Retrospective clinical series collected more citation counts than prospective studies, possibly because of their larger number of patients from the archives of tertiary reference hospitals than prospective randomized studies with small number of subjects.

Classification of the articles in the top 100 list regarding the topic of the study revealed interesting results. The number of papers on inguinal hernias were more than three times of those about incisional hernias. This is somewhat expected given the fact that inguinal hernia repairs comprise the majority of operations for abdominal wall hernias (21,22). However, incisional hernia articles had a higher mean number of citations than papers on inguinal hernias. On the other side, the total number in the list and the mean citation counts for papers about umbilical hernias are lower than those for incisional hernias despite the fact that the share of these two types of hernias within surgical repairs are quite similar. One reason for this situation may be the complexity in repair of incisional hernias together with more frequent and more serious complications following them.

CONCLUSION

Citation counts of hernia related articles from Turkey are relatively low. Hernia is the leading journal for Turkish studies. Inguinal hernia is the most frequent topic, whereas papers about incisional hernias receive more citations than others.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (2): 180-191

Türkiye'den yayınlanan karın duvarı fıtıkları ile ilgili bilimsel makaleler içinde en çok atıf alan 100 makale: bibliyometrik çalışma

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, Türkiye'den karın duvarı fıtıkları ile ilgili yayınlanan makaleler içinde en çok atıf alan 100 yazıyı bulmak ve değerlendirmektir.

Gereç ve Yöntem: Mart 2019 tarihinde Web of Science veri tabanında yapılan tarama ile en çok atıf alan 100 makale belirlendi. Bu makaleler yayınlandıkları dergilere, yayın tarihine, yazarlarına, makale türüne, makalenin odaklandığı konuya ve yayını yapan merkeze göre analiz edildi. Tüm makalelerin Google Scholar'daki atıf sayıları da kaydedildi.

Bulgular: Listedeki 100 makalenin ortalama atıf sayısı 30,50 idi. Makaleler 38 ayrı dergide yayımlanmıştı, en çok makale Hernia dergisinde yer almıştır. Dergilerin etki faktörü ile atıf sayısı arasında ilişki saptanmamıştır. Yazıların 2/3'ü klinik çalışmalardır. Makale türünün atıf sayısı üzerine etkisi yoktu. Kasık fıtıkları 58 makale ile en sık incelenen konuydu. Kesi fıtıkları ile ilgili yayınlar diğer konulara göre daha fazla ortalama atıf sayısına sahipti. En yüksek atıf alan makalenin yayınlandığı Ankara Üniversitesi Tıp Fakültesi aynı zamanda listedeki yayınlar dahilinde en yüksek toplam atıf sayısına ve makale başına en yüksek atıf sayısına sahip merkezdi. Ankara Numune Eğitim ve Araştırma Hastanesi ve İstanbul Üniversitesi Tıp Fakültesi listeye en yüksek sayıda makale veren kurumlardı.

Sonuç: Fıtıklarla ilgili Türk makaleleri nispeten düşük atıf sayılarına sahipti. En çok makalenin yayınladığı dergi Hernia idi. Kasık fıtıkları çalışmalarda en çok incelenen konuydu, ancak kesi fıtıkları ile ilgili yazıların ortalama atıf sayısı daha yüksekti.

Anahtar Kelimeler: Fıtık, karın duvarı, bibliometrik, atıf

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ORIGINAL ARTICLE
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Complications and outcomes of 890 living liver donor hepatectomies at a single center: risks of saving loved one's life

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ABSTRACT

Objective: Living liver donor surgery is a major surgical procedure applied to healthy people with mortality and morbidity risks and does not provide any direct therapeutic advantage to the donor. We retrospectively analyzed the postoperative complication of our living liver donors to figure out the risks of donation.

Material and Methods: Between November, 2006 and December, 2018, a total of 939 living liver donor hepatectomies were performed with no mortality to the living-related donors. Eight hundred and ninety donors with a minimum 1-year follow-up were analyzed retrospectively.

Results: Of the 890 donors, 519 (58.3%) were males and 371 (41.7%) were females. Mean age was 35 years (18-64) and mean body mass index was 25.7 kg/m^2 (17.7-40). Right donor hepatectomy was performed to 601 (67.5%), left donor hepatectomy to 28 (3.2%) and left lateral sector hepatectomy to 261 (29.3%) of the donors. Of the 890 donors, 174 (19.5%) donors experienced a total of 204 early and late complications including life- threatening and nearly life- threatening complications in 26 (2.9%) of them. Intraoperative complication occurred in 4 (0.5%) donors. Right donors hepatectomy complication rate (23.3%) was higher than left donor (14.3%) and left lateral sector donor hepatectomy (11.5%).

Conclusion: All donor candidates should be well-informed not only on the details of early and late complications of living liver donation, also possible outcomes of the recipient. In addition to detailed physical evaluation, preoperative psychosocial evaluation is also mandatory. Comprehensive donor evaluation, surgical experience, surgical technique, close postoperative follow-up and establishing a good dialog with the donor allows better outcomes.

Keywords: Living donor hepatectomy, complications, outcomes, living liver donor transplantation, life-threatening complications

INTRODUCTION

Liver transplantation (LT) is currently the only lifesaving and definitive treatment for end-stage liver disease, acute liver failure, some metabolic diseases and some liver tumors. Despite remarkable recipient outcomes, a significant number of people die on the waiting list. One strategy used to counter-balance organ shortage has been the utilization of living donor liver transplantation (LDLT), which is the only option in a region with insufficient deceased donor support. Studies consistently demonstrate that LDLT is equivalent to deceased donor liver transplantation (DDLT) in terms of patient and allograft survival (1). Although LDLT was initially considered in 1969 (2), the first real attempt took place in 1988 (3,4). Over the past two decades, while attempts continued in Western countries, significant progress was achieved in Asia, where religious and cultural beliefs do not allow deceased donation to significantly contribute to the donor pool (5).

Although LDLT is a potentially life-saving operation for the recipient, with similar outcomes to DDLT, living liver donor hepatectomy (LLDH) is a major surgical procedure with morbidity and mortality risks, which is applied to healthy people. In addition, donor surgery does not provide any direct therapeutic advantage to the donor. The donor undertakes these risks to save the life of a loved one. This report retrospectively analyzed postoperative donor complications and outcomes to evaluate the risks of living liver donation at an experienced center in a region with insufficient deceased donor support.

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MATERIAL and METHODS

Between August 2006 and November 2018, 1,126 LTs (766 adult, 340 pediatric) were performed at a single center, 939 from living related donors and 187 from deceased donors. The first LDLT was performed in November 2006. During this period, 939 LLDH patients were discharged with no mortality. Of the 939 living related donor-recipient pairs, 126 (13.4%) were from 20 different foreign countries. The first 890 LLDH cases, performed between November 2006 and December 2017 with a minimum 1-year follow-up, were retrospectively analyzed (Figure 1). Data were collected including donor age, gender, body mass index (BMI), graft type, operation time, length of hospital stay and donor complications. Complications were scored using the modified Clavien classification of surgical complications and adapted donor morbidity classifications (6-8). SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA) was used for the analysis.

Donor Evaluation and Selection

Requirements for donor candidacy included age > 18 years and good health condition with no comorbidities. By the Turkish Health Ministry Organ Donation Ethics Committee policy, potential donors are required to be first-degree relatives (parents, children), second-degree relatives (grandparents, siblings, grandchildren), or third- or fourth-degree relatives (uncles, aunts, nephews, cousins) of the intended recipient. Spouses and other Ethics Committee-approved related patients are also considered as potential donors (Table 1). This standard also applies to donor and recipient candidates from foreign countries, in which case donor evaluation is undertaken only after a formal document has been received from their government proving close consanguinity of the donor and recipient. In addition, all formal documents require approval from their Embassy or Consulate in Turkey. During the evaluation in this study, candidates were informed about all LLDH procedures, risks of surgical complications, and expected recipient outcomes with the family members. In addition, they were informed that they could decline continuation of the evaluation at any time. Most LLDH candidates had a body mass index (BMI) < 30, but in rare emergency cases, donors with BMI >30 were also considered. All candidates underwent extensive preoperative work-up including blood type, extensive biochemistry, coagulation, urine, hepatitis A, B, C and D virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, pregnancy (for females), venereal disease, and factor 2 and factor 5 Leiden mutation tests. Donor candidates > 40 years of age underwent echocardiography and cardiology evaluation, and if a smoker, respiratory function testing and pulmonary examination were performed. All donor evaluations included hepatology and psychiatric examinations. In addition, thoracic and abdominal computed tomography (CT) and electrocardiography were performed in all candidates. CT assessed liver volume, parenchyma and vascular structures. The biliary system was evaluated by magnetic resonance cholangiopancreatography (MRCP). Donors with remnant liver volume > 30% and remnant liver weight:donor weight ratio > 0.5% were considered candidates for donation. Most were approved if the graft weight:recipient weight ratio (GWRBR) was > 1%. If the GWRWR was > 0.8%, donation was only considered in emergencies and was rarely approved. Donor livers with > 10% steatosis were not accepted, but a diet and exercise program was suggested, with re-evaluation and reconsideration possible. In rare cases, liver biopsy was performed to determine the true steatosis stage.

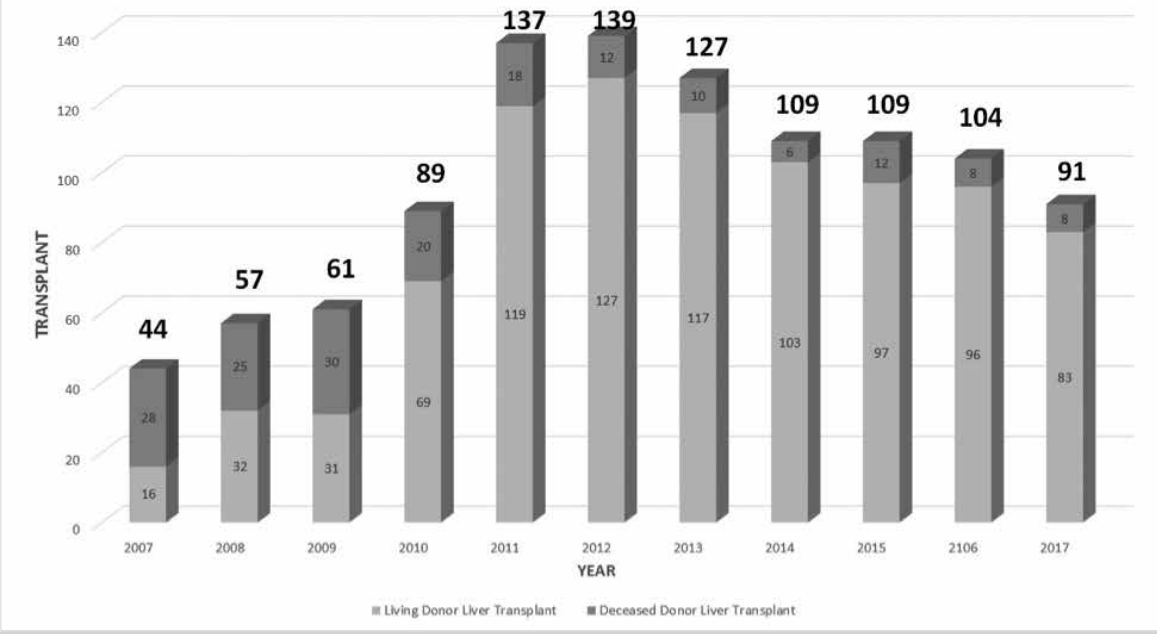

Figure 1. Transplant numbers between 2007 and 2017 in Memorial Sisli Hospital.

Table 1. Donor demographics	
Demographic features	
Mean age (years)	35 (range 18-64)
Sex (n, %)	
Male	519 (58.3%)
Female	371 (41.7%)
Mean BMI (kg/m^2)	25.7 (range 17.7-40)
Relationship with recipient (n, %)	
First grade relatives	526 (59%)
Second grade relatives	143 (16%)
Third & fourth grade relatives	144 (16%)
Ethical committee approved	77 (9%)
Donor hepatectomy type (n, %)	
Right hepatectomy	601 (67.5%)
Left hepatectomy	28 (3.2%)
Left lateral sector hepatectomy	261 (29.3%)
Mean operation time (hours/minutes)	
Right hepatectomy	5 h and 9 m
Left hepatectomy	6 h and 12m
Left lateral sector hepatectomy	4 h and 13 m
Medium hospital stay (days)	7 (range 5-58)

Surgical Procedure and Postoperative Care

All donors were admitted to the hospital one day prior to surgery and underwent examination by the surgical team. Preoperative signed informed consent was obtained in call cases. Two hours prior to surgery, low molecular weight heparin (LMWH) (Clexane 4000 IU/0.4 mL or Clexane 6000IU/0.6 mL sc injection; Sanofi Aventis Pharma, Istanbul, Turkey) was administered to all donors according to body weight for thrombosis prophylaxis and was continued for one week postoperatively. Most donor hepatectomies (96%) were performed by two surgeons (K.A. and Y.Y.); 4% was performed by other team members or clinical fellows. All hepatectomies were performed under the supervision of an experienced transplant and hepatopancreaticobiliary surgeon.

In most cases, a median J-shaped incision was made. In some left lateral sector donors, a small bilateral subcostal or upper median incision was made. Exploration of the liver and abdominal organs was performed in all cases. If exploration findings were normal, the right or left lobe of the liver was mobilized according to graft type. The right or left hepatic vein was isolated according to graft type. All other hepatic veins larger than 5mm which drained directly to the inferior vena cava were protected. The right or left hepatic artery and right or left portal vein were isolated, and cholecystectomy was performed. Following cholecystectomy, cholangiography was performed through the cystic duct stump to evaluate the biliary system anatomy. In most cases, the right bile duct was cut before parenchymal division, and the left bile duct was cut after parenchymal division. In some cases, the right bile duct was cut after parenchymal division. Parenchymal dissections and divisions were performed using Cavitron Ultrasonic Aspirator (CUSA System 200 Macrodissector; Cavitron Surgical System, Stamford, CT, USA) and bipolar electrocautery. The Pringle maneuver was never used during parenchymal division, and central venous pressure was held below 5 cm H2O. A hanging maneuver was used in all cases. The middle hepatic vein was left with the remnant or taken with the graft according to the volumes and branches of the middle hepatic vein. After completing parenchymal division, the graft was removed by transecting the hepatic artery, portal vein and hepatic vein branches of the graft. The hepatic artery stump in the donor was tied with 4/0 silk sutures, and the hepatic vein stump was closed with 4/0 prolene. The portal vein stump was closed with 6/0 prolene and the bile duct stump was closed with 6/0 polydioxanon (PDS) sutures. The biliary system and cut surfaces were always checked with cholangiography and air test after the closure of the bile duct stump. The remnant left liver lobe was always fixed to the diaphragm after right donor hepatectomy. A silastic drainage tube was inserted in all cases, and surgery was completed with closure of the abdomen.

Following extubation in the operating room, all donors were taken to the intensive care unit and monitored closely for one day. Liver function tests were performed every day for one week and prophylactic antibiotics were given for the first two days. The nasogastric tube was removed on postoperative day 1 and oral feeding started on postoperative day 2 for most of

the donors. Urinary catheter was removed on postoperative day 1, and central venous catheter was removed on postoperative day 4. In order to reduce postoperative atelectasis and deep vein thrombosis (DVT), early mobilization with preoperative embolism stockings and spirometer breathing exercises were started. An abdominal ultrasound was performed on donors with unexpected high liver enzymes, high International Normalized Radio (INR), bile leak or abdominal pain. The silastic drainage tube was removed at uncomplicated cases between postoperative day 3 and 6 according to the amount of drainage and findings. Post-discharge, all donors were followed in clinic with liver function tests and physical examination at 2 weeks and 1, 2, 3, 6, 9 and 12 months after surgery. After one year, donors were instructed to contact clinic if they had any problems or complications related to surgery.

Donors always underwent Doppler ultrasound for ALT > 800 (U/L) or INR > 2.5. We always perform MRCP in donors whose alkaline phosphatase (ALP), GGT and total bilirubin do not start to normalize within 10 days after surgery. We support the donor liver after the procedure with fresh frozen plasma if INR is > 2 and with human albumin if albumin is < 3 g/dL. During the first 4 days postoperatively, we support the liver with high-glucose solutions. We give prophylactic antibiotics to all donors during the first postoperative 48 hours. If there are any infection findings or any postoperative complications that might increase the risk of infection, we continue with antibiotic treatment.

RESULTS

Of the 890 donors, 519 (58.3%) were males and 371 (41.7%) females. Mean age was 35 years (range 18-64), and 27 (3%) donors were older than 55, including 9 donors (1%) at > 60 years of age. Mean donor BMI was 25.7 (range 17.7-40), 95 donors had BMI > 30, and 12 donors had > 35. Of the 890 donors, 63 (7%) were spouses, 463 (52%) were first-degree relatives (parents and children), 143 (16%) were second-degree relatives (grandparents, siblings and grandchildren), 144 (16%) were third- or fourth-degree relatives (uncles, aunts, nephews and cousins), and 77 (9%) were other ethics-committee approved related donors (Table 1). Of the 890 donors, 601 (67.5%) underwent right lobe donor hepatectomy (RLH), 261 (29.3%) underwent left lateral sector hepatectomy (LLH) and 28 (3.2%) underwent left lobe donor hepatectomy (LDH). Mean operation time for RLH was 5 hours and 9 minutes, for LDH was 6 hours and 12 minutes and for LLH was 4 hours and 13 minutes. Median hospital stay was 7 days (range 5-58 days) (Table 1).

No donor surgery was aborted intraoperatively due to bile duct anatomy or vascular structures. One donor surgery was aborted intraoperatively due to liver findings. In that case, all preoperative testings was normal with no suspicion of liver disease, but during exploration the liver was found to be abnormal. Liver biopsy was performed with the finding of Grade 1-2 fibrosis, and recipient surgery was canceled prior to its start. This donor was referred to the Hepatology Department for follow-up. Another donor surgery was aborted due to cardiac arrest and death of the recipient on the operating table. At that point, half of the donor parenchymal division was finished and the right bile duct was already cut. The donor surgery did not go forward and Roux-en-Y right hepaticojejunostomy was performed without donor hepatectomy. No complication occurred in this donor candidate during the follow-up period.

In two donors, following right donor hepatectomy, Roux-en-Y left hepaticojejunostomy was performed during donor surgery, which was planned preoperatively in one case due to the diagnosis of Type 1a choledochal cysts during the evaluation. In that patient, following right donor hepatectomy, common bile duct resection and Roux-en-Y left hepaticojejunostomy were performed. In the second donor, a bile duct stricture was noted on perioperative control cholangiography after closing the bile duct stump, and Roux-en-Y left hepaticojejunostomy was performed. No complication occurred in this donor during the follow-up period. In one donor, a bile leak was noted after closure of the bile duct stump. Suturing the leak would be unsafe, so a T-tube was placed in the common bile duct in that case. No additional complications occurred after the T-tube was removed. In one donor, the vascular staff loosened the right hepatic vein during the procedure and emergency thoracotomy was required to stop the bleeding; subsequently, a serious pulmonary infection developed, necessitating a > 1-month ICU stay. In one case, early portal vein thrombosis (PVT) occurred due to the closure technique, which was treated surgically within 6 hours without a postoperative problem. Our intraoperative complication rate was 0.5% (2 biliary, 1 early PVT, 1 hepatic vein bleeding).

Of the 890 donors, 174 (19.5%) experienced postoperative complications, including life threatening and nearly life-threatening complications in 26 (2.9%). Surgical treatment was required in 36 donors (4%) due to early or late complications. A total of 204 early and late complications developed in these 174 patients according to the Clavien adapted donor morbidity classification (7,8) (Table 2). Twenty-one donors developed two complications, and four donors developed three or more complications. There were no donor deaths due to LLDH in this series. One donor died years later, following a motor vehicle collision and one donor underwent liver transplantation from a deceased donor due to a new diagnosis of benign recurrent intrahepatic cholestasis (BRIC) 14 months after LLDH. Of note, the recipient of this donor, who had the same diagnosis prior to transplantation, underwent re-transplantation from a deceased donor one year later. One donor was diagnosed with leukemia years after LLDH and underwent treatment. In three donors, psychiatric medical treatments were required for a short time period due to anxiety after LLDH. All of these donors had experienced Grade 3 or 4 complications.

