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Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

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

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INSTRUCTIONS TO AUTHORS

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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.

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Video Articles: We do encourage the submission of the video articles which report interesting cases and technical methods.

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- All videos will be peer reviewed.
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- Article length: It should not exceed 500 words.
- Reference Number: Not to exceed 5 references

Diagnosis, surgical technique and outcome should be summarized. All important steps and aspects of the surgery should be mentioned in the video. If it is a new surgical technique, appropriately labeled and cited video materials may be used. Authors can use a rare case they have encountered, a surgical technique, or videos using modern technological devices.

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

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

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

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.

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

Figures and Figure Legends

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

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

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

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

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

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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.

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

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.

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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.

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Turkish
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FROM THE EDITOR'S DESK
Turk J Surg 2023; 39 (2): VIII
10.47717/turkjsurg.2023.230201

Dear readers of the Turkish Journal of Surgery,

Medicine has been struggling to find a solution to cancer, and cancer surgery is probably by far the field with the most surgical research. Thousands of important studies are published in the literature every year, and oncologic treatment is constantly evolving. Improvements in diagnostic and therapeutic capabilities and increasing experience have made many types of cancers no longer a hopeless disease.

In this issue, there are three important studies related to oncologic surgery, two of which are in the field of breast surgery. In their important study, Günay and colleagues report the results of intraoperative radiotherapy in early-stage breast cancer (1). Breast-conserving surgery and postoperative whole breast radiotherapy is the standard treatment for early-stage breast cancer. However, in recent years, it has been shown that intraoperative radiotherapy applied to the surgical field can reduce local recurrence. I believe everyone interested in the subject will read the experience of Günay and colleagues with great interest.

On the other hand, another important study on breast cancer in this issue is the study by Abidi and colleagues from Pakistan (2). Neoadjuvant therapies are now an important part of oncologic treatment strategies, which has led to dramatic progress in many types of cancers, and in some patients, this treatment is so effective that the primary tumor disappears completely. Abidi and colleagues investigated whether axilla dissection was necessary in breast cancer with a complete pathologic response after neoadjuvant therapy. I recommend reading this study with interesting results that may lead to a change in surgical strategy.

Oncologic surgery is indeed a field that is progressing in different directions, and approaches are updated every day. In some cancer types, surgeons are narrowing their surgical options, while in others, they are expanding them. On the one hand, breast-conserving surgery has become the standard in breast cancer, where radical surgeries were previously routinely performed. However, in another type of cancer, Nekarakanti and colleagues from India showed that surgery can prolong survival in stage 4 gallbladder cancer, where surgeries were previously mostly discouraged (3). This study examines patients undergoing surgery for stage 4 gallbladder cancer using a propensity-score matched analysis. I am inviting interested readers to read this inspiring study.

While I wish all our readers a pleasant reading for the articles in this issue of Turkish Journal of Surgery, I do hope that you have a joyful holiday time where you can find opportunities to improve yourself in every sense.

Sincerely,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

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ORIGINAL ARTICLE
Turk J Surg 2023; 39 (2): 89-94

The effects of the use of hyoscine-N-butylbromide during laparoscopic sleeve gastrectomy

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ABSTRACT

Objective: Hyoscine-N-butylbromide is used by some surgeons during laparoscopic sleeve gastrectomy (LSG) to loosen gastric smooth muscles and to provide a more effective LSG. However, evidence-based data on the effects of hyoscine-N-butylbromide in laparoscopic sleeve gastrectomy are limited and its effect on sleeve gastrectomy surgery and weight loss is unknown. The aim of this study was to analyze the effect of intraoperatively administered hyoscine-N-butylbromide on stomach resection volume, weight loss and complications seen in patients undergoing LSG.

Material and Methods: Patients who underwent laparoscopic sleeve gastrectomy due to morbid obesity were included in the study. Intraoperative hyoscine-N-butylbromide was administered to 52 patients (Group 1), not applied to the other 52 patients (Group 2). Age, sex, height, weight and body mass index (BMI) data of the patients were obtained retrospectively. The weight, BMI, percentage of total weight loss (TWL%) and percentage of excess weight loss (EWL%) of the patients were evaluated at postoperative third, sixth and 12th months.

Results: Resected gastric volume (p= 0.111), length of stapler line (p= 0.944), operation time (p= 0.383), hospitalization time (p= 0.494) and postoperative complications (p> 0.05) did not differ between Groups 1 and 2. However, frequency of intraoperative tachycardia (p< 0.001) and hypotension (p= 0.006) in Group 1 was significantly higher than in Group 2. TWL% and EWL% values were similar between the two groups at all-time points. Stapler line leakage was not observed in any patient during the postoperative period.

Conclusion: Intraoperative hyoscine-N-butylbromide use is not effective on weight loss postoperatively in patients undergoing LSG. Although hypotension and tachycardia occured in some of patients, none of the patients had complaints in the early or long-term postoperative period. The use of hyoscine-N-butylbromide during LSG is safe but does not have any effect on weight loss.

Keywords: Morbid obesity, hyoscine-N-butylbromide, laparoscopic sleeve gastrectomy, weight loss

INTRODUCTION

With the increase of incidence of obesity and obesity-related metabolic problems around the world, the rate of bariatric-metabolic surgery is also increasing. There are different types of procedures, but the most common surgical procedure is laparoscopic sleeve gastrectomy (LSG) (1). Although sleeve gastrectomy is a restrictive surgery, it has been shown to be effective not only in the treatment of obesity but also in the treatment of obesity-related comorbid diseases (2). However, the LSG technique is not exactly standardized, and there are still many controversial technical issues. One of these issues is the usage of intraoperative hyoscine-N-butylbromide (3,4).

As an antispasmodic drug, hyoscine-N-butylbromide has been shown to reduce contraction in the gastrointestinal tract during endoscopic procedures that facilitates these procedures (5). With the use of hyoscine-N-butylbromide, it can be thought that the stomach can be loosened and manipulated better during surgery, and thus more part of stomach can be resected. In a study conducted in Türkiye, it has been observed that 17% of surgeons routinely preferred to use hyoscine-N-butylbromide in all of cases during LSG, while 31% of surgeons preferred to use it in some of the cases (6). There is limited information about the usage of hyoscine-N-butylbromide during bariatric surgery. Although there are studies in the literature evaluating postoperative pain, nausea and vomiting with the use of hyoscine-N-butylbromide in LSG, there is no study evaluating the volume of resected stomach and weight loss with the use of hyoscine-N-butylbromide during LSG (7,8). The aim of this study was to analyze the effect of intraoperatively administered hyoscine-N-butylbromide on stomach resection volume, weight loss and complications seen in patients undergoing LSG.

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MATERIAL and METHODS

Patients who underwent laparoscopic sleeve gastrectomy due to morbid obesity, had a body mass index over 40 or had at least one comorbid disease related to obesity with a body mass index over 35 kg/m^2 were included in the study. Patients who underwent another operation in the same session, patients who underwent re-sleeve gastrectomy, patients who were sensitive to hyoscine-N-butylbromide, and those with cardiac disease, glaucoma, and prostatic hypertrophy for whom the use of hyoscine-N-butylbromide was not appropriate were not included in the study. Ethics committee approval was obtained for the study.

Considering the "independent samples t-test" before the study, it was calculated that the bidirectional p value was 0.05, the effect width was d= 0.72, 1-β= 0.95, and the number of patients in the groups was equal, at least 52 patients in both groups, making a total of 104 patients. Hyoscine-N-butylbromide was administered intravenously to one of the groups (Group 1) and no additional medication was applied to the other group (Group 2).

Body mass index (BMI) of all patients were recorded before the operation. The volume of the resected stomach during laparoscopic sleeve gastrectomy, stapler line length, greater curvature length, duration of surgery, presence of intraoperative tachycardia and hypotension, postoperative complications, and length of hospital stay were recorded. Patients' weight, BMI, percentage of total weight loss (TWL%), and percentage of excess weight loss (EWL%) were evaluated at the third, sixth, and 12th months. In order to calculate the resected stomach volume, a pressure gauge was placed inside the resected stomach and the specimen was inflated with saline to a pressure of 20 mmHg. The volume of saline filled into the resected stomach up to this pressure was considered as the volume of the resected stomach.

Surgical Techniques

All surgeries were performed by one of the two general surgeons using the same surgical technique in a single center. The operation was started at the fowler position under general anesthesia. The surgeon takes position between the legs of the patient. A 10 mm trocar is placed at the upper abdomen 1-2 cm above the umbilicus with the Hasson technique. Pneumoperitoneum is performed with 12 mmHg CO_2 insufflation. A 10 mm trocar is introduced at the right upper quadrant and a 12-mm trocar is inserted at the left upper quadrant. A 5 mm trocar is introduced at the left subcostal anterior axillary line. A 5 mm trocar is inserted at the sub-xiphoid area for the liver retraction. A 30° angled scope was used through the supraumbilical port.

First of all, intraabdominal exploration was performed. The stomach was decompressed via a nasogastric tube. Then, the gastroepiploic arch was ligated with a vessel sealing device (Ligasure™, USA). Omental dissection was performed close to the stomach until the angle of his was impaired by ligating the short gastric arteries superiorly and 2-4 cm proximal to the pylorus. The stomach was then lifted towards the anterior abdominal wall. Adhesions in the greater omentum and the posterior surface of the stomach and fundus were released with a vessel sealing device, paying attention to the left gastric artery and its branches, splenic vessels and the proximal part of the pancreas. The dissection was completed after separation of the gastrophrenic ligament and the left crus was completely visualized. Posterior crural approximation was performed with 3/0 silk suture in patients with hiatal hernia. Then, 36 french bougie was advanced into the stomach by the anesthesiologist. At this stage, in patients intended to use hyoscine-N-butylbromide, 20 mg of hyoscine-N-butylbromide was rapidly administered intravenously to the patient. Afterwards, it was ensured that the bougie was placed along the lesser curvature, and the stomach was transected starting from 2-4 cm proximal to the pylorus. Then, 50-100 mL of methylene blue was given through the bougie and the stapler line, which was applied with LSG and evaluated for leakage. Then, a Jackson-Pratt drain was placed along the stapler line and the operation was terminated.

Statistical Analysis

Statistical analyzes were performed using the SPSS version 20.0 (IBM®, Chicago, USA) package program. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk test). Descriptive statistics were expressed as mean and standard deviation, and numbers and percentages in nominal data. Normally distributed variables were analyzed with the independent samples t-test between the two groups, and the variables that were not normally distributed were analyzed with the Mann-Whitney U test between the two groups. Intra-group comparisons were analyzed with the spousal t-test and the Wilcoxon signed rank test. Nominal data were evaluated between the two groups using the Fisher's exact test or the Chi-square test. Comparisons with a p value below 0.05 were considered statistically significant in the statistical analyzes in the study.

RESULTS

A total of 104 patients, 52 patients in each group, were included in the study. Demographic data of the patients are shown in Table 1.

Table 1. Demographic data of the patients

	Group 1 hyoscine-N-butylbromide (+)	Group 2 hyoscine-N-butylbromide (-)	p
Age (year) (avg ± SD)	36.5 ± 11.0	35.8 ± 13.3	0.786†
Sex			0.512††
Female, n (%)	36 (69.2)	39 (75.0)	
Male, n (%)	16 (30.8)	13 (25.0)	
Weight (kg) (avg ± SD)	122.8 ± 18.3	123.1 ± 17.4	0.939†
BMI (kg/m^2) (avg ± SD)	45.1 ± 5.5	45.6 ± 5.0	0.629†

*Independent t-test.
††Chi-square test.

Intraoperative tachycardia (p= 0.001) and hypotension (p= 0.006) were statistically significantly higher in Group 1. However, intraoperative problems due to hypotension and tachycardia were not observed in any of the patients. Hypotension and tachycardia were not observed in any of the patients in the postoperative period.

Resected stomach volume (p= 0.111), stapler line length (p= 0.944), greater curvature length (p= 0.097) were similar between the groups. Usage of hyoscine-N-butylbromide did not shorten the operation time (p= 0.383). Length of hospital stay (p= 0.494) was similar between groups. In Group 1, 30 patients had nausea and 10 patients had vomiting. In Group 2, 32 patients had nausea and nine patients had vomiting in postoperative period. Postoperative nausea rate (p= 0.689), vomiting rate (p= 0.800), nausea duration (p= 0,446), and vomit duration (p= 0.357) were similar between the groups (Table 2).

Leakage or postoperative bleeding was not observed in any of the patients. Mortality was not observed in any of patients.

In both groups, weight, BMI, TWL% and EWL% decreased significantly at third, sixth and 12th months of follow-up (Table 3). Yet, in comparison between the groups, weight, BMI, TWL%, and EWL% were statistically similar at all follow-ups (Table 4).

DISCUSSION

Our study is the first to analyze the effect of usage of hyoscine-N-butylbromide during LSG on the volume of the resected stomach, weight loss and complications in patients who underwent sleeve gastrectomy. In this study, the effect of intraoperative hyoscine-N-butylbromide injection on the resected stomach volume and weight loss up to 12 months postoperatively, and on BMI, TWL and EWL in patients who underwent laparoscopic sleeve gastrectomy was evaluated. No statistically significant difference was observed in terms of resected stomach volume and weight loss between the patients who received hyoscine-N-butylbromide and those who did not.

Table 2. Distribution and comparison of surgical-related features and complications among the groups

Parameters	Group 1	Group 2	p
Resected gastric volume (cc) (avg ± SD)	1430 ± 233	1363 ± 188	0.111†
Staple line lenght (cm) (avg ± SD)	27.7 ± 2.5	27.6 ± 3.0	0.944†
Greater curvature length (cm) (avg ± SD)	59.0 ± 4.3	57.7 ± 3.6	0.097†
Duration of surgery (min) (avg ± SD)	47.7 ± 7.3	49.5 ± 12.7	0.383†
Lenght of hospital stay (day) (avg ± SD)	3.6 ± 0.7	3.5 ± 0.6	0.494†
Intraoperative tachycardia (+), n (%)	41 (78.8)	1 (1.9)	<0.001††
Intraoperative hypotension (+), n (%)	8 (15.4)	0	0.006††
Postoperative nausea (+), n (%)	30 (57.7)	32 (61.5)	0.689†††
Postoperative nausea duration (day) (avg ± SD)	1.0 ± 0.2	1.1 ± 0.3	0.446†
Postoperative vomiting (+), n (%)	10 (19.2)	9 (17.3)	0.800†††
Postoperative vomiting duration (day) (avg ± SD)	1.1 ± 0.3	1.0 ± 0.1	0.357†

†Independent samples t-test.
††Fisher's exact test.
†††Chi-square test.

Table 3. Data of patients' weight, BMI, TWL% and EWL%

		Baseline	Third month	Sixth month	12th month	p†	p††	p†††
Group 1								
	Weight (kg) (avg ± SD)	122.8 ± 18.3	95.7 ± 16.2	85.0 ± 14.9	76.4 ± 13.9	<0.001	<0.001	<0.001
	BMI (kg/m^2) (avg± SD)	45.1 ± 5.5	35.3 ± 5.3	31.4 ± 5.0	27.0 ± 7.1	<0.001	<0.001	<0.001
	TWL% (avg ± SD)		22.0 ± 3.9	31.1 ± 5.0	38.0 ± 6.9		<0.001	<0.001
	EWL% (avg ± SD)		51.7 ± 13.1	71.8 ± 17.1	87.0 ± 18.0		<0.001	<0.001
Group 2								
	Weight (kg)	123.1 ± 17.4	96.4 ± 14.3	83.7 ± 1.7	76.1 ± 11.6	<0.001	<0.001	<0.001
	BMI (kg/m^2)	45.6 ± 5.0	35.7 ± 4.7	30.9 ± 3.8	28.1 ± 3.9	<0.001	<0.001	<0.001
	TWL% (avg ± SD)		21.5 ± 4.8	21.5 ± 4.8	37.9 ± 7.1		<0.001	<0.001
	EWL% (avg ± SD)		49.3 ± 13.8	49.3 ± 13.8	86.2 ± 17.0		<0.001	<0.001

*Paired samples t-test.
†Baseline third month.
††Third month-sixth month.
†††Sixth-12th month analysis.

