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AIMS AND SCOPE

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.

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

The Turkish Journal of Surgery is currently abstracted/indexed by PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Scopus and EBSCO.

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Manuscripts must be submitted via the online submission system, which is available at www.turkjsurg.com. Journal guidelines, technical information, and the required forms are available on the journal's web page.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Surgical Society, editors, editorial board, and/or publisher; thus, the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts submitted to another journal for evaluation but rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

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An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement verifying that written informed consent of the patients and volunteers was obtained following a detailed explanation of the procedures should be included. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee, and the ethics committee approval number should also be stated in the Material and Methods section of the manuscript. It is the authors' responsibility to carefully protect patients' anonymity. For photographs that may reveal the identity of the patient, releases signed by the patient or his/herlegal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;
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.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Turkish Journal of Surgery requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkjsurg.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all responsibility for authorship during the submission and review stages of the manuscript.

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.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to cases that cannot be resolved internally. The Editor-in-Chief is the final authority in the decision-making process for all appeals and complaints.

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MANUSCRIPT PREPARATION

Manuscripts should be prepared in accordance with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2017 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkjsurg.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process by the editorial office staff to ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

- Copyright Transfer Form,

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

during the initial submission. These forms are available for download at www.turkjsurg.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, which should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- 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.

Human Subjects Research

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)"

All references, tables, and figures should be referred to within the main text and numbered consecutively in the order they are referred to within the main text.

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

References

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.

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

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

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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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PREFACE
Turk J Surg 2021; 37 (1): IX-X.
10.47717/turkjsurg.2021.9901

The Pandemic, Statistics for 2020, Journal Targets and Gastric Cancer

When I was appointed as the editorial coordinator of the journal, I pointed out our goals to be reached and the most important one was increasing the quality and visibility of the journal. During the last two years, I believe we have reached that target publishing very high-quality manuscripts with the continuous efforts of the editorial team and the reviewers. I would like to thank all authors for sending their work to the Turkish Journal of Surgery.

2020 will be remembered with the COVID-19 pandemic and unfortunate loses all over the world. Currently, the total number of cases in Turkey is 3.240.577 and total number of deaths is 31.230, including 392 healthcare professionals (1,2).

During the pandemic, we published four issues and 66 manuscripts consisting of 43 original article, 11 case series & case reports and 3 invited reviews. Although we published 66 articles, we received 274 submissions, 114 of which came from 28 different countries. India, United Kingdom, Pakistan, Iran and Georgia were the first five countries.

Out of 274 submissions, 205 were already evaluated and finalized with an acceptance rate of only 21.5 percent (44 accepted and 161 rejected). Sixty-six articles published in 2020 includes 25 accepted papers from 2020.

During 2020, 274 manuscripts were submitted to the journal and evaluated by 74 reviewers. I would like to thank all of them for their efforts. Final decision for the manuscripts reached within an average of 51.23 days including revisions. Total evaluation time was 3.59 days for the assoc editors' first look, 5.79 days for the reviewers, 26.47 days for the assoc editors' decision, 9.26 days for the authors's revision, and 6.12 days for the editor in chief's decision.

Sixteen papers in 2020 underwent statistical evaluation by the statistical reviewer and average review time was 11.62 days. Five were accepted and 3 rejected directly, and 8 were sent to the authors for revision before acceptance.

CiteScore of the journal was 0.56 in 2018 and it rised to 1.0 in 2019 (evaluated in 2020). CiteScore for 2020 will be available in May 2021. In 2017, 76 documents had 127 citations; in 2018, 76 documents had 119 citations and in 2019, 84 documents had 146 citations, therefore the number of citations is also in a rise (3).

In this first issue of 2021, you will find 11 original articles (3 of them are actually case series), 2 case reports and 1 surgical technique. All of them are very good studies; however, I would like to call your attention to 4 articles on gastric cancer (4-7).

Yüksel A et al. compared laparoscopic and open surgery for gastric cancer, and despite being a low volume center for laparoscopic gastric cancer surgery, they concluded that the risks were similar for both techniques (4).

In another case series study by Kayaalp and his team, although the number was too small, it was found that laparoscopic surgery was technically applicable (5).

In another interesting study by Akcakaya et al. on gastric cancer, they showed that there was no impact of E-cadherin expression on tumoral features and survival in gastric cancer; however, -160 C→A polymorphism might influence the expression of E-cadherin in gastric cancer (6).

Ozmen MM et al. compared D2 dissection with D2 plus PALND in patients with advanced gastric cancer and concluded that D2-PALND could be performed safely by experienced surgeons and results in better survival rate especially in patients with advanced disease such as stage IIIA and IIIB (7).

I would also like to take the opportunity to inform you that we will proceed with a new application to Web of Science for inclusion in current contents and SCIE. We will also apply to Pubmed Medline for inclusion. We are currently preparing documents for these applications, and I have every confidence that we will be successful in these steps with the increased quality of the journal.

I extend my sincerest gratitude to every person who has made valuable contributions to the journal. I eagerly look forward to witnessing further advances in the near future.

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Editorial Coordinator, Turkish Journal of Surgery
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FROM THE EDITOR'S DESK
Turk J Surg 2021; 37 (1): XI.
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Dear Authors of the Turkish Journal of Surgery,

We are very pleased to present the first issue of Turkish Journal of Surgery in 2021. An issue is the "end product" of a long and exhausting work of the authors, editorial staff, reviewers and publishing team. The articles you read sometimes have a long history with numerous revisions and improvements upon the suggestions of the reviewers. In this issue, we are glad to open our pages to valuable studies from various disciplines of the surgery.

The term "minimally invasive surgery" was indicated only two decades ago as a new innovative surgical technique whose role was not yet well defined in the daily practice of the surgeons. Subsequent to the enormous worldwide success of laparoscopic cholecystectomy, minimally invasive surgery has become an inseparable part of surgery. Currently, there is not an operation which is not technically "doable" with minimally invasive techniques.

In the March 2021 issue of the Turkish Journal of Surgery, we have four interesting studies on different fields of minimally invasive surgery. A study from the United Kingdom is about hernia surgery. Nahid et al. report their experience on laparoscopic inguinal hernia surgery in regards of two different fixation methods (1). The results of the study show that a mesh application without fixation may be a reliable technique.

Another interesting study of Mehraj et al. is from India (2). The authors report their experience on transanal minimally invasive surgery (TAMIS) in benign and malignant rectum tumors. The role of TAMIS for the management of rectum lesions is not yet well established and we do hope that interesting -and promising- results of this study would be helpful for those interested in colorectal surgery.

Another current hot topic in minimally invasive surgery is the laparoscopic gastric surgery. After the introduction of new devices, together with the growing experience in laparoscopic obesity surgery, there is an increasing tendency now to treat gastric tumors laparoscopically. In this present issue, you have the chance to read two studies from Turkey. Çiçek et al. present their experience in a very specific issue, the laparoscopic management of remnant gastric cancer (3). We do think that the experience of the center on this rare condition is worth reading. Another noteworthy study compares open vs. laparoscopic surgery for the management of gastric cancer (4).

In brief, our readers interested in minimally invasive surgery would find motivating information through these studies. Of course, there are much more to read across the pages of the March 2021 issue.

On behalf of the editorial team, we wish you a good start for 2021 and we are impatient to review your manuscripts.

As I always say: please submit your best work to the Turkish Journal of Surgery!

Best regards,

Kaya SARIBEYOĞLU
Editor,
Turkish Journal of Surgery

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ORIGINAL ARTICLE
Turk J Surg 2021; 37 (1): 1-5

Outcomes on mesh fixation vs non-fixation in laparoscopic totally extra peritoneal inguinal hernia repair: a comparative study

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ABSTRACT

Objective: Inguinal hernia repair is one of the most common general surgical procedure, and laparoscopic approach gained popularity over the open approach. This study aimed to compare the clinical effects of TEP inguinal hernioplasty with or without mesh fixation. The primary outcome was acute post-operative pain.

Material and Methods: A retrospective comparative study on a prospectively collected data was conducted in a large DGH in England between January 2017 and December 2019 on 47 patients. The patients were divided into two groups. In group A, mesh fixation was performed with absorbable tackers and in group B no fixation was performed. Patients were followed up to 18 months postoperatively. Data was collected on post-operative pain, cost, recurrences and time taken to return to normal activities. Patients with lower midline scar and complicated inguinal hernias were excluded.

Results: Out of the 47 patients 53% (n= 25) were in group A and 47% (n= 22) in group B. All the patients in both groups were male. The mean postoperative pain score at 72h in group A was 7.12 (SD 1.13) and 4.91 (SD 1.23) in group B ($p< 0.001$). Group B patients have taken shorter time to return to normal activities in comparison to group A ($p< 0.001$), while recurrence (2%) rate is higher in group B ($p> 0.05$).

Conclusion: Pain and time taken to return to normal work postoperatively were significantly less in the non-fixation group. The study recommends non-fixation over fixation as it is feasible, cost-effective, causes less post-operative pain and no differences in terms of recurrences.

Keywords: İnguinal hernia, laparoscopic, mesh, fixation, non-fixation, chronic pain

INTRODUCTION

Inguinal hernias are a significant cause of patient morbidity. It is the most common type of hernia, accounting for 75% of all the abdominal wall hernias. The prevalence of repair ranges from 10 per 100 000 of the population in the United Kingdom to 28 per 100 000 in the United States (1). It has been estimated that over 20 million inguinal hernia operations are carried out each year throughout the world. The lifetime risk is approximately 27% in males and 3% in females (1). Several methods of inguinal hernia repair have been described and have been evolved over time (2,3). Historically, the first operations for inguinal hernias were performed by the end of the 16th century. In the early 1980s, minimally invasive techniques for inguinal hernia repair were first reported, adding another modality to the management of these hernias (4). Laparoscopic approach of inguinal hernia repair has gained popularity over open approach due to reducing postoperative pain, shorter hospital stay, decreased incidence of urinary retention and earlier return to normal activities (5). National Institute for Health and Care Excellence (NICE) guidelines also advocates the superiority of the laparoscopic approach over open inguinal hernia repair (6). Two laparoscopic techniques have become the mainstay for the repair of these hernias: Trans Abdominal Pre-Peritoneal repair (TAPP) and Totally Extraperitoneal (TEP) repair. Both approaches have been proven to be effective, however, several fundamental differences exist when comparing the two approaches (7-9).

Mesh placement is the most frequently debated issue of TEP or TAPP operation. Mesh can be placed without fixation or can be fixed into place with tackers. However, these metal tackers increase the cost, operative times and there is an increased incidence of

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chronic groin pain (2-16%) (5,10-14). One of the main concerns for non-fixation is mesh displacement or migration and subsequently increasing the chances of recurrence. However, several recent studies have shown that non-fixation of the mesh does not lead to an increase in recurrences. Moreover, it has the advantages of shorter operative time and less chronic groin pain when compared to tacker fixation (5,10-14).

The aim of this study was to compare the clinical effects of laparoscopic TEP inguinal hernioplasty with or without mesh fixation. Primary outcome was acute post-operative pain. Secondary outcome measures included time taken to return to normal activities, cost, complications and recurrence rates.

MATERIAL and METHODS

A retrospective study on a prospectively collected data was conducted in a large District General Hospital in South-East England between January 2017 and December 2019 on 47 patients with inguinal hernias presenting electively for TEP inguinal hernia repair with accepted written consents. Group A (25 patients) underwent TEP with mesh fixation by absorbable tackers versus Group B (22 patients) who received TEP with mesh non-fixation. Data was collected on post-operative acute and chronic groin pain, recurrences, time taken to return to normal daily activities, cost and any other complications. Timely post-discharge follow-ups were conducted up to 18 months through telephone on the third post-operative day and regular outpatient clinics appointment in 6 months and 12 months interval.

All adult patients with uncomplicated inguinal hernias were included. Exclusion criteria included lower midline scars and complicated (obstructed or strangulated) inguinal hernias. All patients received a single intravenous dose of 1.2 gm. Co-amoxiclav before induction as prophylaxis. The procedure was done under general anesthesia. We did employ urinary bladder catheterization pre-operatively. All procedures performed in this study were in accordance with the ethical standards of trust, and the study was discussed by the local research committee. However, ethical approval was not required as there is no deviation from the current practice and both techniques are widely practiced in the UK. Informed consent was obtained from all individual participants. The study complies with the current laws of the UK.

Surgical Technique

Access to the preperitoneal space was obtained by a 10-mm infraumbilical port placement anterior to the posterior rectus sheath. Once the access was confirmed, dissection of the preperitoneal space was initiated with a balloon dissector to place a 10-mm 30° telescope. The pneumo pressure was 12 mmHg. Two 5-mm ports were placed in the midline, one three finger breadths above the symphysis pubis and the other in between the 10-mm port and 5-mm supra-pubic port, and the entire posterior floor was dissected. Once enough space was created to visualize the pubic symphysis medially, the cord structures entering the deep ring laterally, and adequate lateralization till Anterior Superior Iliac Spine, the hernia was addressed. For indirect hernias, cord dissection was done to isolate the sac completely. Direct hernia defects were identified and contents in the hernia defect were reduced. Once hernia was completely reduced, rolled 12 × 15 cm polypropylene mesh was introduced via the 10-mm port. The mesh was spread to cover the entire myopectineal area to cover the defect. The lower edge must extend well below the level of the inguinal ligament. The lateral part of the patch folded over and extended beyond the iliac vessels. In bilateral hernias, a similar mesh was placed bilaterally. The mesh was fixed with absorbable tackers, medially on Cooper's ligament and laterally near anterior superior iliac spine. This step was not performed during the mesh non-fixation period. The procedure was completed after complete desufflation under vision until creeping of the peritoneum and its filling over the mesh, ensuring that the inferior border of the mesh will not roll up and closing the port sites with appropriate sutures. Early ambulation was encouraged. The patients were advised to undergo regular daily activities except for lifting heavy weights or involving in strenuous activity/exercise for at least 6-8 weeks.

Statistical Analysis

Statistical analysis was performed using SPSS software version 25. Data was expressed as mean ± standard deviation (SD). Comparisons of quantitative data in both groups were analyzed using t-test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Total eligible patients for the study was 54, however, later 7 patients were excluded. Of the 47 patients, 53% (n= 25) were in Group A and 47% (n= 22) in Group B. All the patients in both groups were male with an overall mean age of 56 years (range: 22-83 years). In group A (fixation group), unilateral hernias were 28% (n= 7) and bilateral hernias were 72% (n= 18), whereas in Group B (non-fixation group), unilateral hernias were 18% (n= 4) and bilateral hernias were 82% (n= 18), ($p > 0.05$) (Table 1).

Visual analogue pain scale (VAPS) given to patients were used post-operatively at 72 hours for pain assessment via telephone. Mean postoperative pain score in Group A was 7.12 ± 1.13 and 4.91 ± 1.23 in Group B, ($p < 0.001$) (Figure 1).

Mean time taken to return to normal activities for group B was 4.68 ± 1.62 in comparison to Group A 6.24 ± 1.33, ($p < 0.001$) (Table 2). The extra cost of the operation for each patient in Group A was approximately GBP 300 for NHS England, which is the added cost for absorbable tackers.

There was one recurrence (2%) encountered in the 18th month follow-up in Group B ($p > 0.05$), which was statistically insignificant. No cases needed conversion to open hernia repair, and there were no bowel and visceral injuries in our study. No patients developed seroma, hematoma, urinary retention or infection. No cases with

Table 1. Patient demographics and characteristics of hernia		
Variables	**Fixations (n= 25)**	**Non-fixation (n= 22)**
Age (years)		
Mean	58	55
Sex		
Male	25	22
Female	0	0
Unilateral Hernias (%)	7 (28%)	4 (18%)
Bilateral Hernias (%)	18 (72%)	18 (82%)

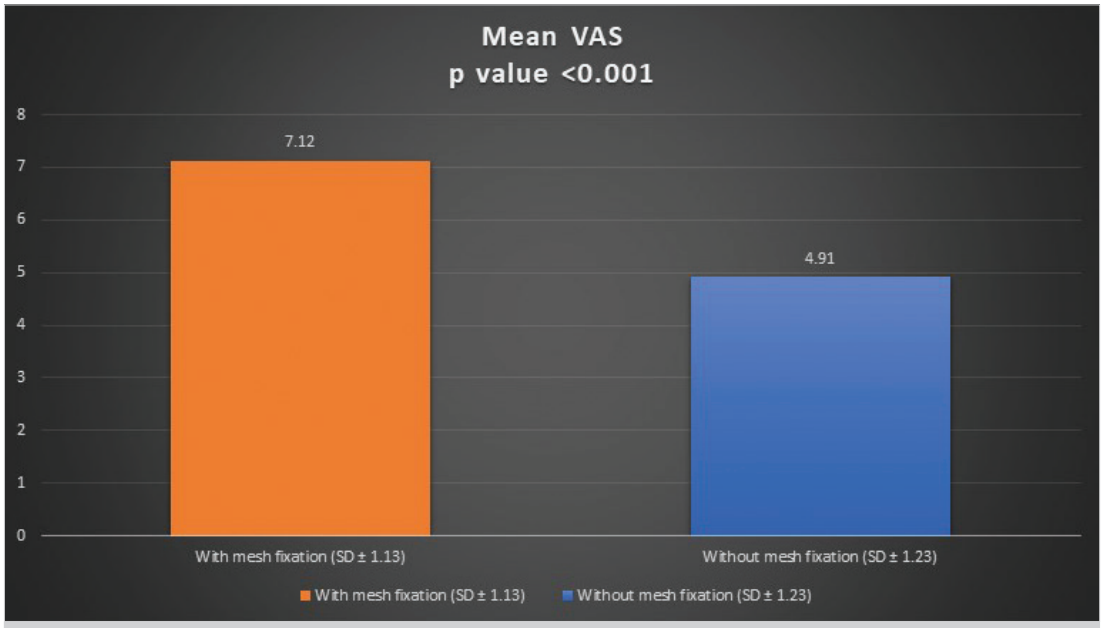

Figure 1. Comparison of post-operative pain in two groups at 72 hours.

Table 2. Comparison between the two groups according to time taken to return to normal activities			
Return to normal activities	**Group A (n= 25) [n (%)]**	**Group B (n= 22) [n (%)]**	**p**
2-3 days	1 (4%)	6 (27%)	<0.001
4-5 days	4 (16%)	10 (46%)	<0.001
6-7 days+	20 (80%)	6 (27%)	<0.001
Mean ± SD	6.24 ± 1.33	4.68 ± 1.62	
Median	7	5	

chronic groin pain in this study were encountered in both groups with 15-18-month follow-up.

DISCUSSION

Laparoscopic hernia repair is now recommended for primary inguinal hernia, recurrent inguinal hernia repair and bilateral inguinal hernia (2,3,6). Laparoscopic Totally Extraperitoneal (TEP) repair has gained popularity over Trans Abdominal Pre-Peritoneal repair (TAPP) repair as it does not involve breach into the peritoneal cavity and subsequent risks of visceral injuries (7-9). Inguinal hernias are being considered effectively treated by the TEP laparoscopic approach allowing bilateral repairs in the same sitting by minimally invasive technique. Understanding the posterior inguinal canal anatomy is essential to perform a laparoscopic TEP (17).

In this study, our aim was to ascertain patients' functional outcomes after a laparoscopic TEP between mesh fixation and non-fixation. Many studies advocate the superiority of the mesh non-fixation over the fixation (15-17,19-21). However, it has remained debatable and controversial. The main concerns for non-fixation are mesh migration and the recurrence rate. In TEP, stabilization of the nonfixated mesh placed between anterior wall

of the abdomen and peritoneum is based on sandwich effect created between tissues. Mesh stabilization without fixation has been well described in the literature (19-21). Meta-analyses have also comprehensively concluded that the recurrence rates are not increased by non-fixation of the mesh (15-18,20). Moreover, the non-fixation procedure can avoid the risk of vessel and nerve injury associated with tacker fixation. Postoperatively within two weeks, the proliferation of mesenchymal cells occurs in the mesh, and in the next two months, the tissue starts to incorporate into the mesh and adequate amount of collagen develops. This eventually strengthens permanent stabilization of mesh in the preperitoneal area.

Several methods of mesh fixation have been described and practiced such as surgical adhesives (Fibrin glue), self-fixating mesh and mechanical fixation (Tackers or sutures). The main reason for fixation is to avoid migration and theoretical recurrences. However, the use of fibrin sealant may lead to fibrin glue reactions, but many studies have proven its efficacy as safe (15,22,23). Suture fixation is barely practised as it is time-consuming and has not shown any benefits over non-fixation or tacker fixation. Tackers are the most common method of mesh fixation. They can be both absorbable and non-absorbable. The main concerns are post-operative acute and chronic pain due to greater risks of nerve injury (5,10,14,19,22). The use of fixation devices in the conjoint tendon or the pubic tubercle can be a causative factor for postoperative pain and discourage early ambulation. Approximately 2-16% of patients may experience persistent pain after laparoscopic inguinal hernia repairs. This may again promote seroma formation and increase hospital stay. Our study also found increased pain scores in the fixation group when we assessed pain at 72h post-surgery and this was statistically significant (Figure 1).

In our study, we also looked at the time taken by the patients to return to their normal activities postoperatively. Non-fixation group took a statistically significant shorter time in comparison to the fixation group in return to their daily activities. Cost is the other issue that needs to be considered while using tackers, and our study indeed showed tackers cost additional money compared to non-fixation. Several meta-analyses and RCTs have shown that non-fixation of mesh leads to decreased cost (16,17,20).

A very important finding in this study was that the non-fixation of mesh did not lead to increased recurrence. This is in agreement to the results of randomized trials and meta-analysis looking at non-fixation of mesh (7,15-17,19-21). Moreover, the superiority of nonfixation method in terms of avoiding potential nerve damage as well as limiting surgical expenses has been acknowledged.

CONCLUSION

Laparoscopic TEP repair for inguinal hernia is recommended for both direct and indirect inguinal hernias as providing a safe operative technique with early recovery and return to normal activities. Our results support the findings of researchers and demonstrate that laparoscopic TEP inguinal hernia repair performed without mesh fixation is a reliable technique. We recommend non-fixation over fixation as it is feasible, cost-effective, causes less post-operative pain and no differences in terms of recurrences. Our study is limited by its limited number of patients and relatively short follow up period. Also, patients were not randomized using RCT, which introduced potential selection bias. However, selection bias is a confounding factor.

Ethics Committee Approval: All procedures performed in this study were in accordance with the ethical standards of trust, and the study was discussed by the East Kent Hospitals University NHS Foundation Trust, UK.

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Author Contributions: Concept - R.F., A.K.N.; Design - A.K.N.; Supervision - R.F., A.K.N.; Materials - A.K.N., R.F.; Data Collection and/or Processing - All of authors; Literature Review - A.K.N.; Writing Manuscript - A.K.N.; Critical Reviews - R.F.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2021; 37 (1): 1-5

Laparoskopik total ekstra-peritoneal inguinal herni tedavisinde sabitlemeli ve sabitlemesiz meş uygulamalarının sonuçları

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William Harvey Hastanesi, Genel ve Kolorektal Cerrahi Kliniği, Ashford, Birleşik Krallık

ÖZET

Giriş ve Amaç: Inguinal herni onarımı en yaygın cerrahi işlemlerden biri olmakla birlikte laparoskopik yaklaşım açık yaklaşıma göre daha büyük popülariteye sahiptir. Bu çalışma, sabitlemeli ve sabitlemesiz meş yerleştirilen TEP inguinal hernioplastinin klinik sonuçlarını araştırmaktı. Primer sonuç ise akut postopertif ağrı idi.

Gereç ve Yöntem: Prospektif olarak toplanan verilerden retrospektif karşılaştırmalı bir çalışma Ocak 2017 ve Aralık 2019 tarihleri arasında İngiltere'de 47 hastada uygulandı. Hastalar iki gruba ayrıldı. Grup A'da absorbe olabilen zımbalarla meş sabitlemesi uygulanırken Grup B'de bu tür bir sabitleme uygulanmadı. Hastalar postoperatif 18. aya kadar takip edildi. Postoperatif ağrı, maliyet, nüks ve normal faaliyetlere dönüş açısından veriler kaydedildi. Alt orta hat skarı ve komplike inguinal hernisi olan hastalar çalışma dışında tutuldu.

Bulgular: Kırk yedi hastanın %53'ü (n=25) Grup A'da %47'si ise (n= 22) Grup B'de idi. Her iki gruptaki tüm hastalar erkekti. Grup A'da 72. saatte postoperatif ağrı skoru 7.12 (SD 1.13), Grup B'de 4.91 (SD 1.23) idi (p< 0,001). Grup A hastalarına nazaran, Grup B hastaları daha erken sürede normal faaliyetlerine döndü (p< 0.001) ancak Grup B'de nüks oranı (%2) daha yüksekti (p> 0,05).

Sonuç: Postoperatif ağrı ve normal faaliyetlere dönüş sabitleme yapılmayan grupta anlamlı derecede daha düşüktü. Çalışmamızın sonuçları, uygulanabilir ve uygun maliyetli olduğundan ve daha az postoperatif ağrıya sebep olmasından ve nüks açısından herhangi bir fark göstermemesinden ötürü sabitlemesiz meş yerleştirme işlemini önermektedir.

Anahtar Kelimeler: İnguinal herni, laparoscopik, meş, sabitleme, kronik ağrı

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ORIGINAL ARTICLE
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Transanal minimal invasive surgery (TAMIS): safety and feasibility for the resection of benign and malignant lesions of the rectum

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ABSTRACT

Objective: Radical surgery for rectal tumours has high morbidity. Local excision of such tumours can be achieved without compromising oncologic safety. However tumours that are not accessible to local excision can be approached using Transanal Minimal Invasive Surgery (TAMIS). The aim of our study was to assess feasibility of TAMIS procedure in terms of complications, operating time, resection margin positivity, hospital stay and local recurrence rate.

Material and Methods: Forty eight patients with benign adenomas or early stage adenocarcinoma, within 4 to 12 cm from anal verge who were subjected to TAMIS over a period of 3 years were included in the study. Short and long term outcomes were assessed.

Results: TAMIS was performed for 36 benign adenomas and 12 adenocarcinomas, which were located at an average distance of 6.2 cm from anal verge. The mean operating time was 72 minutes. There were no intraoperative complications.1 (2.08%) patient suffered post operative bleeding, which was managed conservatively. 2 (4.16%) patients developed acute urinary retention who required indwelling catheterisation. Resection margin was positive in 3 (6.25%) benign cases. Average hospital stay was 2.7 days. Local recurrence occurred in 2 (4.16%) villous adenoma patients (after 11 and 13 months), whereas in malignant patients there was no recurrence at a follow up period ranging between 12 to 36 months.

Conclusion: TAMIS is a safe and feasible procedure for benign tumours and early rectal cancers, located in low and middle rectum.

Keywords: Tamis, tubulovillous adenoma, early rectal cancer

INTRODUCTION

Radical surgery for rectal tumours has high morbidity. Local excision of such tumours can be achieved without compromising oncologic safety. However, tumours that are not accessible to traditional local excision or endoscopic resection can be approached using either Transanal Endoscopic Microsurgery (TEMS) or Transanal Minimal Invasive Surgery (TAMIS).

TEMS is superior to conventional Transanal excision with regard to completeness of excision (1,2), but its equipment is costly and not available in many centres especially in developing nations with limited resources. Therefore, despite being in use for more than two decades, it has not been adopted by many colorectal surgeons across the globe.

TAMIS, on the other hand, has the advantage of being done using conventional laparoscopic instruments. Since its first description in 2010 by Sam Atallah et al. (3), who reported this technique safe and effective for resection of adenomas and early rectal cancers, TAMIS procedure has gained popularity among more and more surgeons all over the world. Besides the conventional laparoscopic instruments, a special port for inserting these instruments through the anal opening is required, which is available as Single Incision Laparoscopic surgery (SILS™ port, Covidien, Mansfield, MA, USA), Single Site™ (SSL) device (Ethicon, Cincinnati, OH) and specifically designed for TAMIS, Gelpoint Path™ (Applied Medical, Rancho Santa Margarita, CA).

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Aims and Objectives

The primary outcome of our study was to assess the feasibility of TAMIS procedure in terms of operating time, intraoperative and postoperative complications, resection margin positivity, hospital stay, and local recurrence rate.

MATERIAL and METHODS

This was a prospective study carried in the Department of Colorectal Surgery at Sher I Kashmir Institute of Medical Sciences, Srinagar for a period of 3 years. All patients with a preoperative diagnosis of benign adenoma or early-stage adenocarcinoma (T1, N0, M0) within 12 cm from the anal verge were included in the study. Besides, one patient with multiple comorbidities with low performance status who was bleeding actively per rectum and had a T3N0M0 lesion was also subjected to resection using TAMIS procedure. Preoperative staging in cases of adeno carcinoma was done using Magnetic resonance imaging (MRI) for the pelvis and Contrast enhanced computed tomography (CECT) for the abdomen and chest. Complete colonoscopy was done routinely to rule out any synchronous lesions. Full bowel preparation was used in majority of the patients one night prior to surgery, except a few (not suitable or refused) who received rectal enema on the evening preceding and on the morning of the day of surgery. Surgery was performed under general anaesthesia in all patients. Patients were kept in modified lithotomy or jack knife prone position depending on the site of lesion. Initially, we used SILS™ port for transanal access in 14 patients and later shifted to Gelpoint Path™ in others (Figure 1). Gel port gives a better manoeuvrability for instruments as compared to SILS port. Pneumo rectum was created using CO_2, which was set at a pressure of 15 to 18 mm Hg. Since there was no smoke removing apparatus (Air seal®) available, an extra knob available on the gel port was opened to get rid of the excess smoke as and when needed. Most of the patients were operated in lithotomy position, though there was slight difficulty in operating lesions in the upper half, but were managed as such; however, 3 patients, in whom the location was at 11 (in 2 patients) and 1 o'clock position, were operated in prone jack knife position. There are certain difficulties one may encounter during the procedure because of large size of the lesion, high up lesions and anatomical location of the lesion in the upper half of the operating field. Standard laparoscopic instruments were used. Resection of the lesion was done using mono polar electro cautery and harmonic scalpel. Full thickness excision was done in all cases with an aim to achieve 1 cm clear margin. The resultant defect was closed using V Lock™ (Covidien) 3-0 absorbable suture on 26mm needle in continuous fashion (Figure 2) without changing the pressure (15-18mm Hg). Light pack was kept in the rectum. Resected specimen was properly labelled and sent for histopathological examination. Light diet was started in the evening and followed by soft diet the next morning. The patients were regularly examined for any sign of bleeding. After discharge from hospital, the patients were again seen at two weeks and one month postoperatively and thereafter, in every 3 months. At every 3-month follow up, a proper digital rectal examination and proctoscopy were done to detect any local recurrence. Colonoscopy was done yearly. Follow up period ranged from 12-36 months.

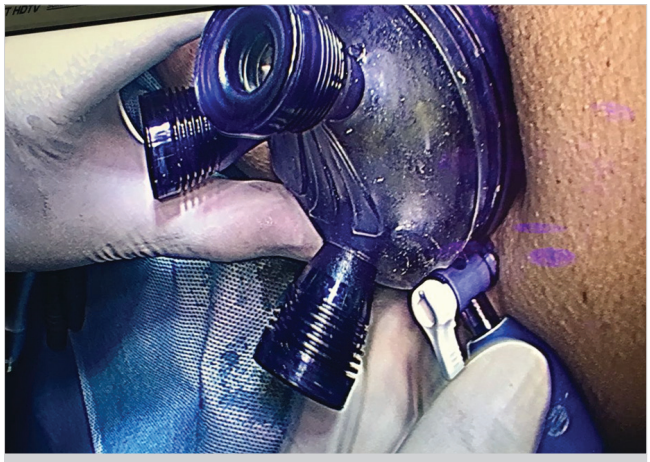

Figure 1. Gel point path port along with three trocars.

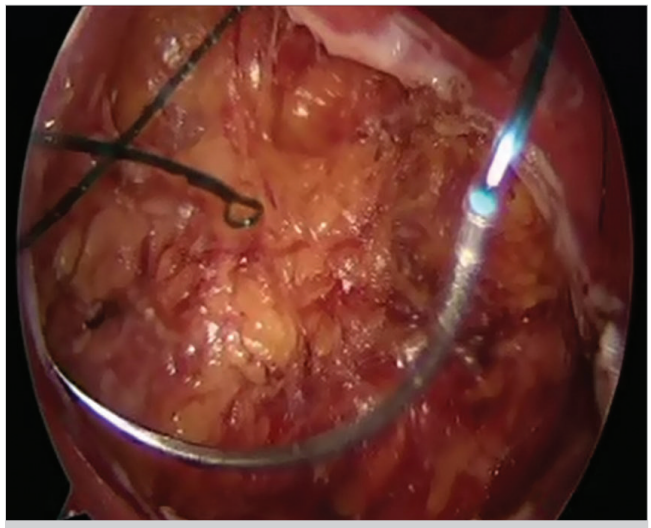

Figure 2. Suturing the rectal defect.