Table 2. Complications according to adapted Clavien classification (204 complications in 174 donors)

Grade	Number of the patients and %	Complications and number of the patients
Grade 1	112 (12.6%)	Wound problems (bedside and medical treatment) : 49 Vomiting (remarkable-medical treatment) : 23 Ascites & Pleural effusion (medical treatment) : 17 Bile leak (spontaneously resolved) : 8 Pain (remarkable-medical treatment) : 8 Sub-ileus (Follow-up) : 7
Grade 2	15 (1.7%)	Pulmonary embolism (minor-medical treatment) : 2 Pneumonia & atelectasis (medical treatment) : 4 Diarrhea (medical treatment) : 2 Urinary infection (medical treatment) : 4 Anxiety (medical treatment) : 3 Vertigo (medical treatment) : 2 Cardiac arrhythmia (medical treatment) : 1
Grade 3 3 a 3 b	70 (7.8%) 35 (3.9%) 35 (3.9%)	Pleural effusion & abdominal collection (percutaneous drainage) : 20 (3a) Gastric ulcer bleeding (endoscopic treatment) : 1 (3a) Bile leak (percutaneous drainage only) : 6 (3a) (PTC-D & ERCP-S) : 4 (3a) * (surgical treatment - hepaticojejunostomy) : 1 (3b) * (surgical treatment - surgical drainage) : 4 (3b) Biliary stricture (PTC-D & ERCP-S) : 4 (3a) * (surgical treatment - hepaticojejunostomy) : 2 (3b) * Bleeding (surgical treatment and transfusion) : 11 (3b) Incisional hernia (surgical treatment) : 11 (3b) Wound problems (surgical treatment) : 3 (3b) * Intestinal obstruction (surgical treatment) : 2 (3b) * Intestinal perforation (surgical treatment) : 1 (3b)
Grade 4 4a 4b	7 (0.8%) -	* Pulmonary embolism (medical treatment -ICU) : 2 (4a) * Portal vein thrombosis (late – medical treatment) : 1 (4a) (early – surgical treatment) : 1 (4a) * Bleeding (thoracotomy and pneumonia) : 1 (4a) * Temporary Liver failure (plasmapheresis) : 1 (4a) * Liver transplantation (BRIC) : 1 (4a)
Grade 5	-	-

* life-threatening & nearly life- threatening complications (in 26 donors – 2.9 %).
PTC-D: Percutaneous transhepatic cholangiogram and biliary drainage.
ERCP-S: Endoscopic Retrograde Cholangio-Pancreatography and stent replacement.
BRIC: Benign recurrent intrahepatic cholestasis.

Twelve (1.3%) of our donors experienced perioperative bleeding. Early postoperative bleeding was noted by drain output in the other 11 of these donors. Twenty-one (2.4%) of our donors experienced biliary complications, of which 8 were minimal bile leaks which resolved spontaneously in 3 to 20 days by following drain output only. In the other 13 (1.5%) donors, 21 invasive procedures were performed to resolve the problems. In 6 donors, biliary stricture occurred, most following a bile leak (n= 5); two of these required treatment by hepaticojejunostomy.

One of our donors, aged 50, experienced temporary liver failure and underwent plasmapheresis during the first week after the procedure. This patient's total bilirubin level reached 19.0 mg/dL and INR 1.7 during the first week after the procedure. This

Table 3. Donor complication rates according to subgroups

Donors subgroups	n (complication)/n (subgroup)	Complication %
All donors	174/890	19.5 %
Age ≥ 60	2/9	**22.2 %**
Age ≥ 55 and < 60	3/16	18.8 %
BMI ≥ 35 kg/m^2	2/12	16.5 %
BMI ≥ 30 kg/m^2 and < 35 kg/m^2	19 / 95	20.0 %
Right donor hepatectomy	140/601	**23.3 %**
Left donor hepatectomy	4/28	14.3 %
Left lateral sector donor hepatectomy	30/261	11.5 %

donor also experienced complications including minimal bile leak, wound infection and incisional hernia. In addition to this case, in other 17 donors, total bilirubin reached a level between 10 and 15 mg/dL and INR reached 1.5 to 2.0. In six of these patients, biliary complication was diagnosed and treated. In the other 11 donors, total bilirubin levels and all liver functions normalized within 7 to 20 days after the procedure, with the same complication rate (18.2%).

In 43 donors, INR levels reached a level between 2 and 3; in 5 due to warfarin treatment (4 PE and 1 early PVT). In 38 donors, INR reached this level during the first one to four days postoperatively and normalized after support treatment. In 16 donors, alanine aminotransferase (ALT) reached a level over 1000 U/L, and in 44 donors over 800 U/L. Seven of the donors with ALT > 1000 U/L were left lateral sector donors who had a normal Doppler ultrasound. In our 45 donors, gamma-glutamyl transferase (GGT) reached a level over 1000 U/L and in 112 donors between 500 and 1000 U/L. Only 11 of these donors were diagnosed with a biliary complication, and all normalized within 45 days postoperatively.

Donor complication rate was 22.2% in donors > 60 years of age and 18.8% in donors 55 to 60 years of age. Donor complication rate was 16.7% in (1 donor complication was a wound infection and a second one was a PE requiring an ICU admission) donors with BMI > 35 kg/m^2 (n= 12) and 20% in donors with BMI between 30 and 35 (n= 95). In one case, a minor PE occurred. In our RLH donors, the complication rate was 23.3%, which was higher than that for LDH (14.3%) and LLH (11.5%) (Table 3).

DISCUSSION

LDLT is the only alternative to DDLT in regions that do not have enough deceased donors (DD) to meet the needs of their waiting lists. LDLT has also become an alternative life-saving method that reduces patient waiting time and mortality on the waiting list in regions that do have good DD support. Although recipient outcomes after LDLT are similar to those after DDLT, donor safety is still the most important discussion, and LLDH carries a significant risk of morbidity and mortality for the otherwise healthy donor.

The incidence of morbidity and mortality after LLDH is not well known because reporting is not standardized and relies on single center, or in some countries, registry reports. Mortality rate has been reported to be 0.1% to 0.3% (9-11). Results of a worldwide survey conducted among 148 programs performing LDLT, with 71 (48%) programs in 21 countries completing the survey, including 11,553 LLDH, has been published by Cheah YL, et al. (12). According to this survey, donor mortality rate was 0.2% (23/11,553) with the majority of deaths occurring within 60 days of surgery, and all but four deaths were related to donation surgery. A data review of more than 300 articles, including nearly 6000 LLDH, has reported an overall mortality rate of 0.2% (10,13). Many single-center experiences with the same complication rate have been reported from Turkey and other countries (8,9,14-19).We reported briefly our complications in the first 419 LLDH cases in a previous manuscript (20). Including these reported cases, in our first 939 living liver donors, no death occurred related to surgery or complications in our program. Our donor candidates were given an estimated mortality rate of 0.1% and 0.2%.

The complication rate after LLDH varies widely in the literature, between 9 and 40% (8,9,12,14-19,21,22). Among our donors, 19.5% experienced complications, comparable with the literature. We reported multiple types of postoperative complications, including several low morbidity complications such as diarrhea, vertigo, cardiac arrhythmia, remarkable pain and vomiting. All complications are important when surgery is being performed in a healthy individual and does not provide any direct therapeutic advantage. The main focus of living donation is to protect donor safety and minimize the risk of potential complications. Although there are no ideal criteria for safe living liver donation, it is agreed that donors must be between 20 and 50 years of age, have a BMI < 30 kg/m^2, have no evidence of liver steatosis or chronic disease, and have a remnant liver volume of > 30%. In addition, remnant liver weight to donor body weight ratio must be over 0.5% (15). However, most transplant centers accept donors who do not meet all these criteria depending on the recipient's health situation and deceased donor possibility (23,24). As with our center, many centers utilize living

liver grafts from donors older than 50 years of age. We know that liver regeneration capacity decreases in older patients, and related to that, the effect of donor age on donor and recipient outcomes after LDLT remains unclear (15,25,26). In the literature with successful outcomes for both donor and recipient, an LDLT has been reported from 76-year-old female living liver donor to her 75-year-old husband (24). Nine of our donors were between the ages 60 and 65, and 16 were between the ages of 55 and 59. According to our experience, the complication rate was slightly higher (22.2%) in donors between the ages of 60 and 65, which is comparable to the literature (Table 3). With different age cut-offs, different results have been reported in the literature, and it has been concluded that age factor should never be considered as an isolated exclusion criteria for LLDH (23,24,27). Also, twelve of our donors had a BMI > 35 kg/m2, and complication rate was 16.7% in these donors (Table 3). Although overall complication rate was not higher in our high BMI (> 30 kg/m^2) donors, the rate of PE, which is a major life-threatening complication, was higher. PE is one of the most important causes of death in the literature. It is important to eliminate predisposing factors. Early mobilization, LMWH and preoperative embolism stockings were important to decrease the risk of PE (8,12,14,28). Donors older than 60 years of age and donors with a BMI of > 30 kg/m^2 should be evaluated if there is not a better candidate. Recipient physical condition is also an important part of the discussion.

Intra-abdominal bleeding is an important life-threatening complication. Operative bleeding should be carefully managed, which is dependent on the experience and skills of the surgeon. Early recognition of postoperative bleeding and early laparotomy if required are very important, as bleeding may be a serious life-threatening complication (16). Twelve (1.3%) of our donors experienced perioperative bleeding. Twenty-one (2.4%) of our donors experienced biliary complications. The literature reports a biliary complication rate of 4% to 9% during LLDH (14,29,30). Gorgan A et al. from the Toronto group have reported a less than 2% bile leak rate in their donors and explained this slightly lower rate than that in previous series by their approach to not drain the abdominal cavity routinely and some subclinical leaks resolving uneventfully (9).

We did not experience any donor deaths, but we performed DDLT to one of our donors. Even though donor LT was not performed due to a complication of LLDH, after this unfortunate experience, we believe that performing genetic testing in donor candidates who are close relatives of a recipient with hereditary diseases is mandatory during the evaluation. LT after LLDH, due to these complications, has previously been reported in the literature and liver failure after LLDH is the main reason for LT with portal vein thrombosis (12,16). Portal vein variations can make both donor and recipient surgery technically challenging and can increase donor risk. The portal vein closure technique and the fixation of the left lobe to the abdominal wall in right hepatectomy donors are important to prevent PVT. We always fix the left lobe by suturing the falciform ligament to the anterior abdominal wall after right donor hepatectomy to prevent the rotation of the left lobe, a potential cause of PVT. In addition, the rate of biliary system variations is higher in donors with portal vein variations, which also increases risk of biliary complication for both donor and recipient (15).

Since the donor is healthy, the safety of the donor is of paramount importance. In addition, minimally invasive approaches are important for functional and cosmetic demands of the donors. Minimizing the incision is an alternative, which has been reported in the literature with same outcomes (9,31). Beginning with donor left lateral sector hepatectomy in 2002 by Cherqui et al. (32), laparoscopic and other minimally invasive approaches are being used today. This seems feasible and safe when performed by a surgeon who is highly experienced in both laparoscopic and hepatobiliary surgery and with an experienced transplant team (33-35).

The use of living donors with previous abdominal surgery may be a surgical issue which challenges the safety of these altruistic donors. There are few studies which have evaluated the impact of previous abdominal surgery on LLDH with the conclusion that previous abdominal surgery cannot be an absolute contraindication to LLDH in the hands of expert surgeons armed with advanced surgical techniques and maximal care (36). We performed LLDH in several donors who had undergone previous cholecystectomy, appendectomy and caesarean section. No serious complication occurred in these donors due to previous surgery.

Though donors were informed about postoperative pain, one-third of them reported that post-procedure pain was greater than anticipated in the immediate postoperative period (37). Our clinical experience also matches up with this. Eight of our donors reported pain as their main problem, without any other complications during the first days after the procedure. Studies have shown that most donors return to their job after a mean duration of 3 to 4 months, and most donors report that they would donate again if necessary (37-39). We focused on the psychosocial effects of the donation with the limited number of donors in our previous reports (40-42), and a clinical study is currently under way at our center which focuses on these questions.

Although LDLT has helped to resolve the problems of many patients, donors themselves gain no medical benefits, but incur the risks of surgical complications, sometimes with negative psychosocial consequences. Reports have shown that 40% of the living liver donors report psychological distress after surgery (12,37,43-45). Our experience shows that donor complications and negative recipient outcomes are major causes of psychological distress. In three of our donors, serious anxiety occurred during the first days after the operation and was treated with psychiatrist support. During long-term follow up, we became

aware of at least two of our donors treated for serious depression. Cheah YL et al.'s worldwide survey has reported that five donor deaths (21.7%) were due to suicide between 2 months and 5 years after donation (12). In addition, the literature suggests long-term monitoring of the mental health of living donors to minimize adverse psychosocial outcomes associated with living liver donation (12,43). Preoperative psychosocial evaluation is very important to avoid negative postoperative psychosocial consequences.

For young female donors, pregnancy is one of the concerns in the years following donation. None of our donors who became pregnant after donation reported a bad experience or a complication due to the living liver donation procedure. We suggest female donors that they wait one year after the procedure to become pregnant.

CONCLUSION

LDLT has become a well-tolerated and safe option when DDLT is not an option. All donors want to save a loved one's life, but the risk of donor morbidity and mortality is a major concern. Surgeon and center experience and higher annual case volume are associated with lower rates of postoperative complications, but LLDH is not a complication-free procedure. All donor candidates should be well informed not only about the details of the early and late risks of living liver donation, but also about possible outcomes for the recipient. In addition to detailed physical evaluation, preoperative psychosocial evaluation is also mandatory. Comprehensive donor evaluation, surgical experience, surgical technique, and close postoperative follow-up and the establishment of a good dialogue with the donor should allow for better outcomes.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013). Authors declared that the content of this manuscript complies with all the rules of the "Call for an end to unethical transplant practices" by The Transplantation Society (Transplantation.2019 Apr;103(4):647.) and The Declaration of Istanbul on Organ Trafficking and Transplant Tourism (Transplantation. 2008 Oct ;86(8):1013-8.).

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ORİJİNAL ÇALIŞMA-ÖZET
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Tek merkezde gerçekleştirilmiş 890 canlı karaciğer donör hepatektomisinin komplikasyonları ve sonuçları: sevdiğin birinin hayatını kurtarmanın riskleri

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ÖZET

Giriş ve Amaç: Canlı karaciğer verici ameliyatı tamamen sağlıklı bireylere uygulanan, vericinin doğrudan terapötik bir kazanç elde etmediği, ölüm ve ciddi komplikasyon riskleri taşıyan büyük bir cerrahi işlemdir. Bu çalışmamızda; canlı karaciğer vericisi olmanın riskini ortaya koymak amacıyla retrospektif olarak canlı karaciğer verici ameliyatı geçirmiş vericilerimizin ameliyat sonrası komplikasyonlarını ve sonuçlarını inceledik.

Gereç ve Yöntem: Kasım 2006-Aralık 2018 tarihleri arasında merkezimizde alıcısı ile yakınlık ilişkisi bulunan toplam 939 karaciğer vericisine, canlı karaciğer verici hepatektomisi mortalitesiz olarak gerçekleştirildi. Bu olgulardan minimum bir yıl takipli 890'ı retrospektif olarak incelendi.

Bulgular: İncelen 890 vericiden, 519 (%58,3)'u erkek, 371 (%41,7)'i kadındı. Ortalama yaş 35 (18-64) ve ortalama beden kütle indeksi 25,7 kg/m2 (17.7-40) idi. Canlı sağ verici hepatektomisi 601 (%67,5), sol verici hepatektomisi 28 (%3,2) ve verici sol lateral sektör hepatektomisi 261 (%29,3) vericide gerçekleştirilmiştir. Vericilerden 174 (%19,5)'ünde toplam 204 komplikasyon görülmüştür. Bunların 26 (%2,9)'sında hayatı tehdit edici komplikasyonlar gelişmiştir. Cerrahi işlem sırasında 4 (%0,5) vericide komplikasyon gelişmiştir. Canlı sağ verici hepatektomisinde (%23,3) komplikasyon oranları, sol (14,3%) ve sol lateral sektör hepatektomisine (%11,5) göre daha fazla gözlenmiştir.

Sonuç: Tüm verici adayları sadece verici ameliyatının detayları, erken ve geç komplikasyonları ile ilgili olarak değil ayrıca alıcının olası sonuçları hakkında da ayrıntılı olarak bilgilendirilmelidir. Ayrıntılı klinik muayene, tetkik ve değerlendirmelere ek olarak psiko-sosyal değerlendirme de kaçınılmazdır. Kapsamlı verici değerlendirilmesi, cerrahi deneyim ve teknik, yakın cerrahi sonrası takip, verici ve yakınları ile kurulacak iyi diyalog daha iyi sonuçları elde etmemizi sağlayacaktır.

Anahtar Kelimeler: Canlı verici hepatektomisi, komplikasyon, sonuç, canlı vericili karaciğer nakli, hayat tehdit edici komplikasyon

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A novel coenzyme-Q approach for the prevention of postsurgical adhesion

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ABSTRACT

Objective: Postoperative intraperitoneal adhesions are an unsolved and important problem in abdominal surgery. In the present study, the probable preventive role of coenzyme-Q in the development of peritoneal adhesions was investigated.

Material and Methods: Sixteen Wistar Hannover male rats weighing 300-350 g were randomly separated into two groups of 8 rats each. The cecum was abraded with a sterile gauze until sub-serosal hemorrhage developed. A patch of peritoneum located opposite to the cecal abrasion was completely dissected. No treatment was given to Group 1. Group 2 received 30 mg/kg coenzyme-Q, which was injected 2 mL intraperitoneally. All the rats were sacrificed on the postoperative 21st day, and after adhesions were scored macroscopically, tissue specimens of the peritoneum and bowel were subjected to histopathological investigation. Tissue and blood specimens were also taken for biochemical analysis to investigate antioxidant efficiency.

Results: Adhesion scores were significantly different between the control group and the coenzyme-Q group (p= 0.001). According to the tissue levels of GSH-Px, MDA, and SOD levels, there was no significant difference between the study groups (p= 0.074, p= 0.208, p= 0.526). According to the plasma GSH-Px and SOD levels, there was significant difference between the groups (p= 0.002, p= 0.001), but the difference was not significant at MDA levels (p= 0.793). The differences between the pathological scores of the control and coenzyme-Q (p= 0.028 for fibrosis; p= 0.025 for inflammation) groups were statistically significant.

Conclusion: This study confirms that coenzyme-Q is the potential application in the prevention of early postoperative adhesions.

Keywords: Coenzyme Q, adhesion, surgery

INTRODUCTION

Peritoneal adhesions are bands of fibrous tissue connecting the abdominal organs to the abdominal wall or each other. Adhesions emerge quickly after the damage to the peritoneum due to surgery, such as trauma, irradiation, or infection (1). Abdominal adhesions are one of the main reasons for postsurgical morbidity and mortality and besides, the incidence rises up to 97% after gynecological and general surgical abdominal operations in the literature (2). The importance of postoperative adhesion formation has become a significant burden socioeconomically (3). Different substances and techniques are used to solve the problem, but unfortunately, an effective solution has not yet been accomplished (4).

Coenzyme-Q-10 is a fat-soluble, vitamin-like compound naturally found in most tissues of the human body that is also a fundamental ingredient for life and health of every living cell, and furthermore, this endogenous cellular antioxidant is a safe and effective therapeutic antioxidant (5,6).

Based on the antioxidant property of coenzyme-Q-10, we aimed to evaluate its beneficial effects to determine the anti-inflammatory process among the experimental postoperative intraabdominal adhesions. We hypothesized that coenzyme-Q-10 is helpful to improve the unmet needs of the consequences of oxidative stress. We considered that we can put a value to the process of intraabdominal adhesion formation.

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MATERIAL and METHODS

Consent was received from the Bagcilar Training and Research Hospital Experimental Animals Production and Research Laboratory Ethical Committee (HADYEK/2013-02/28.01.2013). Sixteen Wistar Hannover male rats (average weight: 300-350 g, age: 6-7 months) were housed individually in wire cages under constant temperature (21 ± 2°C) with a 12-hour light-dark cycle. The animals were allowed free access to water and standard rat chow. Twelve hours before anesthesia, animals were deprived of food but had free access to water until 2 hours before anesthesia. No enteral or parenteral antibiotics were administered during the study.

All rats were sacrificed with high-dose prolonged diethyl ether inhalation (minimum 10 min.) on postoperative day 21.