Table 4. Comparison of weight, BMI, TWL% and EWL% between the groups

		Group I	Group II	p
Weight				
	Baseline	122.8 ± 18.3	123.1 ± 17.4	0.939
	Third month	95.7 ± 16.2	96.4 ± 14.3	0.807
	Sixth month	85.0 ± 14.9	83.7 ± 1.7	0.651
	12th month	76.4 ± 13.9	76.1±11.6	0.919
BMI				
	Baseline	45.1 ± 5.5	45.6 ± 5.0	0.629
	Third month	35.3 ± 5.3	35.7 ± 4.7	0.629
	Sixth month	31.4 ± 5.0	30.9 ± 3.8	0.582
	12th month	27.0 ± 7.1	28.1 ± 3.9	0.339
TWL%				
	Third month	22.0 ± 3.9	21.5 ± 4.8	0.543
	Sixth month	31.1 ± 5.0	31.8 ± 5.4	0.515
	12th month	38.0 ± 6.9	37.9 ± 7.1	0.960
EWL%				
	Third month	51.7 ± 13.1	49.3 ± 13.8	0.380
	Sixth month	71.8 ± 17.1	72.6 ± 14.4	0.818
	12th month	87.0 ± 18.0	86.2 ± 17.0	0.818

*Independent samples t-test.

The purpose of the use of hyoscine-N-butylbromide during LSG is to loosen the stomach, thus facilitating stomach manipulation, and the idea of removing a wider stomach volume with the relaxation of the stomach. Hyoscine-N-butylbromide is an anticholinergic drug with high affinity for parasympathetic muscarinic receptors on smooth muscle cells of the gastrointestinal tract. Intravenous form of hyoscine-N-butylbromide is preferred in gastroscopy and colonoscopy

because it reduces contraction and provides better visualization of the mucosa (9). It has been shown that the duration of colonic intubation time is shortened in patients premedicated with hyoscine-N-butylbromide for colonoscopy (10). However, in our study, it was observed that the use of hyoscine-N-butylbromide did not affect the duration of surgery. Therefore, contrary to the benefit seen in colonoscopy procedures, it is not possible to say that LSG is easier or faster in patients treated with hyoscine-N-butylbromide.

One can think that loosening the stomach will lead to wider stomach resection so patient will lose more weight. In order to analyze this, we compared the resected stomach volumes between the groups in our study. No statistical difference was detected between the groups for resected stomach volume. In order to detect efficacy of usage of hyoscine-N-butylbromide during LSG on resected stomach volume, it is better to measure ratio of resected stomach to whole stomach rather than measuring volume of resected stomach. However, it is technically difficult to measure the whole stomach volume before operation so we just measured the volume of the resected stomach that gives us information about the differences between the groups.

In our study, the usage of hyoscine-N-butylbromide had no effect on postoperative nausea and vomiting ratios. There is a study in the literature analyzing the effect of hyoscine-N-butylbromide usage for postoperative nausea and vomiting ratios during LSG. In that study, it has been detected that postoperative nausea and vomiting ratios did not change (7).

In our study, the usage of hyoscine-N-butylbromide did not have an effect on either shortening duration of the operation or increasing weight loss of the patient. In addition, no adverse effects were observed due to the use of hyoscine-N-butylbromide. Although hypotension and tachycardia occurred in some of patients, none of the patients had complaints in the early or long-term postoperative period. As a result, the usage of hyoscine-N-butylbromide during laparoscopic sleeve gastrectomy is safe.

CONCLUSION

Usage of hyoscine-N-butylbromide during LSG does not change the resected stomach volume, after one-year follow-up, the amount of weight loss of the patients was not higher than the patients in whom hyoscine-N-butylbromide was not used. The use of hyoscine-N-butylbromide during LSG is safe but does not have any effect on weight loss.

Ethics Committee Approval: This study was approved by Health Sciences University Antalya Training and Research Hospital Clinical Research Ethics Committee (Decision no: 18/13, Date: 08.08.2019).

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ORİJİNAL ÇALIŞMA-ÖZET
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Laparoskopik sleeve gastrektomi sırasında hiyosin-N-bütilbromit kullanımının etkisi

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ÖZET

Giriş ve Amaç: Hiyosin-N-bütilbromit, bazı cerrahlar tarafından laparoskopik sleeve gastrektomi (LSG) sırasında mideyi gevşeterek daha efektif bir ameliyat yapma amacıyla kullanılır. Fakat bununla ilgili literatürde kanıta dayalı bilgi sınırlıdır ve bu ilacın kilo kaybı üzerine etkisi belirsizdir. Bu çalışmanın amacı LSG ameliyatında intraoperatif hiyosin-N-bütilbromit kullanımının rezeke edilen mide, kilo kaybı ve komplikasyonlara etkisini araştırmaktır.

Gereç ve Yöntem: Çalışmaya morbid obezite sebebiyle LSG uygulanan hastalar dahil edildi. Elli iki intraoperatif hiyosin-N-bütilbromit uygulanan hasta Grup 1, 52 hiyosin-N-bütilbromit uygulanmayan hasta Grup 2 olarak kabul edildi. Hastaların yaş, cinsiyet, boy, kilo, vücut kütle endeksi (VKİ) bilgileri kayıt edildi. Ameliyat sonrası üçüncü, altıncı ve 12. ayda hastaların kilo, VKİ, toplam kilo kaybı yüzdesi (%TKK), fazla kilo kaybı yüzdesi (%FKK) kayıt edildi.

Bulgular: Rezeke edilen mide hacmi (p= 0,111), stapler hattı uzunluğu (p= 0,944), ameliyat zamanı (p= 0,383), hastanede yatış süresi (p= 0,494) ve ameliyat sonrası komplikasyonlar (p> 0,05) iki grupta da benzerdi. Grup 1'de intraoperatif taşikardi (p< 0,001) ve hipotansiyon (p= 0,006) daha sık görüldü. TKK ve FKK yüzdeleri tüm takip zamanlarında iki grup arasında benzer orandaydı. Stapler hattından sızıntı hiçbir hastada izlenmedi.

Sonuç: LSG uygulanan hastalarda intraoperatif hiyosin-N-bütilbromit kullanımı, kilo kaybı üzerine etkisizdir. Hiyosin-N-bütilbromit kullanılan hastalarda ameliyat sırasında hipotansiyon ve taşikardi görülse de, hiçbir hastada erken ve geç dönemde buna bağlı bir problem görülmemiştir. LSG uygulanan hastalarda intraoperatif hiyosin-N-bütilbromit kullanımı güvenlidir fakat kilo kaybı üzerine bir etkisi yoktur.

Anahtar Kelimeler: Morbid obezite, hiyosin-N-bütilbromit, laparoskopik sleeve gastrektomi, kilo kaybı

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Video game experience affects performance, cognitive load, and brain activity in laparoscopic surgery training

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ABSTRACT

Objective: Video games can be a valuable tool for surgery training. Individuals who interact or play video games tend to have a better visuospatial ability when compared to non-gamers. Numerous studies suggest that video game experience is associated with faster acquisition, greater sharpening, and longer retention of laparoscopic skills. Given the neurocognitive complexity of surgery skill, multimodal approaches are required to understand how video game playing enhances laparoscopy skill.

Material and Methods: Twenty-seven students with no laparoscopy experience and varying levels of video game experience performed standard laparoscopic training tasks. Their performance, subjective cognitive loading, and prefrontal cortical activity were recorded and analyzed. As a reference point to use in comparing the two novice groups, we also included data from 13 surgeons with varying levels of laparoscopy experience and no video game experience.

Results: Results indicated that video game experience was correlated with higher performance (R^2= 0.22, p< 0.01) and lower cognitive load (R^2= 0.21, p< 0.001), and the prefrontal cortical activation of students with gaming experience was relatively lower than those without gaming experience. In terms of these variables, gaming experience in novices tended to produce effects similar to those of laparoscopy experience in surgeons.

Conclusion: Our results suggest that along the dimensions of performance, cognitive load, and brain activity, the effects of video gaming experience on novice laparoscopy trainees are similar to those of real-world laparoscopy experience on surgeons. We believe that the neural underpinnings of surgery skill and its links with gaming experience need to be investigated further using wearable functional brain imaging.

Keywords: Mental workload, NASA-TLX, laparoscopy, surgical education

INTRODUCTION

Laparoscopic surgery offers substantial benefits to patients, including small incisions, rapid recovery, short hospital stays, and reduced post-operative pain. These translate into increased patient safety and significant economic benefits to healthcare systems. However, laparoscopic surgery is difficult and imposes additional demands on surgeons' perceptual and cognitive abilities. A laparoscopic surgeon operates with an indirect, narrow visual access and minimal tactile feedback. Such conditions require new skills with different learning curves and new training methods beyond the traditional master-apprentice format. It is critical for residents to reach expertise in a safe training environment with documented criteria. There is increasing interest in characterising not only the observed performance but also the cognitive effort and physiological and brain activity profiles of trainees with the ultimate aim of devising better training and assessment methodologies (1-3). While direct observation may indicate that a trainee performs adequately, it may fail to predict the long-term retention of skill or actual performance beyond the training environment, and trainees who perform identically may differ in subsequent real-world performance.

Video games can be a valuable tool for surgery training. Video gamers demonstrate superior eye-hand coordination, faster reaction times, superior spatial visualization skills, high capacity for visual attention and spatial distribution. Both laparoscopic surgery and computer games require eye-hand coordination, visuospatial cognitive ability, attention and perception skills. Individuals who interact or play video games tend to have a better visuospatial ability when compared to non-gamers (4,5).

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Numerous studies suggest that video game experience is associated with faster acquisition, greater sharpening, and longer retention of laparoscopic skills (6-11). Video game playing also appears to have value as warm-up preparatory exercise for surgery. These advantages accrue preferentially to laparoscopic or robotic rather than to traditional surgery (12). Yet, neither the direction of causality nor the mechanisms through which video game experience affects surgery skills are well understood (13). To our knowledge, studies to date investigating these links have exclusively utilized overt performance and behavioural measures. However, given the neurocognitive complexity of surgery skill, multimodal approaches are required.

We investigated the impact of video game playing experience on the performance, subjective task load, and prefrontal (PFC) brain activity of novice trainees and compared them with the corresponding variables in expert surgeons of varying levels of laparoscopy experience. In order to measure performance, we chiefly employed task completion times. For cognitive load, we used NASA-TLX, which has been widely used to measure subjective task load in surgery (14-16). It is a multidimensional ratings scale that provides an overall index of mental workload as well as the relative contributions of six subscales: mental, physical, and temporal task demands; and effort, frustration, and perceived performance. We also used a high-density, wireless functional near-infrared spectroscopy (fNIRS) device, which allowed us to discover hemoglobin concentration changes as a proxy for brain function.

MATERIAL and METHODS

Subjects

Data from thirteen surgeons with varying levels of laparoscopy experience and no video game experience, and 27 students with no laparoscopy experience and varying levels of video game experience were used in this study. The students were subdivided into 12 non-gamer students (with no experience in video gaming) and 15 gamer students (with experience in video gaming). Subject demographics are listed in Table 1. Research Ethics Board of Medipol University approved this study (10840098-604.01.01-E.33230), and it was performed in agreement with the Declaration of Helsinki. All participants signed informed consent and could withdraw from the study at any time. Participants had normal or corrected to-normal vision.

Experimental Design

Participants performed standard laparoscopic training tasks including peg transfer (Task 1) and string pass (Task 2) using a laparoscopic trainer box. Peg transfer task involved grasping, lifting and relocating rings from one rod to another using both laparoscopy graspers and was performed on a ring stack base. String pass involved grasping a piece of string and passing it through the holes using both graspers and was performed on a threading base. Data were recorded including time to completion, error rate, and overall work quality. Following the completion of each task, the subjects filled out the NASA task load index (NASA-TLX) questionnaire. At the beginning of the experiment, two 2 minute-long videos demonstrating the tasks were shown on a computer screen to the subject. After the video session, the 15 min training was repeated by each subject for gamers and non-gamers. Further details of the procedure were provided in a recent study where we reported an analysis of the brain activity of surgeons and a subset of the student participants without regard to game playing experience (3). All participants filled out a questionnaire detailing their video game experience including frequency, duration and category. The gamers were divided into three groups based on their replies to the questionnaire: only shooter game group (that played first-person shooter and/or third person shooter and/or role-playing games), only strategy game group (real-time strategy, turn based strategy and multiplayer battle arena games), shooter + strategy game group (both strategy and shooter games).

Imaging and Data Analysis

fNIRS data were collected using a high-density fNIRS device (NIRSIT, OBELAB, Korea) with 24-light sources at 780 and 850 nm and 32 detectors, with a sample rate of 8.138 Hz. The channels overlap with parts of the dorsolateral and ventrolateral prefrontal and the upper part of the orbitofrontal and medial PFC. Completion times of three laparoscopic tasks were recorded. The participants used NASA-TLX to evaluate six criteria: mental, physical, and temporal task demands; and effort, frustration, and perceived performance. Each criterion was scored from 1 to 20. A total mental workload score was obtained from the sum of the criteria scores. In order to analyze the fNIRS data, source-detector pair readings (with a separation of 3.35 cm) at two distinct wavelengths are first converted into hemoglobin concentration changes via the modified Beer-Lambert law, and the average of the task episode are calculated (3). In this paper, standard deviation of oxyhemoglobin concentration changes over an episode is denoted HbO and represents the extent of local cortical activation of a subject during the corresponding experimental episode.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 9 for Windows, GraphPad Software. When conducting regression analysis comparing two numerical variables, linear fit with analysis of variance was used. The descriptive results comparing two groups, such as completion time vs. game experience; completion time vs. laparoscopy experience; NASA total vs. game experience and NASA total vs. laparoscopy

experience, HbO changes contained non-paired data. In order to assess the statistical significance of the difference between the two groups of non-paired results, we used the non-parametric Kolmogorov test. We did not utilize null-hypotheses whose rejection would have required corrections for multiple comparisons or false discovery.

RESULTS

We present the behavioral and subjective metrics as well as the cortical activations of novice students (non-gamer and gamer) and expert surgeons, measured while performing laparoscopy training tasks. Forty participants (27 students, 13 surgeons, mean age 27.1 ± 4.8 years) were enrolled in the study. The participants' demographics, previous experience with laparoscopic surgery and gaming experience are shown in Table 1. Figure 1 compares task completion time, NASA-TLX score, and task-evoked oxyhemoglobin changes in the left prefrontal cortex of the three groups of participants. In Figure 2 and Figure 3, inter-group comparisons of performance and cognitive load that were summarized in Figure 1 are further elaborated within each group. Finally, the subject averaged distributions of cortical activation over the PFC of the participants are shown in Figure 4.