RESULTS

A total of forty-eight patients underwent TAMIS procedure. Mean age of the patients was 51.07 years (25-72 years). Average size was 3.9 cm (1.2-8 cm). Average distance from anal verge was 6.2 cm (4-12 cm). Mean operating time was 72 min (46-110 min). There were no intra operative complications. Postoperatively, 1 patient developed bleeding per rectum on the evening of surgery and required one unit of packed red blood cells. However, bleeding stopped after conservative management. Two patients developed acute urinary retention following surgery which was managed by indwelling the catheter. One patient developed peritonitis following TAMIS for recurrent villous adenoma. This

Table 1. Characteristics of malignant patients

Patients No	Age/Sex	Pre-op Bx	Post-op Bx	LVI	PNI	Staging	Post-op Rx
3	72/F	WDA	WDA	+	+	T3N0M0	APR
7	38/M	VALGD	WDA	_	_	T1N0M0	F/U
9	63/F	WDA	WDA	+	+	T2N0M0	TATA
14	70/M	WDA	WDA	+	+	T1N0M0	ACRT
15	68/M	WDA	WDA	_	_	T1N0M0	F/U
19	66/M	WDA	WDA	+	+	T1N0M0	ACRT
20	24/M	VAHGD	WDA	_	_	T1N0M0	F/U
23	50/M	VAHGD	WDA	+	_	T2N0M0	ULAR
34	55/F	WDA	WDA	_	_	T1N0M0	F/U
37	53/M	WDA	WDA	_	_	T2N0M0	TATA
42	65/M	WDA	WDA	+	_	T1N0M0	ACRT
45	69/M	WDA	WDA	_	_	T1N0M0	F/U

M: Male, F: Female, Pre-op Bx: Preoperative biopsy, WDA: Well differentiated adenocarcinoma, VALGD: Villous adenoma with low grade dysplasia, VAHGD: Villous adenoma with high grade dysplasia, Post-op Bx: Postoperative biopsy, LVI: Lymphovascular invasion, PNI: Perineural invasion, T: Tumour, N: Nodal, M: Metastasis, APR: Abdominoperineal resection, F/U: Follow up, TATA: Transanal transabdominal procedure, ACRT: Adjuvant chemoradiotherapy, ULAR: Ultra low anterior resection.

patient was initially subjected to low anterior resection for a huge tubulovillous adenoma at another institute. There was no fragmentation in any of the excised specimens. Mean hospital stay was 2.7 days (2-9 days).

Preoperative biopsy was villous adenoma in 39 (81.25%) patients and well differentiated adenocarcinoma in 9 (18.75%). However, postoperative biopsy revealed villous adenoma in 36 (75%) and well differentiated adenocarcinoma in 12 (25%) patients.

Out of twelve adenocarcinoma patients (Table 1), 3 had T1 tumour with lympho vascular and perineural invasion and were subjected to adjuvant chemo radiotherapy with 45 Gy of radiation over 25 cycles along with oral capecatabine. Three out of 12 adenocarcinoma patients had muscle invasion (T2) on the postoperative biopsy of the resected specimen. All 3 patients underwent Salvage surgery in the form of Transanal abdominal Transanal resection (TATA) in 2 & Ultra low anterior resection (ULAR) in 1. Another patient had a locally advanced lesion (T3N1M0) and was having multiple comorbidities, had advanced age, and was bleeding actively. We took her for TAMIS as a palliative procedure. Postoperative biopsy revealed positive resection margin, and she underwent APR at other institute which was followed by a complicated postoperative course requiring ICU admission and massive blood transfusion. The remaining 5 patients with T1 lesion without any lymphovascular, perineural invasion and well differentiated adenocarcinoma on postoperative histology report are on regular follow up. None of the patients with adenocarcinoma developed local recurrence till date.

Out of the thirty-six villous adenomas, resection margin was positive in 3 patients, and 2 out of these 3 patients had large lesions occupying almost 75 and 80% of circumference, respectively. Both of them were operated in two separate sessions, with an interval of 8 weeks between the sessions. Third patient had microscopic positive resection margin. She is on regular follow up for the last 14 months without any evidence of local recurrence. Other patients are recurrence free at follow up ranging from 12 months to 36 months. Two patients developed local recurrence, one after 11 months and the other after 13 months of initial surgery. First patient had a recurrence at the same site as the previous surgery and it was excised by redo TAMIS and postoperative biopsy revealed villous adenoma. In the other patient, there were two polyps at a separate site which were managed endoscopically with excision biopsy. There was no mortality in our series. Complications encountered during the series are tabulated in Table 2.

DISCUSSION

The concept of local excision of rectal neoplasia evolved long back in 1826 by Jacques Lisfranc (4). Subsequently, the technique was modified by Parks (5), which is still being practiced by most of the colorectal surgeons across the world. However, since the introduction of TEMS into clinical practice (6), it has progressively become the standard for treatment of benign polyps and early neoplasm (7,8) and is associated with fewer surgery-associated morbidities an improved postoperative anorectal function, and a shortened postoperative recovery when compared with open or laparoscopic rectal resections (9,10).

However, TEMS procedure has not gained widespread acceptability among surgeons because of high instrumentation cost and steep learning curve.

TAMIS, as a procedure, is more appealing for the surgeons because of the familiarity of the laparoscopic technique and in-

Table 2. Complications

Age/Sex	Pre-op Path	Post-op Path	Complications	Intervention
68/M	VAHGD	VAHGD	BLEEDING	Blood transfusion
70/M	WDA	WDA	AUR	Indwelling catheterisation
66/M	WDA	WDA	AUR	Indwelling catheterisation
73/M	VAHGD	VAHGD	Leak/peritonitis	Peritoneal mopping with ileostomy
72/F	WDA	WDA	Advanced Stage	Salvage APR
63/F	WDA	WDA	Muscle Invasion (T2)	Salvage TATA Resection
50/M	WDA	WDA	Muscle Invasion (T2)	Salvage ULAR
53/M	WDA	WDA	Muscle Invasion (T2)	Salvage TATA Resection
63/F	VALGD	VALGD	Microscopic positive resection margin	Continuous follow up for 14 months; no recurrence
50/F	VAHGD	VAHGD	Local Recurrence after 13 months	Endoscopic excision
48/M	VAHGD	VAHGD	Local Recurrence after 11 months	Redo TAMIS

M: Male, F: Female, Pre-op path: Preoperative pathology, Post-op path: Post operative pathology, WDA: Well differentiated adenocarcinoma, VALGD: Villous adenoma with low grade dysplasia, VAHGD: Villous adenoma with high grade dysplasia, AUR: Acute urinary retention, T: Tumour, APR: Abdominoperineal resection, TATA: Transanal trans abdominal procedure, ULAR: Ultra low anterior resection, TAMIS: Transanal minimal invasive surgery.

Table 3. Comparison of various studies

Study	Country/Year	No. of pts	Diameter (cm)	DAV (cm)	Op Time (min)	Hosp stay (days)	Morbidity (%)	Mortality (%)	Negative margin (%)
Haugvik et al.	Norway 2016	51	3.2	8	40	1	12	0	47
Keller et al.	USA 2016	75	3.2	10	69	1	5.30	0	NA
Sumrien et al.	UK 2016	28	5	NA	<60	1.5	29	0	82
Verseveld et al.	Netherland 2016	24	6	8Δ	NA	NA	4	0	NA
A. Caycedo Marulanda et al.	Canada 2017	50	2.5	7	73	1.1	16	0	84
Nan Chen et al.	China 2018	25	1.1	8.4	61.3	2.7		0	80
Present study	India	48	3.9	6.2	72	2.7	8.33	0	93.75

Pts: Patients, DAV: Distance from anal verge, Op time: Operation time, Hosp stay: Hospital stay.

struments. One more advantage of TAMIS is that the position of the patient does not depend on the location of the tumour, as we can use an angled scope to visualise throughout the circumference of the rectum. However, it may initially be difficult for a surgeon to operate in the upper half (9-3 o'clock position) because of ergonomics. Nevertheless, with increasing experience, most of the tumours can be managed in modified lithotomy positions. We used modified lithotomy position in majority of the cases except for 3 patients in whom tumour location was between 11 and 1 o'clock position and were done in prone jack knife position. TAMIS is a feasible option for the treatment of rectal tumours and does not impair quality of life postoperatively (11). In our study, initial preoperative biopsy revealed benign disease in 39 patients and adenocarcinoma in 9 patients, but postoperative biopsy detected malignancy in 12 patients. In their series of 32 patients who underwent TAMIS procedure, Ana I Encinas-Muñiz et al. (12) have reported that 4 carcinomas were understaged (33.3%) and 1 adenoma overstaged (6.7%) preoperatively. There were also 3 (25%) carcinomas which were not suspected preoperatively. This assumes importance in the management of colorectal polyps in that preoperatively labelled benign polyps can harbour foci of adenocarcinoma, so one should be vigilant while treating such cases.

In a systemic review by Martinez et al. (13), overall complications following the TAMIS procedure has been found as 7.4%. The conversion rate in 390 cases performed for both benign and malignant lesions was 2.3%. In malignant polyps, the rate of positive margins was 4.4% and the rate of tumor fragmentation was 4.1%. Inadvertent peritoneal entry during TAMIS was reported in 1% of the cases. We encountered one anastomotic site leak in a patient who had undergone low anterior resection for a large tubulovillous adenoma at some other institute. There was a 4x3 cm lesion at a previous anastomotic site. We performed TAMIS and excised the lesion with negative margins and closed the defect using V Loc™ continuous suture. However, on the 3rd postoperative day, the patient showed signs of

peritonitis, and digital rectal examination showed a small defect at the closure site and was confirmed by a rectal dye test (water soluble). Patient was taken for exploratory laparotomy. Feculent material was seen in the peritoneal cavity. Thorough peritoneal lavage was done, and loop ileostomy was created for diversion. This complication can be attributed to the fact that in patients subjected to low anterior resection, peritoneum is divided and pelvic cavity is continuous with the peritoneal cavity, resulting in a generalised peritonitis instead of an otherwise localised pelvic collection. So, we suggest a prophylactic diverting stoma in such patients.

There is no debate over the closure of the rectal defect following excision of rectal neoplasm after TAMIS above the peritoneal reflection; however, there is lack of consensus when the excision is carried out below the reflection. In a recent meta-analysis of 555 patients who underwent excision of the rectal neoplasm by TEMS or TAMIS, 283 had their rectal defects sutured, while as in other 272, it was left open. Closing the defect resulted in significantly decreased rate of post-operative bleeding as compared to leaving the defect open. However, there was no statistical difference in postoperative infection, operative time and length of hospital stay between the two groups (14). In our series, we routinely closed all the defects.

In a recent study, Lee Lawrence et al. have reported a series of 200 elective TAMIS local excision procedures performed in 196 patients for 90 benign and 110 malignant lesions. Overall, a 7% margin positivity and 5% fragmentation rate were observed. Mean operative time for TAMIS was 69.5 minutes. Postoperative morbidity was recorded in 11% of the patients, with hemorrhage (9%), urinary retention (4%), and scrotal or subcutaneous emphysema (3%) being the most common. Mean follow up was 14.4 months. Local recurrence occurred in 6%, and distant organ metastasis was noted in 2%. Mean time to local recurrence for malignancy was 16.9 months (SD 13.2). Cumulative DFS for patients with rectal adenocarcinoma was 96%, 93%, and 84% at 1, 2 and 3-years (15).

In another study from Europe, using TAMIS procedure for 75 patients, overall morbidity has been reported as 20%. Five patients experienced postoperative bleeding, one of whom required tamponade with gauze, two were given blood transfusion (Grade II) and two required no special treatment (Grade I). Local infectious complications were seen in six (8%) patients. One (1.3%) patient was re-operated (TME, Grade IIIb) and five were treated with antibiotics (Grade II) (16).

In our study, there was no intraoperative complication. There was no tumour fragmentation during excision with all lesions removed intact. Overall, 4 (8.33%) patients developed postoperative complications. One patient developed a leak requiring ileostomy, and the other 3 (6.25%) patients developed minor postoperative complications in the form of acute urinary retention in 2 patients and minor bleeding in 1 patient, all managed conservatively. There was no procedure-related mortality in our study. Resection margin was positive in 3 patients with tubulovillous adenoma. No patients with adenocarcinoma had a positive resection margin. Among these, 2 patients had huge lesions which were done in 2 sittings, and positive margins were present during the 1st session. After excising the remaining lesion in the 2nd session, resection margins were negative. In the 3rd patient, resection margin was microscopically involved; however, the patient preferred to be on meticulous follow up instead of redo surgery and does not have any evidence of local recurrence till date for the last 14 months.

In cases of early rectal cancer, the rate of local recurrence is relatively high after local excision alone (17-19). However, the addition of adjuvant chemo radiotherapy after local excision significantly decreases the rate of local recurrence (20,21). Toshiyuki Suzuki from Japan has reported their experience of 65 patients with clinical T1N0M0 rectal cancer who were subjected to local excision followed by adjuvant chemo radiotherapy. Local recurrence occurred in 1 (2%) and distant metastases in 3 patients (6%) at a median follow up of 71 months. They have concluded that multidisciplinary treatment with local excision followed by chemo radiotherapy can be used as a treatment option in selected patients with clinical T1N0M0 rectal cancer (22). In patients with high-risk (tumour size ≥3 cm, resection margin ≤3 mm, lymphovascular invasion, tumour resection by endoscopic mucosal resection or endoscopic sub mucosal dissection) pT1 rectal cancer, adjuvant chemo radiotherapy after local excision could be an effective alternative treatment instead of salvage radical resection. However, patients with pT2 stage have inferior oncological outcomes and should be subjected to completion total mesorectal excision (23). In a recent meta-analysis, Van Oostendorp et al. have evaluated oncological outcomes in 4674 patients of early rectal cancer (pT1-2) who were subjected to local excision followed by either no additional treatment, completion total mesorectal excision or adjuvant chemo radiotherapy. The study has revealed that patients who undergo no additional treatment have a high risk of local recurrence, especially those with high-risk pT1 and pT2 lesions. For high-risk pT1 tumours, the risk of local recurrence after adjuvant chemo radiotherapy is similar to that for completion total mesorectal excision. For pT2 tumours, adjuvant chemo radiotherapy seems less effective than radical surgery (24).

We had twelve adenocarcinoma patients in our series. Three patients with pT1 stage were subjected to adjuvant chemo radiotherapy. The other 3 patients had pT2 disease and underwent completion total mesorectal excision. Five patients had pT1 disease with no high-risk pathological factors and did not undergo any further treatment. One patient had a locally advanced rectal cancer who presented to us with massive tumour bleed. She underwent palliative resection of the tumour in view

of her multiple comorbidities for the control of bleeding. Later on, she underwent abdominoperineal resection at some other hospital. No recurrence was reported among these patients at follow up ranging from 12-36 months.

Local recurrences following transanal excision is one of the biggest limitations of the procedure because of the constraints of proper space, which has ultimately led to the development of newer procedures like TEMS and TAMIS. In cases of benign diseases, local recurrence rates range from 4 to 10.3%. (14,25,26). In our study, local recurrence occurred in 2 (8.33%) patients at 11 and 13 months respectively following primary surgery. Follow up period ranges from 12 to 36 months. In the first patient, recurrence occurred at a previously operated site, while in the other patient, there were 2 small lesions at a different location as compared to previous operated site. In the first case, redo TAMIS was done and pathology revealed tubulovillous adenoma and the other patient was managed with endoscopic removal of the tumour. To our knowledge, this is the first reported series of TAMIS from subcontinent, and our outcomes (Table 3) are consistent with most of the studies carried out worldwide (27-32).

CONCLUSION

TAMIS is a safe and feasible surgical technique used for the excision of both benign and early malignant lesions that are not accessible to conventional transanal or endoscopic resection. Short and midterm complications are within acceptable limits. It is a cost effective as well as a technically simpler procedure compared to TEMS. TAMIS can be used for resecting larger benign lesions in multiple sittings. However, literature comparing TAMIS with radical resection for malignant rectal tumors is limited and needs to be studied more in the future.

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ORİJİNAL ÇALIŞMA-ÖZET
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Transanal minimal invaziv cerrahi (TAMIS): benign ve malign rektum lezyonlarının rezeksiyonunda güvenilirliği ve uygulanabilirliği

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ÖZET

Giriş ve Amaç: Rektal tümörler için radikal cerrahi yüksek morbiditeye sahiptir. Onkolojik güvenlikten ödün vermeden bu tümörlerin lokal eksizyonu gerçekleştirilebilir. Ancak lokal eksizyonla erişilemeyen tümörlere transanal minimal invaziv cerrahi (TAMIS) uygulanarak ulaşılabilir. Çalışmamızın amacı TAMIS prosedürünün uygulanabilirliğini komplikasyonlar, ameliyat süresi, rezeksiyon sınır pozitifliği, hastanede kalış süresi ve lokal nüks oranı açısından değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 3 yıllık bir süre boyunca TAMIS uygulanan, *anal verge*'den 4-12 cm uzaklıkta, iyi huylu adenomu veya erken evre adenokarsinomu olan kırk sekiz hasta dahil edildi. Kısa ve uzun vadeli sonuçlar değerlendirildi.

Bulgular: *Anal verge*'den ortalama 6,2 cm uzaklıkta bulunan 36 iyi huylu adenom ve 12 adenokarsinom için TAMIS uygulandı. Ortalama operasyon süresi 72 dakikaydı. Herhangi bir intraoperatif komplikasyon gözlenmedi. 1 (%2,08) hastada postoperatif kanama görüldü, konservatif tedavi ile yönetildi. 2 (%4,16) hastada kalıcı kateterizasyon gerektiren akut idrar retansiyonu gelişti. İyi huylu üç (%6,25) olguda rezeksiyon sınırı pozitifti. Ortalama hastanede kalış süresi 2,7 gündü. Takip süresi 2 ile 36 ay arasında değişiyordu. Lokal eksizyon yapılan 2 (%4,16) villöz adenom hastasında (11 ve 13 ay sonra) lokal nüks meydana geldi.

Sonuç: TAMIS, alt ve orta rektumda yerleşmiş iyi huylu tümörler ve erken evre rektal kanserler için güvenli ve uygulanabilir bir prosedürdür.

Anahtar Kelimeler: TAMIS, tubulovillöz adenom, erken evre rektum kanseri

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Acute pancreatitis: predictors of mortality, pancreatic necrosis and intervention

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ABSTRACT

Objective: Several predictive scoring systems are used in the prognostication of acute pancreatitis (AP). However, the quantity of evidence of these prognostic systems in the Indian population remains sparse. The aim of our study was to evaluate the usefulness of such prognostic scores to predict mortality, incidence of pancreatic necrosis and intervention in AP.

Material and Methods: This was an observational study of patients diagnosed with AP between June 2012 and November 2013 in a tertiary referral center in India. Vital signs, biochemical tests and CT-findings were recorded to identify SIRS, Ranson's score and CT-severity index at diagnosis. Chi square test was used to compare incidence of mortality, pancreatic necrosis, and intervention between mild versus severe acute pancreatitis groups.

Results: A total of 100 patients with AP were treated during out study period. Ranson's score more than 7 and presence of pancreatic necrosis were significantly associated with increased mortality ($p< 0.05$). SIRS, CTSI score more than 7, inotropic support, and complications were more frequently associated with patients with necrosis. Prophylactic antibiotics did not decrease mortality, but decreased intervention rate ($p< 0.05$). Presence of systemic inflammatory response syndrome (SIRS), Ranson's score > 7, necrosis, inotropic support and presence of complications were associated with a greater rate of interventions including surgery and percutaneous procedures ($p< 0.05$).

Conclusion: We validate SIRS, Ranson's, and CTSI score as prognostic markers for AP in the Indian population. These predictors, when used in combination, can direct early monitoring and aggressive management in order to decrease mortality associated with severe AP.

Keywords: Acute pancreatitis, prognostic score, Ranson's score, CT-severity index, necrosis, SIRS

INTRODUCTION

Acute pancreatitis (AP) is one of the most common causes of inpatient admission worldwide, with an annual incidence of 15-36 among 100,000 persons (1). With advances in our understanding of the pathophysiology of AP, outcomes have improved over the last few decades. However, severe forms of AP are still associated with a high morbidity of 25-70% (2) and a mortality rate of 13.5% (3). Early prognostication of AP is crucial to reduce morbidity and mortality in such patients. Several prognostic biochemical, imaging and clinical scores have been created for treating AP in the past. These include but are not limited to Ranson's score (4), CT-severity index (CTSI) (5), BISAP (6), SOFA (7), Glasgow (8), APACHE-II (9), to name a few. Although many studies comparing the effectiveness of these scoring systems have been conducted worldwide, there is sparse evidence in the Indian subcontinent.

Our aim was to demonstrate the predictive effect of clinical signs and scoring systems in identifying AP patients at the highest risk of mortality, pancreatic necrosis, and need for intervention.

MATERIAL and METHODS

Patient Selection

This study was conducted at a tertiary referral center in Mumbai, India from June 2012 to November 2013. We included all patients between 18 and 70 years of age who presented to our outpatient department or emergency department for the first time with clinical presentation suggestive of AP. Patients were excluded if they

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were diagnosed as acute or chronic pancreatitis or if they presented following any surgical or percutaneous intervention at an outside facility or after five days of initial symptom onset.

Covariates and Outcomes

Demographic information including age, gender, history of chronic alcohol intake and gallstone disease was obtained. On admission, vital signs including temperature, pulse, blood pressure, respiratory rate, and lab investigations such as white blood cell count (WBC), random blood sugar (mg/dl), and C-reactive protein (CRP, mg/L) were recorded. Ranson's score at admission was calculated using biochemical and clinical parameters. We did not calculate the Ranson's score at 48 hours, as we preferred the ability to predict who would have severe AP without having to wait two days for an elevated Ranson's score. In conjunction with Ranson's score at admission, presence of systemic inflammatory response syndrome (SIRS) was identified on the basis of the following parameters: temperature, pulse, respiratory rate, and white blood cell counts (10). Contrast enhanced CT of the abdomen was obtained on day fifth of symptom onset. Based on clinical evaluation by the attending surgeon, patients were started on prophylactic antibiotics prior to any form of imaging. Both local and systemic complications were recorded.

Ranson's score was utilized to demonstrate biochemical severity and CTSI was used to grade radiological severity. Hence, a comprehensive triumvirate assessment was made combining clinical and biochemical (SIRS and Ranson's score) and radiological findings (CTSI score). Ranson's score more than 3 was considered as severe (4), and CTSI more than 7 was considered severe (5).

The main outcomes of this study included mortality, rate of intervention and presence of parenchymal necrosis. Intervention included any form of surgical or percutaneous intervention that the patient underwent during the in-patient course. The proportion of pancreatic necrosis was broken down into involvement of less than and more than 30% of the parenchyma on imaging.

Statistical Analysis

Continuous variables were represented as median with range, and categorical variables were represented as frequency with percentages. Categorical variables were analyzed using Pearson Chi square test or Fishers Exact test. All statistical analysis was performed by SPSS (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc) and significance was defined as p-value less than 0.05.

RESULTS

Patient Demographics

A total of 100 consecutive patients diagnosed with AP were included in the study. Baseline patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Parameter	n (%) or median (with range)
Age (years)	36.5 (18-75)
Sex	
Male	74 (74%)
Female	26 (26%)
Etiology	
Alcoholic	64 (64%)
Gallstone	28 (28%)
Idiopathic	8 (8%)
Pancreatic necrosis	
No necrosis	58 (61%)
<30% parenchymal necrosis	10 (10%)
>30% parenchymal necrosis	27 (28%)
SIRS*	77 (77%)
Intervention	
Surgery	13 (13%)
ERCP*	2 (2%)
Image guided drainage	3 (3%)
Non-image guided drainage	2 (2%)
Status at discharge	
Alive	95 (95%)
Dead	5 (5%)

*SIRS: Systemic inflammatory response syndrome, ERCP: Endoscopic retrograde cholangiopancreaticography.

Factors Associated With Mortality

Ninety-eight patients fell into mild Ranson's score category, of which 3 died (3%) (Table 2). Only two patients had a severe Ranson's score and both died (100%). There was a significant association between Ranson's score and mortality (p= 0.004). Presence of pancreatic necrosis resulted in mortality in five patients (5/42, 12%). There was a significant association between necrosis and mortality (p= 0.022).

There was no association between mortality and the following parameters: SIRS (p= 0.52), CTSI (p= 0.563), inotropic support (p= 0.215), ventilatory support (p= 1), CRP (p= 0.6), random blood sugar (alcoholic pancreatitis, p= 0.31; gall stone pancreatitis, p= 0.14), antibiotic use (p= 0.353), and complications (p= 0.578).

Factors Associated With Pancreatic Necrosis

Among those who developed SIRS, 49% had pancreatic necrosis, whereas among those that did not have SIRS, only 18% had necrosis (Table 3). SIRS was more commonly associated with necrosis (p= 0.006). All patients who had a severe CTSI score > 7 had necrosis (21/21, 100%, p< 0.0001). 83% of patients (n= 10/12) who were on inotropic support had pancreatic necrosis. There was a significant relationship between the need for inotropic support and necrosis (p= 0.002).

Table 2. Factors associated with mortality

Parameter	Alive	Dead	p
SIRS*			
Absent	23 (100%)	0 (0%)	0.52
Present	72 (93.5%)	5 (6.5%)	
Ranson's score			
Mild	95 (97%)	3 (3%)	**0.004**
Severe	0 (0%)	2 (100%)	
CT-severity index			
Mild	76 (96%)	3 (4%)	0.563
Severe	19 (90%)	2 (10%)	
Pancreatic necrosis			
Absent	58 (100%)	0 (0%)	**0.022**
Present	37 (88%)	5 (12%)	
Inotropic support			
Yes	10 (83%)	2 (17%)	0.215
No	85 (96%)	3 (4%)	
Ventilator support			
Yes	1 (100%)	0 (0%)	1
No	85 (96%)	3 (4%)	
C-reactive protein			
<150 mg/L	23 (88%)	3 (12%)	0.6
>150 mg/L	4 (80%)	1 (20%)	
Random blood sugar			
Alcoholic pancreatitis			0.31
<200 mg/dl	63 (95%)	3 (5%)	
>200 mg/dl	1 (66%)	1 (34%)	
Gall stone pancreatitis			0.14
<220 mg/dl	26 (100%)	0 (0%)	
>220 mg/dl	1 (50%)	1 (50%)	
Antibiotic use			
Prophylactic antibiotics	40 (97%)	1 (3%)	0.353
Therapeutic antibiotics	41 (93%)	3 (7%)	
Complications			
Absent	68 (95%)	3 (5%)	0.578
Present	27 (93%)	2 (7%)	

*SIRS: Systemic inflammatory response syndrome.

Eighty-five patients received either prophylactic or therapeutic antibiotics. Prophylactic antibiotics was less frequently associated with presence of necrosis (3/41, 7%, p< 0.0001). Five patients out of 58 (18%) without pancreatic necrosis developed local or systemic complications, whereas 24 of 37 patients (65%) with necrosis developed complications. There was a significant relationship between pancreatic necrosis and complication rate (p< 0.0001).

Out of 56 patients with no complications, 3 patients (5%) had pancreatic necrosis <30% and 53 patients (95%) did not have necrosis. Out of 12 patients with complications, 7 patients (58%) had pancreatic necrosis <30%; complications included respiratory complications (2/7, 28%), infected necrosis (1/7, 14%), ascites (1/7, 14%), and pseudocyst (3/7, 42%). The remaining 5 patients (42%) did not have necrosis and developed complications including respiratory complications (5/5, 100%) and pseudocyst (1/5, 20%). There was a significant association between necrosis (none vs <30%) and complication rate (p= 0.00015).

Among 11 patients with no complications, 3 patients (27%) had pancreatic necrosis <30% and 8 patients (73%) had necrosis >

Table 3. Factors associated with pancreatic necrosis

Parameter	Necrosis	No necrosis	p
SIRS*			
Absent	4 (18%)	19 (82%)	**0.006**
Present	38 (49%)	39 (51%)	
Ranson's score			
Mild	40 (41%)	58 (59%)	0.34
Severe	2 (100%)	0 (0%)	
CT-severity index			
Mild	21 (26%)	58 (74%)	**<0.0001**
Severe	21 (100%)	0 (0%)	
Inotropic support			
Yes	10 (83%)	2 (17%)	**0.002**
No	32 (36%)	56 (64%)	
Ventilator support			0.238
Yes	1 (100%)	0 (0%)	
No	41 (41%)	58 (59%)	
C-reactive protein			
<150 mg/L	16 (61%)	10 (39%)	0.67
>150 mg/L	2 (40%)	3 (60%)	
Random blood sugar			
Alcoholic pancreatitis			
<200 mg/dl	30 (49%)	31 (51%)	0.554
>200 mg/dl	2 (67%)	1 (34%)	
Gall stone pancreatitis			
<220 mg/dl	5 (18%)	22 (82%)	0.051
>220 mg/dl	1 (100%)	0 (0%)	
Antibiotic use			
Prophylactic antibiotics	3 (7%)	38 (93%)	**<0.0001**
Therapeutic antibiotics	24 (54%)	20 (46%)	
Complications			
Absent	8 (13%)	53 (87%)	**<0.0001**
Present	24 (83%)	5 (17%)	
Complications	No necrosis	<30% necrosis	
Absent	53 (95%)	3 (5%)	**0.0001**
Present	5 (42%)	7 (58%)	
Complications	<30% necrosis	>30% necrosis	
Absent	3 (27%)	8 (73%)	1
Present	7 (22%)	24 (78%)	

*SIRS: Systemic inflammatory response syndrome.

30%. Out of 31 patients with complications, 7 patients (22%) had pancreatic necrosis <30%. Twenty-four patients (78%) that had necrosis > 30% had complications including respiratory complications (15/24, 62%), infected necrosis (7/24, 30%), ascites (5/24, 21%), and pseudocyst (5/24, 21%). There was no association between extent of necrosis (<30% vs >30%) and complication rate (p= 1).

There was no significant association between pancreatic necrosis and Ranson's score (p= 0.34), ventilator support (p= 0.238), CRP (p= 0.67), and random blood sugar (alcoholic pancreatitis, p= 0.554; gall stone pancreatitis, p= 0.051).

Factors Associated With the Rate of Intervention

Eighteen percent of the patients with SIRS required intervention, compared to 9% of patients without SIRS who required the

Table 4. Factors associated with the rate of intervention

Parameter	No intervention	Intervention	p
SIRS*			
Absent	63 (82%)	14 (18%)	**0.0345**
Present	21 (91%)	2 (9%)	
Ranson's score			
Mild	84 (86%)	14 (14%)	**0.0484**
Severe	0 (0%)	2 (100%)	
CT-severity index			
Mild	68 (86%)	11 (14%)	0.2735
Severe	16 (76%)	5 (24%)	
Pancreatic necrosis			
Absent	55 (95%)	3 (5%)	**0.001**
Present	29 (69%)	13 (31%)	
Inotropic support			
Yes	78 (89%)	10 (11%)	**0.001**
No	6 (50%)	6 (50%)	
Ventilator support			
Yes	83 (84%)	16 (16%)	0.661
No	1 (100%)	0 (0%)	
C-reactive protein			
<150 mg/L	18 (69%)	8 (31%)	1
>150 mg/L	3 (34%)	2 (66%)	
Random blood sugar			
Alcoholic pancreatitis			0.507
<200 mg/dl	50 (82%)	11 (18%)	
>200 mg/dl	2 (67%)	1 (36%)	
Gall stone pancreatitis			
<220 mg/dl	24 (89%)	3 (11%)	0.724
>220 mg/dl	1 (100%)	0 (0-%)	
Antibiotic use			
Prophylactic antibiotics	41 (100%)	0 (0%)	**<0.0001**
Therapeutic antibiotics	31 (70%)	13 (30%)	
Complications			
Absent	22 (61%)	14 (39%)	**0.000028**
Present	62 (97%)	2 (3%)	

*SIRS: Systemic inflammatory response syndrome.

same (Table 4). There was a significant relationship between SIRS and rate of intervention (p= 0.0345). Out of 98 patients with mild Ranson's score, only 14 patients (14%) underwent intervention while both patients (100%) with severe Ranson's score needed intervention. There was a significant association between Ranson's score and the need for intervention (p= 0.0484).

Thirty-one percent of the patients with necrosis required intervention compared to 5% who did not have necrosis. There was a significant relationship between necrosis and rate of intervention (p= 0.001). Fifty percent of the patients who were on inotropic support required intervention, compared to 11% of those who did not require it. There was a significant relationship between inotropic support and rate of intervention (p= 0.001). None of the patients who were administered antibiotics required any form of intervention (p< 0.0001).

Out of 64 patients with no complications, 2 patients (3%) underwent intervention, and out of 36 patients with complications, 14 patients (18%) underwent intervention. There was a significant association between complication and intervention rate (p= 0.000028).

There was no significant relationship between the rate of intervention and CTSI (p= 0.2735), ventilator support (p= 0.661), CRP (p= 1), and random blood sugar (alcoholic pancreatitis, p= 0.507; gall stone pancreatitis, p= 0.724).

DISCUSSION

Severe acute pancreatitis (SAP) develops in 15-25% of the patients diagnosed with AP (11). Such patients have a protracted hospital course with a higher rate of morbidity and mortality (12). Hence, the early identification of severity is one of the most essential steps in the management of AP. Several prognostic scoring indices like Ranson's score, CTSI, Glascow scoring system, APACHE=II, and BISAP score (13) have proven to be useful to ascertain the severity of disease in the past. They have varying sensitivity ranging from 55-90% in predicting severe AP, but the accuracy depends on the cut-off value and time of scoring8. Ranson's and APACHE score are limited by complexity in a number of parameters included but at the same time have maximum likelihood of predicting mortality (14). CTSI score has a similar sensitivity of predicting severity, yet it has limited use in earlier stages of AP as CT findings within 72 hours of symptoms are usually normal, and local complications like hemorrhage and abscess formation occur much later in the course of AP (14). BISAP is a much simpler bed side prognostic score compared to other scoring systems with equivalent predictive value (13).

This study showed that SIRS was not associated with a higher mortality rate. A study by Buter et al. investigating the effect of SIRS and MODS on mortality has concluded that MODS but not SIRS is associated with mortality on multivariable analysis16. The reason for this finding can be explained by the fact that even though transient mild SIRS is common in early stages of AP, it does not translate to mortality but persistent worsening of SIRS score during the inpatient course which indicates progression to sepsis and organ dysfunction would have a higher probability of death.