Study Groups and Surgical Procedure

The rats were randomly divided into two groups of eight animals each. All animals were anesthetized by intramuscular injection of 30 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis, Istanbul) and 5 mg/kg xylazine (Rompun, Bayer, Istanbul). The abdomen was shaved and prepared with povidone-iodine. Under sterile conditions, a midline laparotomy was performed. The cecum was abraded with sterile gauze until sub-serosal hemorrhage developed. A 1 x 1 cm patch of the peritoneum located opposite to the cecal abrasion was completely dissected. In Group 1 (control group), adhesion induction was performed and no treatment was given. In Group 2 (coenzyme-Q-10 group), after adhesion induction, 30 mg/kg coenzyme-Q-10 was injected 2 mL intraperitoneally. Animals were allowed access to food and water after the operation. All operations were performed by the same surgeon. Rats were sacrificed on the postoperative 21st day.

Adhesions were classified by a surgeon who was unaware of the groups according to a diamond adhesion scoring system based on the evaluation of the appearance, extent, and strength of the adhesions (Table 1) (7).

Evaluation of Oxidative Stress

Postmortem liver samples were taken and kept on an ice bath until homogenization. The tissues were homogenized in serum physiologic solution (20 wt/vol), then centrifuged at 4000 g for 15 minutes (min), and upper clear supernatants were used in the assays. All the procedures were performed at 4°C throughout the experiments. Protein level of the clear supernatants was studied by the biuret method. Oxidative stress makers were measured as following; Malondialdehyde (MDA) levels (nmol/g), glutathione-peroxidase (GSH-Px) (U/g) and superoxide dismutase (SOD) (U/g) levels by micro ELISA method. All Elisa kits were purchased from ElAab Science Co. Ltd. All plates were read on 450 nm wavelength in DAR800 ELISA reader (8-10).

Histopathological Evaluation

Histopathological analyses were carried out in the Pathology Department of Bağcılar Training and Research Hospital. Histopathological examination was performed by using light microscopic (Olympus BX51) analyses. The samples obtained from the abraded cecal tissue and the adjacent peritoneal tissue were fixed in 10% neutral buffered formalin solution for two days. Tissues were washed in running water and were dehydrated with increasing concentrations of ethanol. After dehydration, specimens were placed into xylene to obtain transparency and embedded in paraffin. Embedded tissues were cut into 5 µm-thick sections and were stained with hematoxylin and eosin and trichrome. Histopathologic examinations were performed by a pathologist blinded to the study groups. The samples stained with hematoxylin and eosin were examined for inflammation, and the presence of fibrosis was evaluated in the hematoxylin/eosin- and trichrome-stained samples using a semi-quantitative scoring system (Table 2, 3) (11,12).

Table 1. Adhesion scoring system

Score	Extent	Appearance	Strength
0	No	No	No
1	< 25%	Filmy, avascular	Separated easily
2	25-50%	Dense, avascular	Separated by traction
3	50-75%	Dense, capillary vascularization	Sharp dissection needed for separation
4	> 75%	Dense, vascular	Sharp dissection needed for separation

Table 2. Scoring system for inflammation

0: No inflammation
1: Giant cells, lymphocytes, and plasma cells
2: Giant cells, plasma cells, eosinophils, and neutrophils
3: Inflammatory cell infiltration and micro-abscess formation

Table 3. Scoring system for fibrosis

0: No fibrosis
1: Mild
2: Moderate
3: Severe

Statistical Analyses

Data analysis was performed using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program. The differences among the groups were evaluated by Mann-Whitney-U and Chi-square tests, as appropriate. Statistical significance was defined as $p< 0.05$.

RESULTS

Adhesion Scores

Adhesion scores of the groups and statistical evaluation are shown in Table 4. There was a significant difference between the control group and the coenzyme-Q group (p= 0.001).

Oxidative Stress

The tissue levels of GSH-Px, malondialdehyde (MDA), and superoxide dismutase (SOD) levels are shown in Table 5. According to the GSH-Px, MDA, and SOD levels, there were no significant differences between the study groups (p= 0.074, p= 0.208, p= 0.526).

Mean plasma GSH-Px, MDA, and superoxide dismutase (SOD) levels of the groups are shown in Table 6. According to the GSH-Px and SOD levels, there was a significant difference between the groups (p= 0.002, p= 0.001), but the difference was not significant at the MDA levels (p= 0.793).

Histopathological Results

Histological images of the pathological scores are shown in figures A and B. The pathological scores for fibrosis and inflammation are summarized in Tables 7 and 8, and mean pathological scores of the groups are given in Table 9. The differences between the control and coenzyme-Q (p= 0.028 for fibrosis; p= 0.025 for inflammation) groups were statistically significant.

DISCUSSION

Abdominal adhesions are bands of fibrous tissue that can form between abdominal tissues and organs. Abdominal adhesions cause tissues and organs in the abdominal cavity to stick together (12,13). During the normal peritoneal healing period, the balance between fibrin deposition and degradation are crucial for adhesion formation, and the main reason of an intraperitoneal adhesion is mostly considered to be the result of a surgical trauma to the mesothelium and peritoneum which initiates an inflammatory response, followed by release of fibrin-rich exudates and the formation of fibrinous adhesion (13).

Regarding the mechanism of adhesion formation, fibrinolysis and extracellular matrix remodeling, including cell proliferation, migration, differentiation, angiogenesis, and apoptosis, are critical for the regulation of the adhesive process as controlling inflammation at initial stages (7,13,14).

Current up to date studies have reported three main methods for preventing the formation of postoperative adhesions, including reduction of peritoneal trauma by using minimally invasive surgical procedures, such as laparoscopic and robotic surgery; prevention of fibrin formation with pharmacological agents, such as tissue plasminogen activators; and reducing contact between organs and intra-abdominal structures by using barrier methods; however, no single approach or management has been totally satisfactory in reducing the risk of adhesion formation (15,16).

Typically, the expression of adhesion density starts with thin line filmy adhesion which is usually taken down easily by blunt dissection, progressing structure where sharp dissection or energy devices are required and finally firmly adherent, where no surgical anatomical plane is clear (17).

Table 4. Mean adhesion scores of the groups

Groups	Mean adhesion scores	p
Control	3.63 ± 0.52	**0.001**
Coenzyme-Q	1.38 ± 0.92	

Table 5. Tissue antioxidant levels of the groups

	Control	Coenzyme-Q	p
GSH-Px	4208.05 ± 1248.11	3081.86 ± 917.3	0.074
SOD	0.17 ± 0.03	0.16 ± 0.02	0.526
MDA	1.96 ± 2.17	2.55 ± 0.93	0.208

Table 6. Plasma antioxidant levels of the groups

	Control	Coenzyme-Q	p
GSH-Px	0.94 ± 0.15	0.53 ± 0.2	**0.002**
SOD	170.13 ± 20.58	100.37 ± 21.73	**0.001**
MDA	3.6 ± 0.55	3.75 ± 1.19	0.793

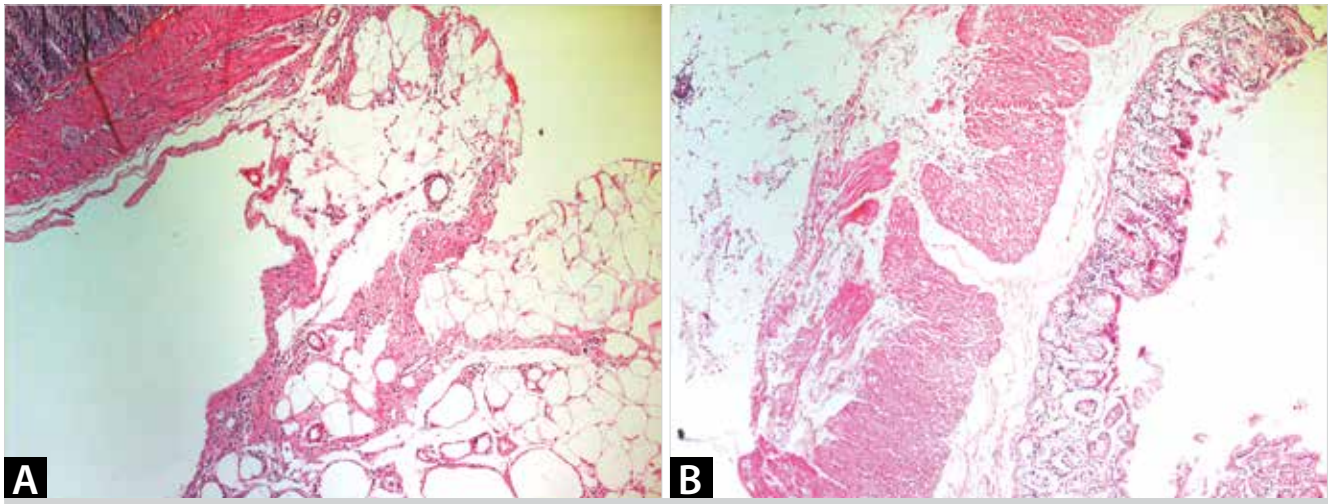

Figure 1. Histopathologic and histochemical findings. (A. HE; x100); this picture shows prominent inflammation (score 2). Upper left: Colonic mucosa. (B. HE; x100); decreased inflammation and fibrosis seen in the coenzyme-Q group.

Table 7. Pathological scores for fibrosis

	Score-0	Score-1	Score-2	Score-3
Control (n= 8)	0	2	5	1
Coenzyme-Q (n= 8)	3	4	1	0

Table 8. Pathological scores for inflammation

	Score-0	Score-1	Score-2	Score-3
Control (n= 8)	0	1	6	1
Coenzyme-Q (n= 8)	3	4	1	0

Table 9. Mean pathological scores of the groups

	Control	Coenzyme-Q	p
Fibrosis	1.9 ± 0.6	0.8 ± 0.7	**0.028**
Inflammation	2 ± 0.5	0.8 ± 0.7	**0.025**

There are reports regarding adhesion incidence following surgical operations as high as 95% (18); however, advances in surgical technology and techniques, such as minimal invasive ones as robotics, can help to minimize the risk of adhesion formation. Moreover, patients undergoing surgery for peritoneal adhesions have increased risk for morbidities due to repeat operations including, anastomotic leakage, enterocutaneous fistulas, small bowel obstructions, and infertility (19,20).

On the other hand, due to re-operations, morbidities and complexity of these operations, cost effectivity is one of the important issues for the management for adhesions. Arung et al. have noted the annual estimated economic impact of peritoneal adhesions about $1.3 billion (21) in the USA, and in another study, Ray et al. have reported that the approximate costs associated with surgical procedures regarding adhesion management exceeded $2 billion without the loss of productivity (22).

Over recent decades, various efforts have been taken against the pathogenesis of adhesion formation. As far we know, the key step of preventing adhesions is the reconstruction of the neo-mesothelial cell layer which requires approximately 5-8 days for parietal peritoneum and visceral mesothelium. During these stages, avoiding fibrinous adhesion formation, preventing the invasion of fibroblasts, and promoting remesothelialization play critical roles in adhesion prophylaxis. When we analyzed the literature, some studies recommend using physical barrier systems to separate injured tissue surfaces during the first few postoperative days (23,24). Barrier systems, including solutions, solid sheets, and in-situ cross-linkable hydrogels are all designed

to reduce the contact between adjacent organs. However, there are cons and pros for every technique as hydrogels applied to the prevention of adhesion have good results, but relatively long gelation time or requirement of UV illumination may be impractical (25). Furthermore, another anti-adhesion method, Seprafilm, is difficult to place in the peritoneal cavity, and after becoming wet, it is difficult to move to the correct position. On the other hand, in recent years, many proteolytic enzymes have been used as anti-adhesive agents including, trypsin, papain, hyaluronidase, streptokinase, and streptodornase (26). The use of fibrinolytic agents that prevent fibrin accumulation has displayed anti-adhesive features, but on the contrary, they have triggered hemostasis problems and degeneration of wound healing (27). In addition to these anti-adhesion techniques, Cakir et al. have reported the use of an enzyme preparation of Clostridium histolyticum that contains collagenases, which are the only proteolytic enzymes that can break up active collagens (28). As mentioned in their study, collagenase removes necrotic tissues, which stick to the wound surface by collagen fibers and prevent wound healing through an enzymatic method. The result of their study was the same as the literature, showing less adhesion and better healing of the peritoneal defect.

Up to date, we know that an ideal method should not only be anti-adhesive, resorbable, and easily applicable with minimally invasive techniques as laparoscopy, but should also adhere to traumatized surfaces without suture or staples, or even oozing surfaces. Compared to other methods, Takagi et al. have developed a powdered anti-adhesion material to resolve these issues (29). In this study, they have noted two main advantages of powder compared with the sheet and liquid materials. First, a powder can be administered in both open and laparoscopic surgery settings, and second, only a minimal dose is necessary because it is easy to administer the powder locally at the desired site to prevent adhesion formation.

Regarding all of these anti-adhesion methods, we used a different technique to manage the collagen synthesis and fibroblast stage of adhesion formation. In wound healing process, the production of reactive oxygen species is vital; however, exposure to excessive reactive oxygen species also induces oxidative stress and impairs wound healing (30).

Coenzyme-Q-10 is an effective fat-soluble antioxidant and essential element of the mitochondrial respiratory chain and a safe material with very low toxicity (31,32). In a recent study, Yoneda et al. have reported that topical application of the reduced form of coenzyme-Q-10 decreased inflammatory reactions in the granulation stage during the wound healing period (33). By using Coenzyme-Q-10 in liquid form intraperitoneally, we determined a significant decrease of fibrosis and inflammation between the study groups.

However, compared to other techniques in the literature, our experimental model evaluated oxidative stress, adhesion and biomarkers in a different way (34,35). We measured the diamond adhesion score and investigated that clinical adhesion formation get decrease by the effect of coenzyme-Q-10 and we also obtained promising results of GSH-Px and SOD regarding anti-oxidant and anti-inflammatory process for pathological adhesion formation, we saw that utilization of coenzyme-Q-10 could be beneficial for intraabdominal protection after surgical procedures.

CONCLUSION

Our study has a potential contribution to reduce postoperative adhesions and apparently showed equivalent efficacy to other available anti-adhesion techniques and materials. We believe that coenzyme-Q-10 can be a good anti-adhesive agent with feasibility, non-toxicity, and effectiveness. Especially, more detailed experimental and clinical large studies are required to test laparoscopic or robotic procedures.

Ethics Committee Approval: Consent was received from the Bağcılar Education and Research Hospital Experimental Animals Production and Research Laboratory Ethical Committee (HADYEK/2013-02/28.01.2013).

Informed Consent: Informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.K.; Design – R.K., S.A.; Supervision – R.K.; Resource – S.A., O.A.; Materials – G.E., S.A.; Data Collection and/or Pro-cessing – S.B., O.A.; Analysis and Interpretation – O.A., G.E.; Literature Review – S.B., Y.A., G.E.; Writing Manuscript – R.K., S.B. Y.A.; Critical Reviews – Y.A.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Cerrahi sonrası yapışıklık önlenmesinde koenzim-Q yaklaşımı

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ÖZET

Giriş ve Amaç: Postoperatif intraperitoneal adezyonlar abdominal cerrahide çözülmemiş önemli bir problemdir. Bu çalışmada, koenzim-Q'nun peritoneal yapışıklık gelişimi üzerindeki muhtemel önleyici etkileri araştırılmıştır.

Gereç ve Yöntem: 300-350 g ağırlığında 16 Wistar Hannover erkek sıçan rastgele olarak her biri sekiz sıçandan oluşan iki gruba ayrıldı. Çekum, subserosal kanama gelişene kadar steril bir gazlı bezle aşındırıldı. Çekal aşınmanın karşısındaki bir periton tabakası tamamen disseke edildi. Grup 1 tedavi almadı. Grup 2 30 mg/kg koenzim-Q, 2 mL intraperitoneal olarak enjekte edildi. Tüm sıçanlar postoperatif 21. günde ötenazi edilerek adezyonlar makroskobik olarak skorlandıktan sonra, periton ve bağırsak doku örnekleri histopatolojik incelemeye tabi tutuldu. Antioksidan etkinliği araştırmak için doku ve kan örnekleri biyokimyasal analiz için alındı.

Bulgular: Adezyon skorları kontrol grubu ile koenzim-Q grubu arasında anlamlı farklılık gösterdi (p= 0,001). GSH-Px, MDA ve SOD düzeylerinin doku düzeylerine göre, çalışma grupları arasında anlamlı fark yoktu (p= 0,074, p= 0,208, p= 0,526). Plazma GSH-Px ve SOD düzeylerine göre gruplar arasında anlamlı farklılıklar gözlendi (p= 0,002, p= 0,001), fakat MDA düzeylerinde fark anlamlı düzeyde saptanmadı (p= 0,793). Kontrol ve koenzim-Q patolojik skorları arasındaki fark (fibrozis için p= 0,028; inflamasyon için p= 0,025) istatistiksel olarak anlamlıydı.

Sonuç: Bu çalışma koenzim-Q'nun erken postoperatif adezyonların önlenmesinde potansiyel uygulama olduğunu doğrulamaktadır.

Anahtar Kelimeler: Koenzim-Q, yapışıklık, cerrahi

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ORIGINAL ARTICLE
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Retrospective analysis of prognostic factors affecting the recurrence and disease-free survival following surgical management of gastrointestinal stromal tumors

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ABSTRACT

Objective: The aim of this study was to evaluate the prognostic factors effecting recurrence risk and disease-free survival of the patients who were diagnosed as gastrointestinal stromal tumor after complete resection of the tumor with or without adjuvant therapy.

Material and Methods: Between the years 2005 and 2013, data of 71 patients including clinical and demographic features, tumor localizations, pathologic examinations, survival and recurrence rates were enrolled into this retrospective study.

Results: Male/female ratio was 1.71, and mean age was 60.27 ± 14.65 years. Forty-two (59.2%) patients had tumor in stomach, 16 (22.5%) in small bowel, whereas 12 (16.9%) had extra-gastrointestinal system and one patient (%1.4) had rectal localization. Modified NIH risk stratification scheme categorized 9 (12.68%) patients in very low-, 12 (16.90%) in low-, 21 (29.58%) patients in moderate-and 29 (40.85%) patients in high-risk group. Twenty-four (33.8%) patients had a metastatic disease at follow-up while 13 (18.3%) patients were metastatic at admission. R0 resection was successfully performed in 51 (71.8%) patients, while R1 resection in 9 (12.7%) and R2 resection in 11 (15.5%) were achieved. Mean follow-up time was 47.12 ± 33.52 months (range, 1-171 months). Nineteen (26.8%) patients demonstrated recurrence with a mean time of 22.16 ± 15.89 months (range, 3-57 months). During follow-up 17 (23.9%) patients were deceased. In univariate analysis, high-risk group, small bowel and extra-gastrointestinal system localization, R1-2 resection, necrosis, positive resection margin and invasion of surrounding tissues, metastatic disease and adjuvant therapy were statistically significant in terms of recurrence. Multivariate analysis presented small bowel and extra-gastrointestinal system localization, R2 resection, mitoses count, invasion and adjuvant therapy as independent prognostic risk factors affecting disease-free survival rates. The 1, 3 and 5 years of disease-free survival rates of the patients were 89.6%, 75.4%, 64.3%, respectively.

Conclusion: As mentioned in the literature, the mainstay of curative therapy of gastrointestinal stromal tumor is surgery. In our study, not only small bowel, extra-gastrointestinal system localization and invasion of surrounding tissues by tumor, but also R2 resection that complicate the local control of the disease were represented as independent adverse prognostic factors for disease-free survival. Unfavourable clinical outcomes of adjuvant therapy over the disease-free survival was linked to higher tumor stage with metastatic disease and emphasized that prospective trials with more cases should be practiced.

Keywords: Gastrointestinal stromal tumors, surgery, prognosis, disease specific survival

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INTRODUCTION

Our knowledge on gastrointestinal stromal tumors (GIST) has increased exponentially as an indicator of progress in medicine, with ground-breaking advances in the diagnosis and treatment of this disease. These tumors were described as leiomyomas, leiomyosarcomas, or leiomyoblastomas in the past. GISTs are now described and accepted as the most common sarcoma of the gastrointestinal (GI) tract as a separate entity. GISTs constitute 1-2% of all GI malignancies and have a clinical course ranging from benign to malignant (1). It can occur anywhere in the gastrointestinal tract, and 60% is in the stomach, 30% in the small intestine, 7% in the large intestine, 5% in the rectum, and 1% in the esophagus (2). It accounts for 2% of gastric tumors and 14% of small bowel tumors, but rarely, primary GISTs of the omentum, mesentery, and pancreas have also been described (3). At least fifty percent of the patients are metastatic on diagnosis, where the liver and peritoneum are the most two common sites of extended disease. GISTs are generally rare tumors between 3000 and 5000 new cases each year, with an annual incidence of 1/14.5 million and

a prevalence of 1/129 million cases (4,5). Median age is 60 years, and it is observed in males with a slight difference.