Figure 1A shows that the surgeons completed the task in a significantly shorter period of time when compared to gamers and non-gamers. A significant difference in completion time was noted between surgeons and non-gamers ($p< 0.01$) confirming the difference between the two groups. Although gamers appeared to be faster, the difference between gamers and non-gamers did not reach significance in Task 1. In Task 2 (not shown), there were similar trends although group differences were not statistically significant. Figure 1B shows that the surgeons had lower NASA-TLX workload scores when compared to gamers ($p< 0.01$) and non-gamers ($p< 0.04$) during Task 1. There was a similar trend for Task 2. Significant difference in task load was seen between gamers and non-gamers ($p< 0.02$). Figure 1C indicates that the left prefrontal cortical activation of surgeons in Task 1 was significantly lower than that of gamers ($p< 0.004$) and non-gamers ($p< 0.02$). As in

Table 1. Group demographics

Group	Number	Median gaming hours per week (range)	Gaming hours per week, mean ± SD	Median age (range)	Median LSE in number (range)	LSE in number mean ± SD
Non-gamer students	12	0 (0-0)	0 ± 0	26.5 (18-30)	0 (0-0)	0 ± 0
Gamer students	15	15 (1-40)	14 ± 12.7	19 (18-32)	0 (0-0)	0 ± 0
Laparoscopic surgeons	13	0 (0-0)	0 ± 0	35 (27-50)	75 (5-350)	116 ± 118.3

LSE: Laparoscopic surgery experience.

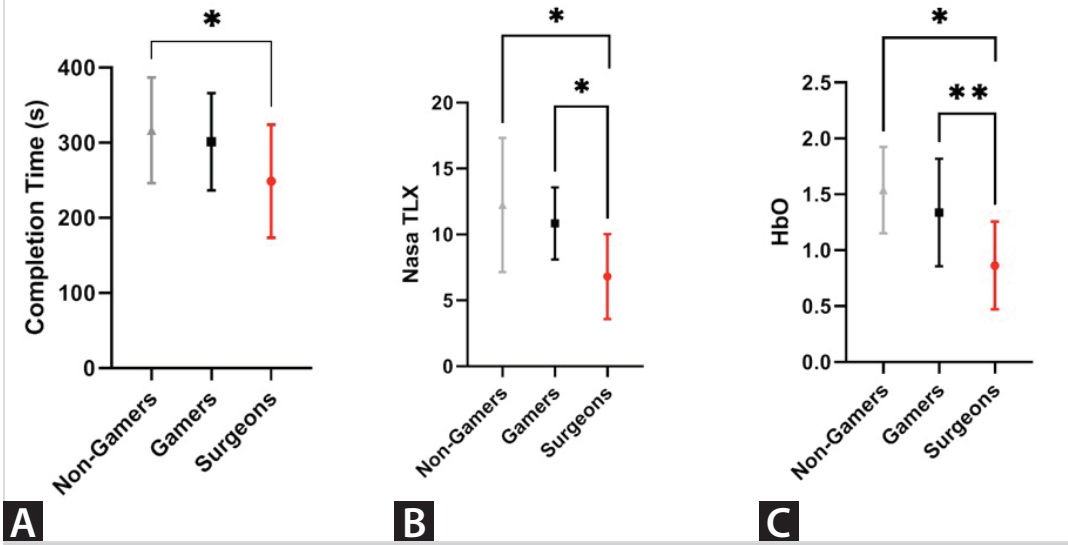

Figure 1. Performance, cognitive load, and prefrontal cortical activations of non-gamer students (gray triangle indicates the median), gamer students (black squares), and surgeons (red circles). The students have no laparoscopy experience and the surgeons have no gaming experience. Error bars indicate sample standard deviations (*$p< 0.05$; **$p< 0.01$). **(A)** Task completion time. **(B)** Mean NASA-TLX score. **(C)** Oxygenated hemoglobin oxyhemoglogin concentration changes in the left prefrontal cortex measured by fNIRS.

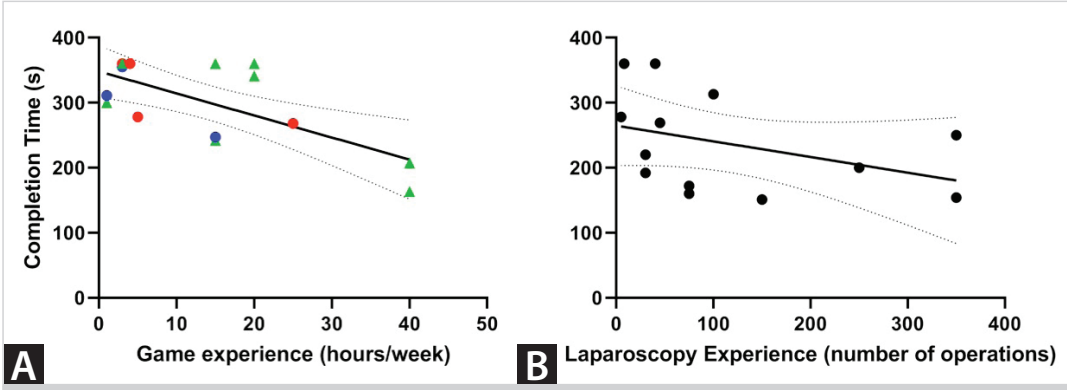

Figure 2. Performance and its dependence on the gaming experience of students and on laparoscopy experience of surgeons. **(A)** Completion time v gaming experience for students. Gamers are shown as only strategy game players (red circles), only shooter game players (green triangle), and both strategy and shooter game players (blue circles). Best fit line to the gamer data is shown (R^2= 0.22, p< 0.01). **(B)** Completion time v laparoscopy experience for surgeons. The solid black line indicate the linear best fit and the dotted lines indicate the 95% confidence interval (R^2= 0.15, p= 0.17).

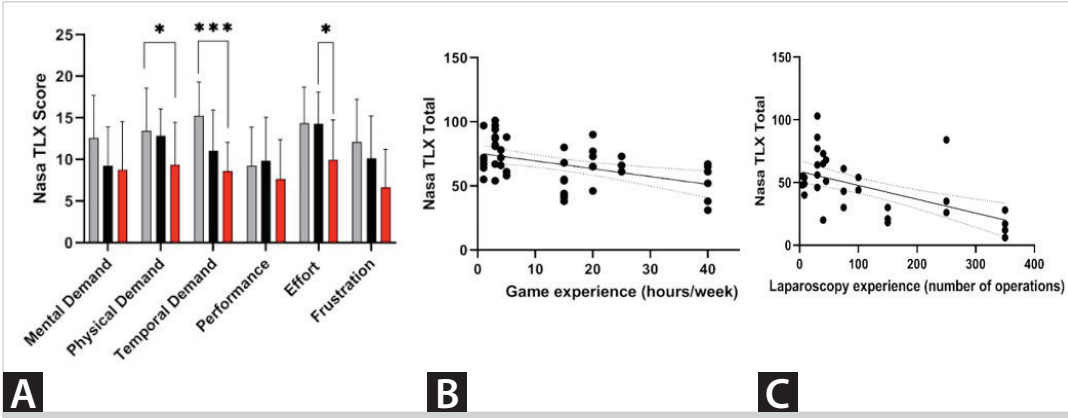

Figure 3. Cognitive load and its dependence on the gaming experience of students and on laparoscopy experience of surgeons (*p< 0.05; ***p< 0.001). **(A)** Individual dimensions of cognitive load shown by the NASA-TLX subscores for non-gamer students (gray), gamer students (black), and surgeons (red). Error bars indicate sample standard deviation. **(B)** Total NASA-TLX score v gaming experience for students (R^2= 0.21, p< 0.001). **(C)** Total NASA-TLX score v laparoscopy experience for surgeons (R^2= 0.36, p< 0.0001). In the scatter plots, the solid black lines indicate the linear best fit to the data points and the dotted lines indicate the 95% confidence interval.

the previous comparisons, Task 2 differences between the groups were similar.

Figure 2A: Through regression analysis, we found a significant association between completion time and gaming experience. The extent of game experience was negatively correlated with completion time (R^2= 0.22, p< 0.01). This figure only presents the results for Task 1. We observed a similarly significant association in Task 2 (R^2= 0.18, p< 0.02). This figure also shows gaming categories which gamers play (the colour coded presentation used to show gaming categories). No significant different was seen between only shooters player vs. only strategy players; only shooters player vs. strategy + shooters players; only strategy players vs. strategy + shooters player and game experience. Figure 2B suggests that more experienced surgeons tended to be faster; however, laparoscopy experience was not significantly correlated with completion time of Task 1 (R^2= 0.15 p= 0.17). Similar results were found in Task 2.

Figure 3A: We show the NASA-TLX subscales that indicate the distinct dimensions of cognitive load. Surgeon had lower scores of the six subscales of the NASA-TLX questionnaire compared to gamers and non-gamers for Task 1. A significant difference in physical (p< 0.02) and temporal demands (p< 0.0007) was noted between surgeons and non-gamers during Task 1. The effort of surgeons was significantly lower compared to gamers (p< 0.05) in completing the tasks. No significant difference was seen between the surgeons, gamers, and non-gamers in performance, frustration and mental demand. In Task 2, no significant difference was seen for pairs of groups in individual subscales. Figure 3B indicates that novice participants with higher game experience reported significantly

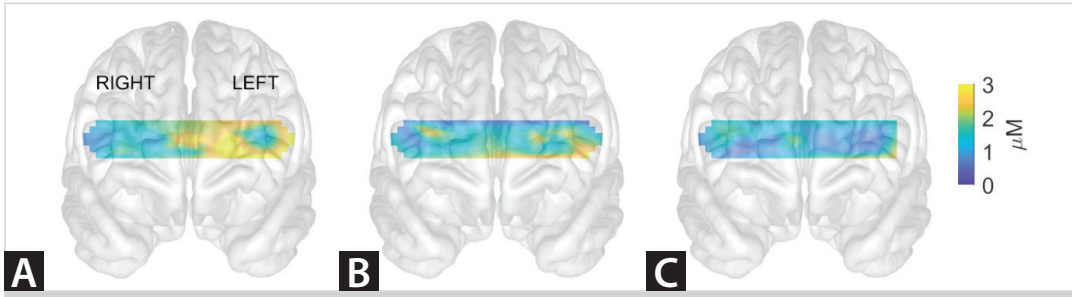

Figure 4. Frontal view of the task-evoked cortical activations measured by fNIRS. The subject averaged topographic distributions of oxyhemoglobin over the prefrontal cortex are shown. **(A)** Non-gamer students. **(B)** Gamer students. **(C)** Surgeons.

lower NASA-TLX workload scores (R^2= 0.21, p< 0.001). Similarly (Figure 3C) we found that more years of laparoscopy experience correlated with significantly lower NASA-TLX workload scores (R^2= 0.36, p< 0.0001). In Figure 3B and Figure 3C, we present NASA-TLX scores for both Task 1 and Task 2. With regard to the topographic distribution of brain activity in three groups, Figure 4 indicates that the left prefrontal cortical activation in non-gamers was substantially higher than that in gamers which, in turn, was somewhat higher than that and surgeons.

DISCUSSION

Our results suggest that some of the effects of video gaming experience on novice laparoscopy trainees are similar to those of real-world laparoscopy experience on surgeons. We showed this by using performance and subjective metrics as well as brain activity. To our knowledge, this is the first study that includes cognitive and brain metrics, and not just behavioural ones, in the investigation of video game experience in relation to laparoscopy skill, and directly compares these to those obtained from expert surgeons.

Taking novice students with no laparoscopy or gaming experience as a baseline, task completion time, self-reported cognitive load, and left PFC activation all were decreased with increasing gaming experience or with greater laparoscopy experience. Some of these inter-group differences were statistically significant and all followed a clear trend. Furthermore, within the group of gamer students, students with greater gaming experience completed the training task significantly faster. In previous studies, video game playing correlated with better surgical technique in medical school students and impacted the traditional skills of knot tying, incision making and suturing (9). Evidence shows that first-person shooter games preferentially enhance attentional control and executive function (5). However, whether a particular genre of video game plays a particular role has yet to be determined in a randomized controlled study. We did not see any difference in the effect of genres of game, likely due to insufficient data. In addition to the effect of game playing on performance, the number of laparoscopy procedures performed in the past may have enhanced surgeons' task performance.

There was a significant negative correlation between the cognitive load and gaming experience in students and laparoscopy experience in surgeons. This result is significant since NASA-TLX scores have been shown to independently predict future OR performance (14). In addition, higher cognitive load during surgery may lead to distraction, consideration of fewer options than those available, or inflexibility in choosing strategies. Low load on the other hand allows greater amounts of data to be processed, leading to appropriate responses to unexpected events (17).

PFC activation provided that clearest inter-group discrimination, particularly with regard to differences between non-gamer and gamer novices. Brain activity in the left PFC, in particular, is reduced as a result of greater gaming or laparoscopy experience. The reduction in activity is consistent with the known dominance of the left hemisphere in motor action regardless of handedness (18), interference processing (19,20) and overall bi-manual coordination (21,22). By contrast, PFC lateralization is reduced in PTSD and other disorders (23). Previous fNIRS studies of laparoscopy skill have indicated that greater skill is accompanied by behavioral automation, which tends to reduce the engagement of executive areas in the PFC (24).

Our study had several limitations. The number of participants was low. A greater number of participants would allow us to rule out or show the significance of some of the trends observed. It may also reveal the differential effects of the genre of video game. Secondly, student participants did not all play the same set of games. More controlled gaming experience may help increase the accuracy and validity of the results. Our results show only correlation and not causation. Underlying factor (such as higher dexterity or motivation) could be causing both higher gaming experience as well as better laparoscopy training performance. This shortcoming may be circumvented by an interventional study that manipulates gaming experience systematically. Lastly, the quantification of video game

experience may have been subject to inaccuracy since it was self-reported. Both in gaming and laparoscopy experience some self-reporting inaccuracy is evident from the fact that there appears to be a bias to report in multiples of fixed values.

CONCLUSION

Our results indicate that multimodal investigations may shed light on how video games affect not only performance in surgery training, but cognitive load and brain activity, as well. The understanding of neural underpinnings of surgery skill and its links with gaming experience will likely increase in the near future as wearable functional brain imaging becomes more widely available.

Ethics Committee Approval: This study was approved by İstanbul Medipol University Non-Invasive Clinical Research Ethics Committee (Decision no: 577, Date: 17.07.2019).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - HOK, AO; Design - HOK, AO; Supervision - HOK; Funding - HOK; Data Collection and/or Processing - HOK; Analysis and/or Interpretation - HOK, AO; Literature Review - HOK; Writer - HOK, AO; Critical Review - AO.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 95-101

Video oyun deneyimi, laparoskopik cerrahi eğitiminde performansı, bilişsel yükü ve beyin aktivitesine etkisinin incelenmesi

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ÖZET

Giriş ve Amaç: Video oyunları cerrahi eğitim için değerli bir araç olabilir. Video oyunları oynayan veya etkileşime giren bireyler, oyun oynamayanlara kıyasla daha iyi görsel-uzaysal yeteneğe sahip olma eğilimindedir. Çok sayıda araştırma, video oyunu deneyiminin laparoskopik becerileri daha hızlı edinme, daha fazla keskinleştirme ve daha uzun süre elde tutmayla ilişkili olduğunu öne sürmektedir. Cerrahi becerisinin nörobilişsel karmaşıklığı göz önüne alındığında, video oyunu oynamanın laparoskopi becerisini nasıl geliştirdiğini anlamak için çok (multimodal) yaklaşımlar gereklidir.

Gereç ve Yöntem: Laparoskopi deneyimi olmayan ve farklı düzeylerde video oyunu deneyimi olan yirmi yedi öğrenci standart laparoskopik eğitim görevlerini yerine getirdi. Performansları, öznel bilişsel yükleri ve prefrontal kortikal aktiviteleri kaydedildi ve analiz edildi. İki acemi grubu karşılaştırırken kullanılacak bir referans noktası olarak, aynı zamanda 13 cerrahın verileri de çalışmaya dahil edildi.

Bulgular: Sonuçlar, video oyunu deneyiminin daha yüksek performans (R^2= 0,22, p< 0,01) ve daha düşük bilişsel yük (R^2= 0,21, p< 0,001) ile ilişkili olduğunu ve oyun deneyimi olan öğrencilerin prefrontal kortikal aktivasyonunun nispeten daha düşük olduğunu gösterdi. Bu değişkenler açısından acemilerdeki oyun deneyimi, cerrahlardaki laparoskopi deneyimine benzer etkiler üretme eğilimindeydi.