We found that SIRS was associated with pancreatic necrosis and an increase in intervention rate which could be considered as a surrogate marker of morbidity. A study by Singh et al. evaluating the role of SIRS on assessing AP severity has found that SIRS predicts AP severity and complications including necrosis with a high sensitivity of 85-100%. The higher the SIRS score on day 1 of admission, the greater the risk of severe AP (17). A study by Gregoric et al. investigating the role of SIRS and IL-6 in AP has found that it correlated with in-hospital morbidity (18). In our study, we studied the effect of SIRS as a prognostic factor as it represents the body's initial inflammatory response to an insult. The insult can be compounded by necrosis which could result to rapid deterioration of the patient's status during hospital stay. Similar sequential insults can cause a maladaptive response leading to multi-organ dysfunction syndrome (MODS). When sepsis supervenes, it can result in worse prognosis.

In this study, higher Ranson's score was associated with higher mortality but not with the presence of pancreatic necrosis. Khanna et al. have conducted a retrospective cohort study comparing various prognostic systems and concluded that Ranson's score was more reliable in determining mortality but not as accurate in predicting pancreatic necrosis compared to CTSI score, CRP and IL-6 on ROC analysis (8). Kumar et al. have similarly studied the predictive value of various prognostic systems and found that pancreatic necrosis was most accurately determined by CTSI followed by APACHE and then Ranson's score by ROC analysis (15). Ranson's score is a composite marker consisting of clinical and biochemical parameters which reflect the systemic status of the patient, hence a good marker of mortality. It is calculated at and within 48 hours of diagnosis, during which parenchymal necrosis development is not complete; which could explain why it is not a better predictor of necrosis compared to CTSI score that quantifies severity based on local complications. In addition, our study showed that Ranson's score was associated with higher intervention rate comprising percutaneous procedures and laparotomy. In our literature review, we did not find similar studies comparing Ranson's score to intervention rate, which can be considered as a surrogate marker of degree of morbidity.

In our study, modified CTSI score was used for assessing severity and was associated with pancreatic necrosis. CTSI score consists of presence of fluid collection in the vicinity of the pancreas and also quantifies the collection or necrosis (19). However, CTSI score was not associated with mortality. A metanalysis conducted by Miko et al. has evaluated the predictive value of mortality between CTSI and other prognostic systems and concluded that CTSI score has a sensitivity of 79% in predicting mortality which was lower compared to APACHE, Ranson, and BISAP score on ROC analysis (19). Similarly, Georgios et al. have compared CTSI, BISAP, Ranson's, and APACHE score in predicting mortality and concluded that CTSI had lower predictive ability compared to APACHE, Ranson's and BISAP score (20). Hence, CTSI may be more important as a radiological marker of severity in terms of local complications like necrosis and hemorrhage in comparison to clinical status of the patient.

Our study showed that pancreatic necrosis was associated with higher morbidity rate in the form of local and systemic complications. Balthazar et al. have studied the prognostic value of CT in predicting severity of disease and concluded that pancreatic necrosis on CT is associated with morbidity in up to 80% of patients (21). Even though our study showed the relationship between necrosis and overall morbidity, it did not depend on the percentage of necrosis. This finding can be due to many reasons. Even though increasing parenchymal necrosis would increase the likelihood of infection or local complications, it does not necessarily lead to systemic complications like pleural

effusion, acute kidney injury (AKI) which may vary by case-to-case basis. Another reason could be that in our cohort, most systemic complications were mild, thus not correlated with percentage of necrosis. Also, we showed that necrosis increases the intervention rate. Pancreatic necrosis requires surgical intervention in 10% of cases, due to infection, hemorrhage, abscess, or bowel perforation (22).

Our study showed that pancreatic necrosis was associated with increased mortality. Overall mortality of AP is around 1-2% in the US population (23) but in severe cases with parenchymal necrosis, mortality is increased to nearly 40% (24). Pancreatic necrosis can lead to a multitude of local complications including infection, hemorrhage, bowel perforation, and fistula formation which considerably increases the mortality rate (25).

Our study put forth that those who had pancreatic necrosis and required intervention needed inotropic support. Alteration in pancreatic microcirculation due to circulating interleukins and TNF-alpha lead to overall fluid sequestration including the pancreatic parenchyma. This can result in hypovolemia coupled with hypoxic damage to the pancreas leading to pancreatic necrosis (26). The resulting hypoperfusion may result in the need for inotropic support. The resulting SIRS, when coupled with gut dysmotility and barrier dysfunction can lead to superinfection of necrosis. In addition, hypovolemia can result in pre-renal azotemia. Other systemic complications include acute respiratory distress syndrome, pleural effusion, anorexia, and electrolyte abnormalities to name a few. All of these complications may increase the overall rate of intervention.

Superinfection of pancreatic necrosis is believed to be due to bacterial translocation from the gut via the enteric blood vessels or lymphatic pathways to the pancreatic parenchyma. Even though the exact mechanism of bacterial translocation is still not clear, various possible mechanisms have been illustrated that include alteration in intestinal flora, impaired gut barrier, or maladaptive immune reponsse (28). Hence, there is a push for administering prophylactic antibiotics in patients with parenchymal necrosis. Our study showed that prophylactic antibiotic use was associated with lesser incidence of necrosis. Pancreatic necrotic patients still continued to have a higher rate of local and systemic complications. A recent meta-analysis has shown that prophylactic antibiotics decreases superinfection of pancreatic necrosis, but does not decrease mortality or rate of intervention (29). Even though prophylactic antibiotics prevent superinfection, they may not decrease the rate of necrosis or other systemic complications. Hence, the use of prophylactic antibiotics in patients with parenchymal necrosis is still controversial.

Our study revealed that the natural progression of AP leading to various systemic and local complications increased the need for intervention. Complications like infected necrosis and peripancreatic necrosis are known to increase the rate of interventions which are mainly necrosectomy (27).

The findings of our study must be elucidated in light of certain limitations. From a statistical standpoint, though this study included a large sample size of 100 patients, power analysis was not performed to determine adequate sample size. This might explain some of the non-significant results. We chose Ranson's score calculated at admission and SIRS as the prognostic markers for this study. Even though the use of Ranson's at 48 hours and other systems like APACHE would be preferred, it was not feasible due to their increased complexity.

To conclude, SIRS, Ranson's score and CTSI prove to be valuable indicators of AP severity in the Indian population. Patients having Ranson's score more than 3, SIRS, and pancreatic necrosis must be carefully monitored in an intensive care unit to achieve better outcomes.

Ethics Committee Approval: The approval for this study was obtained from Seth G.S Medical College and King Edward Memorial Hospital Ethics Committee (Decision no: IEC(II)/OUT/986/14 Date: 03.11.2014).

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ORİJİNAL ÇALIŞMA-ÖZET
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Akut pankreatit: mortalite, pankreas nekrozu ve girişimlerin öngördürücüleri

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ÖZET

Giriş ve Amaç: Akut pankreatit (AP) prognozunu tahmin etmede birkaç skorloma sistemi kullanılmaktadır. Ancak, bu skorlama sistemlerinin Hint toplumundaki kanıt düzeyi kuşkuludur. Bu çalışmanın amacı, bu prognostik skorlama sistemlerinin AP'de mortalite, pankreatik nekroz insidansı ve girişimi öngörmedeki kullanışlılığını değerlendirmekti.

Gereç ve Yöntem: Bu çalışma, Hindistan'da üçüncü basamak bir merkezde Haziran 2012 ve Kasım 2013 tarihleri arasında AP tanısı alan hastaların gözlemsel bir çalışmaydı. Vital bulgular, biyokimyasal testler ve BT bulguları, SIRS, Ranson skoru ve BT-şiddet endeksini belirlemek amacıyla kaydedildi. Hafif ve şiddetli akut pankreatit grupları arasında mortalite, pankreatik nekroz ve girişimsel yaklaşım insidansını karşılaştırmak amacıyla Ki-kare testi kullanıldı.

Bulgular: Çalışma süresince toplamda 100 AP hastası tedavi edildi. 7'den yüksek Ranson skoru ve pankreatit nekroz varlığı yüksek mortalite ile anlamlı düzeyde ilişkiliydi (p< 0,05). SIRS, 7'den yüksek BT-şiddet endeksi skoru, inotrop desteği ve komplikasyonlar nekrozu olan hastalarda daha sık görülmüştü. Profilaktik antibiyoktikler mortaliteyi düşürmese de girişimsel yaklaşım oranını azalttı (p< 0,05). Sistemik enflamatuvar yanıt sendromu (SIRS), Ranson's skoru > 7, nekroz, inotropik destek ve komplikasyon varlığı cerrahi ve perkütan işlemler gibi girişimsel yaklaşımlarla daha yüksek oranda ilişkiliydi (p< 0,05).

Sonuç: Hint toplumunda SIRS, Ranson's skoru ve BT-şiddet endeksini AP prognostik belirteçleri olarak doğruladık. Bu öngördürücüler ek olarak kullanıldığı takdirde, şiddetli AP ile ilişkili mortaliteyi düşürmek için, erken izlem ve agresif tedaviye yönlendirmeyi sağlayabilir.

Anahtar Kelimeler: Akut pankreatit, prognostik skor, Ranson's skor, CTSI, SIRS

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ORIGINAL ARTICLE
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Serial estimation of serum C-reactive protein and procalcitonin for early detection of anastomotic leak after elective intestinal surgeries: a prospective cohort study

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ABSTRACT

Objective: Anastomotic leak can adversely affect the outcome of surgery especially if detected late. The present study was carried out to detect the anastomotic leak early in the postoperative period using serial estimation of procalcitonin (PCT) and C-reactive protein (CRP).

Material and Methods: A single centre prospective cohort study was done on patients undergoing elective gastrointestinal surgery with anastomosis. Serial estimation of serum procalcitonin and C reactive protein was done on the first five postoperative days. Other parameters such as hemoglobin, total protein, albumin and WBC counts were noted perioperatively. Patients were followed up to 60th postoperative day to assess for anastomotic leak, wound infection and other septic foci.

Results: Eighty-four patients were included in the study. Anastomotic leak rate was 26.19% (22/84) and 3/22 patients died in the anastomotic leak group. Wound infection rate was 23.81%. The cut off value of CRP on third postoperative day in detecting anastomotic leak was 44.322 mg/dl with sensitivity of 72.73%, specificity of 66.13% and accuracy of 59.52%. The cut off value for WBC count measured perioperatively in detecting anastomotic leak was 9470 cell/mm^3 with sensitivity of 72.73%, specificity of 56.45% and accuracy of 59.74%. Serum procalcitonin, haemoglobin, total protein and albumin measured were not sensitive enough to detect the anastomotic leak early.

Conclusion: Measuring CRP on the third postoperative day can predict anastomotic leak with a cut off value of 44.32 mg/dl. Patients with raised CRP need careful evaluation to rule out anastomotic leak before deciding on early discharge.

Keywords: C-reactive protein, procalcitonin, anastomotic leak

INTRODUCTION

Anastomotic leak (AL) is the most dreadful complication, which can occur following all intestinal anastomotic surgeries. The incidence of AL following intestinal surgeries is 2-20% (1). The incidence is high in esophagectomy and colorectal surgeries and has been reported as 10% and 2-19% respectively (2,3). Mortality following AL after colorectal and esophageal surgeries are 30% and 30-60% respectively (4,5)70 patients undergoing colorectal surgery were prospectively analyzed in a single-center tertiary teaching hospital. Demographic and surgical data were obtained. Serum procalcitonin was taken before surgery and at day 3 (72 hours. AL can present early or late. It is usually diagnosed between 7 to 12 days postoperatively. Late AL presents after one-month postoperatively (6). It is always the priority of any surgeon to identify these ALs at the earliest possible so as to avoid mortality and morbidity.

AL will lead to bacterial contamination of the peritoneal cavity, which leads to rise in inflammatory mediators such as C-reactive protein (CRP) and procalcitonin (PCT) before it presents clinically. AL can be detected early in elective cases, where wound infection and peritoneal contamination are less due to preoperative bowel preparation and prophylactic preoperative antibiotics. Some studies have reported the role of PCT and CRP for early detection of AL in a group of specific surgery like colorectal and oesophageal surgery (3,4,7-10) it is clinically valuable to detect anastomotic leak early after esophagectomy in esophageal cancer. The purpose of this study is to investigate the associations between routine postoperative laboratory findings and anastomotic leak and to analyze the laboratory findings to find out an independent

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predictive marker for anastomotic leak. In addition, this study compares cases treated with neoadjuvant therapy (NT. However, there are not many reports documenting the efficacy of these parameters in overall alimentary tract surgery.

This study was carried out to determine the role of PCT and CRP plasmatic concentration as an early detector of AL following elective gastrointestinal surgery.

MATERIAL and METHODS

This study was a prospective cohort study carried out in a tertiary centre in India. Institutional ethics committee approval was obtained (JIP/IEC/201/1040). Written Informed consent was taken from all participants in this study, and patients were given full freedom to withdraw at any point of time during the study.

Patients and data collection:

All patients aged more than or equal to 18 years of age, who had undergone elective gastrointestinal surgery with an anastomosis, were included in the study. Patients with fever or focus of sepsis preoperatively, patients who had received intraperitoneal chemotherapy and in patients in whom covering stoma was done with anastomosis were excluded from the study.

All patients, who had fulfilled the inclusion and exclusion criteria, were included in the study after taking informed written consent. Following surgery, blood was collected daily at 8 am on the first five postoperative days for PCT and CRP measurement.

CRP levels were estimated using ELISA kit manufactured by Calbiotech USA® (11). PCT levels were estimated using ELISA kit manufactured by Raybiotech® (12). Normal reference value of PCT as per the kit was less than 0.15 ng/ml, and the normal reference value of CRP was less than 3 mg/l.

Patient data, such as age, sex, telephone number, diagnosis, indication for surgery, previous surgical history, perioperative hemoglobin, total leucocyte counts (TLC), total protein and albumin were recorded. Hemoglobin and TLC were measured using Sysmex Xt-2000i which works on Coulter principle (13). Albumin was measured in Beckman-Coulter AU5800 using spectophotometry method and bromocresol green was used as dye. Total protein was measured in Beckman-Coulter AU5800 using photometric biuret end point method (14). Confounding variables such as surgical site infection and any other postoperative septic foci were also noted. Patients were followed up postoperatively for any signs and symptoms of leak and any other postoperative complications.

AL was defined as any clinical signs of leakage, confirmed by radiological examination, endoscopy, clinical examination of the anastomosis (i.e., palpation of the anastomosis), or reoperation (15). The patient was labeled as having AL if he/she had clinical evidence of leak like peritoneal signs, bile or faecal content in the drain or if ultrasound guided aspiration of the free fluid or localized collection at the anastomotic site revealed bile or faecal matter or if water soluble contrast leak was seen on fluoroscopy or computed tomography.

Serum PCT, CRP, haemoglobin, TLC, total protein and albumin were analysed for the predictability of AL. The incidence of leak following elective intestinal anastomosis in this hospital, the risk factors associated with leak in the population studied, the sensitivity and specificity of serial estimation of serum CRP and PCT to detect leak early were calculated. The patients were followed up on post-operative day (POD) 60 over telephonic interview, and development of enterocutaneous fistula or late post-operative leak were recorded.

Sample Size

Sample size was calculated using the formula, $N = Z2 \times P (1-P) / [d2 \times (1\text{-prevalence})]$ when P was specific. The sensitivity of PCT measured for five post-operative days to predict AL was 100% and specificity was 72%. The specificity of CRP measured for five post-operative days to predict AL was 83% (8). With expected specificity of 72% and expected prevalence of AL as 9.4%, the sample size was calculated as 84 with 95% confidence interval, 10% relative precision. The specificity of PCT was lower than that of CRP. Hence, sample size was calculated using the specificity of PCT. Power of the study was kept at 80%.

Statistical Analysis

All statistical analysis was done using SPSS version 20. Categorical variables such as presence of AL were expressed as proportions. Continuous variables such as PCT, CRP, haemoglobin, total protein, albumin and TLC levels were expressed as mean (SD) or median (IQR) depending upon the normality of distribution. Total protein, albumin, haemoglobin and TLC showed normal distribution. CRP and PCT levels measured on all five days did not follow normal distribution. Receiver Operating Characteristic (ROC) curve was plotted between day specific PCT, CRP, perioperative haemoglobin, total protein, albumin, TLC and the presence of AL, to determine optimum cut-off value for early detection of AL, using sensitivity and specificity. The differences in haemoglobin, total protein, albumin and TLC between AL and NAL patients were analysed using student t test. PCT and CRP was analysed using Mann Whitney U test. p value less than 0.05 was taken as significant.

RESULTS

This study was carried out from January 2017 to December 2018. A total of 84 patients were included in the study. Surgical procedures done for the patients were gastric (42), colonic (13), pancreaticobiliary (20), esophageal (3), stoma closure (4) and small bowel surgeries (2). AL developed among 22/84 patients (26.19%). The distribution of anastomotic leak among various procedures were 12, 3, 6, and 1 in gastric, colonic, pancreaticobiliary and oesophageal anastomosis respectively. AL did not show any statistical difference between sex and different age groups (Table 1). Overall mortality in the study was 5.95% (5/84).

Mortality in the AL group (3/22; 13.64%) when compared to the mortality in the NAL group (2/62; 3.22%) although higher, the difference was not significant (p= 0.076). The overall incidence of postoperative surgical site infection was 20/84 (23.81%). The incidence of wound infection in the AL group was 27.27% and for the NAL group, it was 22.58%. The difference in distribution of wound infection was not statistically significant (p= 0.657). Clinical demographic parameters studied in AL and NAL groups are shown in Table 1.

The median and interquartile range for serum CRP and procalcitonin for all five postoperative days were calculated. The area under the curve calculated for CRP on all five postoperative days was above 0.500 (Table 2).

Mean and standard deviation of haemoglobin, TLC, total protein and albumin were calculated. The area under the curve of TLC was found to be significant (Table 3).

Table 1. Demographic and clinical parameters studied in AL and NAL groups

Patient characteristics	AL group (n= 22)	NAL group (n= 62)	p*
Sex Female (n= 31)	11 (35.48%)	20 (64.52%)	0.138
Male (n= 53)	11(20.75%)	42 (79.25%)	
Age groups 18-45 years (n= 27)	11 (40.74%)	16 (59.26%)	0.074
45-60 years (n= 27)	7 (25.93%)	20 (74.07%)	
More than 60 years (n= 29)	4 (13.79%)	25 (86.21%)	
Mortality	3 (13.64%)	2 (3.22%)	0.076
Wound infection	6 (27.27%)	14 (22.58%)	0.657

AL: Anastomotic leak, Non AL group: Non-anastomotic leak group.
*Chi square test.

Table 2. Comparison of procalcitonin and CRP between AL and NAL groups

Test	POD	Non-AL group Median (IQR)	AL group Median (IQR)	p*	AUC
Procalcitonin	1	210.98 (32.43-657.05)	22.06 (11.54-206.44)	0.009	0.312
Procalcitonin	2	16.27 (49.60-652.02)	26.2 (15.98-212.99)	0.013	0.322
Procalcitonin	3	176.72 (39.17-582.03)	7.55 (7.4-198.45)	0.002	0.274
Procalcitonin	4	216.35 (51.82-625.56)	20.456 (7.25-261.48)	0.017	0.328
Procalcitonin	5	162.64 (33.03-450.16)	15.63 (7.23-352.36)	0.009	0.315
CRP	1	25.04 (16.24-35.14)	34.89 (29.15-54.89)	0.041	0.647
CRP	2	27.82 (16.54-41.61)	34.39 (27.16-38.08)	0.137	0.607
CRP	3	27.09 (16.34-53.98)	44.32 (35.28-61.37)	0.033	0.654
CRP	4	34.90 (16.30-58.07)	51.23 (30.19-51.23)	0.148	0.604
CRP	5	29.44 (16.23-48.98)	45.68 (32.57-48.51)	0.104	0.617

POD: Post operative day, non AL group-non anastomotic leak group, AL group-anastomotic leak group, AUC: Area under the curve, IQR: Interquartile range, CRP: C-reactive protein.
*Mann Whitney U test.

Table 3. Comparison of hemoglobin, total protein, albumin and TLC between AL and NAL groups

Test	Non AL group Mean (SD)	AL group Mean (SD)	p*	AUC
Hemoglobin	10.27 (1.81)	11 (1.76)	0.108	0.355
Total protein	5.6 (1.11)	5.62 (0.92)	0.945	0.452
Albumin	2.96 (0.59)	3.06 (0.63)	0.541	0.417
TLC	10131.94 (4468.81)	12203.64 (4472.41)	0.009	0.641

Non AL group: Non anastomotic leak group, AL group: Anastomotic leak group, AUC: Area under the curve, SD: Standard deviation, TLC: Total leucocyte counts.
*Student t-test.

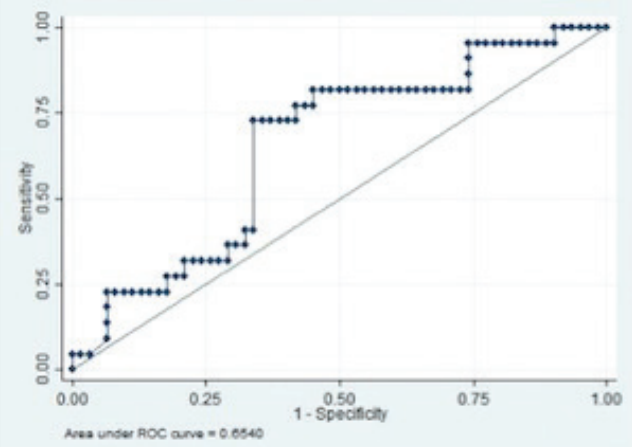

Figure 1. Receiver operating characteristic curve of serum C reactive protein on postoperative day three.

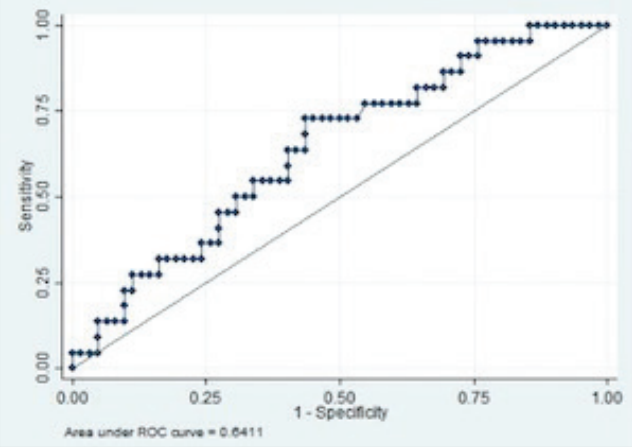

Figure 2. Receiver operating characteristic curve of perioperative total leucocyte count.

AUC for serum CRP was 0.654 on day three reaching the maximum than the other postoperative days. The cut off value was taken as more than 44.32 mg/dl with a sensitivity of 72.73% and specificity of 66.13% (Figure 1) (Table 4). When the cut off value of the perioperative TLC count was taken as more than 9470 cells/mm^3, the sensitivity was 72.73% and the specificity was 56.45%, (Figure 2) (Table 4). AUC was found to be 0.641.

DISCUSSION

AL is a serious life-threatening complication that can occur after a gastrointestinal anastomosis. It is associated with high mortality and morbidity due to the sepsis it causes. Moreover, overall survival reduces as the chance of recurrence of malignancy increases due to delay in adjuvant therapy. Early diagnosis of AL can reduce mortality and morbidity significantly. CRP is an acute phase reactant produced by liver, in response to infection, ischemia and tissue damage (10). It starts to rise two hours following insult and peaks at 48 hours (3). In normal circumstances, the C cells of thyroid gland produce PCT. In sepsis, white blood cells, pancreas, spleen, kidney, colon, adipocytes and the brain produce PCT. It starts rising at 3-4 hours and peaks at 8 to 24 hours (4). In the present study, the aim was to determine whether serological analysis could detect AL prior to its clinical presentation.

The present study showed that the plasmatic concentration of CRP on third POD with a cut off value of more than 44.32mg/dl was significantly associated with AL. Perioperative TLC, more than 9470cells/mm^3 had predicted AL early. Postoperative serum PCT was not an early predictor of AL. Total protein, albumin and hemoglobin level measured perioperatively had no association with AL.

Garcia-Granero et al. have reported about early prediction of AL after colorectal resection using PCT and CRP (8). The study showed that CRP and PCT were reliable predictors from third to fifth postoperative days with AUC more than 0.800. The best predictor was PCT on day five with the cutoff of 0.31 ng/ml, with sensitivity of 100%, specificity of 72%, and negative predictive value of 100% and positive predictive value of 17%. Aiolfi et al. have reported a systematic analysis and Bayesian meta-analysis on five studies including 850 patients on early prediction of esophageal AL using CRP (9). This study showed that CRP values on POD three and five had very good diagnostic accuracy with the AUC of 0.800. The cut off values derived for POD three and five were 17.6 mg/dl and 13.2 mg/dl respectively. Hayati et al. have reported on early prediction of colorectal AL using serum PCT on POD 3 (4). The study showed that PCT cut off value was 5.29 ng/ml with sensitivity of 100%, specificity of 85%, the positive predictive value of 23% and the negative predictive value of 100%. The early predictor of AL associated with pancreaticoduodenectomy surgery was analyzed only in very few studies (16,17). The studies mentioned above showed that the sensitivity and negative predictive value of CRP and PCT in predicting AL of various surgeries was 100%. So, these serological tests can be used to rule out AL, postoperatively. The present

Table 4. Best cutoff value of CRP and TLC along with AUC, sensitivity and specificity for detecting anastomotic leak

Test	POD	AUC	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
CRP	3	0.654	44.32 mg/dl	72.73%	66.13%	30%	75.93%	59.52%
TLC		0.641	9470 cells/mm^3	72.73%	56.45%	28.95%	89.74%	59.74%

CRP: C reactive protein, POD- post operative day, AUC: Area under the curve, TLC: Total leucocyte counts.

study showed that the plasmatic concentration of CRP on third POD was significantly increased in patients with AL and the serial estimation of serum PCT postoperatively was not associated with AL. This may be because of raised postoperative wound infection rate, which is an important confounding factor.

A meta-analysis has shown that the overall incidence of AL was 9% (18). In the present study, it was found that the incidence of AL was 26.19%, which was high as many of the patients in present study had hypoalbuminemia, though it did not show any statistical significance. The mean value of albumin in the present study was 2.96 mg/dl and 3.05 mg/dl in NAL and AL groups respectively.

Zarnescu et al. have reported the risk factors related to AL in colorectal surgery (19). General factors associated with increased chance of AL in colorectal surgery were male gender, malnutrition, serum total protein less than 6g/dl and albumin less than 3.5g/dl, hemoglobin less than 9.9g%, blood transfusions, American Society of Anesthesiologists (ASA) score more than or equal to three, prolonged operating time and chronic steroid therapy. Local factors, which are associated with increased chance of AL, are low rectal anastomosis, less than 6 cm from anal verge, neoadjuvant radiotherapy, intraperitoneal chemotherapy, Hyperthermic intraperitoneal chemotherapy and bevacizumab. In the present study, it was found that risk factors which reflect the general nutritional status of the patient such as hemoglobin, total protein, albumin had no association with the AL. Other risk factors such as neoadjuvant radiotherapy or chemotherapy, surgical techniques, duration of surgery, and chronic kidney disease were not studied in our study.

The present study showed that serum CRP value above 44.32mg/dl on POD three can detect AL with sensitivity of 72.73%, specificity of 66.13%, positive predictive value of 30%, negative predictive value of 75.93% and accuracy of 59.52%. Since the negative predictive value of CRP was more (75.93%), it can be used as a tool to rule out AL. The present study also showed that raised peri-operative TLC is also associated with AL.

The merits of this study are the risk factors associated with AL such as hemoglobin, total protein and albumin were also analyzed. The other causes of raised CRP and PCT such as wound infection was also considered and analyzed. The duration of follow up was also long i.e., 60 days to include delayed postoperative complications.

The limitation of this study is the high wound infection rate in the study population, which may be because of poor nutritional status of the patients and the malignant nature of the disease.

CONCLUSION

The plasmatic concentration of more than 44.32mg/dl of CRP on POD three, and >9470 cells/mm^3 of postoperative TLC were found to detect the AL early with a high negative predictive value. So, this can be utilized for discharging patients early after elective gastrointestinal surgeries. However, serum procalcitonin was not found to be a predictor of anastomotic leak. Risk factors such as low serum total protein, albumin and hemoglobin were not associated with anastomotic leak.

Ethics Committee Approval: The approval for this study was obtained from Jawaharlal Institute of Postgraduate Medical Education and Research Ethics Committee (Decision no: JIP/IEC/2016/1040 Date: 16.02.2017).

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ORİJİNAL ÇALIŞMA-ÖZET
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Elektif bağırsak cerrahisi sonrası anastomoz kaçağının erken tespiti için serum C-reaktif proteininin ve prokalsitoninin seri tetkiki: prospektif kohort çalışma

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ÖZET

Giriş ve Amaç: Anastomoz kaçağı, özelikle de geç tanı konulduğunda cerrahi sonuçlarını kötü etkileyebilir. Bu çalışmada, anastomoz kaçağının postoperatif erken dönemde tespit edilmesi için C-reaktif protein (CRP) ve prokalsitonin (PCT) seri değerlendirmesi kullanılmıştır.

Gereç ve Yöntem: Anastomoz uygulanmış elektif gastroinstestinal cerrahi hastalarını içeren tek merkezli prospektif bir çalışma yürütüldü. İlk beş postoperatif günde C-reaktif protein (CRP) ve prokalsitonin (PCT) seri olarak incelendi. Hemoglobin, total protein, albümin ve beyaz küre sayısı gibi diğer parametreler perioperatif olarak not edildi. Hastalar anastomoz kaçağı, yara enfeksiyonu ve diğer septik odakları değerlendirmek üzere cerrahi sonrası 60. güne kadar takip edildi.

Bulgular: Çalışmaya 84 hasta dahil edildi. Anastomoz kaçağı oranı %26,19 idi (22/84) ve anastomoz kaçağı grubunda 3/22 hasta kaybedildi. Yara enfeksiyon oranı %23,81 idi. Anastomoz kaçağını tespit etmede CRP cut-off değeri 44,322 mg/dl iken duyarlılık %72,73, özgüllük %66,13 ve doğruluk %59,74 olarak ölçüldü. Ölçülen serum prokalsitonin, hemoglobin, total protein ve albumin değerleri anastomoz kaçağının erken tespiti için yeterince duyarlı değildi.

Sonuç: Üçüncü postoperatif günde CRP ölçümü anastomoz kaçağını 44,32 mg/dl'lik cut-off değeri ile öngörebilir. Yüksek CRP değeri olan hastalarda erken taburculuğa karar vermeden önce anastomoz kaçağının elenmesi gerekmektedir.

Anahtar Kelimeler: C-reaktif protein, prokalsitonin, anastomoz kaçağı

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Risk factors for conversion to open surgery in laparoscopic cholecystectomy: a single center experience

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ABSTRACT

Objective: This study aimed to demonstrate the demographic characteristics for laparoscopic cholecystectomy surgeries performed in the general surgery clinics of our hospital and to identify the rate of conversion to open surgery and the main reasons for convert to open surgery.

Material and Methods: Medical records of a total of 1.294 patients who underwent laparoscopic cholecystectomy in our hospital between October 2013 and May 2017 were retrospectively reviewed, and the rates of conversion to open surgery based on age groups were recorded.

Results: Of these patients, 1191 were females (92.0%) and 103 (7.9%) were males. Mean age was 48.6 ± 13.2 (range: 18 to 89) years. Indications for surgery were cholelithiasis in 1195 patients (92.4%), acute cholecystitis in 56 patients (4.4%), and gallbladder polyps in 43 patients (3.3%). The procedure was conversion to open surgery in 41 patients (3.16%), while 12 (0.9%) developed intraoperative complications. There was no mortality. Mean length of hospital stay was 1.2 (range: 1 to 6) days. The main reasons for conversation to open surgery were as follows: adhesions in the Calot's triangle (n= 3), acute cholecystitis (n= 29), choledocholithiasis (n= 2), adhesions due to previous surgery (n= 1), dissection difficulty (n= 2), organ damage (n= 2), anatomic variation (n= 1), and stone expulsion (n= 1).

Conclusion: Acute cholecystitis appears to be the significant factor increasing the rate of conversation to open surgery during LC procedures. Male sex and older age are the other factors increasing the risk of con- vert to open surgery. However, LC should be still the first choice of intervention.

Keywords: Laparoscopic cholecystectomy, open cholecystectomy, complication

INTRODUCTION

Laparoscopic cholecystectomy (LC) is widely used worldwide as in Turkey and has become the standard approach for the treatment of symptomatic cholelithiasis in recent years (1). Major advantages of LC including reduced postoperative pain, early return to normal physical activity, and improved cosmetic outcomes have made this method the first-line intervention over open cholecystectomy (OC). Several factors, which were previously definitive contraindications for LC, are currently diminished due to the recent improvements both in basic surgical concepts and in the technique used.

In the present study, we aimed to evaluate the outcomes of LC in relation to several clinical parameters and compare data in the light of the literature data.

MATERIAL and METHODS

Medical records of a total of 1294 patients who underwent LC in the General Surgery Clinics of our hospital between October 2011 and October 2016 were retrospectively reviewed. (The study protocol was reviewed and approved by our Institutional Ethical Committee. Consent from our patients treated in our hospital is received to use them in the future when they are operated or treated. Although the study was retrospective, approval was obtained to use the related information. The procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983. IRB number : E-15/622) Data including age and sex of the patients, preoperative diagnosis, (acute cholecystitis- (muphy (+), leucocyto-

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sis, CRP elevation, gallbladder wall thickness is >3mm)) number of patients scheduled for laparoscopic surgery and conversion to open surgery, demographic characteristics of these patients, and the reasons for conversion to open surgery were recorded. The relation between age and sex, preoperative diagnosis, and the decision to convert to open procedure was evaluated. All LC operations were performed by the general surgeons of our clinics using standard four-port entry and under 12-14 mmHg pressure.