In a population-based cohort study from 10 series in the literature, Joensuu et al. have demonstrated disease-free survival (DFS) rates of 1625 patients diagnosed with operable GIST, who were not given adjuvant therapy, within 5th, 10th, 15th and 20th years as 70.5%, 62.9%, 59.9% and 57.3%, respectively (6). Although GIST recurrence is rare during the first 10-year follow-up, most patients recover with surgical treatment alone. Despite previous data, modern imaging modalities facilitate early diagnosis and detection of small metastatic foci. Thus, the patients who are eligible for surgery can be treated by surgery alone without adjuvant treatment for almost 60% of the cases. Surgical outcomes and DFS rates should be increased by providing early diagnosis and independent prognostic risk factors associated with disease recurrence. In this retrospective cohort study, it was aimed to evaluate and investigate the effects of clinical characteristics, adjuvant therapy and complete removal of the tumor with intact surgical margin over DFS rates in patients with GIST.

MATERIAL and METHODS

Patient Selection

The clinical, pathological, and surgical parameters and follow-up records of 71 patients with gastrointestinal stromal tumors who were admitted to the General Surgery Department between January 2005 and December 2013 were reviewed retrospectively. The study was planned in accordance with the decisions of the Declaration of Helsinki, patient rights regulation, and ethical rules. Approval was obtained from the Ankara Numune Training and Research Hospital Scientific Research Evaluation Commission for the study (Date: 29.01.2014, Decision no: 2014-748).

Age, sex, concomitant co-morbid diseases, admission symptoms, operation sort and time, length of hospital stay, tumor location, presence of perforation, tumor morphology, and immunohistochemical interpretations, adjuvant therapy, metastasis and recurrence rates were analyzed to determine the prognostic factors in patient survival.

Patient Groups

Patients were grouped according to age and decades. Tumors were located in the stomach, small intestines, large intestines, and omentum-mesentery. Tumor diameter was determined as ≤ 5 cm, > 5 ≤ 10 cm and > 10 cm. Mitosis rate was the number of mitosis count on a light microscope within an area of 0.152 mm2 at 50 high-power fields (HPF) magnification sites; and divided into three groups ≤ 5, 5-10 and > 10. Tumor histology was interpreted as spindle, epithelioid, and mixt types. Tumor necrosis (present/absent), cellularity (poor/distinct), pleomorphism (poor/distinct), mucosal ulceration (present/absent), in-tumor bleeding (present/absent), and tumor invasion depths were noted. Patients were divided into two groups according to adjuvant therapy history with- or without tyrosine kinase inhibitor.

Follow-up

Patients were followed up with routine whole blood and biochemical tests and abdominal ultrasound/or tomography when necessary within 3-6 month intervals for five years. Recurrence- or metastasis-free patients were followed up annually. Patients with additional complaints during follow-up were evaluated by gastroscopy, colonoscopy and further investigations. Patients with tumor recurrence or metastasis were considered for definitive surgery. Adjuvant therapy with tyrosine kinase inhibitors was maintained for high-risk patients according to the modified NIH consensus criteria. Adjuvant Imatinib treatment was schemed as single dose initially and doubled in progressive disease. Imatinib therapy was maintained for 1 to 3 years under the supervision of the Oncology department. Sunitinib therapy was initiated in imatinib-resistant, progressive disease. Patients were contacted via consultation or telephone within six-month intervals, and follow-up parameters of surviving patients were recorded.

Statistical Analysis

In the literature, prognostic factors were divided into valid groups for the evaluation of survival of stromal tumors, whether there was a significant difference between the groups. DFS was defined as the time from the date of diagnosis until first recurrence. Descriptive statistics are given as mean ± standard deviation. Pearson chi-squared test was performed for comparison of homogeneity between the groups. DFS analysis and survival tables were obtained with the Kaplan-Meier method. Comparison of survival curves was tested with Log-rank test. Prognostic factors with p values < 0.20 in the Log-rank test were entered to the multivariate analysis. Multivariate analysis was performed with Cox-regression test regression. Risk ratios (Hazard ratio) in multivariate analysis within a 95% confidence interval with a p value < 0.05 were noted statistically significant. Statistical analysis was performed using the 'SPSS for Windows' package program.

RESULTS

Forty-eight (67.6%) of the patients were males, with a male/female ratio of 2.08 (48/23). Mean age was 60.27 ± 14.65 years (range: 22-88 years). Admission symptoms including abdominal pain, weight loss, nausea-vomiting, melena, and palpable mass regarding to stromal tumor were evaluated; 12 (16.9%) patients were symptom-free, 15 (21.1%) patients presented at least one, 17 (23.9%) patients presented at least two, 15 (21.1%) patients presented at least three, 10 (14.1%) patients presented at least four, and 2 (2.8%) patients presented all of the complaints. Although the most common complaints were abdominal pain in 50 (14%) patients, abdominal mass in 29 (8%) patients, nausea-vomiting in 33 (9%) patients, most frequent symptoms in the literature regarding GI bleeding were presented only in 12 (3%) patients. In our study, only 15 patients described a single symptom, but several symptoms interlinked to each other due to the complicated clinical course of the disease. There was a sig-

nificant relationship between survival and abdominal pain and mass (p< 0.05). A statistically significant relationship was also observed between recurrence and nausea-vomiting (p< 0.05).

Tumors were located in the stomach in 42 (59.2%) patients, small intestines in 16 (22.5%) patients, omentum-mesentery (extra-GIS) in 12 (16.9%) patients and rectum in 1 (1.4%) patient. There were no colonic or esophageal tumors. One case with extra-GIS location was located at the pancreas. Mean tumor diameter was 7.78 ± 5.53 cm (range 0.4-30 cm). Tumor diameter was < 5 cm in 23 patients, 5-10 cm in 29 patients, and > 10 cm in 19 patients. Forty-two of the cases were spindle cells, 6 were epithelioid cells, and 16 were mixed tumors. According to Modified NIH risk scoring system based on clinical and morphological findings, nine patients were in the very low-risk group, 12 patients were in the low-risk group, 21 patients were in the intermediate-risk group, and 29 patients were in the high-risk group (Figure 1).

A total of 13 (18.3%) patients were metastatic on admission including peritoneal dissemination in 5 (38.4%) patients, metastatic nodules in the liver in 6 (46.1%) patients and in lungs in 1 (7.6%) patient and invasion to the stomach in 1 (7.6%) extra-GIS localized patient. Postoperative metastasis was present in 9 (12.67%) patients, including the liver in 3 (33.3%) patients, peritoneal surfaces in 5 (55.5%) patients, and subcutaneous tissue in 1 (12.67%) patient.

A total of 71 patients were included into the study, and 17 (23.94%) patients died during the follow-up period. Mean follow-up period was 47.12 ± 33.52 months, and the last event was at 1 the 71st month. Overall survival rates of 1st, 3rd, and 5th years were 91.4%, 82.6%, 76.5%, respectively. Recurrence was observed in 19 (26.8%) patients, and mean recurrence time was 22.16 ± 15.89 (3-57) months. DFS rates of 1st, 3rd, and 5th years were 89.6%, 75.4% and 64.3%, respectively (Figure 2). Recurrences were in the stomach in 7 (36.84%) patients, small intestine in 5 (26.31%) patients and extra-GIS in 7 (36.84%) patients. The last recurrence was observed in the 57th month, and the patient died at the 69th month. Twelve (70.58%) of the 17 patients died due to stromal tumor progression and recurrences. Rectum localized GIST was recurrence-free during follow-up. Although gastric localized GISTs presented with more recurrence and recurrence-related death rates, extra-GIS localized tumors presented with lower DFS rates (p< 0.001) (Figure 3).

Eighteen (25.4%) patients presented with the local invasive disease during the operation. R0 resection was achieved in 51 (71.8%) patients, R1 resection in 9 (12.7%) patients and R2 resection in 11 (15.5%) patients. Ten (14.2%) of these patients relapsed, and 5 (7.1%) recurrence-related deaths were observed. Only 2 (2.81%) of the 4 (5.63%) patients, who underwent R0 resection with peri-operative local invasive disease, had positive pathological surgical margins. Eight (11.3%) patients presented with

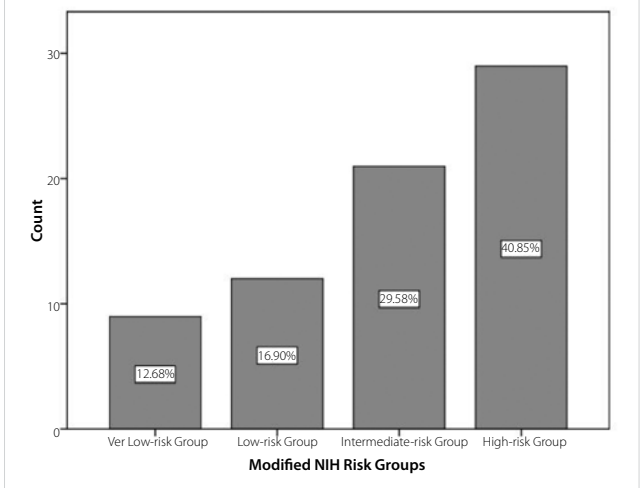

Figure 1. Distribution of the patients according to the modified NIH staging system.

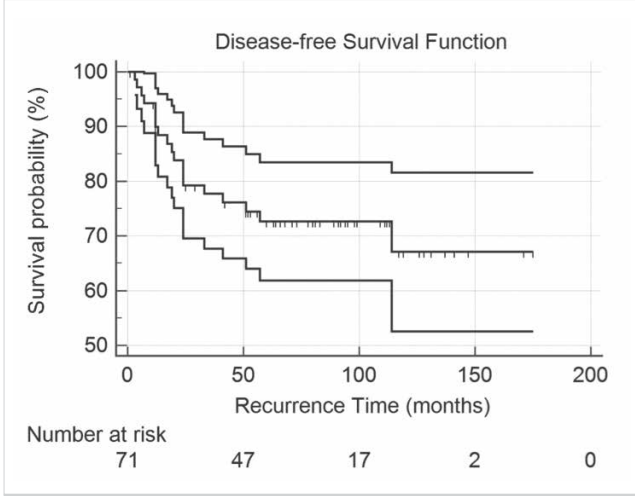

Figure 2. Overall DFS rates of the patients within 95% confidence interval curves.

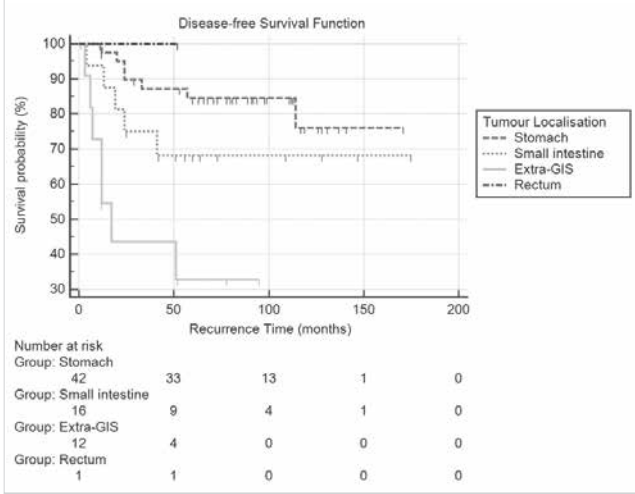

Figure 3. DFS rates of the patients according to tumor localization.

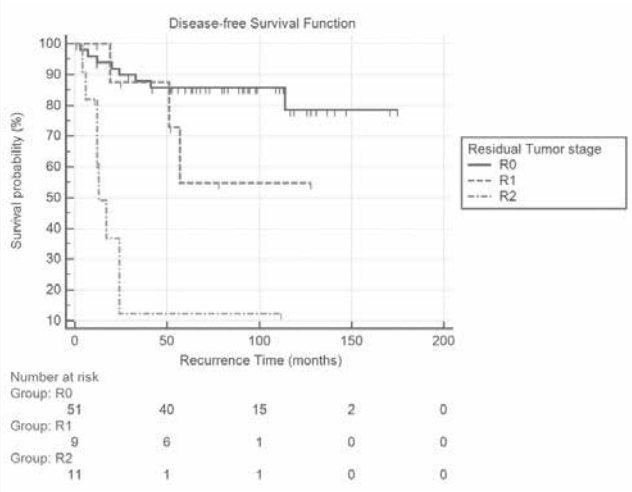

Figure 4. DFS rates of the patients according to residual tumor stage.

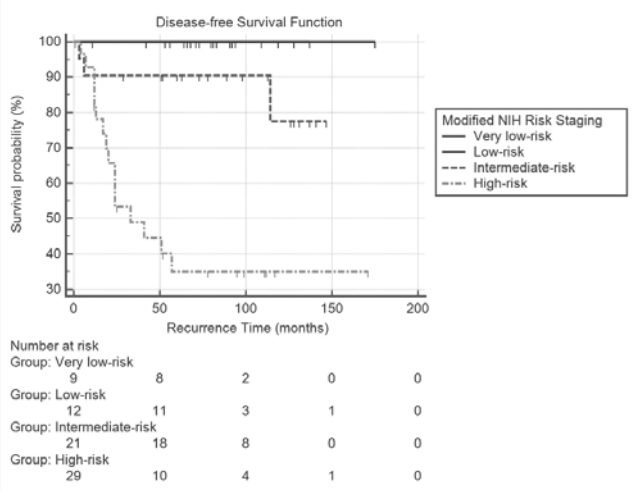

Figure 5. DFS rates of the patients according to the modified NIH risk staging scheme.

restricted perforation during the operation. Tumor rupture was observed in 11 (15.9%) patients, with a mean tumor diameter of 10.91 ± 3.51 cm (range: 4.5-15 cm). Five of the 8 relapsed patients in the R0 resection group, 1 of the 3 relapsed patients in the R1 resection group and 5 of the 8 relapsed patients in the R2 resection group died due to progressive disease. Predicted DFS rates of the patients in the R0 group [141 months, 95% CI (123-160), Log Rank= 28.54, p< 0.001] were significantly higher compared to the R1 [60 months, 95% CI (43-76), Log Rank= 28.54, p< 0.001] and R2 groups [20 months 95% CI (9-32), Log Rank= 28.54, p< 0.001]. DFS rates of residual tumor classification were significantly different between the groups (p< 0.001) (Figure 4). Restricted tumor perforation and tumor rupture were not associated with DFS rates with insignificant p values, 0.380 and 0.208, respectively.

Twelve (63.2%) patients in tumor diameter > 10 cm group relapsed, and 5 of them died. One patient in the tumor diameter < 5 cm group and six patients in tumor diameter 5-10 cm group relapsed, and five of them died. DFS rates of tumor diameter > 10 cm group were significantly lower than the other group of patients [63 months, 95% CI (31-95), Log Rank= 17.75, p< 0.001]. Additionally, tumor local invasiveness and tumor positive resection margin significantly decreased DFS rates (p< 0.002 and p< 0.032). However, tumor invasion depth was not found to be associated with decreased DFS rates (p= 0.488).

Tumor necrosis, moderate and severe cellular atypia, mitosis count 5-10, and > 10 per 50/HPF and desmine were found to be significantly associated with decreased DFS rates (p< 0.005). Tumor histology, mucosal ulceration, central hemorrhage, and immune histochemical markers including CD117, CD34, actin, S-100, Ki-67, NSE were not different between the groups with insignificant p values (p> 0.05).

Modified NIH risk stratification groups of very low-risk and low-risk groups did not present any recurrence or death during follow-up. Three of the 21 patients in the intermediate-risk group, 16 of the 29 patients in the high-risk group relapsed, and three patients in the intermediate-risk group and eight patients in the high-risk group died. First, 3rd, and 5th-year DFS rates for very-low and low-risk groups were 100%. First and 3rd-year DFS rates for the intermediate-risk group were 90.2%, and 5th-year survival rates were 82%. First, 3rd, and 5th-year Disease-free survival rates for high-risk groups were 82.1%, 48.9%, and 34%, respectively. DFS rates were lower in intermediate- and high-risk groups due to 10 (14.8%) of the 12 deaths in the high-risk group and 2 (2.81%) of the four deaths in the intermediate-risk group regarding disease progression or recurrence. DFS rates were found to be significantly different between the risk groups (p< 0.001), and higher risk increases recurrence and decreases recurrence-related survival (Figure 5).

Metastasis was observed in 22 (30.9%) patients during the follow-up period. In this study, 13 (18.3%) patients were metastatic on admission, with liver metastasis in 6 (8.44%) patients, peritoneal metastasis in 5 (7%) patients, lung metastasis in 1 (1.4%) patient and gastric metastasis in 1 (1.4%) patient. Besides, 11 (15.4%) patients developed new metastatic foci during follow-up; 3 (4.2%) in the liver, 5 (7%) in the peritoneum, 2 (2.8%) in the small intestine and 1 (1.4%) in the subcutaneous tissue. Presence of metastasis on admission and tumor progression during follow-up screening were significantly associated with decreased DFS rates (p< 0.001).

Adjuvant tyrosine kinase inhibitor (TKI) therapy was not administered to the very-low and low-risk group, and disease-related death and recurrence were not present in these group of patients. Eighteen patients in intermediate- and high-risk group were administered with TKI, and 11 (61.2%) of the patients died during follow-up. Only 8 (24.2%) of the 33 patients in the intermediate- and the high-risk group without TKI adjuvant therapy presented with recurrence-related death. Disease-free survival rates of patients receiving adjuvant therapy were significantly

different between these groups (p< 0.001). Besides that, disease-free survival rates of the high-risk group without adjuvant TKI therapy and low-risk group with and/or without adjuvant TKI therapy groups were found to be similar. However, DFS rates of the high-risk group with adjuvant TKI therapy were significantly decreased compared to the other groups (p< 0.001). The main factor of this difference was all of the remaining patients were metastatic on admission or progressive during follow-up, except four patients in the high-risk group with adjuvant TKI therapy. DFS rates were significantly different between groups in univariate analysis (p< 0.001).

The univariate analysis of the factors affecting DFS was summarized in Table 1.

Tumor location, tumor diameter, mitosis count, Modified-NIH score, residual tumor stage, per-operative local invasive disease, positive margins, metastasis on admission and follow-up, tumor necrosis, desmine and adjuvant therapy were found to be significant values in the univariate analysis with p value < 0.20 and were entered to the multivariate analysis with Cox-regression models (Table 2).

Multivariate analysis presented recurrence rate and recurrence-related death risks in patients with GIST. Recurrence risk of the small intestine and extra-GIS tumors were found to be 10 and 84 times higher than the gastric tumors. Small intestine and extra-GIS localization of the tumors were determined as unfavorable factors for DFS. Mitosis count < 5 per 50/HPF presented eight times more adverse effect over recurrence risk and increased DFS rates. R2 resection also increases the risk of recurrence and adversely affects DFS up to 38 times. Although locally invasive disease was found to be significant in exploration, its contribution to the development of recurrence was low. It was observed that the risk of recurrence increased fourfold in the high-risk group receiving adjuvant therapy compared to the untreated group.

DISCUSSION

GISTs are rare mesenchymal tumors that are thought to originate from interstitial Cajal cells. GISTs are slightly more common in the male sex with a median age of 60 years (7-9). Gender is not defined as a prognostic factor for survival and recurrence (10,11). Although the majority of the patients in our study were male, a statistically significant relationship was not presented between gender and recurrence. Approximately 70% of the patients are asymptomatic on diagnosis. Presenting complaints are abdominal pain, abdominal mass, weakness, and fatigue due to occult bleeding. As the clinical course of the disease complicates, several symptoms are interlinked to each other. Abdominal mass and pain were found to be strongly associated with the survival in this study. The presence of these symptoms should be noticed in patients with a presumptive diagnosis of GIST in terms of assessing the severity of the disease.