Sonuç: Sonuçlarımız, performans, bilişsel yük ve beyin aktivitesi boyutları boyunca, video oyunu deneyiminin acemi laparoskopi kursiyerleri üzerindeki etkilerinin, gerçek dünyadaki laparoskopi deneyiminin cerrahlar üzerindeki etkilerine benzer olduğunu göstermektedir. Ameliyat becerisinin sinirsel temellerinin ve oyun deneyimiyle olan bağlantılarının, giyilebilir fonksiyonel beyin görüntüleme kullanılarak daha fazla araştırılması gerektiğine inanıyoruz.

Anahtar Kelimeler: Zihinsel iş yükü, NASA-TLX, laparoskopi cerrahi eğitim

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ORIGINAL ARTICLE
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A retrospective study of diagnosis and management of gallbladder perforation: 10-year experience from a tertiary health care centre

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ABSTRACT

Objective: The aim of this study was to perform retrospective analysis of data collected from patients of gallbladder perforations for diagnosis, management and outcome.

Material and Methods: A retrospective analysis of data was carried out for 40 patients of gallbladder perforations from the hospital record of patients who were diagnosed preoperatively and intraoperatively as a case of gallbladder perforation over a period of 10 years and were managed in our surgery unit of a tertiary health care centre. Patients were included irrespective of sex except cases of trauma and patients of the paediatric age group.

Results: Among 40 patients, 26 were females and 14 were males. As per Anderson modification of Neimeier classification, 13 (32.5%) had type 1, 23 (57.5%) had type 2, and four (10%) patients had type 3 perforations and none of the patients had type 4 perforation. Twenty-three patients (57.5%) were found to have fundal perforation, followed by body in 11 patients (27.5%), three (7.5%) in Hartman's pouch while in three patients (7.5%), there were multiple perforations. All patients of type 1 Neimer classification were diagnosed clinically as cases of biliary peritonitis, whereas most cases of type 2 Neimer classification were diagnosed preoperatively by CECT abdomen 12/23 patients (52%) and ultrasound abdomen 10/23 (43.47%). All patients underwent surgery, and there were three mortalities.

Conclusion: In our study, there was female predominance in patients having gallbladder perforation. Of the patients, 52.5% were diabetic and mean age was 55.9 years. CECT abdomen was the most useful modality for diagnosis of type 2 gallbladder perforations. Timely surgical intervention is mandatory for a better outcome of these cases.

Keywords: Acute cholecystitis, gallbladder perforation, biliary peritonitis, operative intervention

INTRODUCTION

Gallbladder perforation is one of the least but potentially fatal complication of acute cholecystitis, with a reported mortality rate of 12-42% (1-3). A low degree of suspicion coupled with a wide range of clinical symptoms makes preoperative diagnosis of gallbladder perforation difficult, more so in our setup with a limited access to radiological investigations such as CECT abdomen or MRCP preoperative, diagnosis is a challenge (4,5). As a result, most of such cases are either managed on the lines of acute cholecystitis or diagnosed on the operating table. This delay in diagnosis increases morbidity and mortality in such patients. Gallbladder perforation is almost always a sequelae of acute cholecystitis, mostly calcular, except for cases of injuries (trauma/iatrogenic) and infections (6). Infections, malignancy, trauma, drugs (e.g. corticosteroids), diabetes mellitus and atherosclerotic heart disease are known predisposing factors for gallbladder perforation (7). A gallbladder perforation may present as free biliary peritonitis or as chronic perforation with an internal fistula. However, the most common presentation is perforation with a localised collection, forming a peri-cholecystic abscess. Niemeier has classified gallbladder perforations into three types; type 1: free perforation, type 2: perforation with localised abscess, and type 3: chronic perforation with cholecysto-enteric fistula (8). Type 4 as cholecysto-biliary or external fistula has been added to the above types (9,10).

We herein present our experience of 40 cases of gallbladder perforation that presented to our hospital from January 2012 to July 2022.

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MATERIAL and METHODS

A retrospective analysis of data was carried out from the hospital record of patients diagnosed preoperatively and intraoperatively as a case of gallbladder perforation and managed in our surgery unit of a tertiary health care centre. Ethical approval for the study was obtained from the institutional ethics committee of the hospital to which the researchers are affiliated (IEC no: IEC/GMC/Cat C/2021/448). Informed consent was obtained from each participant prior to participation in the study. Forty patients were included in this study, who were diagnosed as a case of gallbladder perforation between January 2012 to July 2022. We used Anderson modification of Neimeier classification for gallbladder perforation cases in this study (8).

According to this classification, there are three main clinical subtypes. A fourth type has been suggested by Anderson et al (9).

- Type 1: Acute free perforation
- Type 2: Subacute pericholecystic abscess
- Type 3: Chronic cholecystoenteric fistulation
- Type 4: Cholecystobiliary fistula formation

All patients were included irrespective of sex except cases of trauma and patients belonging to the paediatric age group. History, examination and investigations including CBC, KFT, serum electrolytes, blood sugar, LFT, coagulation profile, X-ray abdomen and chest and USG abdomen were reviewed for all patients. CECT abdomen and MRCP were also reviewed if available during the preoperative period. Intraoperative findings were noted including type of perforation and amount of peritoneal contamination. Postoperative course in hospital including complications and histopathological examination reports were reviewed.

RESULTS

Among forty patients included in this study, 26 were females and 14 were males. Most of these patients were above 50 years of age. As per Anderson modification of Neimeier classification, 23 (57.5%) had type 2 (as shown in Figure 1), 13 (32.5%) had type 1 (as shown in Figure 2) and four patients (10%) had type 3 perforations, and none of the patients had type 4 perforation. Twenty-three patients (57.5%) were found to have fundal perforation, followed by body in 11 patients (27.5%), three (7.5%) in Hartman's pouch while in three patients (7.5%), there were multiple perforations. Associated comorbidities were present in 21 patients (52.5%) as shown in Table 1. Thirteen patients had only diabetes mellitus, six patients had diabetes mellitus and hypertension and two patients had diabetes mellitus, hypertension and CRF. Out of 40 patients who had gallbladder perforation, 21 patients were diabetic. Patients of type 1 gallbladder perforation presented with features of generalised peritonitis and were diagnosed intraoperatively as

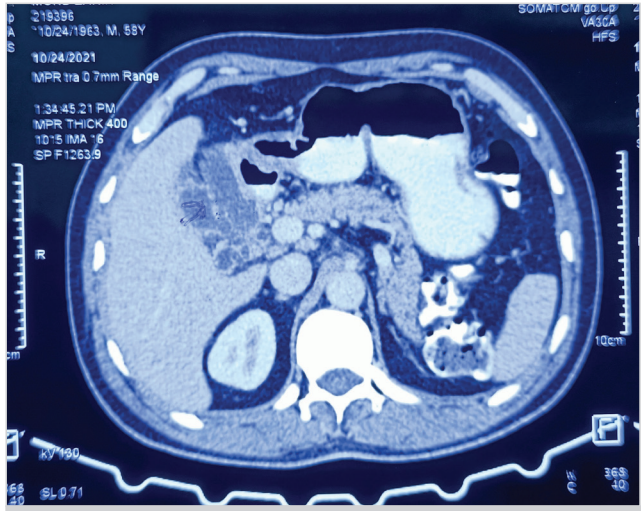

Figure 1. Showing type 2 gallbladder perforation on CECT abdomen.

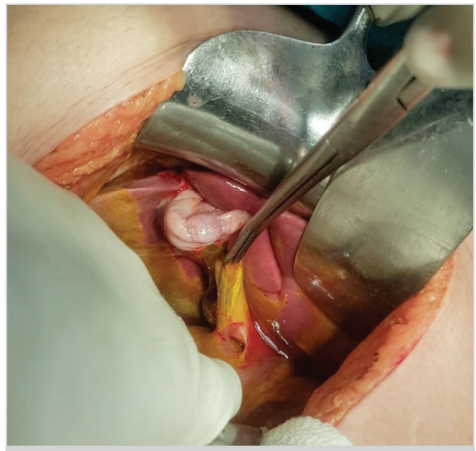

Figure 2. Showing gallbladder perforation in the Hartman pouch.

a case of gallbladder perforation, and type 2 and type 3 gallbladder perforations presented with pain in the right hypochondrium, nausea and vomiting mimicking acute cholecystitis. Type 2 perforations were diagnosed by CECT abdomen in 12 patients and 10 on USG abdomen in patients having non-settling pain, one patient on MRI with MRCP and one patient during surgery, and type 3 perforations were diagnosed during laparoscopic cholecystectomy for non-responding acute cholecystitis in two patients and by MRI and MRCP in two patients. In the present study, 16 patients were diagnosed intraoperatively (including 13 patients of type 1 on laparotomy, two patients of type 3 and one patient of type 2 during laparoscopic cholecystectomy). Thirteen patients were diagnosed by CECT abdomen, 10 cases by USG abdomen and three by MRI and MRCP. All patients of type 1 perforation underwent emergency laparotomy in view of generalised peritonitis and lack of laparoscopic set in the emergency department of our hospital. A total of eight patients (25%) with

type 1 perforation underwent exploratory laparotomy, open cholecystectomy, peritoneal lavage and peritoneal drainage, one patient (3.12%) underwent exploratory laparotomy, open subtotal cholecystectomy, peritoneal lavage and peritoneal drainage and one patient (3.12%) underwent exploratory laparotomy, tube cholecystostomy, peritoneal lavage and peritoneal drainage. Among the 23 patients of type 2 perforation, 17 (73.91%) underwent laparoscopic cholecystectomy and peritoneal lavage, three (13.04%) underwent laparoscopic converted to open cholecystectomy and peritoneal drainage and 3 (13.04%) underwent open cholecystectomy with drainage. Two patients (50%) of type 3 perforation underwent open cholecystectomy and two patients (50%) of type 3 perforation needed laparoscopic to open conversion with duodenal/gastric fistula repair by pedicle omental patch. Cholecysto-duodenal fistula was present in three patients and cholecysto-gastric fistula in one patient. In the present study, a total of three patients (7.5%) died during the course of treatment, two patients in type 1 perforation and one in type 3 perforation. Mean hospital stay was 9.1 days in type 1, 4.4 days in type 2, and 8.2 days in type 3 gallbladder perforation. Histopathological examination showed acute cholecystitis in 16 patients, chronic cholecystitis in 23 patients, and mucinous adenocarcinoma of the gallbladder in one patient, which was investigated during post-operative period and diagnosed as a case of metastatic disease as shown in Table 2.

Table 1. Showing demographic and clinical features along with the type and site of gallbladder perforation

Parameter	Type 1	Type 2	Type 3	Type 4	Miscellaneous
Total no. of cases (n= 40)	13	23	4	-	-
Mean age	56.8	58.4	52.6	-	-
Male:Female ratio	3:6	1:1.5	3:1	-	-
Associated comorbidities	7	11	3	-	-
Site of perforation					
Fundus	13	10	-	-	
Body	5	5	1	-	
Hartmann's pouch	-	-	3	-	
Multiple perforations	-	-	-	-	3

Table 2. Showing modes of diagnosis, operation performed, mortality and histopathology of patients with gallbladder perforation

Neimeier classification	Type 1	Type 2	Type 3
Mode of diagnosis			
USG abdomen	-	10	-
CECT abdomen	-	12	-
MRI and MRCP	-	1	2
Intraoperatively	13	1	2
Surgery performed			
Laparascopic cholecystectomy + PL	-	17	-
Laparascopic converted to open cholecystectomy + PD	-	3	-
Open cholecystectomy + PL + PD	10	3	-
EL + tube cholecystostomy + PL + PD	1	-	-
EL + sub-total cholecystectomy + PL + PD	2	-	-
Open cholecystectomy + repair of duodenal fistula by pedicle omental patch	-	-	3
Open cholecystectomy + repair of gastric fistula by pedicle omental patch	-	-	1
Mortality	2	-	1
Histopathology			
Acute cholecystitis	9	10	-
Chronic cholecystitis	3	13	4
Malignancy	1	-	-

DISCUSSION

Gallbladder perforation is a fatal complication of acute cholecystitis (2), with a reported mortality rate of 12-42% (3). In the present study, there was a female preponderance, with a female to male ratio of 1.8:1, with an average age of 55.9 years at presentation. This is in accordance with the studies performed by Harland et al., Simmons et al., Menakuru et al., Derici et al., Stefanidis et al. and Ergul et al. showing elderly patients being more susceptible to gallbladder perforation especially in the 5th to 6th decade of life (3,11-14). Nevertheless, most studies show a male preponderance as compared to our study (4,12,15). Twenty-one patients (65.62%) in this study had one or more comorbidities present. Wang et al. and Alvi et al. have also postulated that comorbidities like infections, history of steroid intake, diabetes, hypertension and malignancy may be independent risk factors for gallbladder perforation, even in the absence of gallstone disease (16-17). The most common location of gallbladder perforation in our study was the fundus (n= 23, 57.5%), followed by the body (n= 11, 27.5%) and Hartmann's pouch (n= 3, 7.5%). Clinical presentation of gallbladder perforation varies and depends primarily on the location of the perforation. The patient may exhibit features of generalised peritonitis when there is free perforation or may show vague abdominal symptoms when the perforation becomes contained. A localised perforation often mimics the symptoms of acute cholecystitis, therefore making the diagnosis even more difficult (18). Gore et al. have suggested that perforation and abscess formation should be suspected in patients with acute cholecystitis who suddenly become toxic with rapidly deteriorating clinical condition (19). Chen et al. have also suggested that a sudden decrease in pain due to reduction in the intracholecystic pressure might indicate gallbladder perforation (20). The most common method of diagnosis was CECT abdomen diagnosing a total of 12 cases (30%). Abdominal ultrasonography was useful in diagnosing 10 cases (25%). Similar results have been seen by Sood et al. and Kim et al (18,21). However, they have found both modalities equally effective in demonstrating pericholecystic fluid collections, gallbladder wall thickening and cholelithiasis. It is therefore advisable to perform a sonography followed by CECT in a suspected case of gall bladder perforation. MRCP is better at delineating the biliary tree and useful adjunct in diagnosing type 3 perforations (22). In the present study, a total of three (7.5%) patients died during the course of treatment, of whom two patients had type 1 gallbladder perforation and one had type 3 perforation. Most of the deaths occurred due to sepsis. Histopathologic analysis revealed acute cholecystitis in 19 patients, chronic cholecystitis in 20 patients, and mucinous adenocarcinoma of the gallbladder in one patient.

CONCLUSION

In our study there was female predominance in patients having gallbladder perforation. Of the patients, 52.5% were diabetic, and mean age was 55.9 years. CECT abdomen was the most useful modality for the diagnosis of type 2 gallbladder perforations. Timely surgical intervention is a must for better outcome of these cases.

Ethics Committee Approval: This study was approved by Government Medical College, Jammu Institutional Ethics Committee (Decision no: IEC/GMC/Cat C/2021/448, Date: 13.02.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - JI; Design - HW; Supervision - SP; Data Collection and/or Processing - SP; Analysis and/or Interpretation - JI; Literature Review - HW; Writer - JI; Critical Review - SP.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Safra kesesi perforasyonunun tanı ve yönetimine ilişkin retrospektif bir çalışma: Üçüncü basamak bir sağlık merkezinden 10 yıllık deneyim

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, safra kesesi perforasyonu hastalarından tanı, tedavi ve sonuç için toplanan verilerin retrospektif analizini yapmaktı.