Based on preoperative ultrasonography findings, gallbladder wall thicknesses higher than 3 mm were considered to be "thick" and thicknesses equal to or lower than 3 mm were considered to be "normal".

Statistical Analysis

All data were recorded on "SPSS 17.0 for Windows" (SPSS Inc. Chicago IL.) statistical analysis software. For these variables, univariate analysis was performed using chi-square and Student's t-tests. Multivariate analysis was additionally performed for those variables that had statistical significance. P values < 0.001 were considered statistically significant.

RESULTS

Of all patients, 1191 (92.0%) were females and 103 (7.9%) were males. Mean age of females, males and overall study population was 44.8 ± 12.3, 49.6 ± 11.2, and 48.6 ± 13.2 years, respectively. Mean age of the males who underwent LC was significantly higher than females (p< 0.001). In total, the procedure was switched to open surgery in 41 patients (3.16%), including 28 of 1,191 women (2.3%) and 13 of 103 men (12.6%). The rate of conversion to open surgery was higher among men compared to women (p< 0.001). Among the patients who were switched to open procedure, mean age of the women was 51.8 ± 15.1 years and mean age of the men was 57.9 ± 14.8 years, indicating a statistically significant difference (p< 0.05). Mean age of the patients who were switched to open surgery was 54.7 ± 12.9 years, and mean age of the patients who completed the surgery with laparoscopic method was 46.8 ± 13.7 years. Mean age of patients who switched to open surgery was statistically significantly higher p< 0.001. (Table 1).

An evaluation of preoperative diagnoses showed that 1,195 patients were operated for cholelithiasis (92.4%), 56 for acute cholecystitis (4.4%), and 43 for gallbladder polyps (3.3%). The procedure was conversion to open surgery in 18 patients operated for cholelithiasis (1.5%) and in 23 patients operated for acute cholecystitis (41%). The procedure was not switched to open surgery in any patient operated for gallbladder polyps. The rate of switch to open surgery was significantly higher among the patients operated for acute cholecystitis (p< 0.001).

Of the patients operated for acute cholecystitis, 22 were women (1.8% of all female patients) and 34 were men (3.3% of all male patients). The rate of operation due to acute cholecystitis was higher among men than women (p< 0.05).

Mean ages of the patients operated for acute cholecystitis and for cholelithiasis were 51.2 ± 13.0 and 48.4 ± 13.1 years, respectively. Mean age of the patients operated for acute cholecystitis was significantly higher (p< 0.001) Table 2 shows the causes of conversion to open surgery in the absence of a complication. The most common cause was adhesions in the Calot's triangle.

Table 2 presents complications developed during laparoscopic surgery. The procedure was conversion to open surgery in all of those patients. One patient, who had cystic duct injury, was reoperated two days later due to ongoing bile drainage. Stomach-small intestine injuries occurred in two patients due to trocar entry and in two patients during dissection. Primary repair was performed in patients whose injuries occurred due to trocar entry. Primary repair and omentoplasty were performed for other patients. Since the injury was close to the conjunction point of the right and left hepatic ducts in 3 patients with choledochal injury, Roux-en-Y hepaticojejunostomy was performed for these patients. Choledochoduodenostomy was performed for the other patient.

DISCUSSION

The advantages of LC over OC have been long discussed and now, LC has become the first choice (1,2). Until May 2017, all 1294 cases in our hospital underwent LC. When this method was introduced, despite its advantages, it was not considered as a harmless procedure due to high rate of injuries particularly in the main bile ducts (3,4). Acute cholecystitis accounts for almost

Table 1. The association of conversion with age and sex

	n (%)	p
Age (Mean ± SD, y)		
Female	51.8 ± 15.1	**<0.005**
Male	57.9 ± 14.8	
Sex		
Female	28 (2.3%)	**<0.005**
Male	13 (12.6%)	
SD: Standard deviation, y: Year.		

Table 2. Reasons of conversion	
Reason	**n (%)**
Bile leak	7 (17%)
Adhesion in Calot triangle	6 (14%)
Cystic duct injury	4 (9.7%)
Common bile duct stone	4 (9.7%)
Common bile duct injury	4 (9.7%)
Dissection difficulties	4 (9.7%)
Stomach-small bowel injury	4 (9.7%)
Adhesions due to previous surgery	2 (4.8%)
Anatomic variations	2 (4.8%)
Major abdominal vascular injury	2 (4.8%)
Stone loss	2 (4.8%)

20% of all gallbladder diseases, and it is no longer a contraindication for LC (5,6). The incidence of biliary system injuries during LC varies between 0.2-1.4%. This rate, recorded among 11 cases in the present study (0.8%), is consistent with the literature. Among those 11 cases, two had choledochal injury.

Etiology of sex differences in symptomatic cholelithiasis can be multifactorial (9) From a psychosocial perspective, men less frequently refer to a physician at symptom onset compared to women. Similarly, men agree to surgery at a later stage than women. This results in an increase in disease severity. Moreover, higher daily activities of men cause a delay in their referral to a hospital. From a pathophysiological perspective, women can be more sensitive to inflammatory changes associated with cholecystitis compared to men (9). Moreover, anatomic differences and changes in dietary habits may also result in the variability between men and women for cholelithiasis. The most common causes for switch to open surgery were adhesions in the Calot's triangle, acute cholecystitis and bleeding in the present study. In the study of Kausnik et al. (10), adhesions in the Calot's triangle and injuries of the main bile duct have been to be the most common causes of switch to open surgery.

As shown in Table 2, the most remarkable problems in cases switched to open surgery in the absence of a complication were adhesions in the Calot's triangle and difficulties in dissection. Previous upper abdominal surgeries are also risk factors increasing the rate of switch to open surgery (11).

The rate of major complications during LC has been previously reported as 1-3%, and the rate of bile duct injuries has been found to vary between 0 and 0.7% (3). Complications due to Veres and trocar entry have been previously reported in the literature. In a study conducted by Deizel et al. (12), intestinal perforation has been reported as the most common cause of death that occurs after laparoscopic methods. In the present study, four patients received treatment was by open surgery after stomach-small intestine perforations which developed due to trocar entry and dissection.

The rate of conversion to open surgery due to bleeding has been reported as 0-1.9%, and the rate of secondary surgeries has been found to be 0.4% (4-13). In the case series of Shurkalin et al. (14), bleeding has been noted in 0.7% of the patients, and the most common causes of bleeding have been determined intraoperative injuries accompanied by anatomic variations of the vessels (14). Epigastric vessel injury occurred due to trocar entry in two cases in this study; these complications were noticed and successfully treated during the operation. Mortality due to LC is similar to OC and has been reported to vary between 0 and 0.9 % (15-17). Mortality frequently occurs due to concomitant diseases and peritonitis which develop as a result of intraabdominal organ injuries. None of the patients died in our patient series.

Assessment of age and sex distribution of the patients with acute cholecystitis indicated a higher rate of acute cholecystitis among men at all age groups. For both sexes, the rate of acute cholecystitis in the age group of 65 years or older was higher compared to the other age groups, and the difference reached statistical significance for men. Men with acute cholecystitis were younger compared to women.

In the study of Tocchi et al. (18), cholelithiasis complications have been more frequently observed in men, and male sex, as well as ages over 65 years, have been found to be factors negatively effecting operative mortality. Based on some series, higher rates of conversion to open surgery, morbidity and mortality have been reported among older patients (15-19). This is mostly associated with the frequency of cholecystitis episodes and concomitant diseases. Elective LC is recommended for older patients with symptomatic gallbladder stones before they experience an acute cholecystitis episode (20). In the present study, the rate of conversion to open surgery and the rate of complications were higher among patients older than 65 years, and the effect of age on the rate of complications was significant. On the other hand, older age had no significant effect on the duration of operation.

In the present study, acute cholecystitis was found to be the second most common cause of switch to open surgery. In a very large-scale study performed by Vecchio et al. (21) by reviewing data of more than 100.000 patients, the rate of switch to open surgery has been primarily associated with the severity of inflammation.

While patients with acute cholecystitis were initially not found eligible for LC, studies performed later on increased the experience on this procedure and demonstrated that LC can be routinely performed in this patient group as well (22-24). Early cholecystectomy is known to be beneficial also for patients with acute cholecystitis(25). In the present study, the presence of acute cholecystitis and increased wall thickness as shown by

USG were found to be risk factors for switch to open surgery, and their effects also reflected on the complications and duration of operation. These patients constitute the patient group, in whom LC must be performed by paying utmost attention and dissection must be done very carefully.

The rate of gallbladder injuries during LC is higher than the rate observed during open surgery and has been reported to vary between 0.2 and 1.4% (26). Despite all precautions, the best time of repair in case of an injury appears to be during the operation. Hollow organ injuries are also commonly seen complications during LC procedures. Some reports indicate that their incidence may reach up to 0.9% (26). Attention must be paid for such injuries, particularly while constructing the pneumoperitoneum and during the use of cautery. The rate of retroperitoneal major vessel injury due to trocar entry has been reported as 0.05% in the previous studies, and mortality associated with such injuries has been found to be 8.3% (12). Balija et al. (27) have evaluated bile duct variations in patients who underwent LC and detected accessory bile ducts in 52% of their patients. In the present patient series, seven patients who had bladder bed leakage were followed-up by medical means and the leakage was successfully controlled by ERCP in one patient.

Complications due to cystic artery injury, which were previously reported in 0.2-2% of the patients, did not develop in any patient in the present patient series (23).

CONCLUSION

In conclusion, acute cholecystitis appears to be the most significant factor increasing the rate of conversation to open surgery during LC procedures. Male sex, older age, and the presence of acute cholecystitis are the main factors increasing the risk of convert to open surgery. However, LC must still be the first choice of intervention. We believe that the rate of complications will decrease even more, as we gain additional experience in the treatment of acute cholecystitis, in particular.

Ethics Committee Approval: The ethical approval for this study was obtained from Başkent University Medical And Health Sciences Research Board (Date: 02.02.2020 Decision no: 603339-604.01.02/13101).

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Laparoskopik kolesistektomide açığa dönüş risk faktörlerinde tek merkez deneyimi

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ÖZET

Giriş ve Amaç: Bu çalışmadaki amacımız hastanemiz genel cerrahi kliniklerinde yapılan laparoskopik kolesistektomi ameliyatlarının demografik özelliklerini ortaya koymak, açık cerrahiye geçiş oranı ve başlıca nedenlerini irdelemektir.

Gereç ve Yöntem: Ekim 2013-Mayıs 2017 tarihleri arasında hastanemizde laparoskopik kolesistektomi uygulanan toplam 1.294 hastanın tıbbi kayıtları geriye dönük olarak incelendi ve yaş gruplarına göre açık cerrahiye geçiş oranları kaydedildi.

Bulgular: Bu hastaların 1191'i kadın (%92,0) ve 103'ü (%7,9) erkekti. Ortalama yaş 48,6 ± 13,2 (18-89) yıldı. Ameliyat endikasyonları 1195 hastada (%92,4) kolelitiazis, 56 hastada (%4,4) akut kolesistit ve safra kesesi polipleriydi. 43 hasta (%3,3). İşlem 41 hastada (%3,16) açık cerrahiye geçerken, 12 hastada (%0,9) intraoperatif komplikasyon gelişti. Ölüm olmadı. Ortalama hastanede kalış süresi 1,2 (1-6) gündü. Açık cerrahiye geçmenin ana nedenleri şunlardı: Calot üçgeninde yapışıklıklar (n= 3), akut kolesistit (n= 29), koledokolitiazis (n = 2), önceki ameliyata bağlı yapışıklıklar (n = 1), diseksiyon zorluk (n= 2), organ hasarı (n= 2), anatomik varyasyon (n= 1) ve taş çıkarma (n= 1).

Sonuç: Akut kolesistit, laparoskopik kolesistektomi sırasında açık cerrahiye geçiş oranını artıran en önemli faktör olarak görünmektedir. Erkek cinsiyeti, artan yaş ve akut kolesistit varlığı açık cerrahiye dönüş riskini artıran ana faktörlerdir.

Anahtar Kelimeler: Laporoskopik kolesistektomi, kolesistektomi, komplikasyon

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Comparison of open and laparoscopic gastrectomy for gastric cancer: a low volume center experience

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ABSTRACT

Objective: In gastric cancer, laparoscopic gastrectomy is commonly performed in Asian countries. In other regions where tumor incidence is relatively low and patient characteristics are different, developments in this issue have been limited. In this study, we aimed to compare the early results for patients who underwent open or laparoscopic gastrectomy for gastric cancer in a low volume center.

Material and Methods: We retrospectively analyzed the data of patients who underwent curative gastric resection (open gastrectomy n: 30; laparoscopic gastrectomy n: 30) by the same surgical team between 2014 and 2019.

Results: The tumor was localized in 60% (36/60) of the patients in the proximal and middle 1/3 stomach. In laparoscopic gastrectomy group, the operation time was significantly longer (median, 297.5 vs 180 minutes; p< 0.05). In open gastrectomy group, intraoperative blood loss (median 50 vs 150 ml; p< 0.05) was significantly higher. Tumor negative surgical margin was achieved in all cases. Although the mean number of lymph nodes harvested in laparoscopic gastrectomy group was higher than the open surgery group, the difference was not statistically significant (28.2 ± 11.48 vs 25.8 ± 9.78, respectively; p= 0.394). The rate of major complications (Clavien-Dindo ≥ grade 3) was less common in the laparoscopic group (6.7% vs 16.7%; p= 0.642). Mortality was observed in four patients (2 patients open, 2 patients laparoscopic).

Conclusion: In low-volume centers with advanced laparoscopic surgery experience, laparoscopic gastrectomy for gastric cancer can be performed with the risk of morbidity-mortality similar to open gastrectomy.

Keywords: Gastric cancer, laparoscopic gastrectomy, open gastrectomy, complication

INTRODUCTION

Gastric cancer is one of the most common cancers in the world. Although its incidence has decreased today, it is still the third most common cause of cancer-related deaths (1). The only potential curative treatment option in gastric cancer is gastrectomy with lymph node dissection (2). Laparotomy, which is the classical approach, carries serious risks for morbidity, mortality and impaired quality of life (3,4). Therefore, techniques that can reduce these potential disadvantages and risks of the classical approach attract the attention of surgeons in the treatment of gastric cancer.

Laparoscopic gastrectomy was first reported in 1994 by Kitano et al. (5). Since then, laparoscopic gastrectomy has continued to be performed increasingly all over the world, mainly in Asian countries. The effectiveness, feasibility and oncological adequacy of the technique have been demonstrated in various studies (6-8). The majority of these studies are from Asian countries where tumor incidence is high, the tumor is diagnosed at an early stage and a young age with screening programs and cancer surgery is performed in specialized centers (6-8). The experience of laparoscopic gastrectomy is limited in European countries where tumor epidemiology and patient characteristics are different (9,10).

Geographically, Turkey is the crossroads of Europe and Asia. Parallel to that, the incidence of gastric cancer, tumor and patient characteristics are also somewhat between the European and Asian communities (11). In addition, gastric cancer surgery is also performed outside of specialized centers in our country. This situation, together with the relatively low tumor incidence, leads to low patient volume in a single center.

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In this study, it was aimed to compare the early results of patients who underwent open or laparoscopic gastrectomy (total, subtotal) for gastric cancer in our clinic and the oncological adequacy of both techniques.

MATERIAL and METHODS

After approval of the Institutional Ethics Board Committee, the data of patients who were operated consecutively for gastric cancer between January 2014 and December 2019 were collected retrospectively. The diagnosis was made by upper gastrointestinal endoscopy and endoscopic biopsy. Clinical staging was done by using contrast computed tomography (CT). Positron emission tomography (PET) was used in patients with suspected metastasis. Patients with ASA score > 3 and the patients who were operated on by different surgical teams for palliative resection were excluded from the study. Between these dates, 60 patients who underwent curative gastrectomy were included in the study. Until January 2016, open gastrectomy (Open gastrectomy group; n: 30) was performed in all patients and patients whose adjacent organ invasion (cT4b) was shown in preoperative radiological examinations. Laparoscopic gastrectomy (Laparoscopic gastrectomy group; n: 30) was applied to other potential curative patients other than these criteria.

The patients were hospitalized 24 hours before the operation. Deep venous thrombosis prophylaxis (dalteparin sodium 35 IU/kg) was started. Before anesthesia induction, all patients received prophylaxis with 2 grams of first-generation cephalosporin.

Surgery

D1+ lymph node dissection was performed in patients with age ≥70 and comorbid disease, regardless of surgical technique and tumor stage. D2 lymphadenectomy was performed in other patients. Lymph node dissection was performed according to the Japanese gastric cancer treatment guidelines (2).

Laparoscopic Gastrectomy

The operations (total, subtotal) were performed in a French position with five trocars. The surgical team, equipment and the location of the trocars are shown in Figure 1. A total omentectomy was performed in all cases. However, bursectomy was not performed. Lymph node dissection and total omentectomy were performed according to the following stages. The gastrocolic ligament was opened by omentectomy. In the corner of the spleen, left gastroepiploic vessels were dissected (no 4b). Right gastroepiploic vessels (no 4d) and infrapyloric lymph nodes (no 6) were dissected. Gastroduodenal artery was followed in the posterior of the duodenum, and its junction with the hepatic artery was identified. Meanwhile, a window was created for transection in the supraduodenal area. The duodenum was transected with laparoscopic 60 mm linear stapler. Supraduodenal lymph nodes (no.5) were dissected. Right gastric artery was ligated. Targeted lymph node dissection (D1+, D2) according to tumor localization

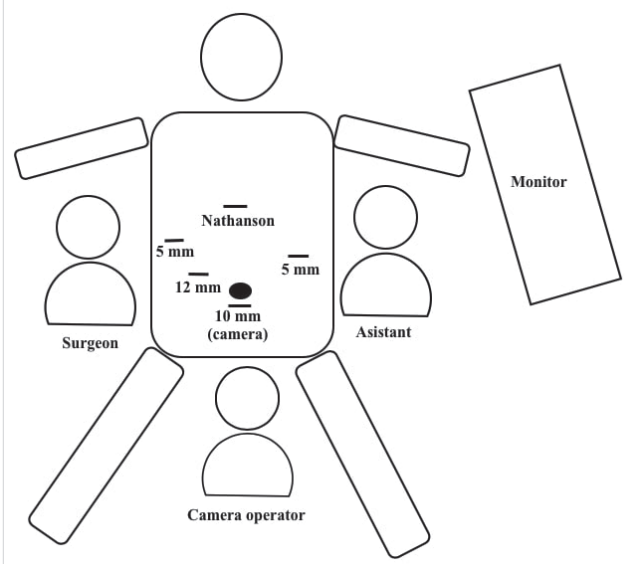

Figure 1. Patient position, placement of equipment and trocars for laparoscopic gastrectomy.

and other factors (age, comorbid status, etc.) was completed as recommended in the Japanese gastric cancer treatment guidelines (2). Dissections were performed with a harmonic scalpel. Intraoperative gastroscopy was performed in all cases in order to determine the surgical margin. All reconstructions were antecolic Roux-en-Y type. In subtotal gastrectomy, standard gastrojejunostomy was performed with a 60 mm endo stapler from the posterior of the remnant stomach. Stapler spaces were closed in double-layers with continuous sutures of 3/0 prolene. Jejunojejunostomy anastomosis was performed with a 60 mm endo stapler at 50 cm distal. Stapler space was closed in double-layers with 3/0 prolene. The specimen was extracted through a suprapubic mini transverse incision. Esophagojejunostomy anastomosis in total gastrectomy was achieved with three different techniques. These were transorally inserted anvil (OrVilTM; Covidien, Mansfield, MA, USA), side-to-side with a linear stapler and transperitoneal double stapler techniques. The specimen was extracted through a suprapubic mini transverse incision in patients who underwent anastomosis with linear stapler, and from the mini-incision in the upper left quadrant where circular stapler were placed in other patients. In all patients, a drain was placed in the abdomen.

Open Gastrectomy

The operations were performed with a midline incision extending under the umbilicus in supine position. Total omentectomy was performed in all patients, but bursectomy was performed in patients who underwent D2 lymph node dissection. Lymph node dissection was performed as in laparoscopic surgery. Reconstruction was performed as retro colic Roux-en-Y or Billroth-II according to the surgeon's preference in subtotal gastrectomy, and Roux-en-Y in total gastrectomy. Gastrojejunostomy was performed with

a linear stapler and esophagojejunostomy with a circular stapler. In the patients who underwent subtotal gastrectomy, one drain was placed in the abdomen, and in the patients who underwent total gastrectomy, two drains were placed.

Postoperative Follow-up

In the laparoscopic group, nasogastric catheter was not used. On the other hand, a nasogastric catheter was used in the open surgery group and was often removed on the 1st or 2nd postoperative day after the first gas discharge. All patients were evaluated by routine laboratory tests (hemogram, biochemistry, CRP) on the 1st, 3rd, and 5th days. In patients for whom intraabdominal pathology was not considered according to clinical findings (physical examination, laboratory) and aspirate from the abdominal drain, oral food was started on the postoperative 3rd day for those who underwent subtotal gastrectomy in the laparoscopic group, postoperative 5th day for those who underwent total gastrectomy, and on the postoperative 4th day for those who underwent subtotal gastrectomy in the laparotomy group, and on the postoperative 5th day for those who underwent total gastrectomy. Patients who had adequate oral intake and no clinical problems were discharged.

Age, sex, body mass index (BMI), previous abdominal surgery status, comorbid diseases, American Society of Anesthesiologists (ASA) score, neoadjuvant therapy status, surgical technique (open, laparoscopic), tumor localization, gastrectomy type (total, subtotal), lymph node dissection type, operative data (operation time, blood loss), morbidity mortality and histopathological examination results of the specimen were recorded for the patients. Complications were grouped according to the Clavien-Dindo Classification (12). Tumor staging was performed according to AJCC 8th Edition (13).

Statistical Analysis

Statistical evaluation was performed with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) program package. Compatibility with normal distribution was assessed by the Shapiro-Wilk test. Numerical variables with normal distribution were expressed as mean +/- standard deviation while numerical variables without normal distribution were expressed as median (Interquartile range (IQR); 25th percentile-75th percentile), and categorical variables were given as frequency (percent). The difference among the groups was determined by the independent-samples t-test for the numerical variables with normal distribution, whereas it was determined with the Mann-Whitney U test for the numerical variables without normal distribution. Correlations between categorical variables were analyzed by the Chi-squared test or Fisher s exact test as appropriate. For a two-tailed hypothesis test, $p< 0.05$ was considered sufficient for statistical significance.

RESULTS

Patient Characteristics

Sixty patients underwent gastrectomy with curative intent (30 open/30 laparoscopic). Thirty-eight patients were (63.3%) males and 22 (36.7%) patients were females. Mean age of the patients was 63.1 ± 11 years. The frequency of male patients was higher in the open gastrectomy group ($p= 0.016$). In total, 8 patients (3 open, 5 laparoscopic) received neoadjuvant chemotherapy. There was no significant difference between the groups in terms of other factors related to patients. Patient characteristics are listed in Table 1.

Table 1. Patient demographics and clinical parameters

Variables	Open (n: 30)	Laparoscopic (n: 30)	p
Age (year)	63.83 ± 11.60	62.40 ± 10.72	.621
BMI (kg/m^2)	22.97 ± 3.77	24.51 ± 4.21	.142
Sex			
Male	24 (80%)	14 (46.7%)	.015
Female	6 (20%)	16 (53.3%)	
ASA score			
I	4 (13.3%)	1 (3.3%)	
II	12 (40.0%)	16 (53.3%)	.348
III	14 (46.7%)	13 (43.4%)	
Previous abdominal surgery			
Yes	5 (16.7%)	1 (3.3%)	.195
No	25 (83.3%)	29 (96.7%)	
Neo-adjuvant chemotheraphy			
Yes	3 (10%)	5 (16.7%)	.706
No	27 (90%)	25 (83.3%)	
Co-morbidity			
=1	9 (30.0%)	9 (30.0%)	
>1	8 (26.7%)	11 (36.7%)	.651
None	13 (43.3%)	10 (33.35%)	

Operative Outcomes and Complications

The tumor was localized in proximal third in 46.7% (28/60) of the cases, middle third in 13.3% (8/60), lower third in 36.7% (22/60), and remnant stomach in 3.3% (2/60) of patients, respectively. Total gastrectomy was performed in 61.7% of the cases (37/60) and subtotal gastrectomy in 38.3% (23/60). D2 lymph node dissection was performed in 78.3% (47/60) of the cases, and D1+ in 21.7% (13/60). In the open surgery group, median operation time was 180 (IQR; 163.75 - 192.5) minutes, while in the laparoscopy group, it was 297.5 (IQR; 257.5-310) minutes. The operation time was statistically significantly shorter in the open surgery group ($p< 0.05$). Median intraoperative blood loss was 150 (IQR; 100-200) ml in open surgery and 50 (IQR; 50-100) ml in laparoscopy ($p< 0.05$). Tumor localization and operative data are listed in Table 2. In three (10%) patients, the laparoscopic procedure was converted to open surgery in the laparoscopic gastrectomy group. The causes of conversion were the total occlusion of the efferent loop and in the end-to-side esophagojejunostomy anastomosis using transorally inserted anvil (Orvil), the injury of the splenic artery during dissection, and nonevaluation of the tumor invasion status laparoscopically. These patients were evaluated in the laparoscopic group.

Although the major complication (≥ grade 3) rate according to the Clavien-Dindo Classification was lower in the laparoscopic surgery group (6.7%) compared to open surgery (16.7%), there was no statistically significant difference between the groups ($p= 0.642$). In the open surgery group, 4 (13.3%) cases were reoperated due to various postoperative complications (bleeding, anastomotic leak, evisceration, spleen ischemia). No patient was reoperated in the laparoscopic gastrectomy group. Anastomotic leak was observed in two patients (6.6%) in the laparoscopic group. These patients were operated on after neoadjuvant chemotherapy. Anastomotic leak was detected radiologically and treated with conservative methods. Anastomotic leak was detected in one patient (3.3%) of the open surgery group. This patient was reoperated due to intra-abdominal sepsis. Mortality was observed in four patients (6.6%) in total. In the open surgery group, mortality was observed in two patients reoperated for anastomotic leak and bleeding due to pancreatic fistula. In the laparoscopy group, mortality was observed in two patients, one who developed ischemic hepatitis due to postoperative portal vein thrombosis and one who developed myocardial infarction. There was no significant difference between the groups in terms of mortality ($p= 0.100$) (Table 3).

Histopathological Outcomes

Median tumor diameter was 6 (IQR; 3-7.5) cm in the open surgery group and 4 (IQR; 2.75-6) cm in the laparoscopy group ($p= 0.033$). Tumor negative surgical margin (R0) was achieved in all cases. 18.3% (11/60) of the cases were evaluated as early-stage and 81.7% (49/60) were evaluated as advanced (≥ T2) gastric cancer. T4 tumor rate was higher in the open gastrectomy group (70% vs 26.7%; p: 0.003). Mean number of lymph nodes harvested was 25.8 ± 9.78 in the open surgery group, and 28.2 ± 11.48 in the laparoscopic group. Although mean number of lymph nodes harvested in the laparoscopic gastrectomy group was high, the difference between the groups was not statistically significant ($p= 0.394$) (Table 4).

DISCUSSION

Laparoscopic gastrectomy for gastric cancer is a difficult and complex procedure. In Asian studies, it has been indicated that the learning curve requires a serious number of cases (50-90 cases) and is a challenging process (14,15). In our clinic, relatively few (15 patients per year) number of curative gastric re-

Table 2. Tumor localization and operative data in patients

Variables	Open (n: 30)	Laparoscopic (n: 30)	p
Tumor location			
Proximal 1/3	15 (50.0%)	13 (43.3%)	
Middle 1/3	3 (10.0%)	5 (16.7%)	
Lower 1/3	11 (36.7%)	11 (36.7%)	.909
Remnant	1 (3.3%)	1 (3.3%)	
Gastrectomy type			
Total	19 (63.3%)	18 (60%)	1.0
Subtotal	11 (36.7%)	12 (40%)	
Dissection type			
D1+	6 (20.0%)	7 (21.7%)	.794
D2	24 (80.0%)	23 (78.3%)	
Reconstruction type			
Roux-en Y	26 (86.7%)	30 (100%)	.112
Billroth-II	4 (13.3%)	0 (0%)	
Operation time (min)	180 (163.75-192.5)	297.5 (257.5-310)	<0.05
Blood loss (ml)	150 (100-200)	50 (50-100)	<0.05

Table 3. Peri-operative outcomes

Variables	Open (n: 30)	Laparoscopic (n: 30)	p
Postoperative Complication			
Yes	12 (40.0%)	9 (30.0%)	.589
No	18 (60.0%)	21 (70.0%)	
Clavien Dindo			
< Grade 3	7 (23.3%)	7 (23.3%)	.642
≥ Grade 3	5 (16.7%)	2 (6.7%)	
Re-operation	4 (13.3%)	0 (0%)	.112
Mortality	2 (6.6%)	2 (6.6%)	1.00

Table 4. Pathological outcomes

Variables	Open (n: 30)	Laparoscopic (n: 30)	p
Tumor size (cm)	6 (3-7.5)	4 (2.75-6)	**.033**
Tumor differentiation			
Poor/Undifferentiated	13 (43.3%)	15 (50%)	
Moderate	12 (40.0%)	11 (36.6%)	.100
Well	5 (16.7%)	4 (13.4%)	
T stage			
T1	5 (16.7%)	6 (20%)	
T2	2 (6.7%)	4 (13.3%)	**.003**
T3	2 (6.7%)	12 (40%)	
T4	21 (70%)	8 (26.7%)	
Number of harvested LN	25.8 ± 9.78	28.2 ± 11.48	.394
N stage			
N0	6 (20.0%)	14 (46.7%)	
N1	7 (23.3%)	3 (10.0%)	
N2	8 (26.7%)	3 (10.0%)	.068
N3	9 (30%)	10 (33.3%)	
Tumor stage (AJCC 8th Edition TNM)			
Stage 1	4 (13.3%)	9 (30.0%)	
Stage 2	7 (23.3%)	8 (26.7%)	.211
Stage 3	19 (63.4%)	13 (43.3%)	

sections are performed compared to Asian countries. In addition, unlike Asian countries, the majority of cases diagnosed in our clinic were found to have advanced gastric cancer (81.7%) predominantly located in the middle-proximal stomach. In our study comparing this group of patients, in LG, although the duration of surgery was longer, intraoperative blood loss was less.

Regardless of the tumor stage (early, advanced), the duration of surgery in LG was longer in most of the studies comparing open and laparoscopic gastrectomy (7,16,17). A standard total omentectomy was performed in our study. The duration of omentectomy was not recorded separately. However, it was observed that omentectomy significantly extended the operation time, especially in laparoscopic surgery. The reason for this may be the location of the omentum in a wide area on the transverse axis in the abdomen, and fixed placement of trocars and devices in laparoscopy. In studies reported in countries where laparoscopic gastrectomy is more commonly performed, the mean duration of operation has been reported as 258-278 minutes (16,17). In these studies, omentectomy was not applied as standard, and extracorporeal reconstruction was performed (16,17). In our study, the mean duration for operation in the laparoscopic group was 283 minutes. Total omentectomy and intracorporeal reconstruction were performed in all cases. Considering these results, it was observed that the operation time was similar to the clinics where laparoscopic gastrectomy was commonly performed.

Randomized controlled studies and meta-analysises have shown that laparoscopic and open gastrectomy was performed with similar morbidity and mortality rates (7,8,18). In our study, no significant difference was found between the two techniques in terms of morbidity and mortality. In studies, morbidity and mortality rates show geographical differences. Morbidity and mortality rates reported in Asian studies are relatively low compared to European studies (19). In our study, it was deter-

mined that the rate of major complications (Clavien Dindo ≥ 3) especially in laparoscopic gastrectomy was similar to that of Asian studies (6,7). In our study, mortality rate was found to be quite higher than these studies. The predominantly advanced stage and proximal location of the tumor may be the reason for this result. Mortality rates in studies of European countries (10) with tumor characteristics similar to our patient group were similar to our results. However, in the open gastrectomy group, the fact that there were more male patients and patients with T4 tumors, and having had bursectomy and the fact that surgical technique (anastomosis technique, etc.) could not be standardized, especially in laparoscopic total gastrectomy, may have affected the morbidity and mortality rates. This should be taken into account when evaluating the results.

The rate of conversion to open surgery can vary geographically, just like morbidity and mortality rates. While the rate of conversion to open surgery has been reported to be between 6.4% to 6.6% in Asian studies (7,15), this rate has been reported as 18% in a European study (9). In our study, the conversion rate to open surgery was 10%. This rate seems to be acceptable when the learning curve and the limited number of cases are considered.

The R0 resection rate and the number of lymph nodes harvested are important indicators in determining surgical quality. When the two techniques were compared in terms of surgical quality, these parameters were similar in the two groups. The absence of tactile sensation in laparoscopic surgery may cause difficulties in determining tumor localization and surgical margins. Tumor positive surgical margin rate in minimally invasive gastrectomy has been reported to be 6.9-7.5% (9,10). In our study, tumor localization and surgical margins were determined by performing routine intraoperative gastroscopy in the laparoscopic group. This approach may be the main factor in achieving tumor negative surgical margin in all cases.