GISTs are classified into four groups in the Modified NIH risk staging system as very low-, low-, intermediate- and high-risk groups according to localization, tumor diameter, and mitotic index (12). Risk staging systems provide invaluable information in predicting the prognosis and clinical course of the disease. In addition, many studies have shown that very low, low, and intermediate-risk groups have similar clinical results and present favorable prognosis. Therefore, in the light of the staging systems, adjuvant therapy with tyrosine kinase inhibitors are considered for patients only in the high-risk group as a conclusion. Risk staging systems have also presented a significant difference between the risk groups in terms of recurrence, overall survival, and DFS (Figure 6). In the literature, the effects of anatomical localization to the overall survival remains controversial. Gastric tumors have been described with better clinical outcomes compared to distal tumors (13,14). Although lower incidence rates of colonic and rectal GISTs complicate the identification of associated risk factors, recent studies have demonstrated that colonic and rectal tumors present worse prognosis rather than the gastric tumors (6,15-17). Prognosis of small intestine localized GISTs is not markedly different from colonic and rectal GISTs at ten years (6). Primary GISTs of the omentum, mesentery, and pancreas are rarely described in the literature; however, they are highly presented in this study and provide an advantage in comparing overall survival and DFS rates. Tumor localization was not found to be statistically associated with overall survival, but tumor recurrence was different between the groups. DFS rates of extra-GIS tumors were significantly lower than the gastric and small intestine tumors. Multivariate analysis demonstrated the recurrence and recurrence-related death risks of the small intestine and extra-GIS tumors up to 10-fold and 84-fold, respectively, compared to the gastric tumors. These results were consistent with those reported in the literature.

Effective treatment of GISTs is still surgery. Clinical manifestations of stromal tumors may vary due to the complicated clinical course of the disease in terms of recurrence risk and metastasis even when the tumor is completely resected with the pseudo-capsule (13,18). In locally invasive disease, en-bloc resection of the tumor with the surrounding organ or complete removal of the tumor with negative margins mainstay the curative surgery for GISTs. In our study, operation was cautiously performed with extensive resection of the tumor with an intact surgical margin, including metastatic foci and local invasive sites. Predicted DFS rates of the patients in the R0 group were significantly higher compared to the R1 and R2 groups. However, residual tumor stage was not statistically associated with the survival but presented as a significant prognostic parameter for disease recurrence. In the literature, there are conflicting reviews over the effects of positive microscopic surgical margins regarding survival (19,20). In the recent Modified NIH (Fletcher) risk staging system, tumor rupture during the operation may alter clinical outcomes and may increase disease stage regardless of any tumor size, localization and mitotic count

Table 1. Univariate analysis of the factors affecting disease-free survival

Variables	N	1st year[a]	3rd year[a]	5th year[a]	Estimated survival[b]	Log-Rank	p
Localization							**0.001**
Stomach	42	88.8	85.5	76	138 (116-160)		
Small intestine	16	93.8	70.8	60.7	88 (61-116)	20.57	
Extra-GIS	12	70.7	37.9	15.6	33 (10-56)		
Rectum	1	-	-	-			
Residual tumor stage							**0.001**
R0	51	91.5	86.3	79.9	141 (123-160)	28.54	
R1	9	-	85.7	42.9	60 (43-76)		
R2	11	81.8	12.3	-	20 (9-32)		
Tumor diameter							**0.001**
< 5 cm	23	100	90	-	118 (102-134)	17.75	
5-10 cm	29	85.9	78.2	-	89 (74-104)		
> 10 cm	19	83.3	44.9	25.6	63 (31-95)		
Mitosis count							**0.006**
< 5/per 50HPFc	46	93	84.2	-	146 (128-164)	10.27	
5-10/per 50HPF	9	-	-	22.9	63 (39-86)		
> 10/per 50HPF	15	80	40	-	41 (24-57)		
Modified NIH groups					119 (99-138)		**0.001**
Very low-risk	9	-	-	-	-		
Low-risk	12	-	-	-	-	18.680	
Intermediate-risk	21	90.2	90.2	82	-		
High-risk	29	82.1	48.9	34	-		
Necrosis							**0.001**
Present	21	84.2	48.1	28.9	47 (30-64)	15.30	
Absent	48	93.8	88.8	85	148 (131-165)		
Margin positive							**0.002**
Present	20	84.1	43.1	34.5	42 (27-57)	9.89	
Absent	51	91.8	86.9	75.5	136 (115-156)		
Local invasiveness							**0.032**
Present	18	88.5	52.5	43.8	55 (36-74)	4.62	
Absent	49	91.4	86.4	74.1	134 (112-155)		
Desmin					35 (22-47)		**0.003**
Present	14	85.7	61.4	-	137 (117-158)	8.63	
Absent	47	97.8	87.4	76			
Metastasis on admission							**0.004**
Present	13	69.2	49.5	33	41 (23-59)	8.45	
Absent	58	94.5	81.4	72.2	131 (111-150)		
Metastasis on follow-up							**0.001**
Var	22	77.3	51.5	27.5	41 (28-54)	14.19	
Yok	49	95.5	87.4	80.7	143 (124-161)		
Progression on CT							
First	18	72.2	52.5	19.7	37 (25-48)	9.20	**0.002**
Second	17	70.6	28.2	9.4	-	34.34	**0.001**
Third	16	75	34.1	12.8	-	24.24	**0.001**
Adjuvant therapy							**0.001**
Present	18	83.3	44.9	28	53 (29-79)	13.46	
Absent	53	92.1	86.7	80	141 (123-160)		
Low-risk group							**0.127**
Adjuvant therapy (+)	3	66.7	-	-	86 (22-151)	2.33	
Adjuvant therapy (-)	39	97.4	-	92	93 (85-100)		
High-risk group							**0.001**
Adjuvant therapy (+)	15	86.7	39.4	19.7	36 (23-50)	11.12	
Adjuvant therapy (-)	14	76.9	59.8	51.3	97 (55-140)		

[a] Survival rates (%), [b] Mean (95% Confidence Interval), [c] High power fields.

Table 2. Cox regression analysis of the factors affecting disease-free survival

Variables	β	Standard deviation	Wald	SD	p	Exp (βp)	95% CI[a] Exp (βp)	
							Lowest	Highest
Localization, Small intestine[c]	2.285	0.776	8.670	1	**0.003**	**9.824**	2.147	44.958
Localization, Extra-GIS[c]	4.428	1.098	16.256	1	**0.001**	**83.738**	9.731	720.590
Mitosis < 5/per 50HPF	-2.023	0.804	6.331	1	**0.012**	**0.132**	0.027	0.640
R2 resection[d]	3.634	1.293	7.897	1	**0.005**	**37.859**	3.003	477.377
Local Invasiveness	-3.453	1.350	6.542	1	**0.011**	**0.032**	0.002	0.446
TKI[b] therapy	1.364	0.655	4.332	1	**0.037**	**3.912**	1.083	14.130

[a] 95% Confidence Interval, [b] Tyrosine kinase inhibitor, [c] Stomach localization is reference group, [d] R0 is reference group.

(6). Tumor rupture has a critical role in abdominal dissemination and disease recurrence. In this study, there was no significant relationship between tumor rupture and tumor recurrence risk, and DFS. However, incomplete surgery and invasion of surrounding tissue increased the risk of recurrence up to 38-fold and adversely affected the DFS rates in multivariate analysis. Approximately 50% of the GISTS are metastatic on admission, and frequently metastasize to the liver and peritoneum, but extra-abdominal metastasis is very rare (21,22). In the literature, peritoneal and liver metastasis at the time of diagnosis indicates poor prognosis, and cases with incidentally detected serosa implants are presented with better outcomes (18). Metastasis on admission and during follow-up was statistically significant in the univariate analysis, but lack of significant data in the multivariate analysis manifested that metastatic disease was not an independent prognostic parameter on DFS. Complete removal of the tumor with the pseudo-capsule and intact surgical margins were presented as the most important prognostic factors over recurrence and DFS.

As a component of risk stratification systems, tumor morphology, immune-histochemistry, and mitotic index are also described as critical prognostic parameters (13,18). Miettinen et al. have demonstrated that spindle cell histology of GIST presents poor prognosis (21). Furthermore, lower cellularity has been described as a useful prognostic factor, while severe nuclear atypia has been mostly seen in aggressive tumors (23,24). In our study, cell type, cellularity, and nuclear pleomorphism had no statistically significant effect on recurrence. Tumor diameter was statistically correlated with both survival and recurrence risk in the univariate analysis. The estimated DFS was found to be lower in patients with tumor size greater than 10 cm. However, multivariate analysis did not present any significant difference between tumor diameter and both overall survival and DFS. Patients with a high mitotic index, > 10 per 50/HPF, are considered in the high-risk group regardless of tumor size (25). In the literature, recurrence risk ratio in patients with mitosis count > 5 per /50 HPF is increased up to 14.6-fold. In our study, high mitotic index presented a significant relationship between survival and recurrence. The increase in mitosis negatively affects DFS. The estimated mean DFS at 95% CI is 41 (24-57) months in patients with mitosis count > 10 per 50/HPF and is lower than the other groups. In multivariate analysis, mitosis count < 5 per 50/HPF decreased the recurrence risk by 8-fold. The mitotic index has been reported in the literature as the most important independent prognostic factor affecting recurrence and survival following surgery (6,15,21), and this data is also consistent with this study. Morphological characteristics of the tumor, including necrosis and hemorrhage in the tumor center, ulceration of the mucosa are common and relatively critical prognostic factors (18,26). In our study, tumor necrosis was observed as a risk factor for recurrence in the univariate analysis, but no statistically significant correlation was found for ulceration and bleeding. The presence of necrosis had a significant effect on DFS, but not as an independent factor alone.

Although surgery plays a pivotal role in GIST treatment, long-term follow-up outcomes have presented unsatisfactory results as the sole treatment option. The introduction of tyrosine kinase inhibitors (TKI) has demonstrated more favored clinical outcomes with the propagation of ongoing phase III randomized clinical trials (27,28). In the literature, 5-year survival following curative surgery with a diagnosis of primary GIST was possible in approximately 54% of the patients, whereas the risk of recurrence increases up to 40% in the second year following the operation (14,29). Although studies have attempted to reveal prognostic factors affecting recurrence, especially the recurrence itself, decreases survival and increases mortality. In this study, recurrence affected survival with unfavorable outcomes compared to the other prognostic markers and increased the recurrence-related death risk up to 30 times in a year.

CONCLUSION

This study evaluated the prognostic parameters of surgical management of GISTs to estimate the risk factors for treatment strat-

egy and prediction of tumor recurrence before and after surgery. Tumor mitotic index was found to be the most effective and invaluable histologic parameter in the prediction of DFS estimates. Extra-GIS and small intestine tumors were both presented with higher recurrence, incomplete surgery and decreased the DFS rates according to the gastric localized tumors. Besides that, regardless of tumor characteristics, R0 resection was described as another important criteria in terms of increasing survival rates and decreasing the risk of recurrence in advanced-stage disease. In patients with a stromal tumor, the main objectives should be prioritized to maintain curative treatment, reduce the risks of recurrence and the burden of metastatic disease and provide a satisfactory quality of life. As mentioned in this study, complete removal of the tumor with intact margins through effective surgical intervention is considered as the most essential factor in the management of GISTs. Although recent studies have propagated tyrosine kinase inhibitors as a potent agent in adjuvant therapy following the surgery to prevent recurrence and improve survival with favorable outcomes in patients with advanced metastatic disease, this study showed limited or no benefit. Therefore, prospective randomized clinical trials involving more patients with comprehensive and trustworthy statistical data are required to determine the most appropriate medical and surgical therapy in terms of multidisciplinary approach.

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ORİJİNAL ÇALIŞMA-ÖZET
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Cerrahi tedavi uygulanan gastrointestinal stromal tümörlü hastalarda nüks ve hastalıksız sağkalıma etki eden faktörlerin retrospektif analizi

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ÖZET

Giriş ve Amaç: Bu çalışmada, hastaların operasyon sonrasında rekürrens riski ve hastalıksız sağkalımına etki eden cerrahi ve cerrahi dışı prognostik faktörlerin ortaya konulması ve tümöral dokunun sağlam cerrahi sınırla birlikte tamamen çıkarılması ve adjuvan tedavi kullanımın sonuçlarının araştırılması amaçlanmıştır.

Gereç ve Yöntem: 2005-2013 yılları arasında gastrointestinal stromal tümör tanısı ile opere edilmiş 71 hastanın klinik ve demografik özellikleri, tümör lokalizasyonu, tümörün morfolojik ve histopatolojik özellikleri, sağkalım ve nüks zamanını içeren verileri geriye dönük olarak kaydedildi.

Bulgular: Yetmiş bir olgunun, erkek/kadın oranı, 1,71 ve yaş ortalaması 60,27 ± 14,65 yıldır. Hastaların tümör lokalizasyonları, 42 (%59,2)'sinde mide, 16 (%22,5)'sında ince bağırsak, 12 (%16,9)'sinde ekstra gastrointestinal sistem, 1 (%1,4)'inde rektumdadır. Modifiye NIH risk sınıflamasına göre, 9 (%12,68)'u çok düşük, 12 (%16,90)'si düşük, 21 (%29,58)'i orta ve 29 (%40,85)'u yüksek risk grubunda yer almıştır. Hastaların 13 (%18,3)'ünde başvuru anında metastaz izlenirken, 24 (%33,8) hastada takipte nüks veya metastaz gelişmiştir. R0 rezeksiyon 51 (%71,8)'inde, R1 rezeksiyon 9 (%12,7)'unda, R2 rezeksiyon 11 (%15,5)'inde sağlanabilmiştir. Ortalama takip süresi 47,12 ± 33,52 ay (aralık: 1-171) olarak izlenmiş olup, nüks izlenen 19 (%26,8) hastanın ortalama nüks zamanı 22,16 ± 15,89 aydır (aralık: 3-57). Takip süresi boyunca 54 (%76,1) hasta sağken, 17 (%23,9)'si yaşamını yitirmiştir. Tek değişkenli analizde yüksek evre, ince bağırsak, ekstra gastrointesinal sistem yerleşimi, R1-2 rezeksiyon, nekroz, çevre doku invazyonu ve cerrahi sınır pozitifliği, metastatik hastalık ve adjuvan tedavi kullanımı nüks riskini artırırken, çok değişkenli analizde hastalıksız sağkalıma ince bağırsak, ekstra gastrointestinal sistem yerleşimi, R2 rezeksiyon, mitoz sayısı, çevre invazyonu ve adjuvan tedavi hastalıksız sağkalım üzerinde bağımsız prognostik faktörler olarak izlenmiştir. Hastaların bir yıllık, üç yıllık ve beş yıllık hastalısız sağkalım değerleri sırasıyla %89.6, %75.4, %64.3 olarak izlenmiştir.

Sonuç: Literatürde tanımlandığı gibi, gastrointestinal stromal tümörlerin küratif tedavisinde en önemli basamak cerrahidir. Çalışmamızda hastalığın ince bağırsak ve ekstra gastrointestinal sistem yerleşimli olması, tümörün çevre dokuya invaze görünümü tümörün lokal kontrolünü zorlaştırmakta ve R2 rezeksiyonla birlikte hastalıksız sağkalım için bağımsız kötü prognostik faktörler olarak izlenmektedir. Adjuvan tedavinin hastalıksız sağkalım üzerinde izlenen olumsuz etkisi yüksek evreli metastatik hastalığa bağlanmakta ve bu yönde daha geniş sayılı ve ileriye dönük çalışmalar yapılması gerekliliğini ortaya koymaktadır.

Anahtar Kelimeler: Gastrointestinal stromal tümörler, cerrahi, prognoz, hastalıksız sağkalım

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ORIGINAL ARTICLE
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Frostbite injuries: independent predictors of outcomes

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ABSTRACT

Objective: Frostbite injuries are important causes of morbidity and mortality after trauma. Epidemiology, injury patterns, and outcomes after frostbite among patients presenting to trauma centers are incompletely defined. The purpose of this study was to delineate patient demographics, clinical characteristics, and independent predictors of outcomes after frostbite.

Material and Methods: Patients with frostbite injury were identified from the National Trauma Data Bank (NTDB) (2007-2014). Demographics, clinical/injury data, and outcomes were collected. Patients were dichotomized into study groups based on intensive care unit (ICU) admission. Univariate analysis was performed with the Mann-Whitney U, Fisher's exact, or Chi-Square test as appropriate. Multivariate analysis using logistic regression determined independent predictors of outcomes.

Results: Over the study period, 241 patients were identified. Median body temperature on admission was 36.3°C (IQR 33.4-36.7). Mortality was 3% (n= 7). ICU admission was required in 101 (42%) patients and 48 (20%) underwent surgical intervention. On multivariate analyses, mortality was predicted by lower admission GCS (p= 0.027) and amputation by higher HR (p= 0.013). Need for ICU admission was predicted by older age (p= 0.010), male gender (p= 0.040), higher HR (p= 0.031) and ISS (p< 0.001), and lower GCS (p= 0.001). Prolonged hospital LOS was predicted by higher heart rate (p< 0.001) and ISS (p< 0.001).

Conclusion: Frostbite injuries are uncommon but can necessitate surgical intervention and cause mortality. Lower GCS and higher heart rate, but not body temperature, portend poor outcomes. These findings can be used to triage patients appropriately upon admission and to better inform prognosis after frostbite injuries.

Keywords: Frostbite, thermal injuries, hypothermia

INTRODUCTION

Frostbite injuries are infrequent but important causes of morbidity and mortality after trauma. In part because of their rarity, frostbite injuries are incompletely defined by the current literature (1). Knowledge of predictors of outcomes, such as mortality and need for amputation, would be useful for prognostication and to anticipate resource utilization after this uncommon mechanism of injury.

The primary objective of this study was to define independent predictors of outcomes [mortality, need for surgical intervention, need for intensive care unit (ICU) admission, ICU length of stay (LOS), and hospital LOS] after frostbite injuries using a large, nationwide patient population from the National Trauma Data Bank (NTDB) (2). The secondary objectives were to define the epidemiology and clinical characteristics of patients who sustain frostbite injuries. Our hypothesis was that worsened physiologic status on presentation to hospital [e.g. lower body temperature, tachycardia, hypotension, diminished glasgow coma scale (GCS) score] would be predictive of poor outcomes after frostbite.

MATERIAL and METHODS

In this retrospective observational study, all patients with frostbite injuries (AIS codes 915000, 915002, 915004, 915006) between January 1, 2007 and December 31, 2014 were identified from the NTDB. The NTDB, run by the American College of Surgeons (ACS), is the largest trauma registry in existence and is comprised of aggregate data from centers across the United States (2). There were no exclusion criteria. Ethics committee approval by the Institutional Review Board of the University of Southern California was obtained. Informed consent was waived due to the study's retrospective observational design of deidentified patient data.

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After patient identification, demographics (age, gender), clinical data [admission heart rate (HR), systolic blood pressure (SBP), temperature, and GCS score], and injury data [Injury Severity Score (ISS)] were collected from the NTDB. Primary outcome was mortality. Secondary outcomes included need for surgical intervention (debridement, amputation), need for ICU admission, ICU LOS, and hospital LOS.

Statistical Analyses

Patients were dichotomized into study groups based on the need for ICU admission or not. Continuous variables are represented as median [interquartile range (IQR)] and categorical variables are given as number (percentage). Univariate analysis was used to compare patient demographics, clinical/injury characteristics, and outcomes between study groups using the Mann-Whitney U test, Fisher's exact test, or Chi-square test as appropriate. Multivariate regression with the enter method included all clinically relevant predictor variables. Data were collected and analyzed using SPSS version 20.0 (IBM Corporation, Armonk, NY). Statistical significance was defined as $p< 0.05$.

RESULTS

Patient Demographics, Clinical Data, Injury Data, and Outcomes

Overall, 241 (< 0.01%) patients with frostbite injury were identified from the NTDB (Figure 1). ICU admission was required in 101 (42%) patients. Median age was 44 years [interquartile range (IQR) 29-58] and 184 (76%) patients were male (Table 1). Median temperature on arrival to the emergency department was 36.3°C (IQR 33.4-36.7). In general, patients were hemodynamically normal and intact neurologically. Median ISS was 8 (IQR 2-14). Overall mortality was 3% (n= 7) (Table 2). Surgical intervention was required in 20% of the patients (n= 48). Overall median hospital LOS was 5 days (IQR 2-10).

Patients Who Required ICU Admission vs. Those Who Did Not

Patients who were admitted to the ICU (n= 101, 42%) tended to be older (48 vs. 41 years, p= 0.008), have a lower admission body temperature (34.1 vs. 36.6°C, p< 0.001), and a lower admission GCS (13 vs. 15, p< 0.001) than patients who were not admitted to the ICU (n= 140, 58%) (Table 1). Patients admitted to the ICU had a higher mortality (7% vs. 0%, p= 0.004), greater need for amputation (9% vs. 3%, p= 0.047), and longer hospital stay (8 vs. 3 days, p< 0.001) than patients not admitted to the ICU (Table 2).