Gereç ve Yöntem: Ameliyat öncesi ve ameliyat sırasında 10 yıllık bir süre boyunca safra kesesi perforasyonu tanısı alan ve üçüncü basamak bir sağlık merkezinin cerrahi ünitesinde tedavi edilen hastaların hastane kayıtlarından safra kesesi perforasyonu olan 40 hastanın verileri retrospektif olarak incelendi. Travma vakaları ve pediyatrik yaş grubu hastalar dışında cinsiyete bakılmaksızın hastalar dahil edildi.

Bulgular: Kırk hastanın 26'sı kadın, 14'ü erkekti. Neimeier sınıflandırmasının Anderson modifikasyonuna göre 13 (%32,5) hastada tip 1, 23 (%57,5) hastada tip 2 ve dört (%10) hastada tip 3 perforasyon vardı ve hiçbir hastada tip 4 perforasyon yoktu. Yirmi üç hastada (%57,5) fundus perforasyonu saptandı, bunu 11 hastada (%27,5) gövde, Hartmann poşunda üç (%7,5) ve üç (%7,5) hastada çoklu perforasyon saptanması izledi. Tip 1 Neimer sınıflandırmasındaki tüm hastalara klinik olarak biliyer peritonit vakaları olarak teşhis edilirken, tip 2 Neimer sınıflandırmasındaki çoğu vakaya preoperatif olarak CECT abdomen 12/23 hastası (%52) ve ultrason abdomen 10/23 (%43,47) tarafından teşhis edildi. Tüm hastalar opere edildi ve üç ölüm meydana geldi.

Sonuç: Çalışmamızda safra kesesi perforasyonu olan hastalarda kadın ağırlığı vardı. Hastaların %52,5'i diyabetikti ve yaş ortalaması 55,9'du. CECT batın, tip 2 safra kesesi perforasyonlarının tanısında en yararlı modaliteydi. Bu vakaların daha iyi sonuçlanması için zamanında cerrahi müdahale zorunludur.

Anahtar Kelimeler: Akut kolesistit, safra kesesi perforasyonu, biliyer peritonit, operatif müdahale

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ORIGINAL ARTICLE
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Circulating tumor DNA for monitoring colorectal cancer: A prospective observational study to assess the presence of methylated SEPT9 and VIM promoter genes and its role as a biomarker in colorectal cancer management

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ABSTRACT

Objective: Methylation status of Septin9 (SEPT9) and vimentin (VIM) genes in circulating tumor DNA of colorectal cancer (CRC) patients is a promising bio-marker for the early detection of CRC. The aim of the present study was to identify the methylation status in promoter regions of the SEPT9 and VIM genes in a cohort of Indian patients with biopsy proven colorectal cancer.

Material and Methods: Forty-five consecutive patients of colorectal cancer were recruited. 10 mL venous samples were collected from each patient and processed for isolation of cell-free DNA, bisulfite conversion of cell-free DNA, polymerase chain reaction (PCR) amplification and detection of SEPT9 and VIM genes.

Results: Partial methylation in vimentin was present in 42.22% of the patients and 57.78% showed no methylation and none of the tumors had complete methylation. Only three (6.66%) patients showed complete methylation patterns in SEPT9 and the remaining 42 (93.33%) tumors showed partial methylation. Considering the two genes together, only three (6.66%) out of 45 showed complete methylation. The association of methylation patterns in both genes (complete, partial, and no methylation) with sex, age, T stage, N stage, M stage, CEA, histology, and location (right or left colon) were explored and none of these parameters were statistically significant.

Conclusion: In our study, only 6.66% CRC patients showed hypermethylation and there was no association of methylation patterns in the both genes (complete, partial, and no methylation) with any of the parameters like age, sex, TNM stage, CEA, and histology.

Keywords: Colorectal neoplasms, cell-free nucleic acids, methylation

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide with 90 per 100.000 people affected by CRC. CRC accounts for 10% of all tumor types worldwide. Five-year survival for colon cancer in different geographical settings range from 28.5% to 57% in males and from 30.9% to 60% in females (1).

Several non-invasive tests like fecal occult blood test (FOBT), fecal immunochemical test (FIT) and carcinoembryonic antigen (CEA) are available for the early diagnosis of CRC but these tests suffer from poor sensitivity and specificity which limits their clinical application (2). The standard screening method of colonoscopy is an invasive test which requires bowel preparation and is uncomfortable leading to poor compliance among patients. Therefore, better tests are required to improve patient compliance (3).

DNA methylation of certain genes is related to the development of colorectal cancer (4). Aberrant methylation of the genome can lead to the silencing of certain tumor suppressor genes which can result in malignant transformation (5). Recently, SEPT9 gene methylation has been recognized as a specific biomarker for colorectal cancer which may be used to screen high risk populations (3). Vimentin is a member of the intermediate filament family and is responsible for maintaining cell shape and integrity of cytoplasm and stabilizing cytoskeletal interactions (6). Human vimentin gene is located on the short arm of chromosome 10 (10p13) and aberrant methylation of vimentin gene may lead to unexpressed vimentin protein which may contribute to CRC pathogenesis (7). Li et al. have shown in their meta-

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analysis of seven studies with 467 CRC patients that vimentin promoter methylation in cancer tissues was significantly higher than in normal or benign tissues (6).

Liquid biopsy based methylated ctDNA for SEPT9 and vimentin genes can be used as a biomarker for detection of cancer (8). Liquid biopsy screening tests are blood based screening tests for early detection of cancer which examine peripheral blood for circulating tumor DNA (ctDNA) which can be present in the earliest stages of tumorigenesis (8). Malignant cells release ctDNA fragments into the bloodstream during apoptosis and represent tumor DNA of cancer cells. These ctDNA are methylated at 5'-cytosine-phosphate-guanine-3' sites (9).

There are no data in the published literature from India on the methylation status of both SEPT9 and vimentin genes in tumors with colorectal cancer. Therefore, this study was taken up to understand the methylation status of these genes in cell-free DNA isolated from the plasma of patients with colorectal cancer in Indian patients.

MATERIAL and METHODS

A prospective observational study was conducted at a tertiary referral center in India from December 2018 to February 2020. The study was approved by the institute ethics committee (Ref. No. AIG/IEC32/10.2018-09). The study was HIPAA compliant and adhered to the tenets of Declaration of Helsinki. A written informed consent was obtained from each patient prior to enrolment.

Patients over 18 years with an established colorectal cancer diagnosis, post neoadjuvant chemo/radiotherapy colorectal cancer patients and metastatic and recurrent colorectal cancer were included in the study. Patients had to be willing to provide oral and written informed consent.

Patients with other associated cancers and patients not willing to provide written informed consent were excluded from the study. During the study period, 75 cases of CRC were diagnosed, 45 patients were included after applying inclusion and exclusion criteria.

The aim of the study was to study the presence of methylated circulating tumor DNA in genes SEPT9 and VIM in colorectal cancer patients in the Indian population and their association with histopathological characteristics, tumor location (left or right) and CEA levels.

Biochemical Analysis

Plasma from 10 mL venous blood was collected in EDTA Vacuette tubes. CEA levels were also measured in all patients.

Isolation of Cell-Free DNA

The samples were equilibrated to room temperature before processing. One mL of serum was taken in an Eppendorf tube to which 100 µL of proteinase K was added. The solution was mixed thoroughly by vortexing. To this solution, 800 µL of Buffer ACL was added and pulse vortexing was carried out for 30 seconds to ensure complete mixing of the sample. This lysate mix was then incubated at 60°C for 30 minutes. After the completion of incubation time, 1.8 mL of Buffer ACB was added to the lysate mix and was mixed thoroughly for 30 seconds.

The sample was incubated on ice for five minutes. About 700 µL of the mixture was loaded onto the QIA AMP Mini column and centrifuged at 10.000 rpm for one minute. This step was repeated until all of the solution had passed through the column. Next, to the column 600 µL of Buffer ACW1 was added and centrifuged. The flow-through was discarded. Later, 700 µL of Buffer ACW2 was added and centrifuged. After centrifugation, a new collection vial was placed and the column was centrifuged at full speed to remove any residual ethanol. The column was then incubated at 56°C to ensure complete drying of the membrane. The QIA AMP mini column was then placed into a new 1.5 mL Eppendorf tube and 100 µL of Buffer AVE was added to the center of the membrane. The column was finally centrifuged at 20.000 g for one minute to elute the cell-free DNA. The sample was stored at -20°C until further use.

Bisulfite Conversion of the Cell-Free DNA

A total concentration of 500 ng of cell-free DNA was taken into a 1.5 µL Eppendorf tube and made up to 20 µL using RNase/DNase free water. To this tube, 130 µL of CT conversion reagent was added and mixed thoroughly and centrifuged briefly to ensure complete mixing of the sample. The sample was then incubated in a thermal cycler with the conditions, 98°C for eight minutes, 64°C for 3.5 hours, and 4°C until further processing. After the completion of incubation, the samples were taken and added to the Zymo Spin IC Column containing 600 µL of M-Binding Buffer. The solution is mixed by inverting the column a few times and centrifuged at 10.000 g for 30 seconds. The flow-through was discarded. To the column, 100 µL of M-Wash Buffer was added and centrifuged at 10.000 g for 30 seconds. Later 200 µL of M-Desulphonation Buffer was added and the column was incubated at room temperature for 20 minutes.

After the completion of the incubation time, the sample was centrifuged and flow-through discarded. Again, 200 µL of M-Wash Buffer was added and centrifuged. This step was repeated twice. The column was placed into a fresh Eppendorf tube and 10 µL of M-Elution Buffer was added, centrifuged at 10.000 g for one minute to elute the DNA. The eluted DNA was stored at -20°C until further use.

PCR Amplification

The isolated cfDNA was evaluated for quantity and quality using the Nanodrop 2000 spectrophotometer. Primers specific

to bisulfite converted DNA were designed for each of the two genes namely SEPT9 and vimentin. The primers used for amplification of vimentin for bisulfite converted DNA was forward 5`-GGGTGAGTTTAGTTTAGATTATTAT3`, reverse 5`-AAAAAAAATCCCCTCCCACTAC3`. The primers used for amplification of SEPT9 for bisulfite converted DNA were, forward 5`-TTAATTAGTTTTATTTGGGGTGAGG and reverse 5`-AAATATAAAAAACTTATATACATAAAAAC3`.

Each PCR was carried out using 2.5 U of Epi Taq polymerase (Takara Bio), 10 pm/µL of both forward and reverse primer, 10 mM of dNTP's, 25 mM of MgCl2 and 5x Taq Buffer in a total of 25 µL. The sample was incubated in a thermal cycler with the PCR conditions: initial denaturation at 95°C for three minutes, denaturation at 95°C for 30 seconds, annealing temperature for vimentin gene 59.9°C and SEPT9 gene was 55.4°C, followed by an extension at 72°C for 30 seconds and a final extension at 72°C for five minutes. The amplicons were checked for their size by loading them on agarose gel. The amplicon sizes of vimentin and SEPT9 genes were 209 bp and 198 bp respectively.

DNA Sequencing

PCR Purification Procedure

Eighteen (18) µL of the amplified PCR product was taken into a 96-well sample plate and 20 µL of AMPure Magnetic beads (Beckman) were added. The PCR product and AMPurebeads were mixed until the color of the solution appeared homogenous. The mix was incubated for five min at room temperature. The sample plate was placed on a 96-well magnetic plate and incubated for two minutes to separate the beads from the solution. The clear solution from the sample plate was discarded. 200 µL of 70% ethanol was added to each well and incubated for 30 seconds. Ethanol was removed carefully without disturbing the magnetic beads. The step was repeated by adding 200 µL of 70% ethanol to each well and incubated for 30 seconds. Ethanol was removed carefully without disturbing the magnetic beads. The sample plate was removed from the magnetic plate and 40 µL of elution buffer was added to the wells. The samples were incubated for five min at room temperature. The reaction plate was then placed on the magnetic plate and incubated for two minutes to separate beads from the elution buffer. The sample was transferred to a new 0.2 mL PCR tube and stored at -20°C until further use.

Dilution of the Amplified PCR Product

The sample was diluted to a given concentration based on the product size of the gene of interest. A 300 bp product was diluted to a concentration of 33 ng/µL using the elution buffer. After dilution, the dye termination cycle sequencing was carried out for the samples.

Dye Termination Cycle Sequencing

PCR mix: About 0.5 µL of primer, 2 µL of DTCs (quick start master mix, Beckman), water 0.1-2.5 µL and DNA template 0.1- 2.5 µL were added to make a total volume of 5 µL. The sample was set up for the dye termination cycle sequencing step in the thermal cycler with the following conditions: 96°C for one minute, 50°C for 20 seconds, and 60°C for four minutes for a total of 40 cycles.

Ethanol Precipitation

The sequencing reaction was transferred to an appropriately labeled 0.6 mL microcentrifuge tube and was mixed thoroughly. Then 60 µL of 95% ethanol was added from -20°c freezer and mixed thoroughly. Immediately it was centrifuged at 14.000 rpm at 4°C for 15 minutes. The pellet was rinsed twice with 70% ethanol and centrifuged immediately at 14.000 rpm at 4°C for 2-3 minutes. After centrifugation, the supernatant was removed carefully with a micropipette. It was allowed to completely dry at room temperature for 10 minutes. The sample was re-suspended in 40 µL of sample loading solution. Sample preparation for loading: The re-suspended sample was transferred to the appropriate wells of a 96-well sequencing plate. One drop of light mineral oil was added. The sample was loaded into the instrument.

Statistical Analysis

Clinical data were collected using a separate study proforma (attached). All the data were entered into MS EXCEL for further analysis. Descriptive measures like median and interquartile range (IQR) were derived for continuous variables and categorical variables were expressed as % frequency distribution. The outcome measure by clinical parameters was compared by using Fisher's exact test and Chi-square test. Analysis was carried out by statistical package for social sciences (SPSS 21st version) and graphed quick calculator software. A p value <0.05 was considered as significant with two-sided.

RESULTS

Clinical and Demographic Characteristics

General demographic and clinical characteristics of the study group are as shown in Table 1. Median age of the study group was 53 years comprising predominantly males. The majority in the study group presented with tumors in the right colon 20 (44.4%) with a median CEA level of 4. Among the 45 patients, five had undergone emergency surgery. Based on pathological characteristics, 14 (31.2%) had T4 disease, 23 (41.1%) had lymph nodes (LNs) positive disease, 13 (28.6%) had lymphovascular invasion.

Table 1. Clinical and demographic characteristics of the study group

		Number (n)	Percentage (%)
Age (years)	Median	53 (18-46)	
Sex	Male	32	71.1
	Female	13	13
Diagnosis	Right colon	20	44.4
	Left colon	9	20
	Sigmoid	8	17.7
	Rectum	8	17.7
Histology	Lymphovascular invasion	13	28.9
Tumor (T)	T1	2	4.4
	T2	9	20
	T3	18	40
	T4	14	31.2
Node (N)	N1	15	33.3
	N2	4	8.9
	NO	22	48.9
Metastasis (M)	Yes	5	11.1
	No	40	88.9
Presentation	Emergency	5	11.1
	Elective	40	88.9
CEA	Median	4	
	IQR	2.2-7.1	
	Min	1.2	
	Max	128	

The Methylation Status-Vimentin Gene

A total of 12 methylation sites were identified in the study group and the details are as presented in Figure 1. Methylation status ranged from no methylation to partial methylation and complete methylation across these 12 sites. While tumors from twenty-five patients (26/45; 57.78%) showed no methylation, 19 (42.22%) samples showed partial methylation and none of the tumors exhibited complete methylation.

Association of Methylation Patterns in the Vimentin Gene with Clinical, Demographic Characteristics and Tumor Location

The association of methylation patterns in the vimentin gene (complete, partial, and no methylation) were explored for clinical and demographic characteristics. None of the parameters like sex, age, T stage, N stage, M stage, CEA-median, histology was statistically significant and are presented in Table 2. Vimentin methylation was present in 12 (60%) right sided tumors compared to eight (32%) left sided tumors (p= 0.060).