The width of lymph node dissection is a debated subject. D2 lymphadenectomy is the standard approach in >T1 tumors in Asia and has been shown to provide a survival advantage over D1 lymphadenectomy (20). In our clinic, the general approach is to perform D2 lymphadenectomy in all cases due to the inability to distinguish early gastric cancer in the preoperative period and the fact that the majority of cases are advanced gastric cancer. However, considering the high morbidity and mortality rates reported in cases with D2 lymphadenectomy in European studies (21,22), D1+ lymphadenectomy was preferred in selected cases of elderly age (≥70 years) with severe comorbid disease. The Italian Research Group for Gastric Cancer treatment guideline (23) likewise recommends D1 or D1+ lymph node dissection in selected cases (high-risk patients) where D2 lymph node dissection cannot be performed. A minimum of 15 lymph nodes are recommended to be harvested for correct staging and prognostic evaluation in gastric cancer (24). In our study, an average of 28 lymph nodes were harvested in LG and 25 in open gastrectomy. These results show the adequacy of lymph node dissection. Contrary to studies (25,26) reporting that fewer lymph nodes are harvested in laparoscopy, in our study, more lymph nodes were harvested in LG. The fact that a larger field of view in laparoscopy enables careful and detailed dissection may explain this difference.

Reconstruction in laparoscopic gastrectomy is one of the most difficult stages of the procedure. Unlike Asian countries, in the West, complex laparoscopic bariatric procedures are widely applied (27). These procedures provide an important experience, especially with regard to intracorporeal gastrojejunostomy anastomosis. With such experience, reconstruction was performed easily and safely in laparoscopic subtotal gastrectomy in our clinic. However, esophagojejunostomy anastomosis is a difficult and complex procedure. Many different techniques for laparoscopic esophagojejunostomy have been described in the literature (28). In our clinic, this type of anastomosis has not been standardized yet. Esophagojejunostomy was achieved with three different techniques in our study. In clinics like ours with a limited number of cases and still on the learning curve, the complexity and difficulty of this type of anastomosis should be taken into consideration.

Our results demonstrate the technical feasibility of laparoscopic gastrectomy for gastric cancer in low volume centers with advanced laparoscopic experience. However, in our study, lack of data of survival rates led to continued concerns about oncological adequacy. One of the important limitations of our study is the bias in patient selection. There are few studies in the literature regarding laparoscopic gastrectomy in adjacent organ invasive tumors (T4b) (29). This is because; disruption of normal anatomy due to invasion and abnormal neovascularization may make the laparoscopic approach difficult (30). We prefer open surgery in these patients because of the fact that we are on the learning curve and laparoscopic approach is more complex in these tumors. This is the main cause of bias in our study. In addition, the small number of patients, being a retrospective study, and the lack of data on postoperative recovery profile (pain score, quality of life, etc.) are other factors of limitation of our study.

CONCLUSION

According to the results of this study in which patients with advanced gastric cancer were operated on, laparoscopic gastrectomy for gastric cancer can be performed in low volume centers if the team is experienced in advanced laparoscopy because it does not increase surgical morbidity.

Ethics Committee Approval: The approval for this study was obtained from Healt Sciences University Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2019-98 Date: 14.11.2019).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2021; 37 (1): 33-40

Mide kanserinde açık ve laparoskopik gastrektominin karşılaştırılması: Düşük hasta volümlü merkez deneyimi

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ÖZET

Giriş ve Amaç: Mide kanseri için laparoskopik gastrektomi, Asya ülkelerinde yaygın olarak yapılmaktadır. Tümör insidansının nispeten düşük ve hasta özelliklerinin farklı olduğu diğer bölgelerde, bu konudaki gelişmeler sınırlıdır. Bu çalışmada, düşük hasta volümlü bir merkezde mide kanseri için açık veya laparoskopik gastrektomi yapılan hastaların erken dönem sonuçlarının karşılaştırılması amaçlandı.

Gereç ve Yöntem: Aynı cerrahi ekip tarafından 2014 – 2019 tarihleri arasında küratif mide rezeksiyonu yapılan hastalara (açık gastrektomi n: 30; laparoskopik gastrektomi n: 30) ait veriler retrospektif olarak inceledik.

Bulgular: Tümör, hastaların %60 (36/60)'ında proksimal ve orta 1/3 midede lokalizeydi. Laparoskopik gastrektomi grubunda ameliyat süresi istatistiksel anlamlı olarak daha uzundu (median 297,5 vs 180 dakika; p< 0,05). Açık gastrektomi grubunda intraoperatif kan kaybı (median 50 vs 150 ml; p< 0,05) daha fazlaydı. Tüm vakalarda tümör negatif cerrahi sınır sağlandı. Laparoskopik gastrektomide açık cerrahiye göre ortalama çıkarılan lenf nodu sayısı fazla olmasına rağmen gruplar arasındaki fark istatistiksel anlamlı değildi (sırasıyla 28,2 ± 11,48 vs 25,8 ± 9,78; p= 0,394). Majör komplikasyon oranı (Clavien-Dindo ≥ grade 3) laparoskopik grupta daha azdı (%6,7 vs %16,7; p= 0,642). Dört hastada (2 açık grup, 2 laparoskopik grup) mortalite görüldü.

Sonuç: İleri laparoskopik cerrahi deneyimi olan düşük hacimli merkezlerde, mide kanseri için laparoskopik gastrektomi, açık gastrektomiye benzer morbidite – mortalite riskiyle yapılabilir.

Anahtar Kelimeler: Mide kanseri, laparoskopik gastrektomi, açık gastrektomi, komplikasyon

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ORIGINAL ARTICLE
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Association of CDH1 -160 C → A and -347 G→ GA polymorphisms and expression of E-cadherin and gastric cancer: A case-control study

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ABSTRACT

Objective: The loss of function of the E-cadherin (CDH1) gene with -160 C→A and -347 G→GA polymorphisms is regarded as a critical step for gastric cancer. It was aimed to investigate possible association of these polymorphisms and immunoexpression of E-cadherin with gastric cancer.

Material and Methods: Gastric adenocarcinoma patients and individuals with benign gastric pathologies were included in this case-control study. Demographic data and pathological findings were recorded. Immunohistochemical staining of E-cadherin expression and analysis of -160 C→A and -347 G→GA polymorphisms were done. Differences between allele frequencies of -160 C→A and -347 G→GA polymorphisms and expression of E-cadherin were the primary outcomes.

Results: There were 78 gastric cancer patients (Group A) and 113 individuals with benign gastric pathologies (Group B). The number of male patients and mean age were higher in Group A ($p< 0.001$). -160 C→A and 347 G→GA polymorphisms and their allelic distributions showed no difference between the groups ($p> 0.05$ for all). There was a significant association between -160 C→A polymorphism and grade of E-cadherin expression ($p= 0.013$). There were no significant differences between survival rates with -160 C→A, 347 G→GA and intensity of E-cadherin expression ($p> 0.05$ for all). There was no significant association between -160 C→A and -347 G→GA polymorphisms and gastric cancer.

Conclusion: There was no impact of E-cadherin expression on tumoral features and survival in gastric cancer. -160 C→A polymorphism may influence the expression of E-cadherin in gastric cancer.

Keywords: CDH1 polymorphisms, E-cadherin, gastric carcinoma, immunohistochemical expression, survival

INTRODUCTION

Loss of E-Cadherin encoded by CDH1 gene is known to cause loss of cellular differentiation and intercellular adhesion, which is an early step in neoplastic processes (1, 2). Therefore, CDH1 is regarded as a causative factor for several types of tumors including gastric cancer (3).

Single nucleotide polymorphisms (SNP) of CDH1 gene are associated with an increased risk of gastric cancer (4). Among these, -160 C → A and -347 G→ GA are SNPs located in the promoter region of CDH1 both of which decrease the transcription efficiency of CDH1 gene (3-8). The possible association of these SNPs with gastric cancer has been studied in previous reports (5). Although CDH1 mutations are usually associated with hereditary and/or sporadic diffuse gastric cancer, some reports have also shown these mutations in intestinal gastric cancer cases (9-11). However, conflicting results regarding association and prognostic impact of SNPs were recorded in different ethnic populations (1, 2, 12-15). In addition, the role of these polymorphisms on the expression of E-cadherin in gastric cancer has not

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been studied. We aimed to investigate the possible association of -160 C → A and -347 G→ GA polymorphisms in patients with gastric cancer, immunoexpression of E-cadherin and their impact on prognosis of the gastric cancer patients in the present study.

MATERIAL and METHODS

Study Design

This was a hospital-based case-control study including patients with gastric adenocarcinoma and individuals who required endoscopic evaluation due to dyspeptic symptoms.

Compliance With Ethical Standards

Local ethics committee approval (71306642/050-01-04/296-22.10.2014) was taken. Written consent was obtained from all patients and from individuals with benign gastric pathologies. The study was performed in accordance with the principles of the Declaration of Helsinki.

Setting and Participants

Between January 2015 and April 2018, a series of 125 gastric cancer patients who underwent surgical treatment was included.

Inclusion criteria were gastrectomy for adenocarcinoma with curative intent and the procurement of blood samples. Diffuse or intestinal type all gastric adenocarcinomas were included. Patients with palliative gastrectomy and metastatic disease (n= 18), unsuitable tumor blocks and slides for immunohistochemical studies (n= 3), secondary or recurrent gastric adenocarcinoma (n= 6), lack of laboratory (n= 16) and clinical data (n= 4) were excluded.

By random sampling, individuals with benign gastric pathologies via biopsy with no history of previous cancer, history of cancer in family diagnosed in the first or second degree relatives, and active gastric and duodenal ulcers were recruited from our endoscopy center. Therefore, the participants whose endoscopic evaluation was performed on the first working day of each month during the same interval were consecutively included. As a result, 78 gastric cancer patients (Group A) and 113 individuals with benign gastric pathologies (control group) (Group B) were included in the study. For the control group, these pathologies included chronic gastritis (n= 103, 91.2%), hiperplastic polyp (n= 7, 6.1%) and fundic polyp (n= 3, 2.7%).

Variables

Demographic data and pathological findings including tumor diameter, tumor (T) and lymph node (N) stages, differentiation grade, lymphatic, vascular and perineural invasions and E-cadherin expressions were recorded (16). Patients with signet ring cell and mucinous pathology were grouped as poorly differentiated histology.

E-Cadherin Expression by Immunohistochemistry

Four-micrometer-thick (4 µ) sections of formalin-fixed paraffin embedded tissues were placed on 3-aminopropyletxylene-covered slides.

Subsequently, they were stained with rabbit polyclonal Biocare Medical E-Cadherin antibody in accordance with the manufacturer`s protocol. Briefly, staining was performed on Ventana BenchMark Ultra (Ventana Medical Systems Inc.).

The staining protocol included cell conditioning 1 for 60 min, pre-peroxidase inhibition and primary antibody incubation for 32 min at 37 °C. UltraView Universal DAB Detection Kit (Ventana Medical Systems) was used to detect e-Cadherin protein expression. Tissues were counterstained with Hematoxylin for 16 min and bluing reagent for 4 min. Using the internal positive (normal gastric mucosa) and negative staining controls (lymphocytes), the estimated percentage of the positively stained tumor cells were reported as a scale with three grades: <10% as 0, 10-90% as +1 and >90% as +2. Grouping was performed 0 to 1+ grade as "low" staining (Figure 1-A) and +2 grade as "high" staining for E-cadherin (Figures 1-B, C) (17,18).

An experienced pathologist performed all histopathological evaluations and E-cadherin expressions.

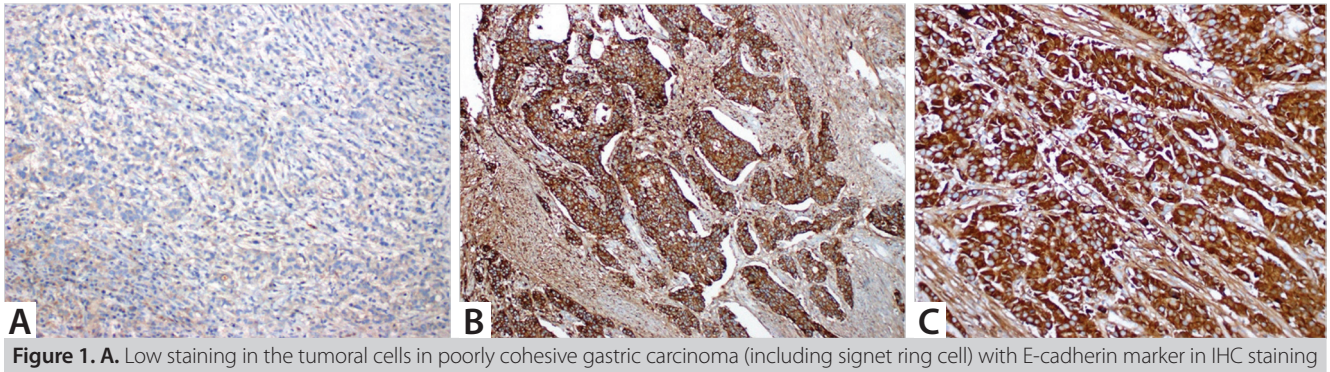

Figure 1. A. Low staining in the tumoral cells in poorly cohesive gastric carcinoma (including signet ring cell) with E-cadherin marker in IHC staining (magnification X200) **B.** High staining in gastric adenocarcinoma cells with E-Cadherin (magnification X200) **C.** High staining in gastric adenocarcinoma cells with E-Cadherin (magnification X200).

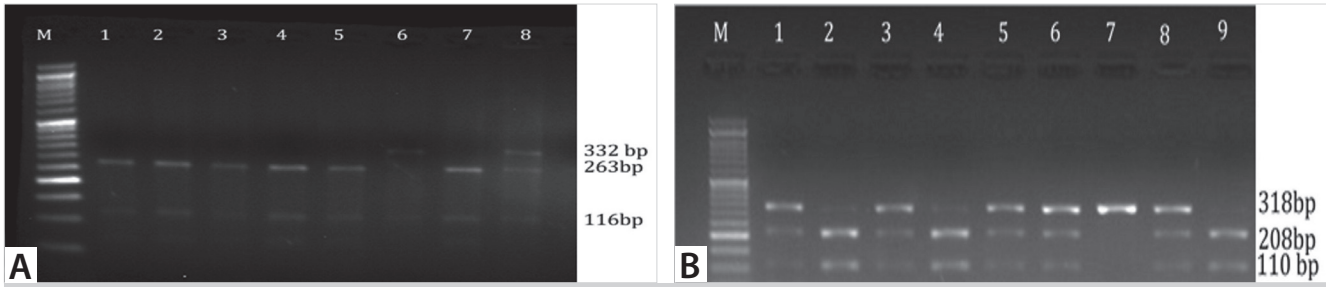

Figure 2. A. Genotyping of E-cadherin, the -347 G→ GA. M: 50bp marker. Lane 1, 2, 3, 4, 5 and 7: GA/GA genotype. Lane 6: G/G genotype. Lane 8: G/GA genotype. **B.** Genotyping of E-cadherin, the -160 C → A. M: 50bp marker. Lane 7: C/C genotype. Lane : 1, 3, 5, 6, 8: C/A genotype. Lane 2, 4, 9: A/A genotype.

Polymorphism Analysis

Genomic DNA samples were extracted from blood samples using white blood cells method of Miller et al. (19) After DNA sample isolation, DNA samples were amplified by polymerase chain reaction for CDH1 –160C/A (rs16260) and CDH1 –347G/GA (rs5030625). Forward- 5'-TGATCCCAGGTCTTAGTGAG-3' and reverse- 5'-AGTCTGAACTGACTT CCGCA-3' were used primers for CDH1 –160C/A (20). For CDH1 –347G/GA, forward-5'-GCCCCGACTTGTCTCTCTAC-3' and reverse- 5'-GGCCACAGCCAATCAGCA-3' were used (21). Restriction fragment length polymorphism analysis was performed using appropriate enzymes. Collected products of CDH1 –160C/A and CDH1 –347G/GA were cut using BstEII (NEB, R0162S) and BanII (NEB, R0119S) restriction enzymes (15 min, 60°C and 2 h, 37°C, respectively) and studied in agarose gel using electrophoresis (2% agarose gel, 25 min and 4% nusieve agarose gel, 40 min, respectively) (Figures 2-A, B).

As a standard approach, negative and positive samples were used during each gel loading, and the experiments were repeated at least twice.

Follow-Up

Follow-up examinations were performed in every 3 months during the first two years and every six months during the following years. Location of recurrences was classified as peritoneal and local recurrence, hepatic and other distant metastasis. End of January, 2019 or the date of death for the relevant patients was the last follow-up date for the study yielding a mean period of 22.4 ± 12.8 months. During this period, three patients (three out of 78 (3.8%)) were lost for survival analysis. Therefore, median follow-up for all patients (n= 75) and the patients who survived (n= 41) was 18 months (ranging from 4 to 49 months) and 30 months (ranging from 14 to 49 months), respectively.

Statistical Analysis

Distribution of -160 C → A and -347 G→ GA polymorphisms in gastric cancer patients with regard to demographic and clinical features was the primary outcome in gastric cancer patients and the individuals in the control group. Differences between allele frequencies of -160 C → A and -347 G→ GA polymorphisms were the secondary outcome. Normally-distributed continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of distribution. Hardy-Weinberg equilibrium was also tested comparing observed frequencies in patients with gastric cancer with expected frequencies in control group. -160 C → A and -347 G→ GA polymorphisms were analysed by using Chi-square test. Haplotype analysis was performed using Haploview (Version 4.2, Broad Institute of MIT and Harvard, USA, 2009). Logistic regression analysis was used to assess the impact of -160 C → A and -347 G→ GA polymorphisms on the development of gastric cancer by using Odds ratio (OR) with 95% Confidence Interval (CI). Association of -160 C → A and -347 G→ GA polymorphisms and expression of E-cadherin to demographic and pathological features was analysed using Chi-square test, Student's t test, and Fisher's exact test. Gastric cancer outcomes such as disease free survival (DFS) and overall survival (OS) were analysed using Cox regression analysis and Kaplan-Meier curves, and a log rank test was used for the comparison of the groups according to survival rates. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

Study Groups

There were 78 gastric cancer patients in Group A, and 113 individuals in Group B (the control group). Mean age was 59.1 ± 11.1 years and 50.3 ± 15.3 years in Group A and B, respectively. There were significant differences regarding age and sex between the groups (p< 0.001 for both) (Table 1).

Mean diameter of the tumors was 6 ± 3.4 cm. T4 and N3 were the most common stages with 47.5% and 50%, respectively. Poorly differentiated histology was detected in 50 patients (64.1%).

Genotype Distribution

Hardy-Weinberg analysis showed that p value for -160 C → A and 347 G→ GA polymorphisms were <0.001 ($\chi 2$: 33.17) and 0.450

Table 1. Demographic data and distribution of -160 C → A and -347 G→ GA polymorphisms

Variable		Overall (n= 191)	Group A (n= 78)	Group B (n= 113)	Chi-square	p
Age*			59.1 ± 11	50.3 ± 15		0.0001
Sex (Male/female)		105/86	61/17	44/69		0.0001
-160 C → A†	C/C	28 (14.7)	13 (16.7)	15 (13.3)	4.488	0.130
	C/A	137 (71.7)	50 (64.1)	87 (77)		
	A/A	26 (13.6)	15 (19.2)	11 (9.7)		
-347 G→ GA†	G/G	149 (78)	60 (76.9)	89 (78.8)	2.929	0.345
	G/GA	40 (20.9)	16 (20.5)	24 (21.2)		
	GA/GA	2 (1.1)	2 (2.6)	0 (0)		
-160 C → A†	C allele	193 (50.5)	76 (48.7)	117 (51.8)	0.533	0.451
	A allele	189 (49.5)	80 (51.3)	109 (48.2)		
-347 G→ GA†	G allele	338 (88.5)	136 (87.2)	202 (89.4)	0.518	0.439
	A allele	44 (11.5)	20 (12.8)	24 (10.6)		

*: mean ± SD, †: n (%).

Table 2. Haplotype analysis of CDH1 polymorphisms in the study groups

Haplotype associations	Frequency (%)	Patient, control (%)	Chi square	p
-347 G: -160C	0.494	0.469, 0.510	0.631	0.427
-347 G: -160A	0.391	0.403, 0.383	0.145	0.704
-347 GA: -160A	0.103	0.110, 0.099	0.125	0.724
-347 GA: -160C	0.012	0.018, 0.007	0.934	0.339

Table 3. Association of -160 C → A and -347 G→ GA polymorphisms with intensity of E-cadherin expression

		E-cadherin expression†			
Genotype		Low	High	Chi-square	p
-160 C → A	C/C	3 (23.1)	10 (76.9)	10.157	0.013
	C/A	27 (54)	23 (46)		
	A/A	12 (80)	3 (36)		
-347 G→ GA	G/G	34 (43.6)	26 (33.3)	2.706	0.679
	G/GA	8 (10.25)	8 (10.25)		
	GA/GA	1 (1.3)	1 (1.3)		

†: n (%).

(χ2: 1.60) for Group B, respectively. For Group A, p values of 0.044 (χ2: 6.24) and 0.768 (χ2: 0.53) were calculated for -160 C → A and 347 G→ GA polymorphisms, respectively. Haplotype associations of the polymorphisms were not statistically significant in Group A and Group B (Table 2) (D':0.799, LOD:2.61, r2:0.085).

Distribution of -160 C → A and -347 G→ GA polymorphisms in Group A and Group B is shown in Table 1. None of the polymorphisms (-160 C → A and 347 G→ GA) and allelic distribution showed significant difference in the genotype. Logistic regression analysis showed no significant association for risk of gastric cancer considering variant genotypes of -160 C → A and 347 G→ GA polymorphisms (OR: 0.832, p: 0.520, 95% CI: 0.475-1.458 and OR: 0.844, p: 0.614, 95% CI: 0.436-1.633, respectively).

Genotype Distribution and Tumoral Features of Gastric Cancer

Only significant association was between -160 C → A polymorphism and grade of E-cadherin expression (p=0.013) (Table 3). There were more patients with A/A and C/C haplotypes in patients with low and high E-Cadherin expressions, respectively. There was no significant association between tumor diameter,

T stage, N stage, grade, lymphovascular invasion, perineural invasion and grade of E-cadherin expression and the polymorphisms (p>0.05 for all).

Immunoexpression of E-cadherin

Distributions of E-cadherin positive staining were grade 0 in 17 (21.8%), grade 1+ in 25 (32.0%) and grade 2+ in 36 (46.2%). Low and high staining for E-cadherin expression was detected in 42 (53.8%) and 36 (46.2%) patients, respectively. There was no signicant correlation between the intensity of E-cadherin expression and age, sex, diameter, T stage, N stage, grade, lymphovascular invasion and perineural invasion (p> 0.05 for all).

Survival and Recurrence

Twenty-nine recurrences (38.7%) and 34 deaths with a mortality rate of 45.3% were detected. Mean length of DFS and OS were 20.3 ± 13.9 months and 22.4 ± 12.8 months, respectively. Overall survival rate at the end of the follow up time was 54.7%. Cox regression analysis revealed no significant differences between survival rates of the patients with -160 C → A and -347 G→ GA polymorphisms and intensity of E-cadherin expression (p= 0.253, p= 0.639 and p= 0.625, respectively). Kaplan Meier analysis showed similar OS for all (log rank, p= 0.219, p= 0.468 and p= 0.648 for OS, respectively). Most common locations for recurrences were hepatic and peritoneal carcinomatosis in 12 (41.4%) and 11 patients (37.9%), respectively. There was no significant association between DFS and -160 C → A, -347 G→ GA and grades of E-cadherin (p> 0.05 for all).

DISCUSSION

This case-control study showed that there was no significant association between -160 C → A and -347 G→ GA polymorphisms and development of gastric cancer. Presence of significant differences between the groups with regard to age and sex and dysequilibrium of -160 C → A polymorphism might be important. Although a significant association was detected between -160 C→A polymorphism and grade of E-cadherin expression, their impact on survival of gastric cancer has not been shown.

In this study, we found a significant deviation from Hardy-Weinberg equilibrium both in the control group and the patients. Although it has been regarded as an evidence of genotyping error, there have been several explanations including selection bias for controls, relatively small sample or population sizes and real genetic effects caused by assortative mating i.e., selection, ran-random mating, or migration, inbreeding caused by consanguinity and population stratification (22-24). An excess of heterozygosity (homozygote deficiency) can be due to copy number variations while population stratification always leads to heterozygote deficit. Wang et. al. (25) have reported that healthy individuals as controls may not accurately represent overall population when disease is common in population leading type I error probabilities for primary disease and/or secondary phenotype-associated genetic markers. Therefore, our results in relation with -160 C → A polymorphism should be considered based on these explanations. In order to overcome such problems for case-control studies, use of pooled control samples and extended likelihood-based approaches including Chen and Chatterjee's methods and extended mixture Hardy-Weinberg proportion tests result in validity of Hardy-Weinberg equilibrium (23-25). Calculation of Hardy-Weinberg equilibrium along with genotype distribution data has been recommended (26). In addition, although it is costly and useful only in specific genotyping errors caused by technical artifacts, repeated genotyping of the same probands can also be preferred. Therefore, future case-control studies with appropriate statistics and population genetic concepts are needed.

Polymorphisms within gene promoter regions may cause profound effects on the transcriptional efficiency of the genes (22). It has been known that there were more than one hundred different CDH1 gene polymorphisms in association with gastric cancer (27). Most of these polymorphisms were non-missense mutations and detected in patients from low-risk areas for gastric cancer. Huge inconsistency in the polymorphism of -160 C → A was found in the previous studies (22). It was suggested that ethnic differences may have a role in association with absence or presence of -160 C→A polymorphism (13, 22, 28). Although presence of such associations was shown especially in Asian populations (6-8), other studies have failed to prove effect of CDH1 gene polymorphisms (4, 12, 13). There was a significant recessive effect of A allele for gastric cancer only in Asian studies in the meta-analyses of Cui and Li (2, 28). In addition, researchers have reported that significant differences were usually based on studies with a total number of patients and controls less than 300 (2). However, another meta-analysis failed to confirm association between -160 C→A polymorphism and risk of gastric cancer (29). Therefore, type and frequency of different CDH1 mutations should be evaluated by considering ethnic and geographic differences.

Researchers have suggested that sex distribution and different age groups may also affect results of such polymorphism studies (1,15). Due to significant differences in the groups regarding sex distribution, we could not reach on a conclusion. Previous studies have also reported that there were significant differences in relation with types of gastric cancer as sporadic diffuse or intestinal and sex distribution (1,30). However, meta-analyses and several studies have failed to show such associations (2,13). Therefore, we analysed all gastric cancer types as one group in the present study.

We examined -160 C→A and -347 G→GA polymorphisms. However, we found no significant association between these two polymorphisms and in the development of gastric cancer. Chu et al. (1), Borges et al. (8) and Al-Moundhri et al. (7) have shown

a significant association between -160 C→A polymorphism and gastric cancer in Taiwanese, Brazilian and Omani populations, respectively. Lin et al. (30) have shown the association of CDH1 rs121964871 C>G polymorphism with susceptibility of gastric cancer. Akbas et al. (15) have established that

-160 C → A polymorphism was not associated with gastric and esophageal cancers in a Turkish population. Although the patients in Akbas's study (15) comprised of both gastric and esophageal cancers with adenocarcinoma and squamous cell carcinoma, subgroup analysis has not been performed. Therefore, our study is the first study to evaluate effect of CDH1 polymorphisms on gastric adenocarcinoma patients in a Turkish population.

Controversial results have been reported regarding -347 G → GA polymorphism in gastric cancer. Borges et al. (8) have reported a higher risk of gastric cancer in patients with 347 GA allele. Chen et al. (6) have found no association with gastric cancer risk in accordance with the present study. Therefore, due to detection of controversial results between studies performed in different parts of the world may necessitate future studies with larger sample sizes.

Abnormal expression of E-cadherin has been previously studied (17). In these studies, abnormal expression was shown to be between 38% to 57%. In the present study, rate was 53.8% in accordance with others. Although Torabizadeh et al. (17) have reported a significant correlation between abnormal expression of E-cadherin and other tumoral features, only significant association was between -160 C → A polymorphism and staining intensity of E-cadherin expression in the present study. In previous studies, E-cadherin mutation was regarded as a predictive factor for tumor invasiveness, however, we found no such association in our study (31).

Zhang et al. (29) have found no significant associations of -160 C→A and -347 del→A polymorphisms on survival contrary to -73 A → C. Membari et al. (4) have reported that patients with AC genotype had lower survival rates. However, low number of patients in this study may prevent the achivement of significant results. In the present study, we found no association between polymorphisms and survival. Large scale studies with longer follow up may clarify possible association between gene polymorphisms and survival of gastric cancer.

It has been shown that low expression of E-cadherin is associated with poor pathological features (18). In addition, low E-cadherin expression has been significantly associated with a lower 5-year-survival. However, we could not find any significant association between intensity of E-cadherin expression and tumoral features. Evaluation of E-cadherin expression has been performed by different methods (17, 18, 29-33). Therefore, methodological differences may have some impact on this issue.

In this study, we did not find significant differences between survival rates and the overall survival of the patients with -160 C → A and -347 G→ GA polymorphisms and E-cadherin expression intensity. A relatively shorter follow-up time, as 30 months for survivors, might be a factor to reach significant associations. It has been reported that the availability of mortality data for each study is the primary factor affecting the length of follow-up time (34). In this context, this study's follow-up time was not a controllable variable as part of the study design. Shorter follow-up times have been speculated as a significant predictor for rapidly changing health conditions in older populations. Verlato et al. (35) have analyzed short-term (the first two years) and long-term risk factors in gastric cancer. They reported that mortality from recurrence of gastric cancer peaked one year after the curative surgery. In advanced T and N stages, there was earlier mortality peaks. Lauren histotype was shown to exert a delayed effect on survival. Based on this study's findings, our follow-up time may be considered adequate due to the presence of advanced T and N stages in the majority of the cases and the low incidence of diffuse-type gastric cancer (three cases, not given data).

Significant demographic differences between the groups were main limitations in the present study. A relatively shorter follow-up time might be regarded as another limitation. Due to selection criteria of the control group, uncontrollable differences might occur. In addition, inherent selection bias due to presence of dysequilibrium of -160 C→A polymorphism was another limitation. A relatively shorter follow-up time might be regarded as another limitation.

CONCLUSION

Presence or absence of association between -160 C → A and -347 G→ GA polymorphisms and development of gastric cancer depends on geographic and ethnic variations. -160 C → A and -347 G→ GA polymorphisms may not play a a major role in this Turkish population. Although there was no impact of E-cadherin expression on tumoral features and survival in gastric cancer, -160 C → A polymorphism may influence expression of E-cadherin in gastric cancer.

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ORİJİNAL ÇALIŞMA-ÖZET
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CDH1 -160 C → A ve -347 G → GA polimorfizmleri ve E-kaderin ekspresyonunun mide kanseri ile ilişkisi: Bir vaka-kontrol çalışması

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ÖZET

Giriş ve Amaç: E-kaderin (CDH1) geninin -160 C → A ve -347 G → GA polimorfizmleri ile fonksiyon kaybı, mide kanseri için kritik bir adım olarak kabul edilmektedir. Bu polimorfizmlerin ve E-kaderin immünekspresyonunun mide kanseri ile olası ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Mide adenokarsinomu olan hastalar ve benign mide patolojileri olan bireyler bu vaka kontrol çalışmasına dahil edildi. Demografik veriler ve patolojik bulgular kaydedildi. E-kaderin ekspresyonunun immünohistokimyasal boyaması ve -160 C → A ve -347 G → GA polimorfizmlerinin analizi yapıldı. -160 C → A ve -347 G → GA polimorfizmlerinin allel frekansları ve E-kaderin ekspresyonu arasındaki farklar birincil sonuçlardı.

Bulgular: 78 mide kanseri hastası (Grup A) ve benign mide patolojisi olan 113 birey (Grup B) vardı. Erkek hasta sayısı ve ortalama yaş grup A'da daha yüksekti ($p< 0,001$). -160 C → A ve 347 G → GA polimorfizmleri ve allelik dağılımları gruplar arasında fark göstermedi (tümü için $p> 0,05$). -160 C → A polimorfizmi ile E-kaderin ekspresyonunun derecesi arasında anlamlı bir ilişki vardı ($p = 0,013$). -160 C → A, 347 G → GA ile hayatta kalma oranları ve E-kaderin ekspresyonunun yoğunluğu arasında anlamlı fark yoktu (tümü için $p> 0,05$). -160 C → A ve -347 G → GA polimorfizmleri ve mide kanseri arasında anlamlı bir ilişki yoktu.

Sonuç: E-kaderin ekspresyonunun tümör özellikleri ve mide kanserinin sağkalımı üzerine etkisi yoktu. -160 C → A polimorfizmi, mide kanserinde E-kaderin ekspresyonunu etkileyebilir.

Anahtar Kelimeler: CDH1 polimorfizmleri, E-kaderin, gastrik karsinoma, immünhistokimyasal ekspresyon, sağkalım

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ORIGINAL ARTICLE
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D2 vs D2 plus para-aortic lymph node dissection for advanced gastric cancer

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ABSTRACT

Objective: Gastric cancer is a common malignancy worldwide. Effective treatment by interdisciplinary cooperation is important, and surgery still plays an important role.

Material and Methods: In a ten-year period, 355 patients were diagnosed to have gastric cancer. One hundred and sixty-two patients with a median (range) age of 58 (23-83) years were eligible for the study. There were 107 patients in D2 and 55 patients in D2 lymphadenectomy plus para-aortic lymph node (PALN) dissection group. The two groups were compared in terms of complications, morbidity, mortality and long-term survival.

Results: Length of stay was 12 (8-34) days for D2 and 14 (8-42) days for D2 plus PALND. Total number of operative mortality was 8/162 (5%), and it was not different between the groups. Twenty patients (18%) had complications in D2 group and 9 (17%) patients in D2 plus PALND group. Overall survival was also similar between the groups, but patients with T3-T4 tumors, patients with stage IIIA and IIIB disease had better survival with D2 plus PALN dissection. We found that the depth of invasion, PLN, ratio (PLN/TLN), stage and LND were all prognostic variables.