Independent Predictors of Outcomes

Mortality: On multivariate logistic regression, only lower admission GCS was independently predictive of mortality (p= 0.027) (Table 3).

Need for surgical intervention: No independent predictors of the need for debridement were identified. Higher admission HR was independently predictive of the need for amputation (p= 0.013).

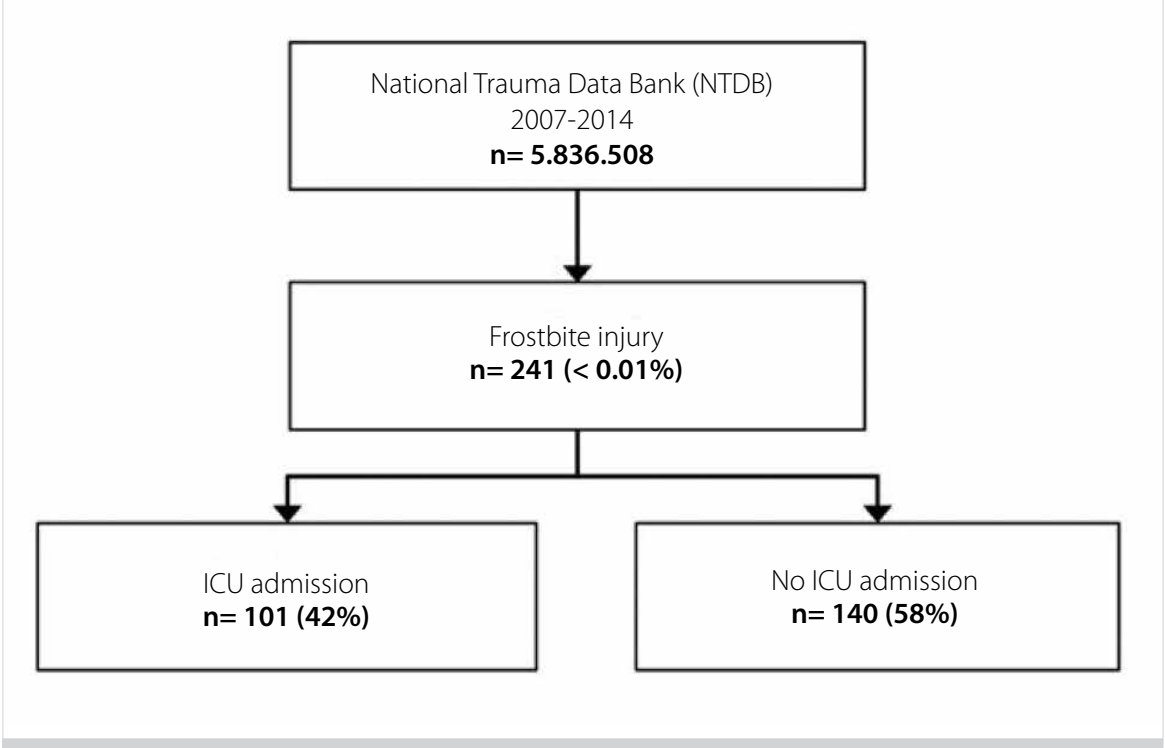

Figure 1. Study algorithm.
ICU: Intensive care unit.

Table 1. Baseline patient demographics, clinical data, and injury data

	Total patients (n= 241)	ICU admission (n= 101, 42%)	No ICU admission (n= 140, 58%)	p
Age (years)	44 (29-58)	48 (37-63)	41 (28-55)	0.008
Gender (male)	184 (76%)	81 (80%)	103 (74%)	0.283
HR (bpm)	96 (84-108)	95 (83-108)	96 (85-95)	0.546
SBP (mmHg)	133 (117-149)	130 (111-149)	134 (122-149)	0.165
Temperature (^{0}C)	36.3 (33.4-36.7)	34.1 (30.6-36.3)	36.6 (34.1-35.9)	< 0.001
GCS	15 (13-15)	13 (6-15)	15 (15-15)	< 0.001
ISS	8 (2-14)	14 (7-21)	5 (1-9)	< 0.001

ICU: Intensive care unit; patient was admitted to ICU after presentation to the emergency department, HR. Heart rate, Bpm: Beats per minute, SBP: Systolic blood pressure, GCS: Glasgow Coma Scale score, ISS: Injury Severity Score.
Continuous variables expressed as median [interquartile range]; p-value calculated with Mann-Whitney U-test. Categorical variables expressed as number (%); p-value calculated with Fisher's Exact Test or Pearson Chi Square Test as appropriate.

Table 2. Univariate analysis of outcomes

	Total patients (n= 241)	ICU admission (n= 101, 42%)	No ICU admission (n= 140, 58%)	p
Mortality	7 (3%)	7 (7%)	0 (0%)	0.004
Need for surgical Intervention	48 (20%)	23 (23%)	25 (18%)	0.414
Debridement	43 (18%)	19 (19%)	24 (17%)	0.737
Amputation	13 (5%)	9 (9%)	4 (3%)	0.047
Upper extremity	4 (2%)	3 (3%)	1 (1%)	0.312
Lower extremity	11 (5%)	8 (8%)	3 (2%)	0.056
Hospital LOS	5 (2-10)	8 (4-16)	3 (2-6)	< 0.001
ICU LOS	0 (0-3)	3 (2-7)	-	-

ICU: Intensive care unit; patient was admitted to ICU after presentation to the emergency department, LOS: Length of stay in days.
Continuous variables expressed as median [interquartile range]; p-value calculated with Mann-Whitney U-test. Categorical variables expressed as number (%); p-value calculated with Fisher's Exact Test or Pearson Chi Square Test as appropriate.

ICU admission and LOS: The need for ICU admission was predicted by older age (p= 0.010), male gender (p= 0.040), higher admission HR (p= 0.031) and ISS (p< 0.001), and lower admission GCS (p= 0.001). Longer ICU LOS was predicted by older age (p< 0.001); male gender (p= 0.030); higher HR (p< 0.001) and ISS (p< 0.001); and lower SBP (p= 0.003) and GCS (p< 0.001) (Table 4).

Hospital LOS: Higher admission HR (p< 0.001) and ISS (p< 0.001) were independent predictors of prolonged hospital LOS.

DISCUSSION

Frostbite, wherein skin is exposed to freezing temperatures and injured by cold thermal energy, is relatively common in some parts of the world, with a lifetime incidence in colder climates of approximately 10% (1,3,4). Most of the available data on frostbite injuries originate from small case series from the military or from adventurists (5-10). The generalizability of these studies, particularly in terms of their applicability to the general population, remains unclear. Existing literature is scarce on patient epidemiology and severity of illness after frostbite injury among civilians. Additionally, independent predictors of outcomes, such as the need for surgical intervention, ICU admission, and mortality, are undefined.

This study examined a nationwide patient population sustaining frostbite injuries and found that frostbite is an infrequent cause of presentation to American hospitals. Patients who suffered from these injuries tended to be middle aged men. Despite exposure to freezing temperatures, most were normothermic upon presentation to the Emergency Department. Mortality in this population was low but surgical intervention, either with debridement or amputation, was required in 20% of the patients. These data would suggest that systemic sequelae after frostbite injuries are infrequent but that local complications such as tissue necrosis and infection are relatively common.

Elevated heart rate and lower GCS on presentation to hospital were almost uniformly associated with poorer outcomes, including mortality, need for surgical intervention, need for ICU admission, and prolonged hospital stay. Other risk factors

Table 3. Multivariate analysis of outcomes (categorical variables)

	OR	95% CI	p
Mortality			
Age (years)	1.039	0.979-1.103	0.211
Gender (male)	< 0.001	< 0.001-> 999.999	0.997
HR	1.019	0.979-1.060	0.355
SBP	0.991	0.967-1.014	0.432
Temperature (^{0}C)	1.056	0.812-1.373	0.683
GCS	0.776	0.620-0.971	0.027
ISS	1.052	0.962-1.150	0.266
Debridement			
Age (years)	0.981	0.960-1.002	0.074
Gender (male)	1.045	0.444-2.458	0.920
HR	1.012	0.994-1.030	0.184
SBP	1.011	0.997-1.025	0.116
Temperature (^{0}C)	0.994	0.843-1.173	0.947
GCS	1.000	0.885-1.131	0.995
ISS	1.016	0.973-1.060	0.471
Ambutation			
Age (years)	1.002	0.967-1.038	0.916
Gender (male)	3.949	0.467-33.390	0.207
HR	1.040	1.008-1.073	0.013
SBP	0.995	0.973-1.017	0.662
Temperature (^{0}C)	1.314	0.941-1.834	0.110
GCS	0.853	0.702-1.037	0.110
ISS	1.030	0.960-1.105	0.411
ICU admission			
Age (years)	1.028	1.007-1.050	0.010
Gender (male)	2.736	1.048-7.146	0.040
HR	1.021	1.002-1.040	0.031
SBP	0.996	0.963-1.010	0.613
Temperature (^{0}C)	0.935	0.774-1.128	0.481
GCS	0.764	0.651-0.897	0.001
ISS	1.130	1.071-1.192	< 0.001

OR: Odds ratio, CI: Confidence interval, ICU: Intensive care unit; patient was admitted to ICU after presentation to the emergency department. HR: Heart rate in beats per minute. SBP: Systolic blood pressure in mmHg, GCS: Glasgow Coma Scale score, ISS: Injury Severity Score, LOS: Length of stay in days.
Multivariate analysis was performed using logistic regression.

for worse outcomes identified by the present study were older age, male gender, lower SBP on admission, and higher ISS. Interestingly, body temperature on admission was not predictive of any study outcome. Taken together, these findings suggest that many of the clinical parameters known to portend worse outcomes among trauma patients, such as tachycardia, hypotension, depressed neurological status, and older age, also herald worse outcomes among the subset of trauma patients with frostbite injuries.

Limitations of the present study must be acknowledged. Retrospective studies are inherently limited by their design. Additionally, the NTDB lacks sufficient granularity to identify the depth or severity of the frostbite injury, information which may be useful in prognostication after injury (11). Finally, nonsurgical treatment strategies, such as the type of rewarming employed or the use of thrombolytics, are not coded by the NTDB. Therefore, the effect of management strategy on outcomes after frostbite is not captured by this study.

CONCLUSION

Frostbite injuries are infrequent among the American civilian population. Despite having a very low mortality rate, approximately half of the patients with frostbite will require ICU admission and one fifth will require surgical intervention. Although a number of independent predictors of poor outcomes were

Table 4. Multivariate analysis of outcomes (continuous variables)

	RC	95% CI	p
ICU LOS			
Age (years)	0.010	0.004-0.015	< 0.001
Gender (male)	0.248	0.024-0.472	0.030
HR	0.008	0.004-0.013	< 0.001
SBP	-0.005	-0.009 - -0.002	0.003
Temperature (^{0}C)	0.015	-0.029-0.058	0.506
GCS	-0.078	-0.111 - -0.045	< 0.001
ISS	0.043	0.032-0.055	< 0.001
Hospital LOS			
Age (years)	0.004	-0.003-0.011	0.318
Gender (male)	0.163	-0.133-0.459	0.278
HR	0.011	0.005-0.017	< 0.001
SBP	-0.003	-0.008-0.001	0.162
Temperature (^{0}C)	0.012	-0.046-0.069	0.693
GCS	-0.020	-0.064-0.023	0.358
ISS	0.050	0.035-0.065	< 0.001

RC: Regression coefficient, CI: Confidence interval, ICU: Intensive care unit; patient was admitted to ICU after presentation to the emergency department. HR: Heart rate in beats per minute, SBP: Systolic blood pressure in mmHg, GCS: Glasgow Coma Scale score, ISS: Injury Severity Score, LOS: Length of stay in days. Multivariate analysis was performed using logistic regression.

identified, higher heart rate and depressed GCS on admission in particular portended worse outcomes. Clinicians should be especially vigilant with patients who arrive to the ED with these clinical features after frostbite injury. The knowledge of patient epidemiology, clinical characteristics, and predictors of outcomes imparted by this study may be useful in planning resource utilization and to better inform conversations with patients and families about prognosis after frostbite injury.

Ethics Committee Approval: Ethics committee approval by the Institutional Review Board of the University of Southern California was obtained (Approval granted January 28, 2019; Approval number is: HS-19-00015).

Informed Consent: Informed consent was waived due to the study's retrospective observational design of deidentified patient data.

Author Contributions: Concept – M.S., V.C.; Design – M.S., V.C., C.F., Z.W., M.D.T.; Supervision – M.S.; Resource – M.S., K.I., D.C., D.D.; Materials - M.S., K.I., D.C., D.D.; Data Collection and/or Processing - M.S., V.C., C.F., Z.W., M.D.T.; Analysis and/or Interpretation - M.S., V.C.; Literature Search M.S.; Writing Manuscript – M.S., V.C., K.I.; Critical Reviews – C.F., Z.W., M.D.T., D.C., D.D.

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ORİJİNAL ÇALIŞMA-ÖZET
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Donuk travmaları: gidişatın bağımsız belirleyicileri

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ÖZET

Giriş ve Amaç: Donuk travmaları travma alanının önemli mortalite ve morbidite nedenlerinden biridir. Travma merkezlerine başvuran hastaların epidemiyoloji, yaralanma şekilleri ve donukların gidişatı yeterince bilinmemektedir. Bu çalışmanın amacı, hastaların demografik ve klinik özellikleri ile birlikte donuk travması sonrası bağımsız gidişat belirleyicilerini ortaya koymaktır.

Gereç ve Yöntem: Donuk travması olan hastalar, ulusal travma veri bankası (2007-2014) kullanılarak belirlendi. Hastalar yoğun bakım ünitesi (YBÜ) yatışlarına göre çalışma gruplarına ayrıldı. Tek değişkenli analiz, uygun görüldüğü şekilde Mann-Whitney U, Fisher's Exact veya ki-kare testleri ile uygulandı. Lojistik regresyon kullanılan çok değişenli analiz, bağımsız gidişat belirleyicilerini belirledi.

Bulgular: Çalışma dönemi içerisinde toplam 241 hasta bulunmuştur. Başvuru esnasındaki ortanca vücut ısısı 36,3°C idi (IQR 33,4-36,7). Mortalite %3 olarak saptanmıştır (n= 7). 101 (%42) hasta YBÜ'ye kaldırılırken 48 (%20) hastada cerrahi müdahale gerekmiştir. Çok değişkenli analizde mortalite, daha düşük başvuru GKS (p= 0,027) ve ampütasyonla birlikte olan yüksek kalp hızı (KH) ile (p= 0,013) ilişkisi gösterilmiştir. YBÜ yatış gereksiniminin ileri yaş (p= 0,010), erkek cinsiyeti (p= 0,040), yüksek KH (p= 0,031) ve İSS (p< 0,001) ve düşük GKS (p= 0,001) ile ilişkisi gösterilmiştir. Uzamış hastanede yatış süresi ise, daha yüksek KH (p< 0,001) ve İSS (p< 0,001) ile birlikte görülmektedir.

Sonuç: Yaygın olmamakla birlikte donuk yaralanmaları cerrahi müdahale gerektirebilir ve mortalite ile sonuçlanabilir. Vücut ısısından çok düşük GKS ve yüksek KH kötü prognoza işaret etmektedir. Bu bulgular, başvuru esnasında hastaların triyajlarını uygun şekilde yürütmek ve donuk yaralanmaları sonrası prognozu daha iyi öngörmek için kullanılabilir.

Anahtar Kelimeler: Donuk, termal yaralanmalar, hipotermi

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CASE SERIES
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Study of therapeutic results, lymph node ratio, short-term and long-term complications of lateral lymph node dissection in rectal cancer patients

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ABSTRACT

Objective: This study aimed to assess disease free survival, lymph node ratio (LNR) and complication rate among advanced mid to low rectal cancer patients (stage 2-3) who underwent total mesorectal excision (TME) and lateral lymph node dissection (LLND) at the Iran Cancer Institute in 2016-2018.

Material and Methods: The study was carried out on 32 patients treated by curative surgery and lateral lymph node dissection at the Iran Cancer Institute from 2016 March to 2018 March. Chi-square test was used to assess the distribution of dichotomous clinical outcomes by sex. We also used Breslow test in Kaplan-Meier approach to estimate 1-year disease free survival and corresponding 95% confidence intervals (CI).

Results: Of the 279 dissected lymph nodes by TME, 42 nodes (in mesorectal) and of the 232 dissected lymph nodes by LLND, 7 nodes (in iliac, para-iliac and obturator) were positive for metastasis. Higher local recurrence was observed in men (three patients) compared to women (one patient) which was not statistically significant (p= 0.878). We also observed higher 1-year disease free survival rate in women (1-year disease free survival= 93.3%) compared to men (1-year disease free survival= 82.4%), which also was not statistically significant (p= 0.356). 1-year disease free survival rate in patient with negative lymph nodes was 95.5% while respective number in patients with positive lymph nodes was 70% (p= 0.047).

Conclusion: TME with LLND could prolong survival and reduce local recurrence in patients with advanced low rectal cancer. However, large-scale clinical trials are required to evaluate such procedure as a standard in Iran.

Keywords: Rectal neoplasms, lymph node excision, survival, chemoradiotherapy

INTRODUCTION

Total mesorectal excision (TME) is known as the standard treatment for advanced low rectal carcinoma. It is reported that adoption of TME could be of benefit for patients with low rectal carcinoma (1-3). TME could decrease local recurrence and increase survival. Previous studies have supported the effectiveness of TME. However, it is reported that 5-40% of low rectal cancer patients having undergone this technique experience local recurrence after surgery and prognosis in such patients still remains poor (4-6).

It is supposed that poor prognosis of low rectal carcinoma is mainly due to metastasis of lymph nodes outside of the TME field (6-8). Dissection of lateral pelvic lymph nodes is a complementary approach that can be considered as an important fact or to reduce local recurrence and extending low rectal cancer patients' survival. This hypothesis has been investigated in several studies. However, the role of lymph node dissection in terms of prolonging survival of advanced case of low rectal carcinoma is still disputed. In some studies lateral lymph node dissection (LLND) has not depicted survival benefit for low rectal cancer patients, while more recent large scale researches provided supporting evidence for the benefit of LLND (9,10).

In the current study,it was aimed to assess disease free survival, LNR and complication rate among advanced low and middle rectal cancer patients who underwent TME and lateral lymph node dissection at Iran Cancer Institute.

MATERIAL and METHODS

The current research was a case-series study, carried out on 32 eligible patients with advanced stages of lower and mid-rectal cancer (stage 2 and 3) who were treated by

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TME plus LLND at the Iran Cancer Institute. The eligibility criteria included: All patients with stage 2 and 3 of lower and mid-rectal cancer, referring to Iran Cancer Institute from 2016 March to 2018 March who agreed to participate in our study. The exclusion criteria included: metastatic, high rectal and rectosigmoid cancers and unwillingness to participate in the study. The methodology of the study was reviewed and approved by the medical ethics committee of Tehran University of Medical Science (Approval ID: IR.TUMS.VCR.REC.1397.629-Certificate available on demand). Before the study, we assessed whether the patients were eligible to perform LLND according to physical examination, colonoscopy and abdominopelvic and thoracic computed tomography (CT) as a metastasis workup. Prior to study initiation, a written informed consent, addressing that patients could exit the study at any desired time, without negative impact on their future treatment procedure, was completed by each one of them.

In the study group, all patients received chemoradiotherapy as neoadjuvant treatment. All surgical operations were performed using standard open laparotomy with mid-line incision. In the LLND technique, bilateral extraction of para-iliac and obturator lymph nodes was performed (from iliac artery bifurcation to obturator nerve). In order to minimize post-operative complications, complete neurovascular and ureteral exploration was performed for all patients. After surgery, we counted the number of total dissected and positive lymph nodes to estimate LNR. All study participants were actively followed-up for 1 year after surgery and in each post-op examination, we looked for local recurrence, sexual and urinary disorders and death.

Chi-Square test was used to assess the distribution of clinical outcomes by sex. We also reported mean and standard deviation (SD) for continuous investigated variables. Additionally, to calculate disease-free survival in patients with advanced low and middle rectal cancer, Breslow (Generalized Wilcoxon) test was used in Kaplan-Meier approach. All statistical analyses were performed by IBM© SPSS© (Version 22.0.0.0).

RESULTS

Overall, the current study investigated 32 patients with advanced low and middle rectal cancer treated with TME plus LLND at the Iran Cancer Institute, of whom 17 were males and 15 were females. Mean age of the participants was 57.3 (± 13.9) years. Total numbers of dissected lateral lymph nodes by TME and LLND were 279 and 232, respectively. Of the 279 dissected lymph nodes by TME, 42 nodes (in mesorectal) and of the 232 dissected lymph nodes by LLND, seven nodes (in iliac, para-iliac and obturator) were positive for metastasis (Table 1).