The Methylation Status-SEPT9 Gene

A total of four methylation sites were identified in the promoter region of SEPT9 gene and the details are as presented in Figure 2. Methylation status ranged from no methylation to partial methylation and complete methylation across these sites. Three patients (6.66%) showed complete methylation and 42 patients (93.33%) showed partial methylation.

Association of Methylation Patterns in the SEPT9 Gene with Clinical, Demographic Characteristics and Tumor Location

The association of methylation patterns in the SEPT9 gene (complete, partial) were explored for clinical and demographic characteristics. Of partially methylated tumors, 71.4% and 66.7% of completely methylated tumors respectively were advanced (T3 + T4) (2,30). Of partially methylated tumors 90.5%, and 100% of completely methylated tumors were node positive respectively (Table 3) (3,38). Complete methylation was present in three right sided tumors compared to none in left sided tumors (15% versus 0%). Significance (p values) between complete and partial methylation groups could not be calculated because of the very small sample in complete methylation group.

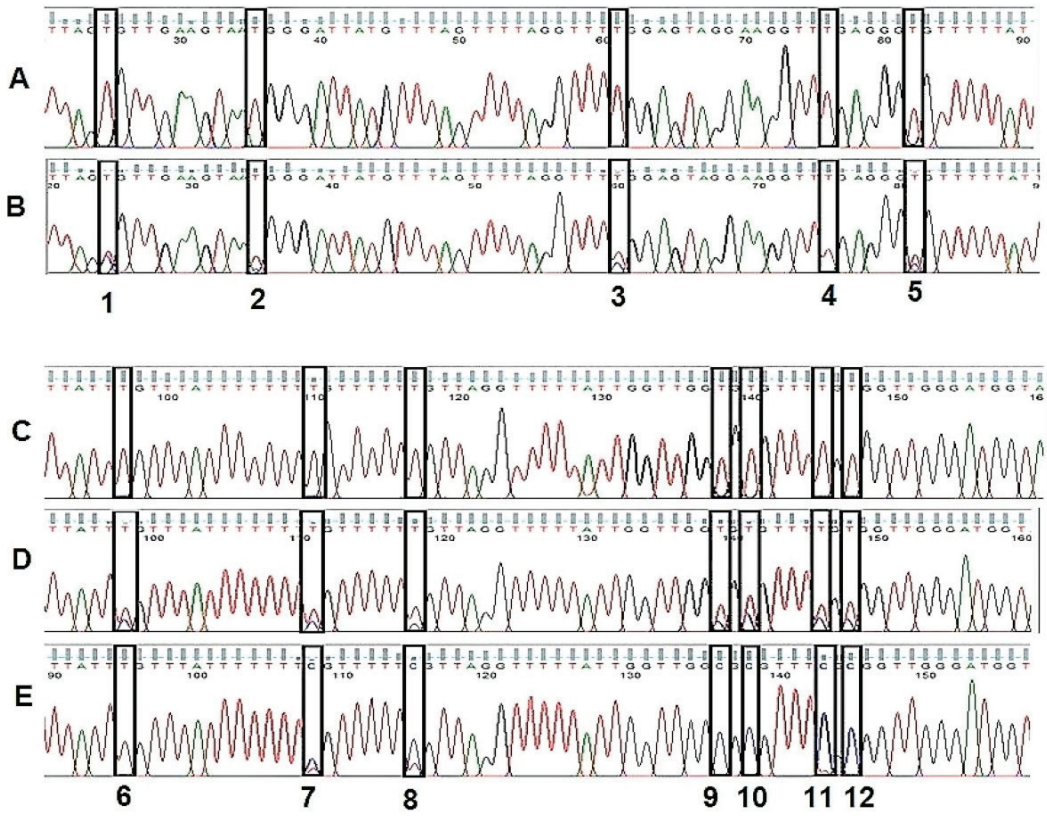

Figure 1. Representative electropherogram depicting different methylation sites (1-2) in the vimentin gene. Panels A-E shows the different methylation status in various sites of the gene. Site A1, A2, A3, A4, A5, B4, C6, C7, C8, C9, C10, C11, C12, E6.

Table 2. Comparison of demographic and clinical characteristics in the vimentin methylation group

		Methylation + (n= 19)		Methylation - (n= 26)		
		Number	Percentage (%)	Number	Percentage (%)	p
Sex	Female	5	26.3	8	30.7	1.000
	Male	14	73.7	18	69.3	
Age	<45	5	26.3	11	42.3	0.351
	>45	14	73.7	15	57.7	
T stage	T1 + T2	3	15.79	8	30.77	0.309
	T3 + T4	16	84.21	18	69.23	
N stage	N0	7	36.84	15	57.69	0.231
	N+	12	63.16	11	42.30	
M stage	M0	17	89.47	21	80.77	0.681
	M+	2	10.53	5	19.23	
Histology	LVI-	13	68.42	19	73.07	0.751
	LVI+	6	31.57	7	26.92	
Stage	1 + 2	7	36.84	14	53.85	0.366
	3 + 4	12	63.16	12	46.15	
CEA (median)	<4	11	63.16	10	38.46	0.349
	>4	7	36.84	14	58.34	

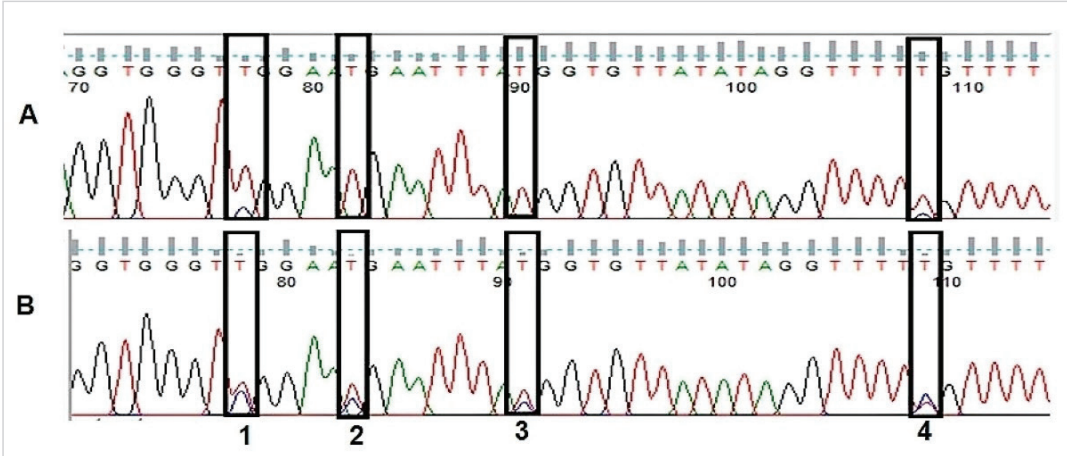

Figure 2. Representative electropherogram depicting different methylation sites (1-4) in the SEPT9 gene. Panels A-B shows the different methylation status at various sites of the gene. Site A2, A3 are the sites with no methylation. Site A1, A4, B1, B2.

Table 3. Comparison of demographic and clinical characteristics in SEPT9 complete and partial methylation group

		Complete methylation (n= 3)		Partial methylation (n= 42)	
		Number	Percentage	Number	Percentage
Age	<45	1	33.3	15	35.7
	>45	2	66.7	27	64.3
Sex	Female	2	66.7	11	26.2
	Male	1	33.3	31	73.8
T stage	T1 + T2	1	33.3	12	28.6
	T3 + T4	2	66.7	30	71.4
N stage	N1	3	100	38	90.5
	N2	0	0	4	9.5
Metastasis	M 0	3	100	37	88.1
	M +	0	0	5	11.9
Histology	LVI +	0	0	13	30.95
	LVI -	3	100	29	69.04
Stage	1 + 2	0	0	21	50
	3 + 4	3	100	21	50
CEA-median	<4	1	33.3	21	53.85
	>4	2	66.7	18	46.15

DISCUSSION

Several different methylation biomarkers have shown good sensitivity and specificity for the early detection of CRC (10). Some of the biomarkers currently under study are SEPT9, IKZF1, and BCAT1, ALX4, VIM. A combination of multiple biomarkers has significantly improved the ability of the plasma methylation test to detect CRC as compared with the measurement of a single marker (11).

SEPT9 gene is located on chromosome 17 at q25.3 (12). According to a systematic review by Nian et al., the sensitivity of methylated SEPT9 gene for CRC ranges from 37% to 88% (13). Another meta-analysis of 19 studies for mSEPT9 to detect CRC has demonstrated a moderate sensitivity of 69% and high specificity of 92% but poor diagnostic performance for precancerous lesions (8). Hu et al., in their meta-analysis of 22 studies with 2271 CRC patients, have shown that the diagnostic value was higher for Asian ethnicity compared to white populations, higher in advanced compared to early stage and higher in CRC compared to adenoma cases (2). Several studies have reported a sensitivity ranging between 30% and 75%, with

a specificity of approximately 90%, using the methylation status of the (SEPT9) gene promoter as a biomarker for detection of early CRC (14).

The PRECEPT clinical study has evaluated the utility of mSEPT9 in plasma for CRC screening and yielded a sensitivity of seventy-six percentage for stages I-IV cancers and 11.2% for advanced adenomas. Specificity was however as high as 91.5% (SAGE-tumor biology May 2018). It has promoter hypermethylation reaching sensitivities ranging from 51% to 90.0%, and the specificity from 73% to 96% in serum or plasma samples of CRC patients (15). In our study, only three patients showed complete methylation patterns in SEPT9 and the majority (43 tumors) showed partial methylation. There were no cases of unmethylated SEPT9 gene. None of the parameters like sex, age, T stage, N stage, M stage, CEA-median, histology was significantly different in complete methylation or partially methylated groups. Hu et al. have shown in their meta-analysis of twenty two studies with 2271 CRC patients that the rate of SEPT9 positivity was higher in advanced CRC cases compared to early stage CRC cases with no significant difference between left and right sided CRC (2). A single center study from Korea has recruited 111 patients of untreated CRC. mSEPT9 in plasma has been detected in only 44 (39.6%) patients unlike our study. The difference in the sensitivity of mSEPT9 among patients with adenomas and those with each stage of untreated CRC was statistically significant (Dukes' staging, p= 0.002 and TNM staging, p= 0.008). The sensitivity of mSEPT9 for each of the stages (I-IV) of untreated CRC patients were 20.7%, 54.1%, 36.6%, and 75.0%, respectively (16).

In our study, 44.5% of the patients showed partial vimentin methylation and 55.55% patients showed no methylation. Lu et al. have shown a vimentin promoter methylation rate of 41.1% in fecal DNA of 56 patients with CRC (17). Li et al. have shown in their meta-analysis of seven clinical cohort studies with a total of 467 CRC patients that the frequency of vimentin promoter methylation in cancer tissues was significantly higher than in normal and benign tissues (cancer tissues vs. normal tissues: OR= 32.41, 95% CI= 21.04 ~ 49.93, p< 0.001; cancer tissues vs. benign tissues: OR= 1.60, 95% CI= 1.05 ~ 2.42, p= 0.028). Ethnicity-stratified analysis has indicated that the frequency of aberrant vimentin promoter methylation was correlated with the pathogenesis of CRC in both Asians and Caucasians (6).

None of the parameters like sex, age, T stage, N stage, M stage, CEA-median, histology and tumor location were statistically significant between the methylated vimentin and non-methylated groups. In contrast, Shirahata et al. have shown in 44 colorectal cancer patients that four (9%) exhibited methylation of the vimentin gene in their serum DNA. Interestingly, methylation was significantly found in the serum of patients with liver metastasis, peritoneal dissemination, and distant metastasis (p= 0.026, p= 0.0029 and p= 0.0063, respectively), suggesting that vimentin methylation in serum might be detected more frequently in patients with advanced colorectal cancer (18).

Limitations of our study are the small sample size and lack of follow-up data.

CONCLUSION

In our study, only 6.66% of CRC patients showed hypermethylation and there was no association of methylation patterns in the both genes (complete, partial, and no methylation) with any of the parameters like age, sex, TNM stage, CEA, location, and histology.

Ethics Committee Approval: This study was approved by Asian Institute of Gastroenterology Ethics Committee (Study-Approval Number: AIG/IEC32/10.2018-09, Date: 06.11.2018).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 107-114

Kolorektal kanseri izlemek için dolaşımdaki tümör DNA'sı: Metillenmiş SEPT9 ve VIM promotör genlerinin varlığını ve kolorektal kanser yönetiminde bir biyobelirteç olarak rolünü değerlendirmek için prospektif bir gözlemsel çalışma

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ÖZET

Giriş ve Amaç: Kolorektal kanser (CRC) hastalarının dolaşımdaki tümör DNA'sındaki Septin9 (SEPT9) ve vimentin (VIM) genlerinin metilasyon durumu, CRC'nin erken tespiti için umut verici bir biyobelirteçtir. Bu çalışmanın amacı, biyopsiyle kanıtlanmış kolorektal kanserli Hintli hastalardan oluşan bir kohortta SEPT9 ve VIM genlerinin promotör bölgelerindeki metilasyon durumunu belirlemekti.

Gereç ve Yöntem: Kırk beş ardışık kolorektal kanser hastası çalışmaya alındı. Her hastadan 10 mL venöz numune toplandı ve hücresiz DNA izolasyonu, hücresiz DNA'nın bisülfit dönüşümü, polimeraz zincir reaksiyonu (PCR) amplifikasyonu ve SEPT9 ve VIM genlerinin saptanması için işlendi.

Bulgular: Hastaların %42.22'si vimentinde sadece kısmi metilasyonla başvurdu ve %57,78'i hiç metilasyon göstermedi ve tümörlerin hiçbirinde tam metilasyon yoktu. Sadece üç (%6,66) hasta SEPT9'da tam metilasyon paternleri gösterdi ve geri kalan 42 (%93,33) tümörün tümü kısmi metilasyon gösterdi. İki gen birlikte ele alındığında, 45'ten sadece üçü (%6,66) tam metilasyon gösterdi. Her iki gendeki metilasyon modellerinin (tam, kısmi ve metilasyon yok) cinsiyet, yaş, T evresi, N evresi, M evresi, CEA, histolojiyle ilişkisi araştırıldı ve bu parametrelerin hiçbiri istatistiksel olarak anlamlı değildi.

Sonuç: Çalışmamızda sadece %6,66 CRC hastası hipermetilasyon gösterdi ve her iki gende (tam, kısmi ve metilasyon yok) metilasyon paternleriyle yaş, cinsiyet, TNM evresi, CEA ve histoloji gibi parametrelerin hiçbir ilişkisi yoktu.

Anahtar Kelimeler: Kolorektal neoplaziler, hücresiz nükleik asitler, metilasyon

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ORIGINAL ARTICLE
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Long-term results of breast cancer patients who received IOERT as boost during BCS: A single-institution retrospective analysis

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ABSTRACT

Objective: Intraoperative electron radiotherapy (IOERT) applied as boost to the tumor bed during breast conserving surgery is advantageous in terms of local recurrence in breast cancer patients. In addition, it has other advantages over the adjuvant boost RT such as no risk of tumor bed change, ease of sequencing radiotherapy chemotherapy, and reduced workload of the radiotherapy clinic. This study aimed to evaluate the long-term results of our patients who were treated with this method in our institution and are still being followed up.

Material and Methods: One hundred and three patients enrolled in this study received IOERT equivalent to 10 Gy as boost during BCS and were subsequently given adjuvant WBI according to the biological subtype of the tumor systemic therapy. These patients were analyzed using their files and hospital records. Patients were evaluated for overall survival, local recurrence, distant metastasis, and cosmetic outcome (using LENT-SOMA scale).