Conclusion: This study showed that D2 plus PALN dissection for advanced gastric cancer can be performed as safely as a standard D2 dissection by experienced surgeons without increasing postoperative morbidity and mortality. D2 plus PALN dissection should be preferred in the advanced stage of the disease (IIIA-IIIB) as it increases the rate of survival.

Keywords: Advanced gastric cancer, D2 lymphadenectomy, D2 lymphadenectomy plus para-aortic lymph node dissection, morbidity, mortality, prognosis

INTRODUCTION

Gastric cancer is a common malignancy world-wide, and the 5-year survival rate in patients with gastric cancer is still poor despite improved survival due to early detection, rational lymphadenectomy and several therapeutic modalities (1). Effective treatment by interdisciplinary cooperation is important, and surgery is currently considered the best manner to treat gastric cancer. The extensiveness of lymph node dissection is, however, unclear, and there is no world-wide consensus (2-8). Extended (D2-3) lymph node dissection has improved survival in Japan (7,9,10). However, the results of European studies are somewhat controversial (11-18).

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s (19). This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches) (20). Superextended lymph node dissection (D3 dissection) has been used in advanced forms gastric cancer in many Japanese centers with the aim of eliminating metastatic lymph nodes, not only in the first and second tiers, but also in the third tier (around the upper abdominal aorta) (21).

D2 dissection for gastric cancer is a standard surgical procedure in Japan and is associated with excellent early and late results (20,22), whereas it is still controversial in the West (23). All four randomized Western trials have failed to show any survival benefit for D2 dissection while finding an association between D2 dissection and

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increased morbidity and mortality (11,12,17,18,24) although D2 dissection is already accepted as the standard procedure for resectable gastric cancer in many countries (13,25,26).

Success with D2 resection has led to the evolution of a superextended lymphadenectomy, and several feasibility studies evaluating dissection of para-aortic lymph nodes have been performed (6,21,27-29). This procedure is performed by selected centers, and D3 dissection has been practiced to improve the survival for advanced gastric cancer in these centers (21,29-31).

Very few studies from Western centers have compared D2 and D3 dissection in the surgical treatment of gastric cancer (32-34).

In the present study, we aimed to assess the value of radical surgery in gastric cancer by comparing D2 and D2 lymphadenectomy plus para-aortic lymph node (PALN) dissection.

MATERIAL and METHODS

A prospective trial was designed to compare two surgical techniques: the extended lymphadenectomy (D2) and the superextended lymphadenectomy (D2 plus PALND) for gastric cancer. Data were collected prospectively and analyzed on a retrospective manner.

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". Written informed consent was obtained from patients who participated in this study.

Patients

In a 10-year period, 355 patients were admitted to our unit with a diagnosis of gastric adenocarcinoma.

The inclusion criteria for this study were as follows: 1) patients who received curative resection; and 2) patients who underwent extended (D2) lymph node dissection, or superextended (D2 plus PALND) lymph node dissection.

The exclusion criteria included: 1) patients who received a palliative operation; 2) patients with distant metastasis; 3) patients with intraperitoneal dissemination; 4) patients with previous gastrectomies; and 5) patients with poor performance status.

Based on the inclusion and exclusion criteria, 193 patients were excluded from the study and 162 (107 males) patients with a median (range) age of 58 (23-83) years were eligible for the study. Due to world-wide acceptance of D2 lymph node dissection (LND) as the treatment of choice, there were 107 patients in D2 and 55 patients in D2 plus PALN dissection group (Figure 1).

Surgical Methods

All operations were performed by a specialized surgical team with a standardized surgical technique.

During laparotomy, the eligibility of patients was verified by inspecting the tumor resectability, feasibility of a potentially curative resection. Depending on the tumor location in the stomach and intraoperative verification of tumor-free margins, patients were qualified for total, subtotal gastrectomy. Splenectomy was performed routinely for tumors located in the upper-third of

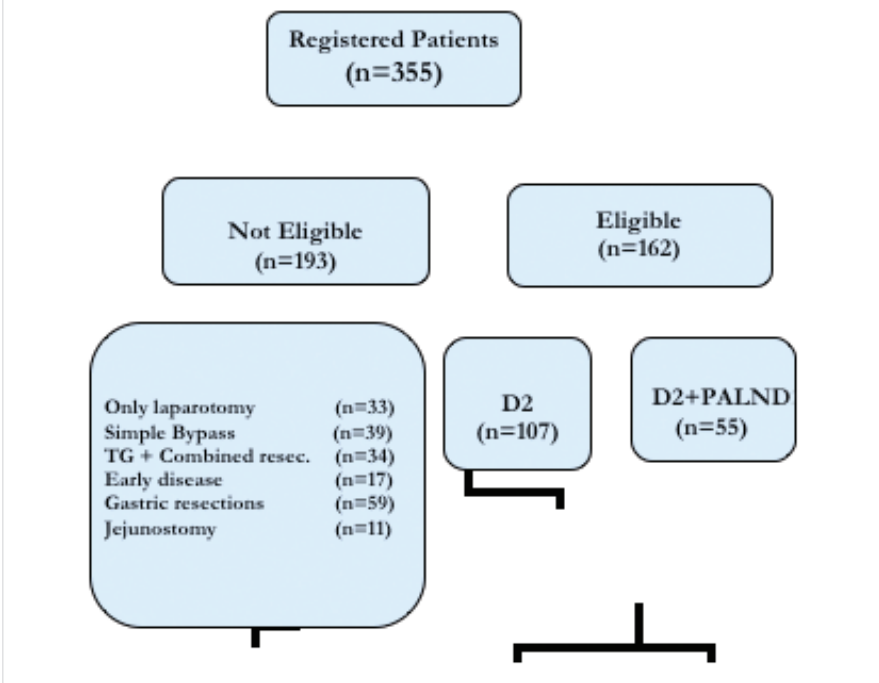

Figure 1. Categories of the registered patients, type of surgery and type of lymph node dissection.

the stomach, and resection of the tail of the pancreas was optional. In other patients, the spleen was removed according to surgeon preference. Gastrectomy was always completed by the removal of the greater omentum and parigastric lymph nodes. The type of lymphadenectomy was selected by the surgical team according to the criteria described by the Japanese Gastric Cancer Association (JGCA) (35). The D2 lymphadenectomies were performed in accordance with the fifth English edition of the JGCA (35). D2 plus PALN dissection were performed as described previously (36).

Evaluation of Operative Morbidity and Mortality

Resected specimens were examined carefully for accurate pathologic staging according to the JGCA rules (35). The following information was included on the case report form for prospective data collection concerning the major groups of operative morbidity: anastomotic leakage, intraabdominal abscess, pancreatic fistula, pneumonia, and others (wound infection, wound dehiscence, pulmoner embolism, MI etc.). Hospital mortality was defined as postoperative death of any cause within 30 days, death within the same hospitalization.

A follow-up of patients was performed according to our standard protocol (every 3 months for first 2 years and then every 6 months at least 5 years), which included tumor-marker studies, endoscopic examinations, ultrasonography, computed tomography, and chest radiography.

The two groups were compared in terms of complications, morbidity, mortality and long-term survival. Effect of the type of dissection as well as the diameter of the tumor, T-stage, number of total and positive lymph nodes (TLN and PLN) and survival according to tumor stage were also analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 for Windows. Comparisons of clinicopathological differences were made using a Chi-square test for discrete variables. Rate of occurrence of events were evaluated using Fisher's Exact test. Cumulative survival rate was calculated using the Kaplan-Meier estimation and examined by the log-rank test. Survival curves compared by Chi-square test. A p-values less than 0.05 was considered to be significant.

RESULTS

Patient demographics, complications and tumor characteristics are presented in Table 1. The two groups were well balanced, as there were no significant differences in their baseline data. The age and sex distribution of the patients was comparable in both groups. Length of stay was 12 (8-34) days for D2 and 14 (10-42) days for D2 plus PALND. The total number of operative mortality was 8/162 (5%), and it was not different between the groups. Twenty patients (18%) in D2 group and 9 (17%) patients in D2 plus PALND group had complications. The number of removed lymph nodes were related to dissection and it was 30(10-86) for D2 and 41 (12-98) for D2 plus PALN dissection. PLN/TLN ratio was similar in both groups (Table 1).

Patients were followed up for a period of 75 (22-130) months. We observed better overall survival with D2 plus PALND than D2 (Figure 2). Patients with T3-T4 tumors (Figures 3-4) had better survival with D2 plus PALN dissection than D2 alone. Patients with Stage IIIA also had better survival with D2 plus PALND than D2.

Although the survival rates were similar in patients with Stage I-II and IV, it was significantly better after D2 plus PALN dissection in patients with Stage IIIA (Figure 5) and IIIB disease (Figure 6).

We found that depth of invasion (T)(T small number 1, 2 is better than 3, 4), positive lymph node (LN(-) is better), lymph node ratio (PLN/TLN <0.2 is better than >0. 3), stage (lower the stage better the survival) and lymph node dissection (D2+ PALND is better than D2) were all prognostic variables (Table 2).

DISCUSSION

Gastric cancer still remains a major health problem, and numerous aspects of surgical treatment still remain unresolved. Despite improvements in local control and empirical chemotherapy, prognosis particularly for advance stage patients remains poor worldwide. New therapeutic strategies are needed.

Treatment of advanced gastric cancer has become much more sophisticated and complicated than ever. New directions in cancer biology research and new randomized trials promise to reach the goal of an individualized approach (37,38). Recently, the decision has been reached that the only possibility for curative treatment of gastric cancer remains surgical resection. For many years, it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. Theoretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure (17,39). Such resection, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into a systemic disease, or if resection increases morbidity and mortality substantially (17,39,40). From this point of view, several studies have generally compared D1 dissection with D2 dissection (11-13,24). However, only a few studyies have compared D2 dissection with D3 dissection (20,27,32-34,36,41-43). Therefore, in this study, we prospectively compared D2 dissection morbidity, mortality and outcome with those of D2 plus PALN dissection.

There is a wide variation in operative morbidity and mortality following gastric cancer surgery among countries and institutions (20). The presence of comorbid disease that affects patient fitness for surgery, surgical experience of the operator, and the workload volume seem to be important factors (20).

Table 1. Patient demographics

Variable	D2 (n= 107)	D2+PALND (n= 55)	p
Age	59.3 (23-83)	58 (32-75)	ns
Sex (M/F)	76/31	40/15	ns
Complications	20 (18%)	9 (17%)	ns
Wound infection	4	1	
Leakage	4	2	
Abscess	4	2	
Wound dehiscence	2	1	
Pancreatic fistula	0	1	
Pneumonia	4	1	
Pulmonary embolism	1	1	
MI	1	0	
Operative mortality	5 (5.2%)	3 (4.9%)	ns
Hospital stay (day)	12 (8-34)	14 (10-42)	ns
Tumor size (cm)	7.9 ± 3.4	7.1 ± 3.7	ns
TLN	30 (10-86)	41 (12-98)	0.02
PLN	4 (6)	7 (9)	ns
PLN/TLN	0.17 ± 0.3	0.17 ± 0.2	ns
Histologic type			ns
Diffuse	45	19	
Intestinal	53	29	
Unclassified	9	7	
Depth of invasion			ns
T1	0	0	
T2	28	14	
T3	60	32	
T4	19	9	
Stage grouping			ns
I	0	0	
II	29	14	
IIIA	38	18	
IIIB	35	18	
IVA	5	5	

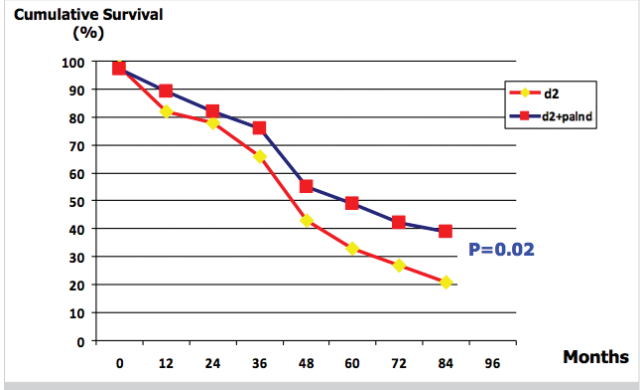

Figure 2. Overall survival curves in patients with D2 and D2 +PALN dissection.

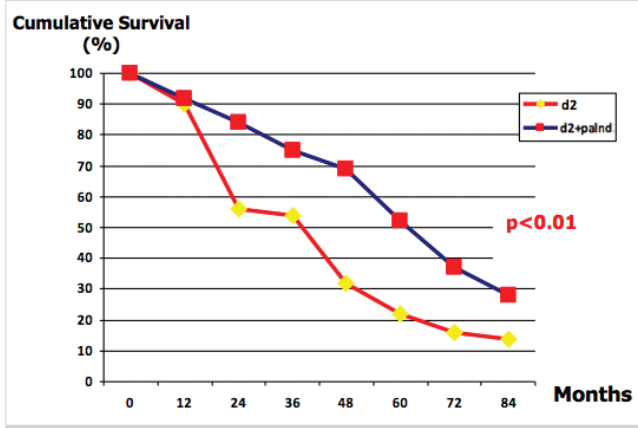

Figure 3. Survival curves in patients with T3 tumors.

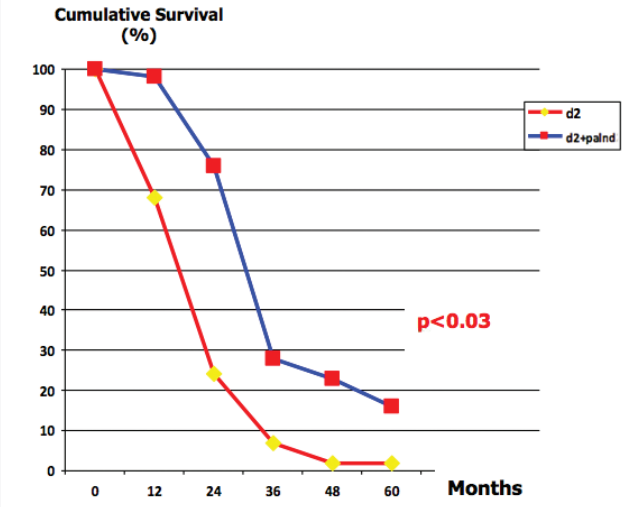

Figure 4. Survival curves in patients with T4 tumors.

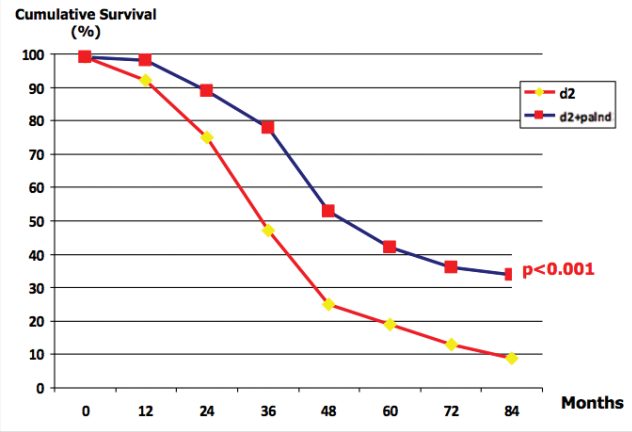

Figure 5. Survival curves in patients with stage IIIA.

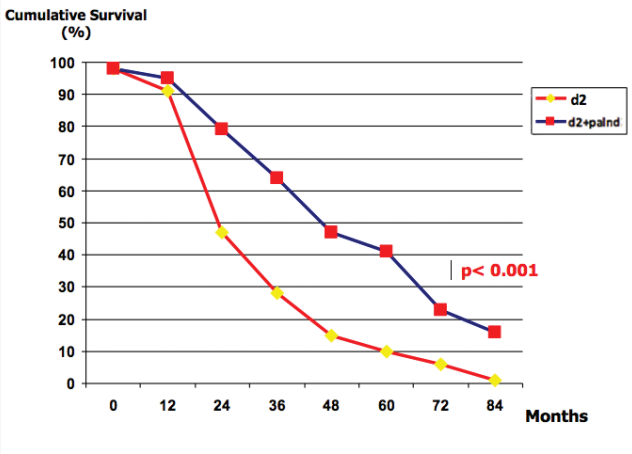

Figure 6. Survival curves in patients with stage IIIB.

of abundant data (43). For gastric cancer, only potentially curative resection (R0) achieves good outcomes, and, in view of the distribution of lymph node metastases, D1 gastrectomy is insufficient for advanced gastric cancer (41). On the other hand, safety outcomes after more extended lymph node dissection (ie, D1 vs. D3, or D2 vs. D3) were analyzed in a few studies (20, 27, 32-34, 36, 41-43, 46).

In JCOG9501 study (36), a total of 523 patients have been assigned to compare the treatment of D2 versus D3 (D2 + PALND) lymph node dissection. The results have shown that surgical mortality rate was very low in both groups (0.8%). No significant difference was found between the two treatment groups in terms of 5-year recurrence-free survival (62.6% vs. 61.7%, respectively), but the overall perioperative complication rate in the D3 group was higher than that in the D2 group (28.1% vs. 20.9%, respectively) (36). These trials have shown that there was no significant survival rate benefit for performing PALN dissection in curable gastric cancer patients and simultaneously revealed its association to a higher surgical morbidity. They have reported that gastrectomy with D2 lymphadenectomy has been considered as the standard routine lymphadenectomy for locally advanced gastric cancer (36).

However, the effect of the D3 dissection on gastric cancer patients with PALN metastasis is still debatable (47). D3 lymphadenectomy may be beneficial in some patients with PALN metastasis, but more research is needed for appropriate patient selection.

Some studies have shown that incidence of metastasis to para-aortic lymph node could be around 20% (48), and the 5-year survival rate for patients with para-aortic node metastasis undergoing para-aortic node dissection could be up to about 20%. Therefore, the rationale of therapeutic para-aortic lymphadenectomy for advanced gastric cancer is suggested for further evaluations (48). D2 plus para-aortic lymphadenectomy after neo-adjuvant or conversion chemotherapy could be considered as a promising treatment for patients with para-aortic lymph nodes involved (48).

Bencivenga et al. (49) have reported that the debate concerning the role of "prophylactic" super-extended lymphadenectomy apparently came to an end after the publication of the JCOG 9501 trial that found no survival advantage when D2 lymphadenectomy was extended to PALNs in patients with T2b, T3, and T4 gastric cancer (36). Consequently, prophylactic D2 plus PALN dissection is no longer recommended as a first-choice treatment for patients with curable gastric cancer in the Japanese guidelines. However, it should be remembered that the baseline prevalence of 16 metastases in that trial was rather low (8.5%), probably because it only enrolled patients without macroscopic metastases to PALNs, and the control group underwent D2 lymphadenectomy extended to the posterior nodal stations (12p, 13, and 14v), which are not usually resected in the case of a conventional D2 (19).

Table 2. Prognostic variables after surgery

Variable	5-year survival (%)	p
Age		ns
< 60	41.2	
> 60	39.4	
Sex		ns
Male	49.2	
Female	51.4	
T		0.001
T2	52.5	
T3	37.4	
T4	19.8	
Histologic type		ns
Intestinal	50.2	
Diffuse	48.5	
Unclassified	45.8	
Location		0.003
Upper	37.7	
Middle	50.2	
Lower	61.7	
Stage		0.001
II	47.4	
IIIA	28.5	
IIIB	25.3	
IV	15.1	
LN		0.0001
+	31.3	
-	64.5	
LN ratio (PLN/TLN)		0.001
< 0.2	46.3	
> 0.3	24.1	
LND		0.02
D2	33.1	
D2 plus PALND	49.4	

Liang and Deng have reported (50) the following indications for D2+PALND candidates: 1) patients in good condition with no serious organ dysfunction; 2) patients without peritoneal dissemination or liver metastases; 3) patients with pathologic N2, N3a and N3b stage disease or positive No.9 LN; 4) patients with Borrmann type III/IV disease; and 5) patients with upper-middle third or occupied more than one-third. However, they recommend that D2+PALND should be carried out only in cancer centers equipped with surgeons with extensive experience for extended LN dissections, because there are some risks in some rare situations, such as complications like formation of chylous fistula. In addition, multiple methods should be used in selecting suitable cases for further study.

Dong and Deng have also reported that (51) prophylactic D2 + PALND has not shown a survival benefit, but improved survival with therapeutic PALND may benefit from related clinicopathological factors. Then, based on the survival benefit of PALND, given that many clinicopathological factors were reported to be highly related to PALN involvement, it is necessary to verify the lymphatic flow to PALNs in gastric cancer and define accurate predictors for PALN metastasis and then explore indications for PALND. To date, CS chemotherapy combined with surgery plus extensive lymphadenectomy is considered the standard treatment for advanced gastric cancer in Japan. Therefore, neoadjuvant and adjuvant chemotherapy must not be ignored in the treatment of PALN metastasis. In the future, multimodal therapy including PALND combined with appropriate chemo-

therapy and with other therapies, such as conversion surgery or radiotherapy, remains to be evaluated in the form of a clinical trial to obtain improved prognosis and as few complications as possible (51).

A recent study has clearly shown that standard D2 and extended D3 dissection can be performed safely without any increase in postoperative morbidity and mortality (20,41). Both morbidity and mortality rates and the percentage of individual complications in our trial showed no significant differences between the D2 and D2 plus PALND groups. Hospital stay was also similar in both groups in our study. In the light of these results, we confirm that D2 plus PALN dissection may be performed in specialized centers with an acceptable operative risk.

In this study, we observed a positive linear correlation between removed lymph node and more extensive lymph node dissection (Table 1). Some authors have suggested that better disease control could be achieved through "inducing a reduction of metastatic nodes ratio" just by extending the number of dissected nodes (13,52-54). Schwarz et al. (55) believe that their results for a therapeutic benefit as a result of extended lymph node dissection, even in patients with more advanced yet resectable gastric cancer. They showed that stage-based survival prediction of advanced gastric cancer without distant metastases depends on total lymph node number and number of negative lymph nodes (55). Kunisaki et al. (43) have also shown that the incidence of lymph node recurrence in the surgically dissected area was significantly lower in D3 patients. They suggest that D3 gastrectomy might be effective for metastatic lymph nodes in the para-aortic regions (43).

In our study, we also observed a positive relation between more lymph node positivity and T-stage. Shen et al. (56) have showed that greater numbers of dissected lymph nodes could lead to a better prognosis in patients with pT3N2 disease and even in patients with pT3N3 disease. These findings indicate the important impact of thorough lymph node dissection on survival, even in patients with pT3N3 gastric cancer, who believed to have incurable disease (56).

Several papers have reported a correlation between survival benefits and D3 lymph node dissection (20,32,41,43,57,58). Kunisaki et al. (43) suggest that D3 dissection may confer a survival advantage with respect to D2 dissection in patients with tumor diameters measuring 50-100 mm and pN2 disease.

In our survival analyses, we observed three results: First, better overall survival with D2 plus PALND than D2. Second, better survival with D2 plus PALND in T3-T4 tumors. Third, better mean survival and 5-year survival in stage IIIA - IIIB. This might imply that D2 plus PALN dissection does contribute to improved survival at advanced stage of gastric cancer.

In early stages of the disease, D2 is safer and better, D2 plus PALN dissection should be preferred in an advanced stage of the disease as it increases the rate of survival. Although D2 plus PALND patients had slightly longer hospital stay, extended lymph node dissection performed without any increase on morbidity and mortality.

We observed that depth of invasion (T), positive lymph nodes (PLN), lymph node ratio (PLN/TLN), stage and lymph node dissection are prognostic variables. From all prognostic variables, only lymph node dissection influenced by the surgeon. Our results were in agreement with those of the Japanese and support the efficacy of extended lymph node dissection in surgical management of gastric cancer for the Western patients as well.

In conclusion, this study put forth that D2 plus PALN dissection for advanced gastric cancer can be performed as safely as a standard D2 dissection by experienced surgeons without increasing postoperative morbidity and mortality. D2 plus PALN dissection should be preferred in the advanced stage of the disease (IIIA-IIIB) as it increases the rate of survival.

Ethics Committee Approval: Ethics committee approval was obtained.

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ORİJİNAL ÇALIŞMA-ÖZET
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İleri evre mide kanserlerinde D2 ve D2+ para-aortik lenf nodu diseksiyonu sonuçlarının karşılaştırılması

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ÖZET

Giriş ve Amaç: Mide kanseri dünya çapında yaygın bir malignitedir. Disiplinler arası işbirliği ile etkili tedavi önemlidir ve cerrahi hala önemli bir rol oynamaktadır.

Gereç ve Yöntem: Kliniğimizde on yıl içinde 355 hastaya mide kanseri teşhisi kondu. Medyan yaşı 58 (23-83) olan 162 hasta çalışmaya uygundu. D2'de 107 hasta ve D2 lenfadenektomi artı para-aortik lenf nodu (PALN) diseksiyon grubunda 55 hasta vardı. İki grup komplikasyon, morbidite, mortalite ve uzun süreli sağkalım açısından karşılaştırıldı.

Bulgular: Hastanede kalış süresi D2 için 12 (8-34) gün ve D2+ PALND için 14 (8-42) gündü. Toplam operatif mortalite sayısı 8/162 (%5) idi ve gruplar arasında farklı değildi. 20 hastada (%18) D2 grubunda komplikasyon, 9 hastada (%17) D2+ PALND grubunda komplikasyon vardı. Genel sağkalım gruplar arasında da benzerdi, ancak T3-T4 tümörleri olan hastalar, evre IIIA ve IIIB hastalığı olan hastalar ve daha yüksek PLN/TLN oranı olan hastalar D2+ PALN diseksiyonu ile daha iyi sağkalım gösterdi. İnvazyon derinliği, PLN, PLN/TLN oranı, evre ve LND'nun bağımsız prognostik değişkenler olduğunu bulduk.

Sonuç: Bu çalışma, D2+ PALN diseksiyonunun ileri evre mide kanseri için, postoperatif morbidite ve mortaliteyi arttırmadan deneyimli cerrahlar tarafından standart bir D2 diseksiyonu kadar güvenli bir şekilde yapılabileceğini göstermiştir. D2+ PALN diseksiyonu, sağkalım oranını arttırdığı için hastalığın ileri evresinde (IIIA-IIIB) tercih edilmelidir.

Anahtar Kelimeler: İleri evre mide kanseri, D2 lenf nodu disseksiyonu, D2+palnd lenf nodu disseksiyonu, prognoz

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Laparoscopic gastrectomy in remnant gastric cancer

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ABSTRACT

Objective: Remnant Gastric Cancer (RGC) describes cancers occurring in the remaining stomach and/or anastomosis in the follow-up after gastric cancer or benign gastric surgery. RGC is diagnosed in esophago-gastroscopy follow-ups of patients who underwent this surgery in the past. Again, the increase in the success of gastric cancer surgery and following medical treatments has increased the incidence of RGC in long-term follow-up after gastric cancer surgery. Laparoscopic surgery has been also reported in few cases. In the present study, the purpose was to present the results of the first five patients that underwent laparoscopic total gastrectomy due to RGC in our clinic.

Material and Methods: The patients who underwent laparoscopic gastric cancer surgery between November 2014 and December 2018 were evaluated retrospectively.

Results: Mean age of the patients was 62.4 years (ranging between 49 and 74 years). Two of these patients had a surgical history due to gastric cancer and 3 due to peptic ulcer. Surgery was completed laparoscopically in all patients. In the early period, one patient had to undergo re-surgery due to stenosis in Jejuno-Jejunostomy, and the patient died. One patient underwent laparotomy due to colonic stenosis in the second month after the surgery. Recurrence was detected on the 140th and 180th days of follow-up in the other two patients.

Conclusion: Laparoscopic surgery is a technically applicable method in RGC; however, it is also a risk factor for past surgical postoperative complications. Early recurrence in this group of patients requires a comparison of open and laparoscopic surgery.

Keywords: Stomach cancer, minimal invasive surgery, laparoscopy, completion gastrectomy, total laparoscopy, remnant stomach neoplasm

INTRODUCTION

Remnant Gastric Cancer (RGC) is a pathology in the remaining stomach in patients undergoing gastric surgery with benign and/or malignant etiology, and its current treatment is surgery. The increase in the frequency of laparoscopic applications after primary gastric cancer surgery has brought with it the application of these applications in RGC to the agenda. Laparoscopic surgical procedures have been reported in a limited number of RGC cases, and early period and oncological results of these cases are limited. In our study, the purpose was to discuss the postoperative period and oncological results of the patients undergoing laparoscopic surgery with the diagnosis of RGC together with the literature data.

MATERIAL and METHODS

Patients Characteristics

A total of 133 patients underwent laparoscopic surgery due to gastric cancer between November 2014 and December 2018, and 5 of these patients underwent surgery with a diagnosis of RGC. Approval was obtained from the Non-Interventional Clinical Research Ethics Board of İnonu University. Preoperative, intraoperative, and postoperative results of these cases were evaluated. Mean age of the patients was 62.4 years (ranging between 49 and 74 years). The time after previous surgery was median 24.25 years (ranging between 9 and 38 years).

Surgical Procedure

Pneumoperitoneum was created with Veres from the upper left quadrant in patients with upper-lower umbilical median incision. Working trocars of 10 mm were placed under the umbilical point, 10 mm from the lower right quadrant, 5 mm from the upper right quadrant, and 10 mm from the lower left quadrant. Liver Ecar-

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teur was not used in patients in whom the liver was adhered to the diaphragm. The adhesions to the front abdominal wall were separated. The bowel ANSs of the Retrocolic Bill Roth II gastro-enterostomy anastomosis were incised and closed with linear stapler. The Retrocolic ANSs were separated from the transvers colon. The great curvature was released with the remaining omentum. The small curvature lymph nodes were dissected, and included in the pieces. The esophagus was dissected and closed with a linear stapler. Then, esophago-jejunostomy was performed intracorporeally with ante-colic hand as single-layer 3/0 prolene. Anastomosis was tested with methylene blue, and no leakage was detected. Jejuno-Jejunostomy was performed intracorporeally with linear stapler between the ANSs coming from Treitz and 100 cm distal part of the esophago-jejunostomy anastomosis manually with a single-layer 3/0 prolene or with 3/0 prolene, and the opening in the anastomosis was closed with stapler 3/0 prolene. The pieces were removed supra-pubically.

RESULTS

Laparoscopic Total Gastrectomy was performed in 5 patients due to RGC. Two patients had distal gastrectomy and Bill Roth II Reconstruction due to gastric cancer, 2 patients had distal gastrectomy due to peptic ulcer and Bill Roth II Reconstruction, and 1 patient had a history of gastroenterostomy (Table 1). When the durations between previous surgical history and cancer development of the patients were evaluated, the interval after gastric cancer was observed as 35 and 38 years, and the interval after ulcer surgery was 9 and 15 years. Tumor placement was detected in the remnant stomach in 3 patients, and in the anastomosis line in 2 patients (Table 1).

Surgery was completed laparoscopically in all patients. Surgery duration was 396 minutes (ranging between 360 and 420), and the amount of bleeding was median 160 ml (ranging between 100 and 400) (Table 2). Three patients had D2 and 2 patients had D1 lymph node dissection. Esophago-jejunostomy anastomosis was performed manually and intracorporeally, Jejuno-Jejunostomy anastomosis was performed by hand intracorporeally in 3 patients and intracorporeally with stapler in 2 patients. Oral intake of the patients following surgery was started in median 2.6 days (ranging between 1 and 7). Postoperatively, one patient underwent open exploration again due to atelectasis and stenosis in Jejuno- Jejunostomy anastomosis, and the patient died in the postoperative follow-up period (Table 3). Hospital stay was

Table 1. Patient characteristics

Case	Age	Sex	BMI (kg/m^2)	Reason for previous surgery	Type of previous gastrectomy	Interval (years)	Tumor location
1	74	F	17.8	Gastric ulcer	DG + Billroth II	NA	Remnant
2	49	F	20.2	Gastric cancer	DG + Billroth II	15	Remnant
3	58	M	27	Gastric cancer	DG + Billroth II	9	Anastomosis
4	62	M	20.7	Gastric ulcer*	DG + Billroth II	38	Anastomosis
5	69	M	20.5	Gastric ulcer	GE	35	Remnant

DG: Distal gastrectomy, GE: Gastro-enterostomy, *additional surgery: appendectomy, sigmoid volvulus surgery.
Gastrectomy AND laparoscopy* AND ("remnant gastric cancer" OR "gastric remnant cancer" OR "gastric stump cancer")

Table 2. Perioperative data

Case	Operation time (min)	Blood loss (ml)	LN disection	Anastomosis (E-J and J-J)	Open convertion
1	360	100	D2	E-J (H), J-J (S)	-
2	390	100	D1	E-J (H), J-J(H)	-
3	420	100	D1	E-J (H), J-J (S)	-
4	390	100	D2	E-J (H), J-J(H)	-
5	420	400	D2	E-J (H), J-J (S)	-

LN: Lymph node, E-J: Esophago-jejunostomy, J-J: Jejuno-jejunostomy, H: Hand, S: Stapler.

Table 3. Postoperative data

Case	Food intake (days)	Hospital stays (days)	Complication	Mortality
1	1	34	Atelectasis, Stenozis J-J	+
2	1	15	Urinary tract infection	-
3	2	10	-	-
4	2	7	-	-
5	7	18	Arrhythmia	-

J-J: Jejuno-jejunostomy.

Table 4. Pathological results

Case	cStage	Tumor size (mm)	Number of retrieved LN	Positive LN	TNM	Pathology
1		13x10x10	25	0	T1N0M0	Hyperplastic polyp
2		50x40x10	6	0	T4N0M0	Signet ring cell carcinoma
3		30x15x8	15	11	T3N2M0	Poorly cohesive carcinoma
4		130x80x21	36	11	T4aN3aM0	Poorly cohesive carcinoma
5		40x40x20	22	0	pT3N0M0	Well-differentiated adenocarcinoma

LN: Lymph node.

median 16.8 days (ranging between 7 and 34 days). When the pathology results of the patients were evaluated, the number of lymph nodes excised was median 20.8 (ranging between 6 and 36) and the number of positive lymph nodes was median 4.4 (ranging between 0 and 11) (Table 4).