In the first year following surgery, for each studied patient, carcinoembryonic antigen (CEA) level was screened every three months. At the end of the first year, colonoscopy and double-contrast thoraco-abdomino-pelvic CT scan was performed on all of the studied patients. In general, lymph node dissection associated complications was observed in one male patient with impotency. Respective number was 0 in females (p= 0.910). Higher local recurrence was observed in men (three patients) compared to women (one patient) which was not statistically significant (p= 0.878). We also observed higher 1-year disease free survival rate in women (93.3%) compared to men (82.4%), which again, was not statistically significant (p= 0.356). In addition, 1-year disease free survival was calculated for patients with negative and positive lateral lymph nodes. 1-year disease free survival rate in patient with negative lymph nodes was 95.5% while respective number in patients with positive lymph nodes was 70% (p= 0.047) (Figure 1). Neither any unexpected bleeding during surgery nor any post-op hematoma or urinary complications were observed in participants.

Table 1. Characteristics of the study participants (n= 32)

Sex	
Male	17 (53.1%)
Female	15 (46.8%)
Age	
Mean (SD)	57.3 (13.9)
Total number of dissected lymphnode	
TME	279
LLND	232
Mean (per patient)	15.97
Total number of positive lymph node	
TME	42 (15.0%)
LLND	7 (3.0%)
Mean (per patient)	1.53

SD: Standard deviation, TME: Total mesorectal excision, LLND: Lateral lymph node dissection.

DISCUSSION

Lateral pelvic lymphadenectomy is one of the treatments for patients suffering from advanced low rectal cancer. However, a universal agreement about its effectiveness is still lacking and there is no global agreement on whether lymph node dissection could be beneficial for low rectal cancer patients or not. Therefore, different approaches to such patients are used among surgeons worldwide. For instance, lateral pelvic lymphadenectomy is being used as arecommended treatment in Japan, while it is not frequently performed in western societies (6,11-13).

In the current study, we found tan estimated 12.5% for local recurrence in participants, which is consistent with previous studies reporting local recurrence rate in patients who had total mesorectal excision ranging from 5% to 40% (4,14-17). Yokoyama et al. have reported local recurrence in 3.0% of patients with LLND, while in patients without lymphadenectomy, it was 12.2% (18).

The percentage of 1-year disease free survival for patients treated by TME and LLND and was 87.5% in our study. Although this

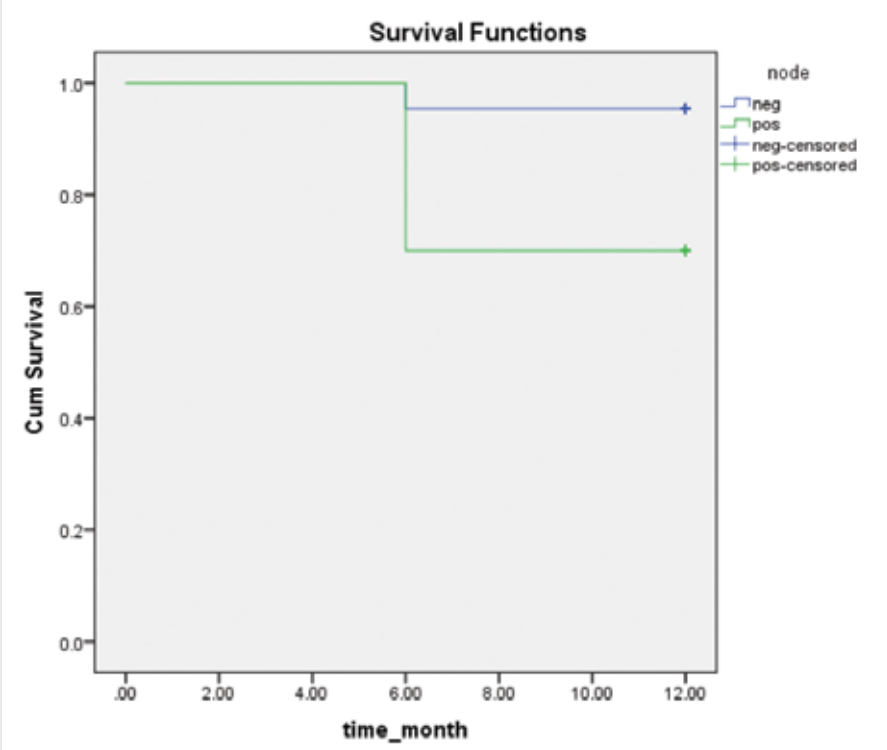

Figure 1. Disease-free survival rate of patients with advanced low rectal carcinoma admitted at Iran Cancer Institute by lymph node involvement.

number was partially higher in women than men, no statistically significant difference was observed. This finding is consistent with previously performed studies as well (19-21).

We examined 232 lateral lymph nodes, seven of which were positive for metastasis (3.0%). This findingis substantially lower compared to the previous studies, reporting lateral pelvic lymph node involvement from 38.0% to 71%. This could be the result of neoadjuvant chemoradiotherapy all of the studied patients received prior to surgery. We were unable to find any other attributable factors to the low number of positive lymph nodes in our cases. Therefore, this finding needs further testing in future studies. In addition, in recent studies, lateral lymph node (LLN) involvement rate has been reported 14.6% and 19.1% (Wu and Yokoyama), which is closer to our results (6,18). Positive LLN is associated with increased risk of local recurrence, which consequently reduces survival in advanced low rectal cancer patients (6). There is some evidence indicating that LLND provides better outcomes regarding both local recurrence and survival in patients diagnosed with negative lateral pelvic lymph nodes (6,7,18,19). Sugihara et al. have reported a significant difference in 5-year survival rate after surgery in patients with negative and positive lymph node dissection (7). Our current study also showed asignificantly higher 1-year disease free survival rate in negative lymph node patients (95.5%) compared to patients with positive LLN (70%), which is compatible with previous studies (7,8).

Lymph node dissection is not a procedure without complication. It generally increases operation time and blood loss. Hence, patient selection for LLND must be regarded as an important factor to receive better results in terms of both local recurrence and survival rate in low rectal cancer patients (18).

We encountered some limitations in our study which should be considered while interpreting the results. First of all, small number of study participants along with short follow-up time might have resulted in overestimated survival rates in patients who had TME + LLND. Secondly, as the current study was a case-series, there was no comparison group. Therefore, we believe that the findings of this study should be reevaluated in future clinical trials, as there are alternative treatments for advanced low rectal cancer including mere TME and preoperative chemoradiotherapy.

In conclusion, it seems that TME with LLND could prolong survival and reduce local recurrence in patients with advanced mid and low rectal cancer as the results of current study support the effectiveness of lymphadenectomy in terms of survival improvement of mid and low rectal cancer patients.

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Ethics Committee Approval: The methodology of the study was reviewed and approved by the medical ethics committee of Tehran University of Medical Science (Approval ID: IR.TUMS.VCR.REC.1397.629-Certificate available on demand).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.M.; Design - H.M., A.B.; Supervision - H.M., R.O.; Materials - A.B.; Data Collection and/or Processing - A.B., M.A.B.; Analysis and/or Interpretation – A.B.; Literature Search – M.A.B.; Writing Manuscript – A.B.; Critical Reviews – R.O., H.M.

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

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OLGU SERİSİ-ÖZET
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Rektum kanseri hastalarında lateral lenf nodu diseksiyonunun terapötik sonuçlarının, lenf nodu oranının ve kısa-uzun dönem komplikasyonlarının değerlendirilmesi

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, 2016-2018 yılları arasında İran Kanser Enstitüsünde total mezorektal eksizyon (TME) ve lateral lenf nodu diseksiyonu (LLND) geçiren ileri evre orta-alt rektum kanseri hastalarında (2-3. Evre) hastalıksız sağkalım, lenf nodu oranı (LNO) ve komplikasyon oranını değerlendirmektir.

Gereç ve Yöntem: Bu çalışma Mart 2016-Mart 2018 tarihleri arasında İran Kanser Enstitüsünde küratif cerrahi ve lateral lenf nodu diseksiyonu ile tedavi edilen 32 hasta üzerinde yürütüldü. Cinsiyete göre ikili klinik sonuçların dağılımını değerlendirmek için ki-kare testi kullanıldı. Ayrıca, %95 güven aralıklarına karşılık gelen bir yıllık hastalıksız sağkalımı hesaplamak için Kaplan-Meier yaklaşımında Breslow testi kullanıldı.

Bulgular: TME ile diseke edilen 279 lenf nodundan 42 (mezorektal)'si ve LLND ile diseke edilen 232 lenf nodundan yedisi (iliyak, para-iliyak ve obturator) metastaz için pozitif tespit edilmiştir. Kadınlara oranla (bir hasta) erkeklerde (üç hasta) daha yüksek oranda lokal nüks izlenmiş ancak bu oran istatistiksel açıdan anlamlı bulunmamıştır (p= 0,878). Yine istatistiksel olarak anlamlı olmasa da erkeklere kıyasla kadınlarda daha yüksek bir yıllık hastalıksız sağkalım oranı tespit edilmiştir (erkekler: %82,4, kadınlar: %93,3, p= 0,356). Negatif lenf nodu olan hastada bir yıllık hastalıksız sağkalım oranı %95.5 iken aynı oran pozitif lenf nodu olan hastalarda %70 idi (p= 0,047).

Sonuç: LLND ile TME, ileri evre alt rektum kanseri hastalarında lokal nüksü azaltabilir ve sağkalımı uzatabilir. Ancak, bu tür bir müdahaleyi İran'da standart tedavi olarak kabul etmek için büyük ölçekli klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Rektal neoplazma, lenf nodu eksizyonu, sağkalım, kemoradyoterapi

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CASE REPORT
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Inlet patch mimicking unstable angina pectoris

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ABSTRACT

The ectopic stomach mucosa island in the proximal esophagus, which is generally known as the inlet patch or cervical inlet patch, is called as the heterotopic gastric mucosa of the esophagus. Despite its asymptomatic progress, it may cause chest pain, shortness of breath and difficulty in swallowing due to the acid secretion from the ectopic mucosa. The study aimed to present a patient who underwent coronary angiography with an unstable angina pectoris diagnosis by cardiologists for gastric chest pain but found an inlet patch in gastroduodenoscopy.

Keywords: Inlet patch, unstable angina pectoris, differential diagnosis

INTRODUCTION

The heterotopic gastric mucosa (HGM) of the esophagus, also known as the inlet patch (IP), is a clinical entity described first in 1805 by Schmidt as the ectopic gastric mucosa located in the proximal esophagus (1). In the reported endoscopical studies, the incidence varies from less than 1% to 13.8%. This rate increases to 70% in autopsy studies (2,3). Although IP is generally considered as congenital, there are also those who think that it is acquired (4,5).

Although most IPs are asymptomatic, they can cause chest pain and shortness of breath when they are acid-releasing (6). IP should be considered in the differential diagnosis of patients with chest pain complaints.

CASE REPORT

A 42-year-old male patient applied to our policlinic with complaints about cough, back pain and burning in stomach and throat ongoing for a long time. The patient said his complaints diminished after drinking anti acid syrups. The patient, who underwent in-depth anamnesis, said he applied to the emergency service of our hospital a week ago with severe chest pain, shortness of breath and excessive sweating. The patient did not have any underlying diseases and he smoked 2 packs of cigarettes a day and as his father also had a story of heart attack. The patient's enzyme and troponin were inspected at the emergency service. Although the results were normal and there was no problem in his electrocardiography, he was diagnosed with unstable angina pectoris and he was given urgent coronary angiography by the cardiology unit. The patient who had no problem following the treatment was discharged on the next day.

Upon this, after the patient was interviewed and the consent was obtained for gastroduodenoscopy, the procedure was performed under mild sedation. In gastroduodenoscopy, there were areas with erythema and oval-shaped, flat, velvety mucosa with approximately 0.5 x 1 cm of perimeter in the esophagus at 20 cm, which was separated from the peripheral esophageal tissue by sharp borders (Figure 1), and biopsy was taken from here. As there was doubt about the heterotopic gastric mucosa in the esophageal lesion and antral gastritis in the patient, proton pump inhibitor was administered to the patient. Pathologic result was chronic gastritis with mucous and

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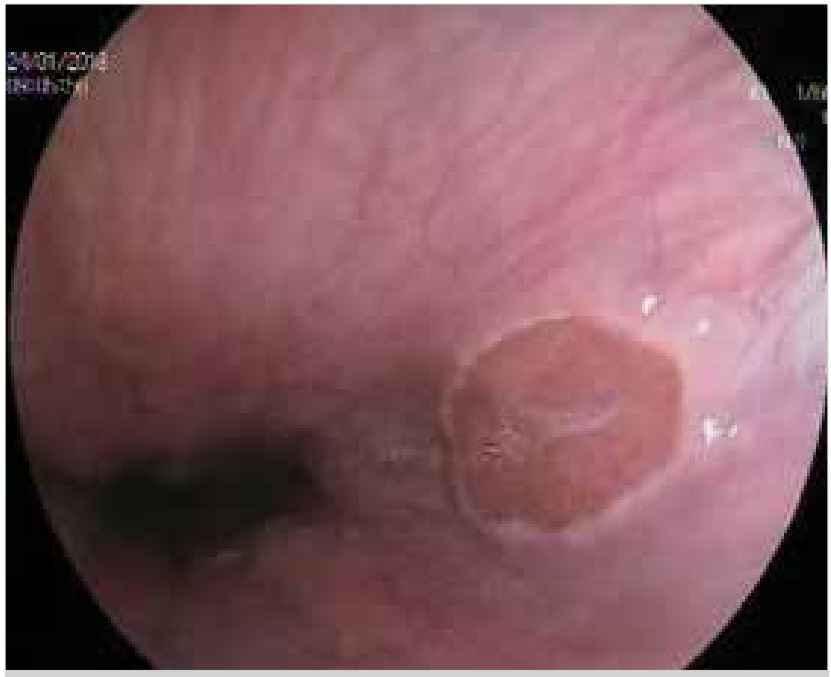

Figure 1. The endoscopic image of the oval-shaped, flat, velvety, heterotopic gastric mucosa which is separated from the peripheral oesophageal tissue by sharp borders.

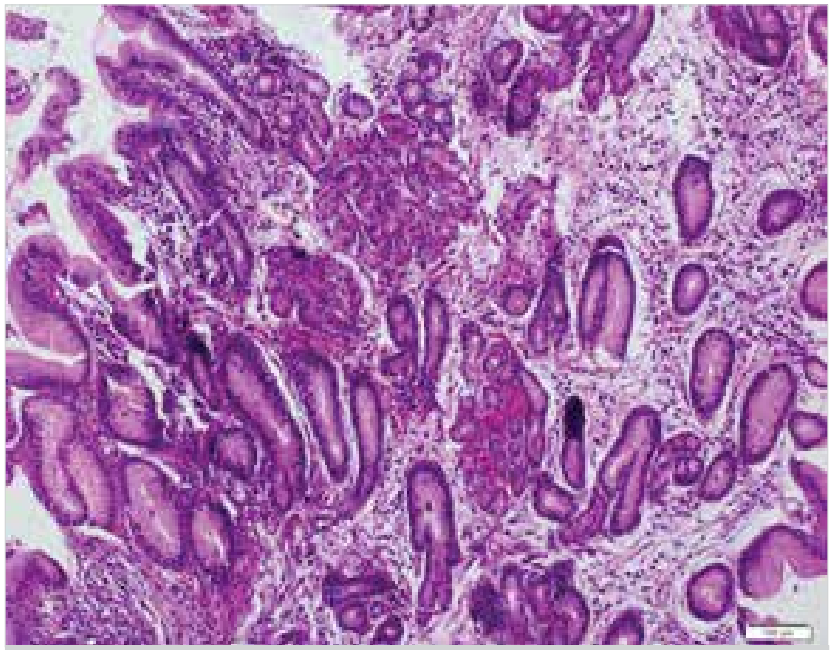

Figure 2. Typical IP image in which there are mucous and parietal cells in the photomicrograph (Haematoxylin eosin staining, original expansion x100).

parietal cells, and Helicobacter pylori were not observed in histology similar to the stomach corpus (Figure 2). These endoscopic and pathologic findings reminded us of HGM, to name in other words the IP, as the diagnosis.

DISCUSSION

Heterotopic gastric mucosa might be raised slightly from the surface, collapsed from the surface or flat, smooth surface or nodular. Microscopically, it is salmon-colored and velvety in ap-

pearance, changing from 2-3 mm to 4.5 cm in size. It can be seen as a single piece or multiple pieces separated from the normal mucosa by sharp boundaries (7). We also conducted a biopsy with the pre-diagnosis of IP as we saw a smooth velvety area, separated by a sharp boundary from the mucosa in the 20th cm as described above while we were performing gastroduodenoscopy to our patient.

The most common histologic type of IP is cardia or oxyntic type of mucosa, and acid production can also be seen from the current gastric mucosa in some phenomena according to the type of the mucosa below. In some patients, laryngopharyngeal reflux is caused by the proximity to the upper esophageal sphincter (8). *Helicobacter pylori* colonization in IP is described up to 82% in some studies. Apart from that, atrophy, metaplasia, dysplasia and even carcinoma of HGM are described (9,10). In the pathology result of our patient, cells similar to the stomach corpus were observed and helicobacter pylori and intestinal metaplasia were not observed.

Many of the cervical IPs are asymptomatic; however, esophagitis, ulcer and web, which are associated with acid secretion, and pain in the chest and throat, dysphagia, sensation of globus and dyspnea -as a result of contraction in the esophagus- may develop (6). Probably, our patient developed esophageal irritation dependent on acid secretion and in turn reflux symptoms and pain in the chest. Recurrent unstable angina pectoris symptoms of our patient lead cardiologists to coronary angiography. We are of the opinion that this case is important to expand the awareness of IP and evaluation of differential diagnosis of esophageal diseases in patients with angina pectoris by emergency physicians and cardiologists.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.T., E.A.; Design - T.T., G.T.; Supervision - T.T.; Materials - T.T.; Data Collection and/or Processing - T.T., M.S.; Analysis and/or Interpretation – T.T., E.A., M.S., G.T.; Literature Search – T.T., E.A..; Writing Manuscript – T.T., G.T.; Critical Reviews – T.T., M.S.

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OLGU SUNUMU-ÖZET
Turk J Surg 2020; 36 (2): 229-232

Unstabil anjina pektorisi taklit eden inlet patch olgusu

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ÖZET

Genellikle inlet patch ya da servikal inlet patch olarak bilinen proksimal özofagustaki ektopik mide mukozası adası, yemek borusunun heterotopik mide mukozası olarak adlandırılır. Asemptomatik olmasına rağmen, göğüs ağrısına, nefes darlığına ve ektopik mukozanın asit sekresyonuna bağlı yutma güçlüğüne neden olabilir. Sırta vuran göğüs ağrısı nedeniyle kardiyologlar tarafından unstabil anjina pektoris ön tanısıyla koroner anjiyografi yapılan fakat gastroduodenoskopisinde inlet patch tespit edilen hasta sunulmuştur.

Anahtar Kelimeler: Inlet patch, unstabil anjina pektoris, ayırıcı tanı

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CASE REPORT
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Pancreatic inflammatory myofibroblastic tumor presenting with extracolonic obstruction

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ABSTRACT

Inflammatory myofibroblastic tumor is a rare soft tissue tumor which can be detected in many parts of the body. Its etiology and clinical behavior are not fully understood, and its treatment is controversial. This study aimed to present the management of a pancreatic tail case presenting with extracolonic obstruction findings. Unblock distal pancreatectomy + left surrenalectomy + left hemicolectomy + splenectomy operation was made with R0 resection principles. Although there are some medical treatments reported in children and unresectable tumors in the medical literature, complete surgical resection following oncological principles seems to be the most important and main treatment modality in the treatment of inflammatory myofibroblastic tumors. However, inflammatory myofibroblastic tumor has many aspects that are not yet clearly understood, and it is a disease being continuously researched.

Keywords: Myofibroblastic, pancreas, mass

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is a rare soft tissue tumor which can be detected in many parts of the body. Its etiology and clinical behavior are not fully understood, and its treatment is controversial (1-5). Although this unusual disease has a relatively good prognosis, its differential diagnosis from other malignant diseases is challenging. In our study, we presented the management of a pancreatic tail case presenting with extracolonic obstruction findings. The aim of this study was to discuss our patient that had IMT originating from the tail of pancreas in light of the literature.