Results: Median age was 53,5 (27-74), mean follow-up time was 75 (48-106) months. Mean pathological tumor size was 18 mm (4-30), 90 of the patients had invasive ductal carcinoma, eight of them were lobular and five of them had mixed histological structure. Ninety-three of the patients presented histological grade II, 15 grade III; 74 patients were luminal A-like, 15 luminal B-like, eight HER2 positive and six triple negative breast cancer. According to the LENT-SOMA scale, 35 had grade 0, 42 each had grade I, 23 had grade II, and two had grade III. All patients underwent whole breast irradiation after surgery, 81 received chemotherapy and 90 endocrine therapy. There was one local recurrence, distant recurrence was seen in four patients and one patient died of non-breast cancer causes. Overall survival was %99, and event free survival %96.

Conclusion: IOERT for breast cancer treatment during BCS is a safe option with low chronic toxicity and the cosmetic outcome gets better over time.

Keywords: Breast cancer, breast conserving surgery, boost radiotherapy, intraoperative electron radiotherapy, LENT-SOMA

INTRODUCTION

Currently, breast conserving surgery (BCS) and radiotherapy (RT) have become the standard approach in every case who is eligible for BCS regardless of stage in the regional treatment of breast cancer. Whole breast irradiation (WBI) as adjuvant therapy and boost RT applied to the tumor bed effectively control the tumor bed and around 1-2 cm where local recurrences are most common (1-4).

Thanks to the developments in the field of radiotherapy, intraoperative electron radiotherapy (IOERT) is an important option to reach the required effective dose in the tumor bed in a short time during the operation, which is applied as a boost to the tumor bed by direct visualization during breast-conserving surgery and is advantageous in terms of local recurrence in patients with breast cancer. In addition, it has other advantages over the adjuvant boost RT, such as no risk of tumor bed changes. After the final pathology report, the treatment plan may differ in chemotherapy (CT) and RT sequence and may require modification. The marker clip, which is placed in the original location of the tumor during surgery, can be displaced in the postoperative period because of the seroma and etc., and focus on a different area in boost planning, also healthy breast tissue can be exposed to extra RT (4-7). It gives an excellent sequencing chance where adjuvant chemotherapy takes precedence over external boost RT, IOERT is more likely to have local control (5,7). When compared with external adjuvant boost RT, it has been reported that there is a positive difference in favor of the patient, especially in terms of

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local recurrence after four years (8-10). In our previous study, the average follow-up period was three years, and local recurrence was less in the group that underwent IOERT (7). Another advantage is that by shortening the duration of adjuvant RT, it contributes to the correct use of time and resources allocated for the treatment of other patients treated in the same center (1,2,5,7).

The aim of this study was to evaluate the long-term results of our patients who were treated with this method in our institution and are still being followed up.

MATERIAL and METHODS

One hundred and three patients who were treated with the diagnosis of breast cancer in our clinic between October 2013 and June 2018 were included in this study. After a treatment plan was made in the multidisciplinary breast cancer committee, the patients were selected among those eligible for IOERT. They received IOERT as boost during BCS followed by WBI and, if necessary, systemic therapy. IOERT as boost, an electron equivalent to 10 Gy was applied via Mobetron with an average 865 (773-954) monitor unit (MU) and 90% reference isodose with 6 MeV energy (Table 1). Mobetron® (registered trademark of IntraOp Medical, Inc., USA) is an electron linear accelerator designed to deliver electron beam IOERT to treat cancer during surgery. These patients were analyzed using their files and hospital records. Patients were evaluated for overall survival, local recurrence, distant metastasis, and cosmetic outcome.

The risks of overall survival, local recurrence and event-free survival were performed by the Kaplan-Meier method and late effects normal tissue/subjective objective management analytic [LENT-SOMA (V06-7/2003)] scale was used for cosmetic scoring (Table 2) (7). The study was approved by the ethics committee of the hospital, with the decision dated 17.10.2022/278.

Table 1. Patient and tumor characteristics

Patient and tumor characteristics	**n= 103**
Age (median) range (27-74)	53.5
Follow-up time	75 (48-106)
Tumor diameter (mm)	18 (4-30)
T1a	3
T1b	16
T1c	66
T2	18
Histology- Invasive ductal Invasive lobular Mixt	 90 8 5
Tumor grade (0-III)	2
Luminal A	74
Luminal B	15
HER2 neu positive	8
TNBC	6

Table 2. LENT-SOMA scale V06, 7/2003, for breast carcinoma radiotherapy: Post radiation fibrosis

Grade 0	None
Grade I	Rarely palpable/increased density
Grade II	Definite increased density and firmness
Grade III	Marked density, retraction and fixation

RESULTS

Median age was 53.5 (27-74) years and mean follow-up was 75 (48-106) months. Mean pathological tumor size was 18 (4-30) mm, 90 of the patients had invasive ductal carcinoma, eight had lobular and five had mixed histological structure. Ninety-three of the patients presented histological grade II, 15 grade III; and 74 patients showed luminal A-like, 15 luminal B-like, eight HER2-positive, and six triple-negative molecular subtypes; and finally, 35 of them were evaluated as 0, 42 of them as first, 23 of them as second and two of them as third grade according to LENT-SOMA scale.

All patients underwent whole breast irradiation after surgery, 81 received chemotherapy and 90 received endocrine therapy (Table 2).

While adjuvant treatment of the patients whose loco-regional treatment is completed continues, they are monitored every three months for the first two years and every six months in the following years in terms of systemic and cosmetic outcome. During the follow-up period, one patient died from causes other than breast cancer, one patient showed local recurrence and four patients showed distant metastasis.

A 62-year-old patient died due to sepsis at the hospital where she was treated for a broken femur fracture that occurred after a traffic accident at the end of the postoperative second year. The patient who underwent mastectomy for local recurrence at 92 months had invasive ductal carcinoma in the first operation, the subtype of the tumor was HER 2+, Ki 67 35%, and nuclear grade III. Histopathological examination after mastectomy showed luminal A like invasive ductal carcinoma, nuclear grade II, Ki 67 25%.

The patients with distant metastases were treated with chemotherapy, nephrectomy and radiotherapy, respectively, due to one lung, one liver, one kidney and one bone metastasis. They are still being followed up event free. Overall survival was 99% and event-free survival was 96% (Table 3). When evaluated in terms of total (a), disease-free (b), local recurrence (c), and distant metastasis (d) at 75-month follow-up, the following estimated values with 95% [confidence interval (CI)] were reached:

Table 3. Treatment and follow-up characteristics

Treatment and follow-up characteristics	n= 103, median follow-up for all patients was 75 (range 48-106) months.
BCS	103
SLNB	103
ALND	7
IOERT dose: Gray-equivalent MU= monitor U	10/862
Applicator surface median (mm)	5.4 (4-7)
WBI	103
Adjuvant chemotherapy	81
Adjuvant endocrine therapy	90
Local recurrence/time: 92 M	1 (Mastectomy)
Distant metastasis/time Liver-94.M Lung-88.M Kidney-44.M Bone (Vertebra)-59.M	4 Chemotherapy Chemotherapy Nephrectomy RT
OS DFS	99% 96%
Cosmetic outcome: LENT-SOMA scale	75% excellent- 23% good/satisfactory 2% poor
Grade 0	35
Grade I	42
Grade II	23
Grade III	2

Overall survival; 109.1 ± 0.8, (CI= 107.5-110.7), local recurrence free survival; 109.5 ± 0.4, (CI= 108,6-110,4), disease' other causes'-free survival; 107.6 ± 1.02 (CI= 105.6-109.6), distant disease-free survival 108.1 ± 0.9 months (CI= 106.3-109.9) respectively (Figure 1).

DISCUSSION

BCS followed by WBI is applied as the standard method in the locoregional treatment of early-stage breast cancer. Based on the knowledge that more than 70% of local recurrences occur around the 2 cm radius of the tumor bed's focus, additional doses of Rt have been given to the tumor bed with different methods since 1985 (3). It has been shown in many studies that this approach significantly reduces local recurrence (1,4,6,8). By adding an additional dose of 16 Gy to the tumor bed, the EORTC 'boost versus no boost' trial reported a reduction of the 10-years LR rate from 10.2 to 6.2% (3).

We also know from other published studies that when IOERT is administered as a boost during BCS, it is clear that the risk of local recurrence is relatively low and toxicity rates seem acceptable (2,3,8-11). In other words, the results of patients receiving IOERT as a boost during BCS show the similar or better overall and disease-free survival than postoperative external boost RT. The strongest influence on these results is the effect on the microenvironment, including the microvasculature or cytokine model, without tumor cell proliferation before and during radiotherapy, with the dose delivered as boost directly to the tumor bed immediately after tumor removal during surgery (1,2,9).

Blank et al. have reported that IOERT, as a tumor bed boost during BCS, decreases the risk of local recurrence and that the toxicity rates seem to be acceptable (6). Follow-up of 197 patients who received IOERT as boost, with a median duration of 37 months, had five local recurrences, six secondary cancers, and 11 distant metastases, resulting in a five-year disease-free survival of 81.0% and overall survival of 91.3%. Local recurrence-free survival at three and five years (invasive cancers) was 97.0% (6).

In our series, when we look at the results of the first three-year follow-up, no local recurrence or distant metastasis was detected in the IOERT group, while local recurrence was detected in one patient at the 20th month in the external boost RT arm, and distant metastasis was detected in another patient at the 32nd month. Mean follow-up was 35 and 38 months (7).

The greatest experience for electron-using IOERT is available in a single-institution retrospective study comparing preliminary results of IOERT as boost. Accordingly, the results of the study, although with mild toxicities, have favorable early oncologic outcomes for the breast (8). A retrospective study compared 188 external boost RT with 190 IOERT patients at five-year follow-up, the rate of intramammary recurrence in the external boost group was 4.3% compared to 0% in the IOERT group. This difference was statistically significant and was due to the reduction in true local recurrences previous index quartile (10).

In a series of 46 patients with a median tumor size of 16 mm and mean follow-up of 62 months, there was no local recurrence after equivalent to 10-12 Gy IOERT as boost during BCS, followed by WBI, but two patients (4.3%) showed distant recurrence. In this article, it was reported that the patients were evaluated with Common Terminology Criteria for Adverse Events (CTCAE) 4.0 for chronic radiation toxicity in the late period, fibrosis was detected in six patients, and it was scored as grade II, and there was no patient with grade III (11).

Retrospective analysis of 400 patients with IOERT, followed by whole breast irradiation were in terms of adverse events, evaluated prospectively over a period of up to 15 years (LENT-SOMA scales). Median follow-up was 78 months (2-180). Local recurrence occurred in 15 patients, resulting in a local recurrence rate of 2.0%, 6.6%, and 10.1% at five, 10, and 15 years, respec-

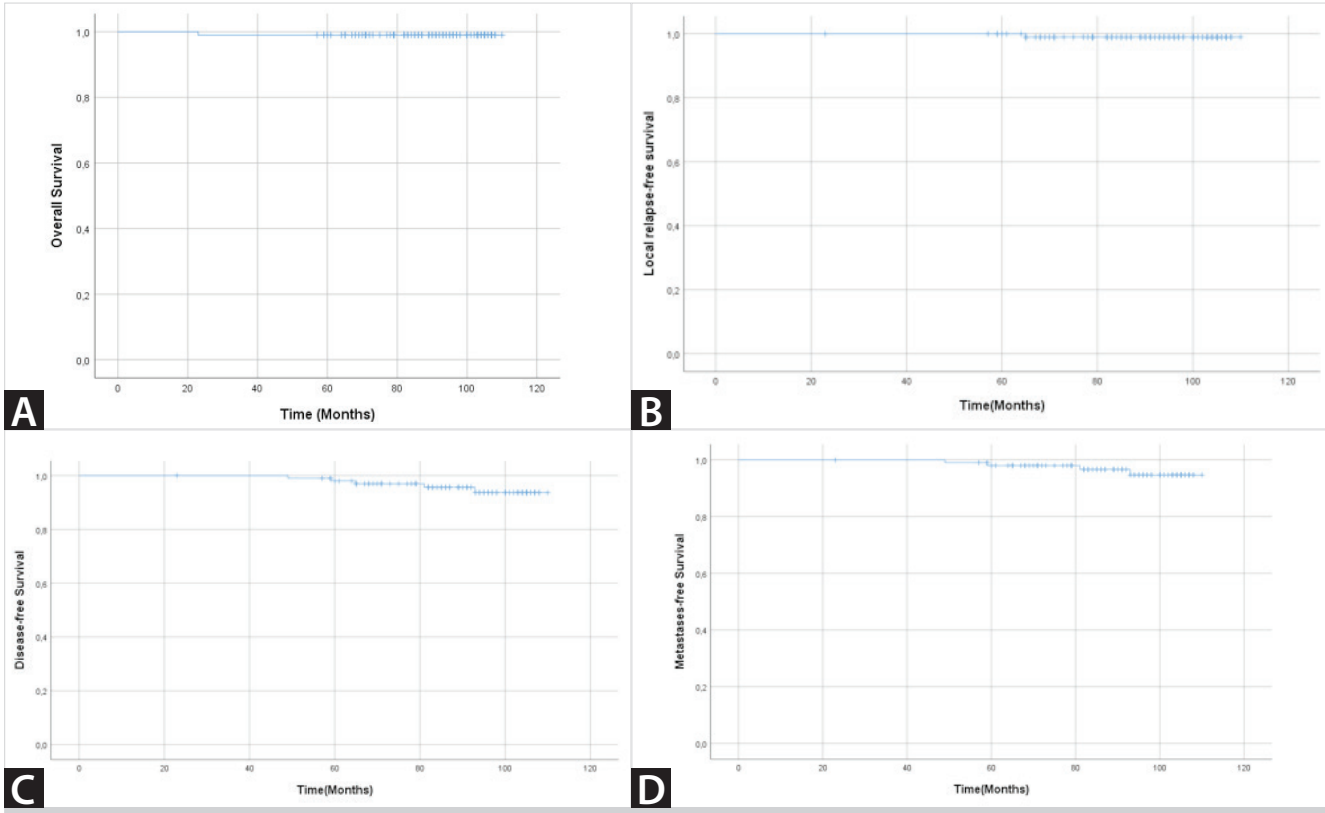

Figure 1. A. Overall survival: 109.1 ± 0.8 (107.5-110.7). **B.** Local recurrence-free survival: 109.5 ± 0.4 (108.6-110.4). **C.** Disease-free survival: 107.6 ± 1.02 (105.6-109.6). **D.** Distant metastase-free survival: 108.1 ± 0.9 (106.3-109.9).

tively. Overall survival rates at five, 10, and 15 years were 92.1%, 81.8%, and 80.7%, respectively (12). Local recurrence and overall survival were found to be better in our patients who had more than six years of follow-up. Side effects were similar to or less than expected from external beam boost RT, both in the Pez et al. series and in our patient group (13).

The results of studies published on this topic are also noteworthy: A correlation between breast size, tumor size, and cosmetic results has been reported. Similar results were obtained in our series and shared in the literature (13).

The series we presented with this study showed very low recurrence rates at an average follow-up of 75 months, as well as very few side effects such as fibrosis and pain. Those with fibrosis were defined as grade II, and the same patients reported pain relief when asked, but these side effects did not increase after three years. In our IOERT series, one patient had local recurrence at the 92nd month and mastectomy was performed, and distant metastasis was detected in four patients, and they are being followed up after their treatment. One of our patients died of a cause other than breast cancer (intra-abdominal sepsis).

Better overall and event-free survival results were obtained in our series when the articles reporting IOERT late outcomes with similar follow-up times were reviewed. These studies, including our series, were designed retrospectively. We believe that this may be due to careful patient selection and better prognostic factors depending on molecular subtypes.