DISCUSSION

The frequency of gastric cancer varies between communities; however, it is among common cancer types. Early diagnosis of gastric cancer is important, and medical treatments applied in the post-operative period have positive effects on patient survival durations. RGC is a pathology in long-term follow-up in the stomach after benign and/or malign gastric surgery. The development of surgical and medical treatment modalities, increased follow-up and controls increase the frequency of RGC. RGC is seen in those with a history of surgery because of benign pathology at an average interval of 25 years, and in those with a history of surgery because of malignant pathology at an average interval of 15 years (1). Patients with a history of gastric surgery should undergo lifelong and regular esophago-gastro duodenoscopy check-ups.

R0 Surgery is the basis and most important prognostic factor of treatment in RGC (2). Increased laparoscopic surgery experience in gastric cancer has brought with it its application in RGC. Laparoscopic surgery was first reported by Yamaha et al. in Remnant Gastric Cancer (3).

Laparoscopic surgery is a technically applicable method in RGC. We believe that intracorporeal anastomosis techniques can be used manually in anastomosis in both primary gastric cancer surgeries and in RGC surgeries. In the literature, short- term results are presented in a small number of cases, and data on follow-up are presented in a small number of cases. In the study conducted by Booka et al., in comparing open and laparoscopic surgeries in RGC, laparoscopic surgery has been found to be advantageous merely in terms of the amount of bleeding (4). Strong et al. have conducted a case control study evaluating 30 laparoscopic and 30 open RGC patients and detected complications in the laparoscopic group at a rate of 26% in the early period and in 43% in the open group. Major complications were observed as colonic leakage in one case in their laparoscopic group, and as delayed gastric evacuation in one case. In the open surgery group; however, intra-abdominal abscesses were observed in two cases as major complications, anastomosis leakage was detected in one case, and intestinal obstruction in one case. When late laparoscopic complications were evaluated, they were not observed in laparoscopic cases, but complications at a rate of 20% were observed as ventral hernia in 3 cases in the open surgery group, nutritional failure was detected in 1 case, chronic abdominal pain in 1 case, wound infection in 1 case and tube jejunostomy was performed to the case that had malnutrition (5).

Kim et al. have reported complications at a rate of 23.5% in the laparoscopic group and 30% in the open surgery group in their study comparing 50 patients with open surgery and laparoscopic 17 patients (6). Major complications were observed in two laparoscopic cases, and leakage was detected in esophago-jejunostomy anastomosis in one case, who was followed-up with parenteral nutrition, and internal herniation was detected in another case who underwent laparoscopic surgical intervention (6). Kwon et al. have conducted a study and compared 58 open and 18 laparoscopic RGC cases in similar groups. They showed similar early and oncological results (7). Although complication rates were 44.8% in open cases, and 33.3% in laparoscopic cases, major complication rates were 15.5% to 16.7%. Major complications were observed in 1 laparoscopic case that had duodenal switch leakage, intra-abdominal bleeding in 1 open case, intra-abdominal abscess in 3 open cases, pulmonary complications in 6 open cases, and anastomosis leakage in laparoscopic 2 and 1 open case (7). In our study, re-surgery was required due to stenosis in Jejuno-jejunostomy anastomosis in the early period, and this case died. Duration of hospital stay was extended in one case due to urinary tract infection. Surgical intervention was required due to stenosis in the transvers colon in 1 case in the late period, and proximal transvers colostomy was opened.

CONCLUSION

Laparoscopic Surgery is a technically applicable method in patients with adhesiolysis in RGC. However, past surgical history complicates the dissection, increasing the duration of surgery. We believe that it also increases complications after surgery. The results of laparoscopy should be investigated and followed-up in a multi-centered fashion in Remnant Gastric Cancer in terms of long-term recurrence and complications.

Ethics Committee Approval: The approval for this study was obtained from Inönü University Health Sciences Non-Interventional Research Ethics Committee (Decision no: 2020/1206 Date: 10.11.2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.Ç., F.S.; Design - E.Ç.; Supervision - F.S., C.K.; Materials - E.Ç., Ö.G., A.Z.; Data Collection and/or Processing - E.Ç., F.S., A.Z., Ö.G.; Literature Review - E.Ç., Ö.G., A.Z..; Writing Manuscript - E.Ç., Ö.G.; Critical Reviews - C.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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ORİJİNAL ÇALIŞMA/OLGU SERİSİ-ÖZET
Turk J Surg 2021; 37 (1): 59-62

Remnant mide kanserinde laparoskopik gastrektomi

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ÖZET

Giriş ve Amaç: Remnant mide kanseri (RMK), benign veya malign nedenli mide cerrahisi sonrası takipte, kalan mide ve/veya anastomozda ortaya çıkan kanserleri tanımlamaktadır. Geçmişte mide cerrahisi geçiren hastalarda özofago-gastroskopi kontrollerinde RMK tanısı koyulmaktadır. Mide kanser cerrahisi ve sonrasındaki medikal tedavilerin başarısındaki artış, mide kanser cerrahisi sonrası uzun dönen takipte RGK görülme sıklığını artırmıştır. Laparoskopik cerrahi az sayıda olguda bildirilmiştir. Bu çalışmada kliniğimizde remnant mide kanseri nedeniyle laparoskopik total gastrektomi uyguladığımız ilk beş hastasının sonuçlarını sunmayı amaçladık.

Gereç ve Yöntem: Kasım 2014 - Aralık 2018 yılları arasında laparoskopik mide kanser cerrahisi uygulanan hastalar retrospektif olarak değerlendirildi.

Bulgular: Hastaların yaş ortalaması ortalama 62,4 (49-74 aralığında) olup ikisinde mide kanseri, üçünde peptik ülser nedeniyle cerrahi öykü mevcut idi. Tüm hastalarda cerrahi laparoskopik olarak tamamlandı. Özofago-jejunostomi elle intrakorporeal, jejuno-jejonostomi anastomozları üç hastada elle intrakorporeal, iki hastada ise stapler ile intrakorporeal yapıldı. Erken dönemde bir hastada jejuno-jejunostomide darlık nedeniyle tekrar cerrahi gerekti ve bu hastada mortalite görüldü. Bir hastada ameliyat sonrası ikinci ayda kolonik stenoz nedeniyle laparatomi yapıldı. Diğer iki hastada takipte 140 ve 180. günlerde nüks saptandı.

Sonuç: Remnant mide kanserinde laparoskopik cerrahi teknik olarak uygulanabilir bir yöntem ancak geçirilmiş cerrahi postoperatif komplikasyonlar açısından risk faktörüdür. Erken dönemde nüks görülmesi bu hasta grubunda açık ve laparoskopik cerrahinin karşılaştırılmasını gerektirmektedir.

Anahtar Kelimeler: Mide kanseri, minimal invaziv cerrahi, laparoskopi, tamamlayıcı gastrektomi, total laparoskopi, remnant mide kanseri

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Primary anorectal malignant melanomas: retrospective analysis of 11 cases in a single center

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ABSTRACT

Objective: Anorectal malignant melanoma is a rare tumor with poor prognosis. In this study, it was aimed to present our surgical results by reviewing the literature retrospectively in 11 patients who underwent surgery for ARMM in our clinic.

Material and Methods: The patients who underwent surgery for anorectal malignant melanoma in Yuksek İhtisas Training and Research Hospital between 2007-2018 were included in the study.

Results: Four patients were males and seven were females. Mean age was 54.18. The tumor was in the rectum in 4 cases, in the anorectal region in 3 cases and in the anal canal in 4 cases. Wide local excision was performed in 3 cases and APR was performed in 8 cases. Four of the cases were stage I, 6 were stage II and 1 was stage III. Mean tumor size was 4.73 cm, and mean tumor depth was 13.6 mm. Mean number of metastatic lymph nodes was 10.37. Median survival was 12 months.

Conclusion: Anorectal malignant melanoma is a type of tumor diagnosed in late and advanced stages due to lack of specific findings. Although ARMM is rare, when rectal bleeding, pain, hemorrhoids and changes in bowel habits are observed, ARMM should be kept in mind.

Keywords: Anorectal malignant melanoma, abdominoperineal resection, wide local excision, prognosis

INTRODUCTION

Anorectal malignant melanoma (ARMM) accounts for less than 1% of all colorectal malignancies and 1-2% of all melanomas (1). Its prognosis is very poor. Median survival is 24 months and 5-year survival is 10% (2). The first case presentation of ARMM was made by Moore in 1857 (3). Patients usually die after metastatic disease. Wide local excision (WLE) or abdominoperineal resection (APR) are the methods of surgical treatment. In a meta-analysis, it has been shown that APR had no superiority to WLE on mean survival, but local recurrence was observed less in APR. Due to the fact that there is no difference in survival in localized disease without lymph node metastasis, WLE provides better life comfort and less morbidity (4).

In this study, it was aimed to present our surgical results by reviewing the literature retrospectively in 11 patients who underwent surgery for ARMM in our clinic.

MATERIAL and METHODS

The patients who underwent surgery for anorectal malignant melanoma in Yuksek İhtisas Training and Research Hospital between 2007-2018 were included in the study. Patients with distant metastasis at the time of diagnosis and who did not accept surgery were excluded from the study. Data were obtained retrospectively from patient files. Patients were evaluated in terms of age, sex, tumor localization, stage, surgery, preoperative investigations, symptoms, tumor size, tumor depth, R0 resection, lymph node metastasis and survival. Surgical approach was preferred according to whether the patient would allow permanent colostomy or not. APR was recommended firstly to all of the patients included in the study. WLE was applied to patients who did not accept APR. Tumor stage (TNM stage) was defined according to the American Joint Committee on Cancer classification (AJCC, 7th edition) .

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SPSS software version 17 (SPSS Inc., Chicago, IL, USA) was used in this study for statistical analysis. Descriptive data were expressed as mean or median (range). Categorical variables were described using frequency distributions. Survival was calculated using the Kaplan–Meier method. Length of survival was calculated as the period from the date of initial operation to the date of death or last follow-up.

RESULTS

Eleven patients who were operated on for anorectal malignant melanoma were included in the study. Four (36.36%) of the cases were males and 7 (63.63%) were females. Mean age was 54.18 (38-67). Rectal pain was present in 3 (27.27%) patients and rectal bleeding was present in 8 (72.72%) patients. Hemorrhoidectomy was performed in 2 of the cases due to rectal bleeding and pathology was reported as malignant melanoma. All patients underwent colonoscopy and abdominal tomography for preoperative evaluation. Four cases underwent PET/CT, 1 case MRI and 2 cases EUS for staging. When evaluated for the location of the tumor, the tumor was in the rectum in 4 (36.36%) cases, in the anorectal region in 3 (27.27%) cases and in the anal canal in 4 (36.36%) cases. Local excision was performed in 3 (27.27%) of the cases, and APR was performed in 8 (72.72%) of the cases. Postoperative complication was observed in only one patient. Ostomy separation was observed, and ostomy revision was performed. Recurrence or metastasis was observed in 4 patients postoperatively. Two of them had recurrence at the local excision site, and the other two patients had multiple liver metastasis. Ten (90.90%) cases died during postoperative follow-up. Median survival was 12 (1-53) months (Table 1). 5-year survival was 9.09%. Four (36.36%) of the cases were stage I, 6 (54.54%) were stage II and 1 (9.09%) were stage III. Mean tumor size was 4.73 (1.5-12) cm. Mean tumor depth was 13.6 (1.3-25) mm.

R0 resection could not be performed in only 1 of the 11 patients included in the study. Wide local excision was performed in 3 cases so lymph node dissection could not be performed (Figure 1,2). Lymph node metastasis was observed in only the remaining 6 of 8 cases. Mean number of metastatic lymph nodes was 10.37 (0-25) (Table 2).

DISCUSSION

ARMMs are rare aggressive tumors that constitute 0.05% of all colorectal tumors (5). They are observed more frequently in the 6th decade and more in females than males (6). Similar results were observed in our study with the literature. In one study, ARMM has been observed in 65% of the anal canal and anoractal

Table 1. Demographic characteristics of the cases

No.	Age	Sex	Symptom	Preop examination	Site	Surgery	Complication	Recurrence or Metastasis	Survival (Month)
1	42	Male	Rectal bleeding	Colonoscopy, CT	Anorectal region	APR (2007)	-	-	7
2	56	Female	Rectal bleeding	Colonoscopy, CT	Anal canal	APR (2008)	-	-	12
3	67	Female	Rectal pain	Colonoscopy, CT	Anorectal region	WLE (2009)	-	+	6
4	43	Male	Rectal bleeding	Colonoscopy, CT, PET/CT	Anorectal region	APR (2009)	-	+	12
5	65	Female	Rectal bleeding	Colonoscopy, CT, MRI	Rectum	APR (2009)	Ostomy seperation	+	17
6	67	Male	Rectal bleeding	Colonoscopy, CT	Rectum	APR (2011)	-	-	1
7	56	Female	Rectal bleeding	Colonoscopy, EUS, CT	Anal canal	APR (2012)	-	+	21 (lost in follow-up)
8	38	Female	Rectal bleeding	Colonoscopy, CT, PET/CT	Rectum	APR (2014)	-	-	53
9	61	Male	Rectal bleeding	Colonoscopy, CT, PET/CT	Anal canal	WLE (2017)	-	-	17
10	46	Female	Rectal pain	Colonoscopy, CT, PET/CT	Anal canal	WLE (2017)	-	-	16
11	55	Female	Rectal pain	Colonoscopy, EUS, CT	Rectum	APR (2013)	-	-	9

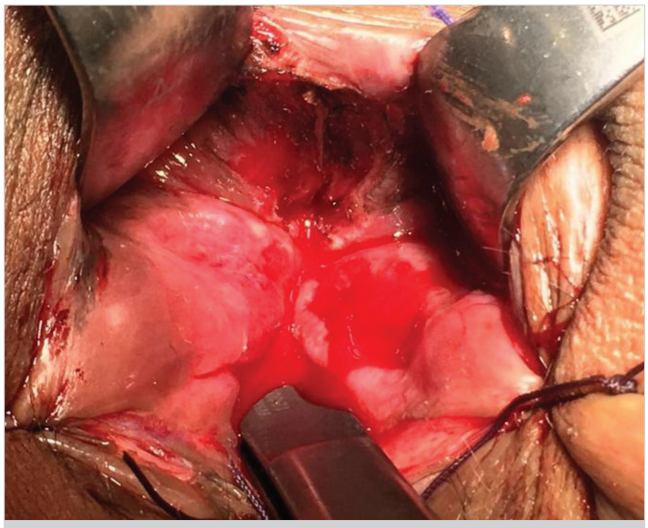

Figure 1. Excision area after wide local excision.

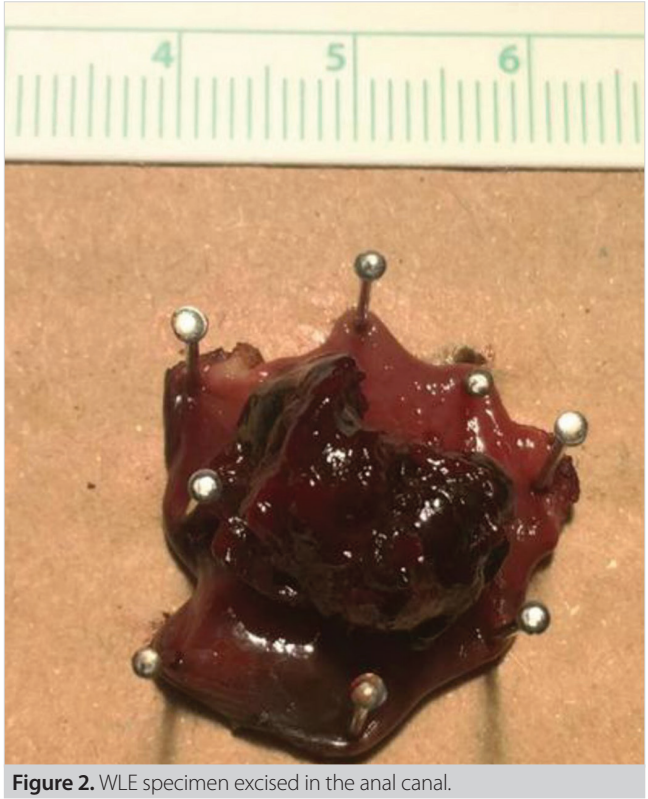

Figure 2. WLE specimen excised in the anal canal.

region, in 35% of the distal rectum, and in our study, the tumor was observed in 36% of the distal rectum (7). Male sex, perineural invasion, depth of invasion, lymph node metastasis and distant metastasis are poor prognostic factors and indicates that the patient's survival will be short.

More than 40% of the patients with submucosal infiltration in ARMM have lymph node metastasis. 5-year survival in patients with lymph node metastasis is close to 0%. Lymphatic spread is to inguinal and/or iliac lymph nodes and perirectal lymph nodes (5). Negative surgical margins in primary mucosal malignant melanoma increase mean survival (6).

Abdominal ultrasonography, endorectal ultrasonography (EUS), computed tomography (CT), magnetic resonance (MRI) and PET/CT are used for staging in ARMM. EUS is used to determine the depth of invasion, abdominal CT is used to detect liver and lung metastasis and MRI is used to determine liver metastasis and depth of invasion (8). PET-CT is recommended for staging in the studies. Due to high metabolic rate of tumor cells and high FDG uptake in malignant melanoma patients, it is an effective method for staging and is superior to other imaging methods (5).

Traditionally, APR is the best treatment option because it provides more local control in ARMM. However, there are retrospective studies showing that mean survival in patients undergoing wide local excision is similar to APR (7). Patients undergoing WLE have more local recurrence, but in the absence of distant metastases, local recurrence can be eliminated by re-excision. In addition, when WLE is performed, a better quality of life is achieved, fewer complications are observed and colostomy does not cause difficulties in life compared to APR patients (4).

When there is mesorectal and mesenteric lymph node metastasis, R0 resection cannot be performed with WLE. Therefore, staging is important before selecting the surgical method. Although MRI and endorectal ultrasonography are effective in evaluating mesenteric lymph node metastasis in rectal tumor, it is not sufficient to evaluate lymph node metastasis in anorectal malignant melanoma. In the study of Wang et al., when tumor size is over 3 cm, WLE should not be performed because of the possibility of lymph node metastasis (9).

Rectal hemorrhage is the most common symptom in ARMM and occurs in 53% - 89% of the cases. Other symptoms are suspected hemorrhoids, pain, anal mass, changes in bowel habits, and itching. High LDH and YKL-40 levels also increase the suspicion of anorectal malignant melanoma. A very small number of patients are examined with mass in the inguinal region (10). In our study, 72.72% of the patients presented with rectal bleeding complaints. Due to the rarity of ARMM and non-specific clinical findings, misdiagnosis is very common. Early symptoms of ARMM may be misdiagnosed with benign lesions such as thrombosed hemorrhoids, hemorrhoids and rectal adenomas. The reasons for misdiagnosis are that clinicians do not have sufficient knowledge, lack of specific clinical findings and difficult pathological diagnosis (11).

Patients present at advanced stages due to nonspecific clinical findings in ARMM. In the study of Hicks et al., half of the cases have been diagnosed in stage II and stage III. In the same study, median tumor thickness was 5.5 mm, and in more than half of

Table 2. Histopathological features of the cases

Patient No.	Stage	Tumor Size (cm)	Tumor Depth (mm)	R0 Resection	Lymph Node Metastasis
1	II	3.5	15	+	6
2	II	3.3	18	+	16
3	I	2.5	12	-	-
4	II	4	25	+	9
5	II	6	9	+	3
6	III	12	20	+	24
7	I	1.5	8	+	0
8	II	6	21	+	0
9	I	2	1.3	+	-
10	I	1.8	1.3	+	-
11	II	9.5	19	+	25

the patients, tumor depth was deeper than 4.0 mm (12). In our study, the rate of stage I patients was found to be 36.36%. Mean tumor depth was 13.6 mm. We believe that mean survival time is lower than the literature due to the higher stage of the patients and more tumor depth in our study.

To conclude, ARMM is a rare and rapidly progressing disease with poor prognosis. ARMM is diagnosed at advanced stages due to lack of specific symptoms and has a low survival rate. Radical surgery provides longer survival advantage in early-stage tumors. ARMM should be kept in mind in patients with rectal bleeding, rectal pain and palpable mass or hemorrhoids since the most important factor in survival is the early diagnosis of the disease.

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ORİJİNAL ÇALIŞMA/OLGU SERİSİ-ÖZET
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Primer anorektal malign melanomları: tek bir merkezde 11 olgunun retrospektif analizi

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ÖZET

Giriş ve Amaç: Anorektal malign melanom kötü prognozu olan nadir bir tümördür. Bu çalışmada, kliniğimizde ARMM ameliyatı geçiren 11 hastada literatürü retrospektif olarak inceleyerek cerrahi sonuçlarımızı sunmayı amaçladık.

Gereç ve Yöntem: 2007-2018 yılları arasında Yüksek İhtisas Eğitim ve Araştırma Hastanesinde anorektal malign melanom nedeniyle ameliyat edilen hastalar çalışmaya dahil edildi.

Bulgular: Dört hasta erkek, yedi hasta kadındı. Yaş ortalaması 54,18 idi. Tümör 4 olguda rektumda, 3 olguda anorektal bölgede ve 4 olguda anal kanalda idi. Üç olguya geniş lokal eksizyon, 8 olguya APR uygulandı. Olguların dördü evre I, 6'sı evre II ve 1'i evre III idi. Ortalama tümör boyutu 4,73 cm ve ortalama tümör derinliği 13,6 mm idi. Ortalama metastatik lenf nodu sayısı 10,37 idi. Ortanca sağ kalım 12 aydı.

Sonuç: Anorektal malign melanom, spesifik bulguların olmaması nedeniyle geç ve ileri evrelerde teşhis edilen bir kanser türüdür. ARMM nadir olmasına rağmen, rektal kanama, ağrı, hemoroid ve barsak alışkanlıklarındaki değişiklikler gözlendiğinde ARMM akılda tutulmalıdır.

Anahtar Kelimeler: Anorektal malign melanom, abdominoperineal rezeksiyon, geniş lokal eksizyon, prognoz

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One of the rare reason of abdominal pain: abdominal wall endometriosis

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ABSTRACT

Objective: Endometriosis is defined as the presence of normal endometrial mucosa abnormally implanted in locations other than the uterine cavity. It is most commonly located in the pelvis but it is also rarely observed in the gastrointestinal tract, lung, liver, kidneys, central nervous system and abdominal wall. Abdominal wall endometriosis (AWE) commonly occurs following a caesarean section or pelvic surgery. The patients consult the physician mostly with complaints of cyclic abdominal pain and a palpable mass in the abdomen. The basic methods in diagnosing AWE are anamnesis and physical examination but ultrasound, computerized tomography, and sometimes magnetic resonance imaging of the abdomen are also used.

Material and Methods: In our study, we retrospectively analyzed 9 patients who underwent surgery at Avcılar State Hospital General Surgery Service between January 2015 and December 2018 with a preliminary diagnosis of AWE and confirmation through pathology results.

Results: Median age of the patients was 32 ± 4.66 and median body mass index (BMI) was 24.6 ± 1.15. Every patient except 1 had a history of cesarean section history. One patient was operated because of recurrence. Patients consulted the hospital with complaints of pain during menstruation and abdominal swelling. The start of the complaints was 4.1 years following C-section. Mostly ultrasound was used for imaging. For treatment, they all received en-bloc mass excision and their pathological diagnosis were compliant with endometriosis. Average surgery time was 40 minutes and average endometriosis lesion dimension was 3.4 cm. It was observed that the lesion extended to the anterior abdominal fascia in 6 of the patients, and 2 patients underwent fascia repair with propylene mesh because of the excessive defect size. No postoperative complication occured in any patient and no recurrence is observed.

Conclusion: In patients with periodic abdominal pain and swelling on the abdominal wall, AWE could be suspected and early diagnosis can be realized by carefully taking medical history and following physical examination, and appropriate radiological examinations and necessary surgical intervention can be performed. The method of diagnosis and treatment is to remove the lesion through wide excision.

Keywords: Endometriosis, abdominal wall, abdominal pain

INTRODUCTION

Endometriosis is defined as the presence of normal endometrial mucosa abnormally implanted in locations other than the uterine cavity. Endometriosis was first described in 1860, and it affects 5%-10% of women population (1,2). It is most commonly located in the pelvis but in 12% of the published cases, it is also rarely observed in the gastrointestinal tract, lung, liver, bladder, kidneys, umbilicus, extremities, central nervous system and abdominal wall (1,3).

Abdominal wall endometriosis (AWE), which was first reported by Meyer in 1903, is rarely observed, but it occurs most frequently following a cesarean or pelvic surgery. The patients consult the physician mostly with complaints of cyclic abdominal pain and a palpable mass in the abdomen (2,4,5). In the presence of the mass found, it can be mixed up with lipoma, abscess, hematoma, hernia, granuloma, desmoid tumor or sarcoma. The basic methods in diagnosing AWE are anamnesis and physical examination but ultrasound, computerized tomography, and sometimes magnetic resonance imaging of the abdomen are used in the differential diagnosis (3,4).

Although there are many theories in AWE etiology, the most accepted one is the direct spread of the endometrium cells through iatrogenic ways and the formation of endometriosis in the surgical field. Cesarean increases AWE formation 27 times in the society, and in recent years, AWE observation rate has increased in parallel with the increase in the cesarean section rate (1,3).

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In our study, it was aimed to examine the diagnosis, treatment and follow-up information of patients diagnosed with AWE pathology at the Avcılar State Hospital for 4 years, following the current literature.

MATERIAL and METHODS

In our study, we retrospectively analyzed 9 patients who underwent surgery at Avcılar State Hospital General Surgery Service between January 2015 and December 2018 with a preliminary diagnosis of AWE and confirmation through pathology results. Demographic information, medical history, complaints, cesarean history, diagnosis and treatment methods, length of hospital stay, pathology results of each patient were taken from their medical files, and their follow-up was recorded through patient controls and phone conversations.

All quantitative data were expressed as mean ± standard deviation. The qualitative variables were defined by frequencies (%). This study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty with approval number 83045809-604.01.02 at 07/07/2020.

RESULTS

Median age of the 9 patients: 32 ± 4.66 years (between 26-40 years), median body mass index (BMI): 24.6 ± 1.15. In 5 patients (55%), BMI was over 25. Every patient except 1 had a history of cesarean section history. One patient was operated because of recurrence 3 years after their first operation in another center.

All of the patients consulted with pain during their menstruation period. Six (66%) patients presented with abdominal distension. The start of the complaints was 4.1 years following C-section. The placement of the lesions was on the left side of the incision in 5 patients (55%), in the center in 2 patients and on the right side in 1 patient. In a patient without a history of surgical operation, the lesion was located on the right suprapubic region.

In imaging, abdominal + superficial ultrasound (US) was used for each patient (Figure 1) Additionally, 3 patients underwent computerized tomography (CT) and 1 patient underwent abdominal magnetic resonance imaging (MRI).

For treatment, they all received en-bloc mass excision and their pathological diagnosis were compliant with endometriosis (Figure 2). Average surgery time was 40 minutes, and average endometriosis lesion dimension was 3.4 cm. It was observed that the lesion extended to the anterior abdominal fascia in 6 of the patients, and 2 patients underwent fascia repair with propylene mesh because of the excessive defect size. Length of hospital stay was 1 day for all patients, no postoperative complications were observed in any patient. All of the patients relieved from symptoms, and no recurrence was observed during the average follow-up of period of 2.3 years.

The determined demographic and clinical data of the patients are shown in Table 1.

DISCUSSION

The presence of ectopic endometrium tissue between the subcutaneous adipose tissue and muscles in the abdominal wall is defined as abdominal wall endometriosis, and its prevalence in the general population is between 0.03% and 1% (5,6). Even though the patients are mostly of reproductive age and with a cesarean section history, cases with abdominal hysterectomy, appendectomy, laparoscopic trocar insertion sites and amniocentesis needle insertion sites have also been reported in AWE-related publications (5,7). In our patients, as stated in the literature, 8 of them had one or more cesarean section history, only 1 patient had no surgical operation history similar to the very rarely observed literature cases reported as a case report.

In patients undergoing surgery, endometriosis is thought to occur through a direct implantation mechanism as a result of insufficient closure of the uterine incision or abdominal wall layers (8).

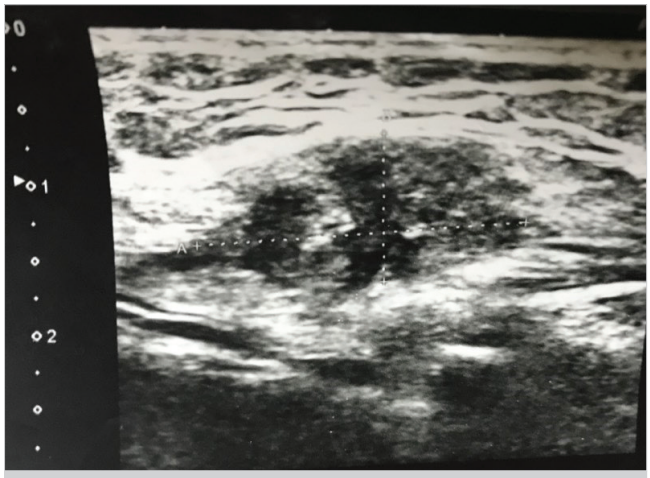

Figure 1. 22x10 mm heterogeneous hypoechoic solid lesion deeply located in the anterior abdominal wall on the US.

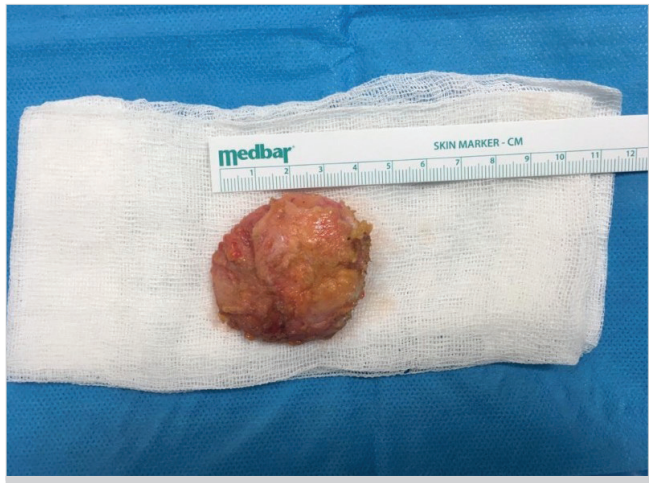

Figure 2. The view of the endometriosis resection piece.

Table 1. Patients's demographic data and study parameters

	N	%	Mean	SD
Patients (n)	9			
Age			32	4.66
Body Mass Index (kg/m^2)			24.6	1.15
<25	4	(44.4)		
>25	5	(55.5)		
Presenting symptoms				
Cyclic abdominal pain	9	(100)		
Mass palpation	6	(66.6)		
Diagnostic tests				
Ultrasound (US)	9	(100)		
Computed Tomography	3	(33.3)		
Magnetic resonance imaging	1	(11.1)		
Treatment				
Surgical resection	9	(100)		
Fascia involvement	6	(66.6)		
Mesh repair	2	(22.2)		
Nodule size (cm)			3.4	
Hospital stay (day)			1	
Duration of follow up (year)			2.3	

Similar to our 28-year-old nulliparous patient, it is considered that primitive pluripotent mesenchymal cells underwent specialized differentiation and caused endometriosis in patients without a history of surgery. It has also been reported that endometriosis may occur through lymphatic or hematogenous spread or coelomic metaplasia and changes in cellular immunity (9).

In order to prevent AWE formation through direct implantation, some techniques are recommended during surgical procedure, especially during cesarean section. These are: preventing the contact of the gases and pads that are used to clean the uterine cavity with the incision area, not comprising the endometrium during the uterine suture, washing abdominopelvic cavity, closing the visceral and parietal peritoneum, and not using the same needles for closing the uterus and abdomen (1,10).

Khan et al. have shown that women with high BMI were more likely to have AWE in comparison to the control group and determined that the reason for this could be not making an appropriate closure of the uterus and abdominal wall in obese patients (8). In our series, 5 patients (55%) presented with a BMI value above 25 in parallel with the publications.

AWE patients spend a long time from the onset of pain to the time of diagnosis and consult to many physicians. They may undergo extra examination during differential diagnosis with incisional or inguinal hernia, lipoma, cyst or soft tissue tumor. All of our patients underwent US, and 3 patients underwent a CT scan and 1 patient underwent an MRI. US is sufficient for the diagnosis of AWE, and the solid hypoechoic appearance including vascular structures is diagnostic in the concomitantly realized Doppler US. Although CT or MRI is not an additional view for diagnosis, they are more useful in evaluating the extent and margins of the lesion (2,11).

Yan Ding et al. have stated that 77% of the AWE is located on the side of the incision and that it is due to the fact that the endometrial cells are less cleaned on the incision edges (12). In our study, it was also observed that 6 (5 left, 1 right) (75%) of the 8 patients presented with incision had the lesion located on the side.

Fine needle aspiration (FNA) accompanied by ultrasound is an effective, inexpensive method that can be used to distinguish benign and malignant during the pre-operative period. In the sample taken with FNA, endometrial-like epithelial cells, stromal cells, and hemosiderin-laden macrophages can be observed. However, the proper diagnosis may not be made for endometriosis that includes fibrosis existing for many years and insufficient sampling. Because of this situation and the risk of creating new implants at FNA entry sites, it is not a preferred method (5,13). Our cases did not include patients with FNA diagnosis.