CASE REPORT

A 61-year-old male patient was admitted to our hospital with abdominal pain. Blood pressure was 100/70 mmHg and Heart rate: 90/min. There was no personal or family history. There was mild distension and moderate sensitivity in abdominal examination. No special condition was detected in other whole-body system examinations. Antral gastritis was found in upper gastrointestinal endoscopy. In colonoscopy, there was an impression of external compression in the descending colon which did not allow proximal transition. Wbc: 9200 10^3/10 µL, hemoglobin: 10.8 mg/dL, and tumor markers (CEA, CA-19-9) were within normal limits. Whole abdominal tomography revealed diffuse wall thickening in the descending colon and marked dilatation of the proximal colon segments. Marked inflammatory changes were observed in fatty tissue in the pericolic area (Figures 1, 2). It was decided to perform laparotomy on the patient for diagnosis and treatment. Exploration revealed a mass of approximately 10 cm, which was thought to be of distal pancreas origin, with 2 cm invasion of the anterior abdomen wall, covering the colonic splenic flexure, left surrenal and splenic ves-

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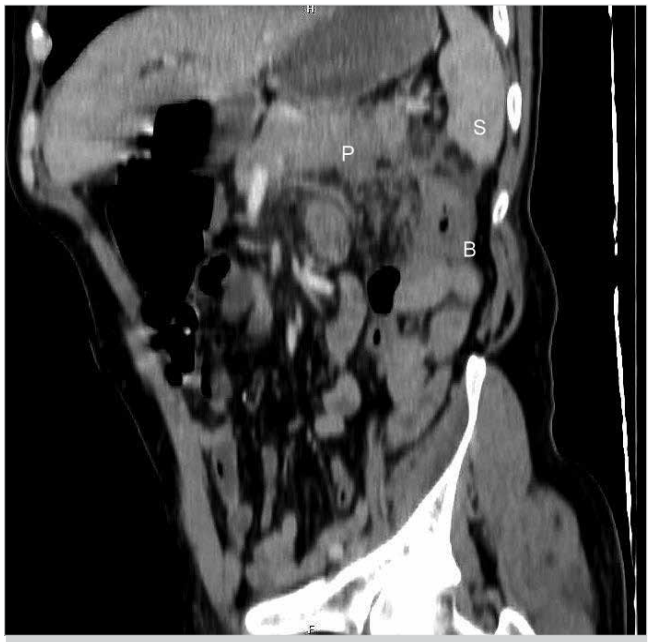

Figure 1. Axial contrast computed tomography: asymmetric wall thickening in the descending colon. Increases in linear branching density from descending colon to the mesenteric tissue, pancreas and spleen (P: Pancreas, B: Bowel, S: Spleen).

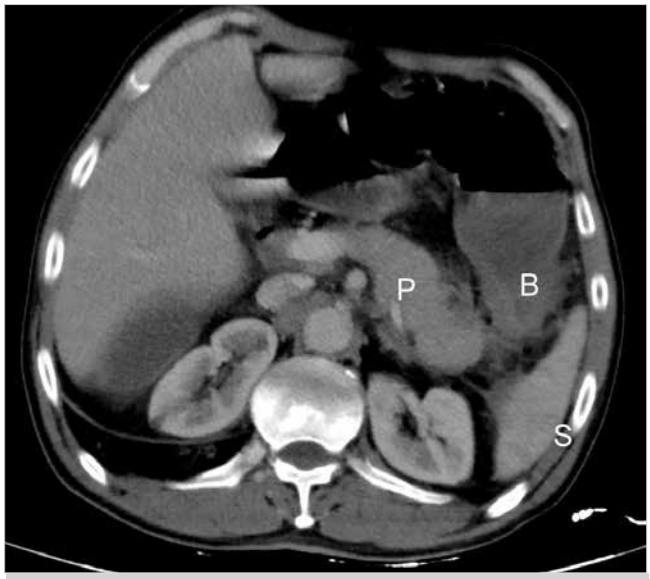

Figure 2. Sagittal re-format computerized tomography: Increases in linear branching density from descending colon to the mesenteric tissue, pancreas and spleen are observed (P: Pancreas, B: Bowel, S: Spleen).

sels, and which was attached to the jejunum adjacent to the treitz ligament, the left kidney parenchyma and mezo via desmoplastic reaction. Considering oncological principles, the desmoplastic adhesions of the tumor with the left kidney and the jejunum in the

Figure 3. En bloc resection including the colon, mesenteric fatty tissue, partial pancreas and adrenal gland.

treitz ligament were separated and the anterior abdominal wall muscle fibers were included into the piece according to R0 resection, and the patient underwent unblock distal pancreatectomy + left surrenalectomy + left hemicolectomy + splenectomy operation (Figure 3). Postoperatively, the patient developed a low flow pancreatic fistula with a daily flow rate of 400 cc. Following oddi sphincterotomy via endoscopic retrograde cholanjio-pancreatography (ERCP), the fistula was closed with medical treatment and follow-up. The patient was discharged on the 16th postoperative day. Resection material was fixed in 10% formaldehyde solution (%10 NB Formaldehyde, Novogen Diagnostik, Istanbul, Turkey) and delivered to the pathology laboratory. On gross examination, macroscopy revealed a colon without any pili due to severe edema of 26 cm on a 15 x 13 x 7 cm irregularly shaped material. A 10 cm mass lesion that encapsulated the colon from the middle section had narrowed the lumen due to compression. The mass had 2 cm surrenal muscle area on one side and 2 cm irregular muscle area on the other side.

On histopathologic examination, a tumoral lesion was observed predominantly consisting of cytologically bland spindle- or stellate-shaped cells loosely arranged in an edematous or hyaline stroma with scattered plasma cells and lymphocytes. Tumoral cells were arranged in a storiform or fascicular growth pattern with a limited infiltrative border neighboring organs. Inflammatory cells were formed in small clusters in some areas. No cytologic atypia, atypical mitotic figures or necrosis were seen. Im-

munohistochemical study revealed in a strong intensity, diffuse positive staining for vimentin and alpha smooth muscle actin; in a weak-moderate intensity, focal positive staining for pancytokeratin and in a weak-moderate, near diffuse positive staining for anaplastic lymphoma kinase (ALK). Positive staining for IgG4 antibody was seen in a few scattered plasma cells. The tumor cells did not stain with IgG4. Likewise, the tumoral cells did not stain with DOG-1, CD117, beta-catenin, desmin and S-100 protein. On the basis of morphologic and immunohistochemical staining results, the case was diagnosed as IMT (Figure 4-7).

No problems were detected in the polyclinic follow-up of the patient and informed consent was obtained for publication. No evidence of relapse or metastasis was observed in the laboratory and radiological tests performed at the 8th month.

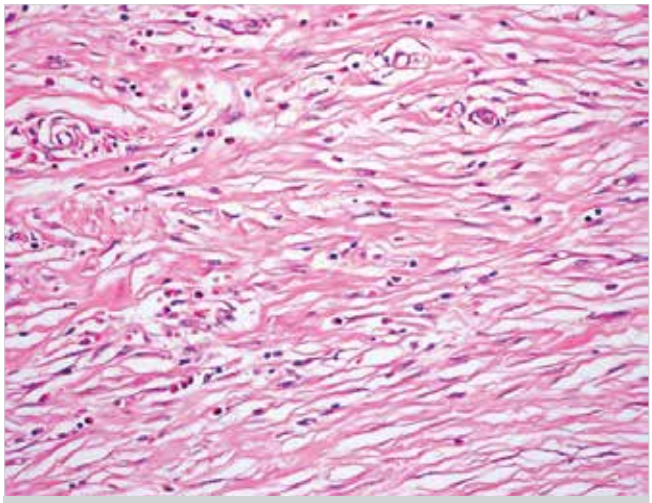

Figure 4. Fibrous tissue bundles of spindle cells between mononuclear inflammatory cell infiltration (H&E x200).

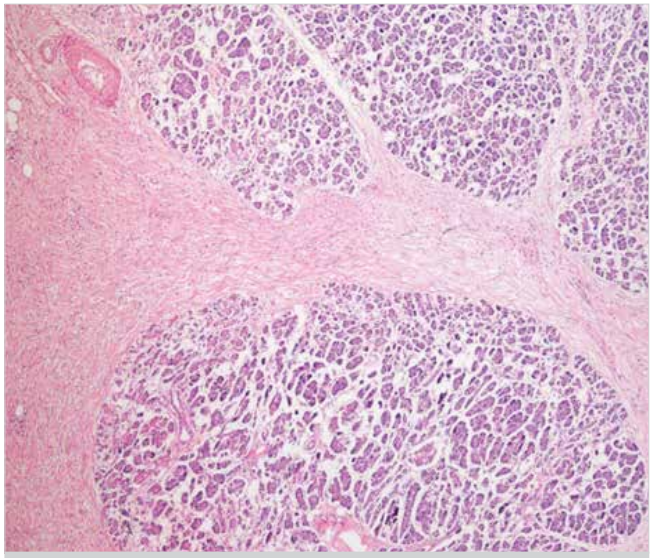

Figure 5. Microscopically fibrous tissue bundles infiltration in pancreatic tissue.

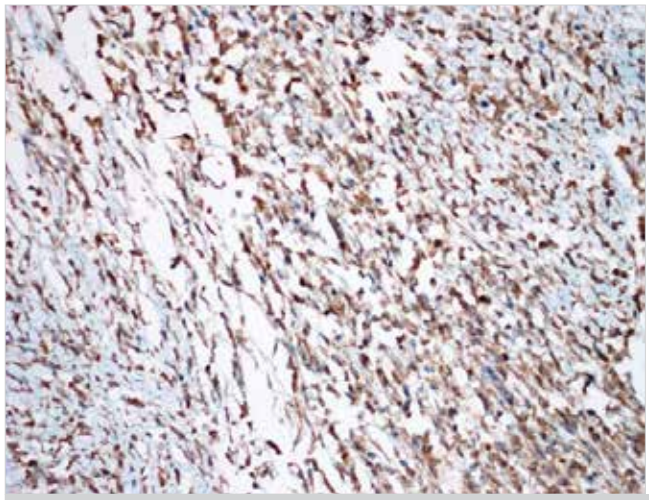

Figure 6. Immunohistochemical ALK positivity in tumor cells (ALK x200).

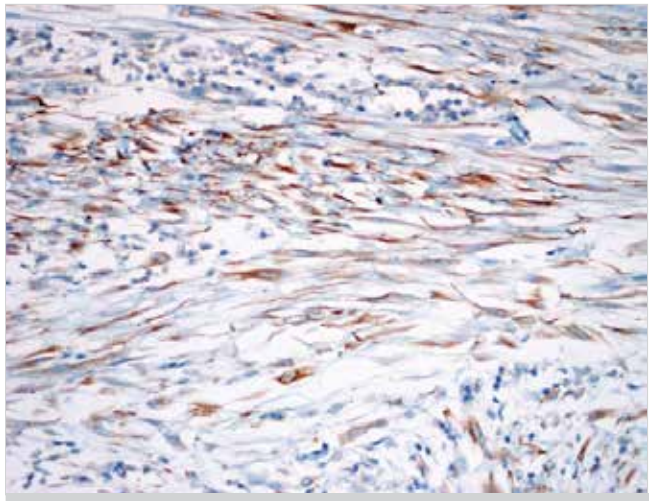

Figure 7. Immunohistochemical PanCK positivity in tumor cells (PanCK x200).

DISCUSSION

IMT is a rare disease. It is known in the literature as inflammatory fibrosarcoma, inflammatory pseudotumor or IMT. Its prevalence in men and women is generally equal, and it is seen in a very wide age range of 0-82 (1-3).

IMT can be seen in many parts of the body. Locations where it can be seen cover a very broad spectrum; including the pancreas, lungs, tongue, heart mediastinum, extremities, liver, small intestine, brain, placenta, pelvis, retroperitoneum, epiglottis, kidney, bladder and testis (3-5). When this disease is located in the pancreas, it can be seen in the tip, body or the tail of the pancreas (1). In our case, it was located in the pancreatic tail.

Clinical symptoms of the disease are associated with its location. It can be detected by radiological tests or examination as a result of non-specific complaints, or it can also present itself with

a mass or associated symptoms, findings or complications (1,6). In our case, the tumor did not cause mass formation radiologically, and presented itself through the complication of colonic obstruction. In addition, there are also atypical cases in the literature presenting with psychiatric disorders such as anorexia nervosa (7).

Although it has been reported in the literature to be generally locally aggressive and non-metastatic, inflammatory myofibroblastic tumor of the pancreas may also show lymphatic metastasis (4). Peritoneal dissemination of stomach-induced IMT has also been shown in the literature (8).

As with many tumor types, radiological or laboratory diagnosis is not possible and histopathological diagnosis is required. This may be a biopsy accompanied by interventional radiology; however, diagnosis is usually made after surgical excision, as in our case.

In cases with pancreatic lesions, surgery is usually performed with laparotomy as in our case, but laparoscopic resection may also be a treatment option (2).

There are cases in the literature where remission is achieved with anaplastic lymphoma kinase (ALK) inhibitors when surgical resection is not possible and also cases showing a good response to methotrexate and vinorelbine chemotherapy (5,9). On the contrary, there are cases showing no response to adriamycin and gemcitabine chemotherapy (6).

Complete surgical resection following oncological principles is seen as the most important and main treatment method in the treatment of this disease (10,11). Postoperative adjuvant therapy is not recommended, but long-term follow-up is required. As a matter of fact, IMT has a local recurrence rate of 15-37% (10,12).

Histopathologic differential diagnosis of this case included fibromatosis (desmoid tumor), extraintestinal gastrointestinal stromal tumor, IgG4-related sclerosing diseases and less likely other tumors with spindle cells. The immunohistochemical reactivity of the spindle and stellate cells for pancytokeratin and ALK and negativity for beta-catenin, CD117, DOG-1 assist in distinguishing IMT from fibromatosis and extraintestinal gastrointestinal stromal tumor. IgG4-related sclerosing lesions are usually a group of disorders ill-defined, entrapping the normal tissues in the vicinity. They tend to have more intense lymphoplasmacytic inflammatory cell infiltration and prominent sclerosis and phlebitis than the typical IMT. Recently, a number of studies have found IgG4-positive plasma cells in IMTs (13). Likewise, IgG4 positivity was detected in a small number of cells in our case.

For other tumors composed of elongated spindle cells arranged in a fascicular or storiform growth pattern, differentiation from IMTs may less likely pose a problem. These entities include fibrosarcoma, leiomyosarcoma and malignant peripheral nerve sheath tumors. These tumors usually contain high cellularity, higher nuclear atypia, more mitotic figures and necrosis than IMTs. Indeed, the immune staining pattern is different these tumors and solves the problem.

Lacoste et al. (14) have reported that high-dose steroid treatment resulted in tumor regression and tumor disappeared in pancreatic inflammatory tumor in children and the disease was not detected during 2-year follow-up.

In conclusion, complete surgical resection following oncological principles seems to be the most important and main treatment modality in the treatment of IMTs. However, IMT has many aspects that are not yet clearly understood, and it is a disease being continuously researched.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.İ., S.K.K.; Design - N.İ., S.K.K., S.Ü.; Supervision - N.İ., S.K.K., S.Ü., S.D.; Materials - T.B., H.G., S.Ü.; Data Collection and/or Processing - N.İ., S.K.K., S.D.; Analysis and/or Interpretation - S.D., S.Ü., O.N.G., H.G.; Literature Search - N.İ., S.K.K., T.B., H.G.; Writing Manuscript - N.İ., S.K.K., H.G., O.N.G.; Critical Reviews - H.G., O.N.G.

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

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OLGU SUNUMU-ÖZET
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Ekstrakolonik tıkanıklıkla seyreden pankreatik inflamatuvar miyofibroblastik tümör

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ÖZET

İnflamatuvar miyofibroblastik tümör, vücudun pek çok bölgesinde görülebilen nadir bir yumuşak doku tümörüdür. Etyolojisi ve klinik davranışı tam olarak anlaşılamamış ve tedavisi tartışmalıdır. Ekstrakolonik obstrüksiyon bulgularıyla seyreden pankreas kuyruk kaynaklı bir olgu sunmaktayız. Hastaya R0 rezeksiyon prensipleriyle distal pankreatektomi + sol sürrenalektomi + sol hemikolektomi + splenektomi operasyonu uygulandı. Tıbbi literatürde, çocuklarda ve unrezektabl tümörlerde bazı medikal tedaviler rapor edilmiş olsa da, onkolojik prensiplerle yapılan komplet cerrahi rezeksiyon inflamatuvar miyofibroblastik tümörün en önemli ve ana tedavi modalitesi olarak görünmektedir. Ancak, tam olarak anlaşılamamış pek çok yönüyle, inflamatuvar miyofibroblastik tümör, araştırılmaya devam edilmektedir.

Anahtar Kelimeler: Miyofibroblastik, pankreas, kitle

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LETTER TO THE EDITOR
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Are PNETs radiotherapy resistant?

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Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors with highly variable biological behaviors and clinical course. Despite being rare, its incidence is steadily increasing over time. In recent years, advances have been made in the treatment of these tumors in parallel to the increase in the incidence of PNETs. Although a multidisciplinary approach is required for the clinical management of PNETs, resection remains to be the single curative treatment in early disease. In retrospective studies, it has been reported that surgical resection alone provides better outcomes than other treatment modalities; however, patients eligible for resection comprise only 39% of the patients (1-3). Chemotherapy, radiofrequency ablation, transarterial chemoembolization, biotherapy, polypeptide radionuclide receptor therapy, anti-angiogenic treatment and selective internal radiotherapy alone can be used in advanced PNETs. However, studies have failed to demonstrate long-term survival benefit in these alternative approaches. Today, there is no effective treatment modality for locally advanced PNETs due to high malignancy potential and resistance to conventional chemotherapy. However, it has been attempted to use targeted therapies such as Everolimus or Sutent, radiotherapy and chemotherapy in combination strategies (1-5).

Although there are several studies attempting to define the role and importance of radiotherapy in PNETs in the literature, many uncertainties are present regarding these tumors. Role of external beam radiation therapy (EBRT) is largely unknown in the management of PNETs, and data are limited to anecdotal reports. In general, it is thought that PNETs are resistant to radiotherapy. However, in recent years, there have been studies indicating that PNETs respond to both radiotherapy and chemotherapy. In a study by Saif et al., radiotherapy (50.4 Gy/1.8 Gy fractions) plus capecitabine or infusional 5'-flurouracyl has been given to patients uundergoing surgery due to locally advanced PNET. Authors have reported that chemoradiotherapy was tolerable and provided good local control in the treatment of PNET (1). In a study by Contessa et al., 36 patients with PNET have been treated by external beam radiation therapy. Authors have reported that no local failure was observed at doses > 32 BED (2 Gy) (2). In a study on patients with pancreatic PNET, Zagar et al. have stratified patients into two groups as patients treated with surgical resection alone and those received combined chemoradiotherapy following surgery. In the combination group, patients received radiotherapy (50.4 Gy/1.8 Gy fraction) plus fluoropyrimidine-based chemotherapy. Authors have reported that there was no significant difference in disease-free survival and overall survival between the groups (4). Another study has compared patients undergoing surgery alone with those that received adjuvant radiotherapy among PNET cases with positive surgical margins. Authors have reported that recurrence rate was comparable between the groups and that radiotherapy could be helpful in achieving local control (5). It has been emphasized that radio-

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therapy is a good palliative modality in patients with unresectable tumor and symptomatic findings (2). In another study, it has been suggested that local radiotherapy can achieve debulking in unresectable or locally advanced tumors (6).

Despite being rare, PNETs are treatable tumors increasingly diagnosed by advancing imaging modalities. They have highly variable clinical course with life expectancy varying from months to years. Several modalities have been used in the management of PNET. Due to lack of prospective, randomized studies, it is unknown which criteria should be used to select treatment modality. In the last decade, significant advances have been achieved in the treatment of PNETs by radiotherapy and chemoradiotherapy. In inoperable or locally advanced PNETs, local control, decrease in tumor burden, regression in clinical symptoms, decelerated disease progression and prolonged progression-free survival can be achieved by radiotherapy and chemoradiotherapy. It will be possible to determine the role of radiotherapy by multicenter, prospective studies with larger sample size, providing relatively uniform analysis and specific assessment of tumor groups. The selection of eligible patients, well-constructed treatment plan, and well-planned clinical and radiological follow-up should be the mainstay of studies in this field.

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