Even though medical treatments with anti-inflammatory agents, oral contraceptives containing progesterone, anti-estrogens such as danazol and gonodotropic analogs such as leuprolide acetate are tried in the treatment of AWE, their success has been

very low and as lesion dimension did not decrease many patients underwent surgical treatment (2,4). Our patients did not have any medical treatment history.

Surgical wide excision is the standard method in AWE treatment and it confirms the diagnosis. Although the intact surgical margin is stated as 1 cm in most publications, there is not a study showing the relationship between the surgical margin and the recurrence (1,5,14). In cases including deeply located fascia, aponeurosis, muscle or peritoneum extension, if the fascia defect is bigger than 3-4 cm following the large resection the insertion of a mesh may be required (14). In our study, all patients underwent wide excision and extension to the fascia was observed in 6 patients, and propylene mesh was used to close the fascia in 2 (22%) patients.

Malignancy development of AWE is very rare and is observed in 1% of the published cases. In publications, older age, postmenopausal period, and tumor diameter greater than 9 cm has been reported as a risk factor for malignancy, and conversion to tumors such as carcinosarcoma, cystadenocarcinoma, and serous papillary carcinoma has been rarely reported (5,15). No malignancy diagnosis or suspicion was found in the pathology diagnoses of our study. We can state that this is related to the patient age being young (average: 32) and lesion dimension being small (average: 3.4 cm).

The limitations of our study are the retrospective design of the stuyd and having a low number of cases, on the other hand, it is significant for us to acquire a rare case serial even though we are not a large center.

CONCLUSION

In conclusion, AWE diagnosis and treatment is a situation that takes a long time and that is rarely observed. In patients with periodic abdominal pain and swelling on the abdominal wall, AWE could be suspected and early diagnosis can be realized by carefully taking a medical history and following a physical examination, and appropriate radiological examinations and the necessary surgical intervention can be performed. The removal of the lesion through a wide excision is necessary for diagnosis and treatment, and the most significant point during manipulation is to make sure that endometriosis does not spread to the surrounding area.

Ethics Committee Approval: The ethical approval for this study was obtained from Cerrahpasa School of Medicine Clinical Research Ethical Committee (Decision no: 83045809-604-01.02- Date: 29.05.2020).

Peer-review: Externally peer-reviewed.

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Karın ağrısının nadir bir nedeni: Karın duvarı endometriozisi

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ÖZET

Giriş ve Amaç: Endometriozis, uterusun dışında başka bir yerde uterus mukozasının bulunmasıdır. En sık pelvis yerleşimli olsa da; nadiren gastrointestinal sistem, akciğer, karaciğer, böbrek, santral sinir sistemi ve karın duvarında da görülmektedir. Karın duvarı endometriozisi (KDE) en sık, geçirilmiş sezeryan veya pelvik cerrahi sonrası oluşmaktadır. Hastalar çoğunlukla siklik karın ağrısı ve karında ele gelen kitle şikayeti ile hekime başvurmaktadır. KDE tanısında anamnez ve fizik muayene temel yöntem olup, ultrason, bilgisayarlı tomografi ve bazen batın manyetik rezonans görüntüleme kullanılmaktadır.

Gereç ve Yöntem: Çalışmamızda Avcılar Devlet Hastanesi Genel Cerrahi Servisinde Ocak 2015 ve Aralık 2018 arasında KDE ön tanısı ile ameliyat edilip patoloji sonuçları ile konfirme edilen 9 hastayı retrospektif olarak inceledik.

Bulgular: Hastaların ortalama yaşı: 32, ortalama vücut kütle endeksi: 24,6 idi. 1 hasta hariç diğer tüm hastaların en az bir kez sezeryan öyküsü vardı. 1 hasta nüks nedenli ameliyat edildi. Hastalar menstruasyon döneminde olan ağrı ve karında şişlik şikayeti ile başvurdu. Şikayetlerin başlama süresi ortalama sezeryandan 4,1 yıl sonra idi. Görüntülemede çoğunlukla ultrason kullanılmıştı. Tedavi olarak tüm hastalara kütle eksizyonu yapıldı; patolojik tanıları endometriozis ile uyumlu idi. Ortalama operasyon zamanı 40 dakika olup endometriozis lezyon boyutu ortalama 3,4 cm idi. Hastaların altısında lezyonun batın ön duvar fasyasına uzanım gösterdiği görüldü, 2 hastaya defekt büyüklüğü fazla olduğu için prolen meş ile fasya tamir işlemi yapıldı. Hiç bir hastada post-operatif komplikasyon izlenmedi, takiplerinde nüks görülmedi.

Sonuç: Dönemsel karın ağrısı ve karın duvarında şişlik olan hastalarda KDE den şüphelenilip , dikkatli bir anamnez ve fizik muayene ve uygun radyolojik tetkikler ile erken tanı konulup gerekli cerrahi müdahale yapılabilir. Tanı ve tedavisinde yöntem lezyonun geniş eksizyonla çıkarılmasıdır.

Anahtar Kelimeler: Endometriozis, karın duvarı, karın ağrısı

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CASE REPORT
Turk J Surg 2021; 37 (1): 73-75

Spleen rupture due to brucellosis

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ABSTRACT

Brucellosis is a common zoonotic infection worldwide; it is caused by infection with the bacterial species Brucella and leads to severe diseases in humans and animals. In Turkey, this bacterial species has not been completely eradicated and is commonly found in animals (such as goats or sheep). Brucellosis can lead to various symptoms, affect multiple systems, and cause splenomegaly in the case of spleen involvement. In contrast to traumatic spleen ruptures, spontaneous spleen ruptures are rare and most commonly occur because of infectious causes. A 52-year-old man was treated at our infectious diseases clinic for Brucella endocarditis. Due to sudden abdominal pain, nausea, vomiting, and vertigo, the patient was evaluated by our team of doctors at the same clinic. The patient had widespread sensitivity in the abdominal region, as well as defense and rebound symptoms. Emergency abdominal tomography revealed a ruptured spleen and widespread hemorrhagic fluid in the abdomen. Exploration revealed multiple ruptures in the spleen capsule. The patient underwent splenectomy and did not experience any complications during the postoperative period. Spontaneous spleen rupture is a rare clinical condition that should be considered in patients who are hospitalized at internal medicine clinics for infectious, hematogenic, and metabolic causes, as well as in those who have sudden abdominal pain and hypovolemia.

Keywords: Brucella, spontaneous spleen rupture, hemorrhagic shock

INTRODUCTION

Brucellosis, caused by infection with the bacterial species Brucella, is a common zoonosis worldwide that can cause severe diseases in humans and animals. Brucellosis can lead to various symptoms, affect multiple systems, and cause splenomegaly in the case of spleen involvement. Due to multiple system involvement, the symptoms and manifestations of brucellosis are generally nonspecific. However, non-specific symptoms, including fever, fatigue, and sweating are common, and hepatosplenomegaly is frequently seen.

The spleen is an immunological organ affected by hematological and non-hematological diseases. Spleen rupture usually occurs because of blunt abdominal trauma. In contrast to traumatic spleen ruptures, spontaneous spleen ruptures are rare and most commonly occur due to infectious causes. Mortality can occur in this patient group due to a delay in diagnosis and treatment (1).

This paper aimed to present a case of spontaneous spleen rupture that occurred secondary to brucellosis but is rarely reported in the literature.

CASE REPORT

A 52-year-old man was treated at our infectious diseases clinic for Brucella endocarditis. Due to sudden abdominal pain, nausea, vomiting, and vertigo, the patient was evaluated by our team of doctors at the same clinic. The patient had no history of trauma. First evaluation revealed that his blood pressure was 70/50 mmHg and his heart rate was 112 beats/minute. The patient had widespread sensitivity in the abdominal region, and defense and rebound symptoms. Hemoglobin level was 8.6 g/dl, and other laboratory parameters were normal. Emergency abdominal tomography revealed a ruptured spleen and widespread hemorrhagic fluid in the abdomen (Figures 1 and 2). The patient underwent emergency surgery. A median incision was used to enter the abdomen. Exploration revealed multiple ruptures in

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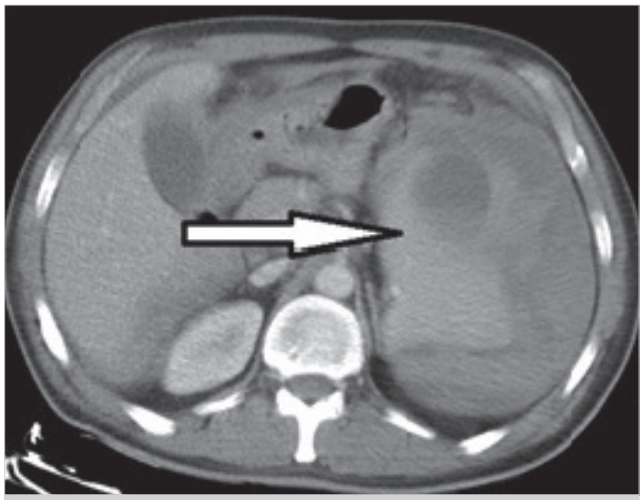

Figure 1. Ruptured spleen (white arrow).

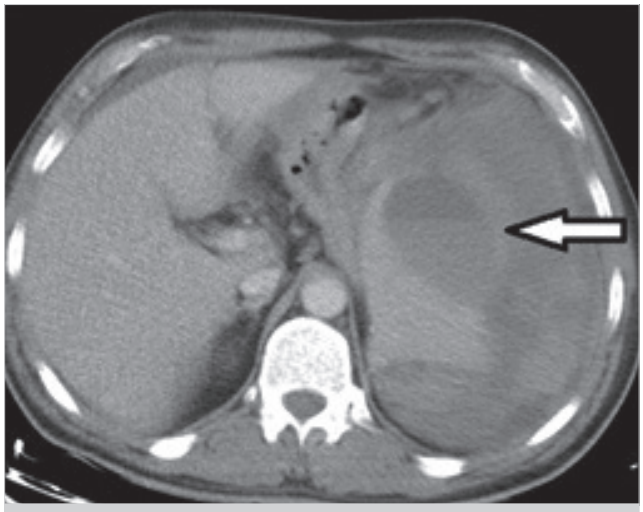

Figure 2. Hemorrhagic fluid (White arrow).

the spleen capsule and approximately 1000 cc of hemorrhagic fluid. The patient underwent splenectomy and experienced no complications during the postoperative period. The patient was then transferred to the infectious diseases department to continue medical treatment.

DISCUSSION

Brucellosis is a zoonotic infection that has not been completely eradicated, and it is commonly found in animals (such as goats or sheep) in Turkey. Transmission from animals to humans usually occurs by direct contact between the secretions of infected animals and the skin, the consumption of unpasteurized milk and dairy products, inhalation of infected aerosols, and conjunctival contact. Despite the common involvement of lymphoreticular system organs, particularly the liver, bone marrow, spleen, and lymph nodes, Brucella infections can also involve different organs and tissues, including the heart, genitourinary system, central nervous system, and joints (2,3).

Due to multiple system involvement, the symptoms and manifestations are generally nonspecific. However, non-specific symptoms, including fever, fatigue, and sweating are common, and hepatosplenomegaly is frequently seen.

Symptomatology studies in Turkey have revealed that the major complaints are fever (43-83%), sweating (65-78%), night sweating (69%), lower back pain (22-33%), headache (28-44%), lack of appetite (34-53%), joint pain (20-76%), muscle pain (56%), fatigue (14-81%), difficulty walking (11-18%), clouding of consciousness (6%), weight loss (2-36%), and numbness in the arms (2%) (4).

The first case of spontaneous spleen rupture was published by Atkinson in 1874 (5). Spontaneous spleen rupture constitutes 1% of all spleen ruptures (6). While the exact cause of spontaneous spleen rupture remains unknown, three mechanisms are considered to play a role in its disease pathogenesis: an increase in intrasplenic pressure due to congestion and hyperplasia of the cells; an increase in intra-abdominal pressure during physiological activities and compression of the spleen by the abdominal muscles; and blockage of vascular structures due to reticuloendothelial hyperplasia (eg., thrombosis, infarction). Interstitial and subcapsular mechanisms can emerge depending on these mechanisms (7,8). Spontaneous spleen rupture can result from infectious causes (malaria, infectious mononucleosis, syphilis, and Brucella infection), hematological causes (anticoagulant treatment, lymphoma, and leukemia), metabolic causes (amyloidosis and sarcoidosis), local causes (splenic vein thrombosis and pancreatitis), and other causes (vomiting and coughing) (9).

Given the high mortality rate of spleen rupture, patients must be diagnosed and treated immediately. Initially, patients have pain in the left upper quadrant, which is followed by sensitivity, and rigidity. Vertigo, vomiting, hypotension, tachycardia, and oliguria can accompany abdominal symptoms, depending on the degree of hemorrhagic shock. Hemorrhagic shock can develop in more than half of patients, if there is no timely intervention (10).

Radiological examination (eg., ultrasonography) can reveal an enlarged, displaced, double-countered spleen, as well as intraperitoneal bleeding. Abdominal tomography can help achieve a definitive diagnosis and enable the detection of hypodense/hyperdense foci, together with intracapsular, perirenal, and intraperitoneal fluid. Additionally, computed tomography can be used to grade the rupture (11). Decisions about treatment depend on the hemodynamic stability of the patient, level of bleeding in the peritoneal space, blood transfusion, and organ damage score.

CONCLUSION

Spontaneous spleen rupture is a rare clinical condition that should be considered in patients hospitalized in internal medicine clinics for infectious, hematogenic, and metabolic causes, and in those with sudden abdominal pain and hypovolemia.

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

Peer-review: Externally peer-reviewed.

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

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OLGU SUNUMU-ÖZET
Turk J Surg 2021; 37 (1): 73-75

Bruselloza bağlı dalak rüptürü

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ÖZET

Brusella, dünyada yaygın olarak görülen bir zoonoz olup, insanlarda ve hayvanlarda ciddi hastalık yapabilme kapasitesine sahiptir. Bruselloz dünyadan tam olarak eradike edilememiş, özellikle ülkemizde keçi ve koyun gibi hayvanlarda yaygın olarak bulunan zoonotik bir enfeksiyondur. Birçok sistemi etkileyebilen değişik semptom ve bulgulara sebep olan brusella, dalakta tutuluma bağlı olarak splenomegaliye de neden olabilmektedir. Spontan dalak rüptürleri ise travma dalak rüptürlerinin aksine nadir görülüp, en sık enfeksiyöz nedenlere bağlı olarak gerçekleşmektedir. Elli iki yaşında erkek hasta brusella endokarditi tanısıyla enfeksiyon hastalıkları kliniğinde yatmakta iken, ani başlayan karın ağrısı, bulantı, kusma ve baş dönmesi şikayeti ile olması üzerine yattığı serviste tarafımızdan değerlendirildi. Karında yaygın hassasiyet, defans ve rebound bulguları mevcuttu. Hastaya acil olarak çekilen karın tomografisinde; dalağın rüptüre ve karın içinde yaygın hemorajik mayi olduğu görüldü. Eksplorasyonda dalak kapsülünde birden fazla alanda yırtık olduğu görüldü. Splenektomi uygulanan ve hastamız postoperatif dönemde sorunsuz takip edildi. Bizim olgumuzda olduğu gibi dahili kliniklerde enfeksiyöz, hematojenik ve metabolik sebeplerle yatan hastalarda ani gelişen karın ağrısı ve hipovolemi durumunda, spontan dalak rüptürü akılda bulundurulması gereken ve nadir klinik bir durumdur.

Anahtar Kelimeler: Brusella, spontan dalak rüptürü, hemorojik şok

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CASE REPORT
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An unusual localization; esophageal melanocytosis

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ABSTRACT

Esophageal melanocytosis is a rare clinical and pathological condition characterized by non-atypical melanocytic proliferation and increased melanin in the esophageal mucosa, which is normally histologically non-melanocytic. Intensive melanin accumulation and hyperpigmentation are necessary for endoscopic recognition. Due to the fact that it is a rare gastrointestinal system pathology, experience and knowledge about its diagnosis, treatment and course are also limited. Although it is argued that chronic stimulating factors have an influence, there is no clear information about its etiology and pathogenesis. Malignant melanomas and melanocytic nevus in particular come to the fore in the differential diagnosis. Opinions and findings indicating that melanocytosis may be a precursor for malignant melanoma make the recognition and follow-up of this clinical and pathological entity more important. In this article, a patient with esophageal melanocytosis diagnosed by endoscopic evaluation is presented, with the aim of increasing the awareness of clinicians, especially endoscopists and pathologists, on this subject.

Keywords: Esophageal melanocytosis, endoscopy, melanoma

This study was presented at the 14th National Hepato- Gastroenterology Congress, 5th National Congress of Gastroenterology Surgery, 1st Euroasian Gastroenterological Association Symposium, 5-8 April 2017, Antalya, Turkey.

INTRODUCTION

Esophageal melanocytosis is one of the very rare pathologies of the gastrointestinal system. It is described as a benign condition characterized by melanocytic proliferation in the basal epithelium of the esophagus, hyperpigmentation, and increased accumulation of melanin in the mucosa (1). It is observed to receive more diagnoses in autopsy series compared to endoscopy-based studies. This is associated with the need for melanin accumulation in very large quantities in the mucosa in order for melanocytosis to become endoscopically visible (2). In addition to this, the extremely rare occurrence of the disease significantly limits the experience of endoscopists with regard to diagnosis and follow-up. In this article, a case of esophageal melanocytosis who was admitted due to dyspeptic complaints was presented, with the aim of increasing the awareness of clinicians on this issue.

CASE REPORT

A 45-year-old male patient presented to our clinic with dyspeptic complaints that had been present for approximately 4 months. There was nothing particular in his personal or family history. No physical anomaly was detected in the physical examination and laboratory tests. The patient underwent an upper gastrointestinal system endoscopy with a Pentax EPK-100p Endoscope (Hoya Comp, Tokyo; Japan). A dark brown-black colored, dotted area of mucosal pigmentation with faint borders and dispersed localization despite being denser in a few foci and taking up almost 1/3 of the lumen was observed along a segment of approximately 2 cm at the distal part of the thoracic esophagus (Figure 1). Multiple biopsies were taken from this area. Sampling with biopsy was done from the antrum because of a hyperemic, speckled and edematous mucosal appearance consistent with antral gastritis. No other pathology was observed endoscopically. In the examination, the gastric antrum samples were evaluated as being consistent with Helicobacter pylori negative chronic gastritis with no atrophy and no metaplasia and showing activation. In the esophageal biopsies, melanin loaded cells in large quantities which were cytolog-

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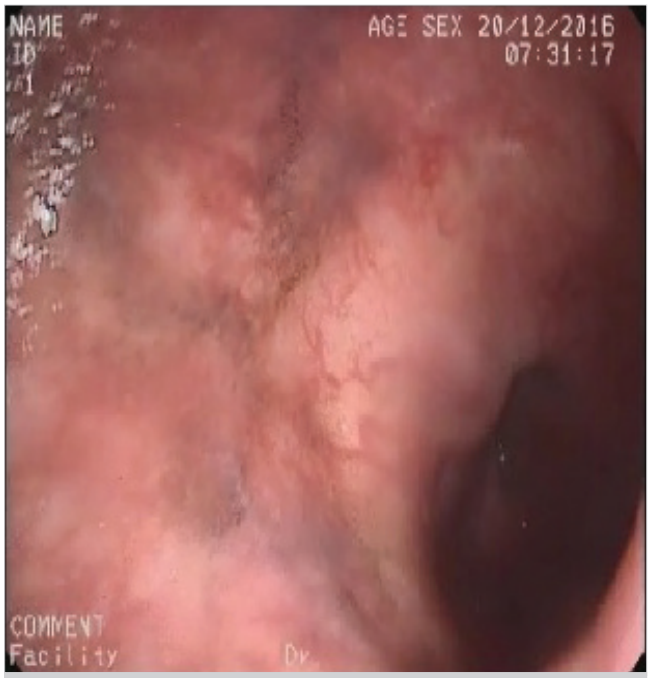

Figure 1. Endoscopic appearance of the area of melanocytosis.

ically non-atypical and consistent with melanocytosis in addition to chronic inflammatory cells in supportive tissue areas that could be seen between the papillae were observed (Figure 2A and 2B). Recommendations for nutritional and lifestyle changes were made to the patient and proton pump inhibitor therapy was initiated. In his follow-up, his dyspeptic complaints were seen to disappear completely. Written consent was obtained from the patient that his medical data could be published.

DISCUSSION

The presence of melanocytic cells in the esophagus was first described by De La Pava et al. in 1963 (3). The rate of melanocytosis in autopsy-based studies ranges from 4% to 7.7%, while studies based on consecutive endoscopy series report this rate to be between 0.07% and 2.1% (1-5).

Histologically, the esophagus mucosa normally does not contain melanocytes. Although the pathogenesis of melanocytosis formation has not been clearly revealed, there are two prominent theories. The first of these argues that melanocytes may have settled in the esophagus through aberrant migration during embryogenesis and the second argues that the stem cells located in the basal layer differentiate into melanocytes as a result of various influences (1,6).

There is no specific symptom or clinical entity pertaining to this pathology, which is usually incidentally diagnosed (2,7). It has been argued that chronic irritant conditions that lead to mucosal damage, such as chronic esophagitis, alkaline reflux and especially gastroesophageal reflux are associated with the disease (1,4-7). Similarly, melanocytic nevus and malignant melanomas presenting with melanin accumulation come to the fore in the differential diagnosis of esophageal melanocytosis. Malignant melanoma, in particular, is a very aggressive tumor with a high metastatic potential and poor prognosis. It is characterized by a histological structure with nuclear atypia, a prominent nucleolus, high mitotic activity and an epithelioid or spindle cell type (1). Melanocytic nevus are distinguished from melanomas by not involving cytological atypia and distinguished from melanocytosis by the presence of pigmented dendritic melanocytes in the subepithelial connective tissue and the lack of junctional melanocytic activity (1,2,8). Esophageal melanocytosis is usually described as a benign lesion that does not require treatment or follow-up (9). Despite this, cases progressing into malignant melanoma have been reported (10-12). There are publications suggesting the clinical and endoscopic follow-up of these patients because it is seen as a lesion that is a precursor for melanoma, it is proposed to follow-up with multiple biopsies (7,12,13).

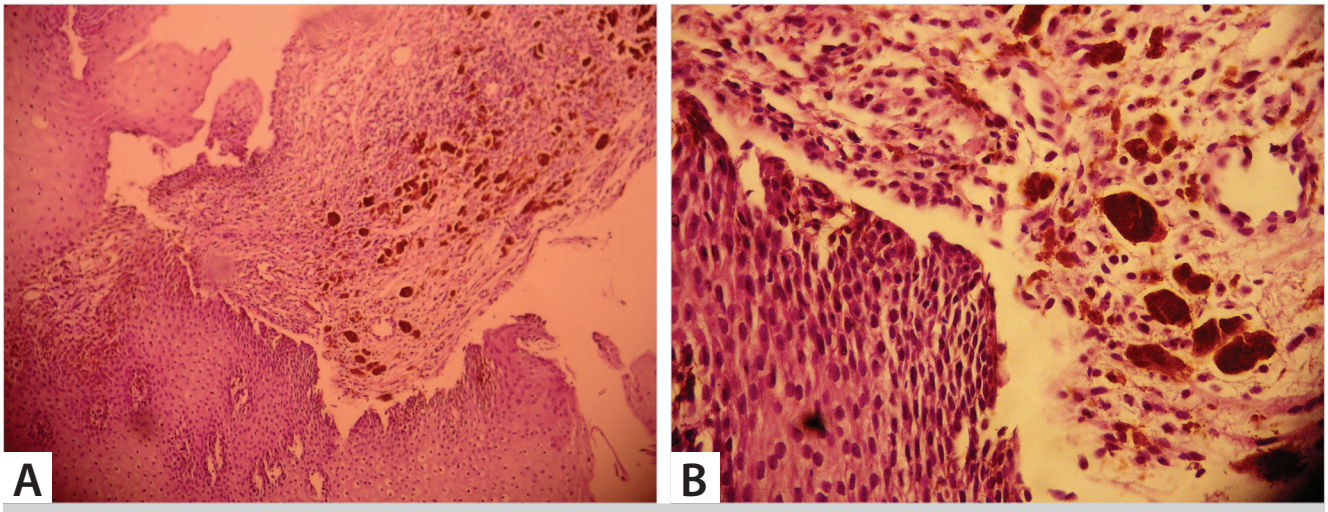

Figure 2A and 2B. Macrophages loaded with pigment under squamous epithelium.

Esophageal melanocytosis is a pathology that has found its place in the literature with a limited number of case reports. Hence, experiences regarding its diagnosis, treatment and prognosis are limited. It is important for endoscopists and pathologists to consider melanocytosis in the differential diagnosis of esophageal pathologies. It is seen that melanocytosis can be a precursor for esophageal malignant melanoma in the findings of literature. Therefore, it is a correct approach to consider these lesions as premalignant esophageal pathologies. Endoscopic follow-up at intervals of 1-3 years is recommended in many premalignant esophageal pathologies, depending on the presence of dysplasia or other risk factors (14). However, as the number of cases is very limited and also the presence of patients who are diagnosed with malignant melanoma two years after the diagnosis of melanocytosis, we believe that the endoscopic follow-up should not be longer than one year. (12). The sharing of experience and information obtained after frequent periodic follow-ups will also contribute to the establishment of a consensus for follow-up strategy of this pathology. Currently, treatments such as endoscopic mucosal resection and radiofrequency ablation, in the treatment of premalignant esophageal lesions, can be performed with high success rates (15). We believe that endoscopic resection treatments should be offered as an alternative in melanocytosis due to the potential for malignant transformation, especially in patients with a limited area of melanocytosis in the esophagus lumen and who are not being eager enough for frequent endoscopic follow-up.

CONCLUSION

We are of the opinion that close endoscopic and pathological follow-up will be appropriate for these patients since there is not adequate information about the course of the disease. It is seen that there are not enough data based on long-term observation yet for the standardization of the follow-up of cases or bringing up endoscopic or surgical treatments. Nevertheless, we consider that endoscopic resection treatments can be applied in appropriate cases when melanocytosis is considered to have potential for melanoma transformation, a very aggressive malignant tumor.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - R.K.; Design - R.K., Z.T.; Supervision - R.K.; Materials - R.K., Z.T.; Data Collection and/or Processing - R.K., Z.T.; Analysis and/or Interpretation -R.K., Z.T.; Literature Search - R.K., Z.T.; Writing Manuscript - R.K.; Critical Reviews - R.K.

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

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OLGU SUNUMU-ÖZET
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Sıradışı bir lokalizasyon; özofageal melanositozis

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ÖZET

Özofageal melanositozis, normalde histolojik açıdan melanosit içermeyen özofagus mukozasında non-atipik melanositik proliferasyon ve melanin artışı ile karakterize, nadir görülen klinik ve patolojik bir durumdur. Endoskopik olarak tanınabilmesi için yoğun melanin birikimi ve hiperpigmentasyon gereklidir. Oldukça ender görülen bir gastrointestinal sistem patolojisi olması nedeniyle tanı, tedavi ve seyri ile ilgili deneyim ve bilgiler de kısıtlıdır. Her ne kadar kronik uyarıcı faktörlerin etkisi olduğu savunulsa da etyoloji ve patogenezi hakkında net bir bilgi bulunmamaktadır. Ayırıcı tanıda özellikle malign melanom ve melanositik nevüs öne çıkmaktadır. Melanositozisin malign melanom için prekürsör olabileceği yönündeki görüş ve bulgular, bu klinik ve patolojik tablonun tanınmasını ve takibini daha da önemli hale getirmektedir. Bu yazıda endoskopik biyopsi ile tanı konulan özofageal melanositozisli hasta sunularak, başta endoskopistler ve patologlar olmak üzere klinisyenlerin bu konudaki farkındalıklarının arttırılması hedeflenmiştir.

Anahtar Kelimeler: Özofageal melanositozis, endoskopi, melanom

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SURGICAL TECHNIQUE
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Management of bile leak from the subvesical duct (Luschka's) during laparoscopic cholecystectomy

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A 60-year-old female patient with resolved biliary pancreatitis was planned for laparoscopic interval cholecystectomy. Before surgery, her vitals were normal and physical examination was unremarkable. There was no associated comorbidity. Her liver function test and serum amylase level were within normal limit. A recent abdominal ultrasound scan had revealed a solitary stone impacted at the neck of gallbladder. At laparoscopy, pericholecystic adhesions were present and gallbladder (GB) was thick-walled. Cholecystectomy was completed after dissection of the Calot's triangle and division of the cystic duct and artery.

Intraoperative inspection of the GB bed revealed continuous bile leak from a small subvesical duct (of Luschka) (Figure 1). Clipping the offending subvesical duct successfully obliterated the bile leak (Figure 2-4) (Supplementary video file 1). An abdominal drain was placed in the subhepatic region. The patient had an uneventful post-operative course. She was discharged on day 3 following surgery after removal of the abdominal drain. At 1 month follow-up, the patient was symptom-free and had normal liver function test. Histopathological examination of the gallbladder specimen was suggestive of chronic cholecystitis.

Post-cholecystectomy bile leak can occur in 0.3–2.7% of cases (1). Cystic duct stump and aberrant subvesical bile duct are the most common sites for bile leak following cholecystectomy (2). It is estimated that approximately 27% of clinically significant bile leaks occur secondary to subvesical bile duct injury. Usually, bile leakage from the subvesical duct tends to be minor and often resolve spontaneously. However, it may seldom cause persistent bile leak resulting in localized or generalized peritonitis with potentially life-threatening consequences (3).

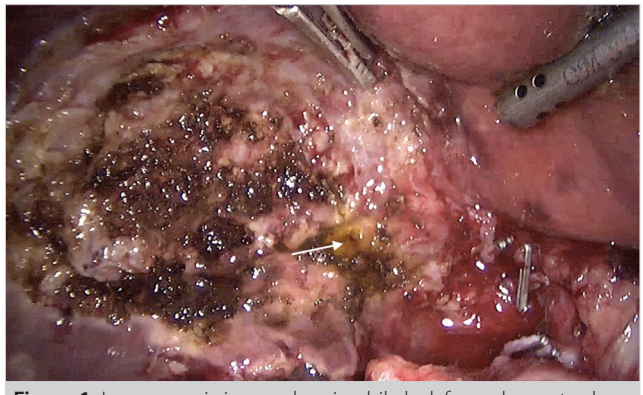

Figure 1. Laparoscopic image showing bile leak from aberrant subvesical bile duct.

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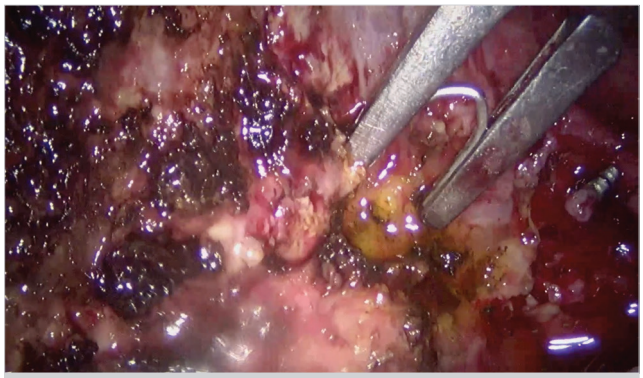

Figure 2. Clip being applied after delineating leaking subvesical duct.

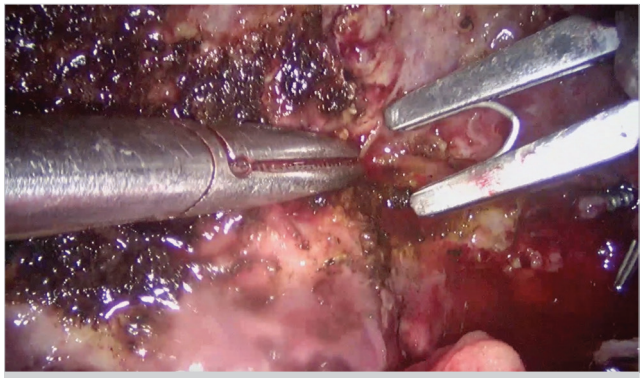

Figure 3. The duct is grasped and gently pulled for proper application of clip.

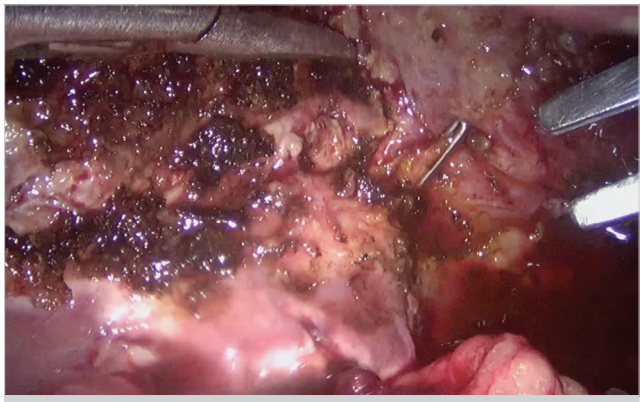

Figure 4. Obliterated aberrant subvesical bile duct after clip placement.

Intraoperative detection of the severed subvesical duct is rare, and most of the cases present during the first postoperative week (2). Common presentations include abdominal distention, pain, fever and occasionally jaundice.

When detected postoperatively, management includes control of the sepsis, drainage of biloma and decompressing the bile ducts. Endoscopic sphincterotomy and biliary stenting is highly effective in treating the persistent bile leaks (4).

Intraoperative detection of the subvesical bile duct injury provides a unique opportunity for timely control of the bile leak and preventing serious complications. Obliteration of the leaking subvesical duct can be achieved with sutures, clip or fibrin glue. Clipping is safe, effective and faster way of managing the bile leak, provided the duct can be clearly delineated.

To conclude, a surgeon should be aware of the risk of subvesical bile duct injury during cholecystectomy and should be prepared to manage it tactfully if detected intraoperatively.

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