In a prospective study, 133 breast cancer patients received IOERT during BCS and compared 112 patients treated with postoperative external boost RT for local recurrence. While recurrences were observed in the IOERT arm at over 100 months of follow-up, the mean time to relapse was much earlier in external boost RT (55.2 months) group. The cumulative risk of IBTR at five and 10 years was 0.8% and 4.3%, respectively. IOERT group comparison with 4.2% and 5.3% after EBRT boost RT. Cosmetic results are significantly better in IOERT group compared to EBRT group and difference remained significant at any time. Cosmetic results are evaluated by both physicians and patients, both were similar and significantly better in IOERT group compared to external boost RT group and difference remained significant at any time (14).

At the end of a mean follow-up period of 36 months, only two of our patients were scored at grade III according to LENT-SOMA. Likewise, there was no change in the following years, and according to our patient records, it was observed that the cosmetic result was better tolerated in grade III patients.

This result is compatible with the data of the articles reported as the late outcome of the IOERT as boost group, namely that the cosmetic result is the same or better in subsequent years and that RT-related side effects occur most frequently in the first three years (5,8,11,12).

CONCLUSION

IOERT for breast cancer treatment during BCS is a safe option with low chronic toxicity and cosmetic outcome gets better over time. It also means less effort for the patient, fewer hospital visits and limits the use of healthcare resources.

Ethics Committee Approval: This study was approved by İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Research Ethics Committee (Decision no: 278, Date: 17.10.2022).

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ORİJİNAL ÇALIŞMA-ÖZET
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Meme koruyucu cerrahi sırasında boost olarak IORT almış meme kanserli hastaların uzun dönem sonuçları: Tek merkez retrospektif analizi

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ÖZET

Giriş ve Amaç: Meme koruyucu cerrahi sırasında tümör yatağına boost şeklinde uygulanan intraoperatif elektron radyoterapi (IOERT) meme kanseri hastalarında lokal nüks açısından avantajlıdır. Biz de bu yöntemle tedavi edilen ve halen takipleri devam eden hastalarımızın uzun dönem sonuçlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya alınan 103 hasta, BCS sırasında boost olarak 10 Gy'ye eş değer IORT aldı. Daha sonra tüm meme ışınlandı ve tümörün biyolojik alt tipine göre sistemik tedavi verildi. Bu hastalar dosyaları ve hastane kayıtları kullanılarak analiz edildi ve genel sağkalım, lokal nüks, uzak metastaz ve kozmetik sonuç açısından LENT-SOMA ölçeği kullanılarak değerlendirildi.

Bulgular: Yaş ortalaması 53,5 (27-74), ortalama takip süresi 75 (48-106) aydı. Ortalama tümör boyutu 18 mm (4-30), hastaların 90'ında invaziv duktal karsinom, sekizinde lobüler ve beşinde mikst histolojik yapı vardı. Hastaların 93'ü histolojik derece II, 15'i III; 74 hasta luminal A,15 luminal B, sekizi HER2 pozitif ve altısı üçlü negatif meme kanseriydi. LENT-SOMA ölçeğine göre 35 kişi 0, 42 kişi 1, 23 kişi 2 ve iki kişi 3 puan almıştır. Tüm hastalara ameliyattan sonra tüm meme ışınlaması yapıldı, 81'i kemoterapi ve 90'ı endokrin tedavisi aldı. Bir lokal nüks oldu, dört hastada uzak nüks görüldü ve bir hasta meme kanseri dışı nedenlerle öldü. Genel sağkalım %99 ve olaysız sağkalım %96 idi.

Sonuç: BCS sırasında meme kanseri tedavisi için IOERT, düşük kronik toksisite ve zaman geçtikçe kozmetik sonuç açısından daha iyi hale gelen güvenli bir seçenektir.

Anahtar Kelimeler: Meme kanseri, meme koruyucu cerrahi, boost radyoterapi, intraoperatif elektron radyoterapi, LENT-SOMA

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ORIGINAL ARTICLE
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Role of serum levels of tumour necrosis factor-like weak inducer of apoptosis (TWEAK) in predicting severity of acute appendicitis

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ABSTRACT

Objective: One of the most prevalent abdominal crises is acute appendicitis (AA). Clinical diagnosis, even for skilled surgeons, is frequently challenging, as indicated by the high proportion of negative investigations. The purpose of this study was to see if serum TWEAK levels might be used to diagnose acute appendicitis.

Material and Methods: Between June 2017 and May 2019, all patients who had surgery with the original diagnosis of AA were included in the study. TWEAK, WBC, CRP, and bilirubin levels were compared.

Results: The levels of WBC, CRP, and bilirubin were compared to pathology. All three blood indicators increased significantly in AA patients. However, no statistically significant difference in the levels of all three blood indicators was seen between individuals with simple AA and those with severe AA. TWEAK plasma concentrations were considerably greater in patients with severe AA than in the healthy control and NAA groups. TWEAK levels were significantly greater in individuals with severe AA compared to patients with simple AA.

Conclusion: Serum TWEAK levels that are elevated may be used to diagnose acute appendicitis as well as prognostic indicators for the severity of appendicitis.

Keywords: Acute appendicitis, inflammation, marker, severity, tumor necrosis factor-like weak inducer of apoptosis

INTRODUCTION

One of the most prevalent abdominal crises is acute appendicitis (AA). Clinical diagnosis is sometimes challenging, even for experienced surgeons, as indicated by the high percentage of negative explorations, which typically approaches 20-30% (1,2). Acute appendicitis is mostly a clinical diagnosis backed by laboratory and imaging tests. Despite the introduction of various clinical scoring systems, their accuracy remains modest and comparable to traditional clinical judgment. Modern imaging may improve diagnostic accuracy, but its usage may be restricted by availability, cost, and radiation exposure. Difficulties in diagnosing acute appendicitis have led to an ongoing search for new diagnostic indicators that may reduce radiation exposure and expenditures (3-6). Patient outcomes are frequently favorable with early identification and correct therapy. However, delayed detection can lead to perforation, which can result in serious consequences such as peritonitis, sepsis, intestinal blockage, abscess development, and reproductive issues. Perforated appendicitis has been demonstrated to significantly increase mortality. However, clinicians must strike a balance between attempts to decrease delayed/missed diagnoses and over-diagnosis, which results in unnecessary treatments (medical/surgical) (7,8).

Chicheportich identified tumor necrosis factor-like weak inducer of apoptosis (TWEAK) as a novel member of the tumor necrosis factor (TNF) superfamily of ligands in 1997. TWEAK has been shown in studies to be a valuable biomarker in a variety of inflammatory and non-inflammatory illnesses (9). In recent decades, there has been a significant increase in the literature regarding the use of TNF inhibitors in the treatment of BD. Therefore, TWEAK has been the focus of attention in current studies (9). TWEAK is a cytokine that is mostly generated by leukocytes and is a

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member of the TNF family. Furthermore, disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis are caused by cellular responses that can be linked to inflammatory pathways triggered by inflammatory multifunctional cytokines like TWEAK (9). TWEAK may have an important role in the pathological remodeling underlying various inflammatory disorders, such as cardiovascular disease and obesity-associated type 2 diabetes mellitus, notably in myocardial remodeling leading to heart failure and acute pancreatitis, according to new data (9).

Therefore, the aim of the present study was to test the diagnostic value of serum levels of TWEAK in acute appendicitis.

MATERIAL and METHODS

All patients who were operated to surgical emergency department with the initial diagnosis of acute appendicitis, were included prospectively between June 2017 and May 2019.

Written, informed consent was obtained according to a protocol approved by local institutional ethical committee. Patients with age <18 years, other acute infections, malignant disease, chronic inflammatory disease (including established or suspected chronic pancreatitis), preexisting chronic organ failure, unstable coronary syndromes, liver failure, chronic obstructive airways disease, and immunosuppressive disorders were excluded due to potential variations in the systemic inflammatory responses and their potential influence on treatment decisions.

After informed consent, routine laboratory studies were obtained in all patients, together with complete blood count and serum chemistry analysis, including CRP levels from the admission blood sample.

All blood specimens were immediately processed after they were drawn and stored in aliquots at -80°C till quantification of sTWEAK.

Serum sTWEAK levels were determined with a commercially available ELISA kit tested for determination of human serum samples (Bender Medsystems, Wien, Austria) according to the manufacturer's instructions. Briefly, a 1:2 diluted test sample was incubated for three hrs at room temperature in wells pre-coated with an anti-human sTWEAK antibody together with a biotin-conjugated anti-human TWEAK antibody. Streptavidin-HRP (horse reddish peroxidase) binds to the biotin-conjugated anti-human TWEAK. Following incubation, wells were washed three times to remove excess antibody, the substrate solution reactive with HRP was added to the wells and incubated for approximately 10-20 min. A colored product is formed in proportion to the amount of soluble human TWEAK present in the sample. The reaction was terminatedby addition of acid and absorbance was measured at 450 nm. A standard curve prepared from seven human TWEAK standard dilutions and subsequently human TWEAK sample concentrations were determined. The absorbance was measured with an automatic ELISA reader (Biochem Immunosystems 100 Cascade Drive, Allentown, PA). Human sTWEAK was detected with this kit at a threshold of 9.7 pg/mL. Intra-assay and inter-assay coefficients of variation were 7.9% and 9.2%, respectively.

All measurements were performed in duplicate.

Data regarding demographic, clinical, radiological, operative, and pathological features were analyzed. The severity of appendicitis, as described in histological examination, was classified as normal (not acute appendicitis, NAA), simple appendicitis, severe appendicitis (in cases of acute appendicitis with periappendicitis or phlegmonous/gangrenous or perforated appendix) similar to the pathologic classification described by Fallon and colleagues (3).

Findings of each marker for overall acute appendicitis, and severe appendicitis were compared to histological findings using the following definitions: sensitivity, (true positive/true positive + false negative); specificity, (true negative/true negative + false positive); positive predictive value, (PPV) (true positive/true positive + false positive); and negative predictive value (NPV), (true negative/true negative ++ false negative).

The receiver operating characteristic (ROC) analysis allows graphical plotting of the sensitivity vs. specify curve to assess the overall performance of the parameter as a diagnostic factor [area under the curve (AUC)] and discern the optimal threshold value. ROC curve analysis was performed for all evaluated. The statistically significant variables were inspected for a cutoff value for optimal diagnostic accuracy [calculated as (true positive + true negative)/N]. Negative and positive predictive values (NPV, PPV) were calculated and recorded. Study population was grouped using the selected variable cutoffs and diagnostic accuracy of overall appendicitis, and severe appendicitis was assessed using Fisher's exact test. Correlation of the variables to the severity of appendicitis, according to operative and pathological reports, was assessed using Spearman's correlation test.

The data were expressed as mean ± SD and 95% confidence interval (CI). Statistical analysis was carried out using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The differences between the groups were estimated using the Chi-square (for gender distribution) and two-tailed unpaired t-test (for normally distributed data). Mann-Whitney U test was used to evaluate serum TWEAK levels in studied groups. A p value of <0.05 was considered to be statistically significant.

RESULTS

The study protocol included 200 patients who underwent operations with diagnosis of AA; all met the eligibility criteria, as well as 50 healthy volunteers. According to the surgery and pathology reports, 168 acute appendicitis (simple & severe AA) and 82 (NAA & control) normal people were detected, respectively. According to the pathology reports, 104 simple AA and 64 severe AA patients were detected. The demographics and clini-

cal presentation are summarized in Table 1. Male gender had a higher rate of acute appendicitis (p< 0.05). While 72 (69.23%) uncomplicated cases and 39 (60.93%) severe appendicitis cases were male, 23 (71.88%) non-appendicitis cases were female.

WBC, CRP and bilirubin levels were compared to pathology. In comparison to the NAA and control groups, all three blood markers increased significantly in patients with simple and severe AA (Table 2). On the other hand, when we compared the levels of all three blood markers between patients with simple and severe appendicitis, there was no statistically significant difference (p= 0.89, p= 0.63, and p= 0.21, respectively).

As shown in Table 2, the mean plasma concentration of TWEAK in patients with severe AA was 945.6 ± 121.2 pg/mL (95% CI 798.93-997.07), significantly higher than that of the healthy control group 385.2 ± 62.9 pg/mL and NAA group 391.7±67.7 pg/mL (p≤0.001). The mean level in simple AA patients (635.4 ± 107.1 pg/mL) (95% CI 541.84-694.25) was also notably higher than that of healthy volunteers and NAA group. Importantly, significantly higher levels of TWEAK were detected in patients with severe AA compared to simple AA.

A correlation was analyzed between the studied markers and the acute appendicitis as recorded in operative and pathology reports. Serum TWEAK levels had the significant sensitivity, specificity, PPV and NPV (Table 3).

Table 1. Comparison of demographics and clinical presentation

	NAA (n= 32)	Simple AA (n= 104)	Severe AA (n= 64)	Control (n= 50)	p
Age	34.3 ± 8.7	32.1 ± 7.8	35.7 ± 8.2	32.3 ± 7.3	0.61
Male sex, n (%)	9 (28.12%)*	72 (69.23%)*	39 (60.93%)*	26 (52%)	0.04*
Duration of symptoms (hours)	33.4 ± 4.7	25.2 ± 4.2	37.0 ± 0.6		0.43
Maximal fever (ºC)	36.8 ± 0.6	37.0 ± 0.7	37.0 ± 0.6	36.7 ± 0.6	0.87
Nauseai, n (%)	19 (59.37%)	67 (64.42%)	38 (59.37%)		0.48
Vomiting, n (%)	16 (50%)	55 (52.88%)	35 (54.68%)		0.38

t-NAA: Not acute appendicitis (normal), Simple AA: Simple appendicitis, Severe AA: Severe appendicitis.
Data are presented as mean ± SD.
(*): Statistically significant difference (p≤ 0.05).

Table 2. Comparison of laboratory findings

	NAA	Simple AA	Severe AA	Control	p
White blood cell count: $x10^9$/L	11.9 ± 4.5	14.2 ± 3.6*	14.6 ± 3.6*	7.2 ± 1.4	0.04*
CRP: mg/L	9.8 ± 2.2	12.4 ± 2.4*	14.1 ± 2.5*	4.2 ± 2.2	0.04*
D. bilirubin mg/dL	0.08 ± 0.03	0.15 ± 0.11*	0.22 ± 0.13*	0.08 ± 0.03	0.04*
TWEAK pg/mL	391.7 ± 67.7	635.5 ± 112.7*	945.6 ± 148.9**	385.2 ± 62.9	0.001*

NAA: Not acute appendicitis (normal), Simple AA: Simple appendicitis, Severe AA: Severe appendicitis.
Data are presented as mean ± SD.
(*): Statistically significant difference (p≤ 0.05).

Table 3. Comparison of the markers in acute appendicitis

	n (250)	Sensitivity	Specificity	PPV	NPV
WBC Positive (149 TP/53 FP) Negative (26 TN/22 FN)	 202 48	87.13%	32.91%	73.76%	54.17%
CRP Positive (135 TP/73 FP) Negative (22 TN/20 FN)	 208 42	87.1%	23.16%	64.9%	52.38%
D. bilirubin Positive (102 TP/89 FP) Negative (52 TN/17 FN)	 191 69	85.71%	36.88%	53.4%	75.36%
TWEAK Positive (159 TP/29 FP) Negative (54 TN/8 FN)	 188 62	95.21%	65.06%	84.57%	87.1%

TP: True positive, FN: False negative, FP: False positive, TN: True negative, PPV: Positive predictive value, NPV: Negative predictive value.

Table 4. Comparison of the markers in appendicitis severity

	n (168)	Sn	Sp	PPV	NPV	Cut-off value
WBC Simple (68 TN/58 FN) Severe (25 TP/27 FP)	116 52	30.12%	71.58%	48.08%	53.97%	14.4 (x10^9/L)
CRP Simple (53 TN/59 FN) Severe (31 TP/25 FP)	112 56	34.44%	67.95%	55.36%	47.32%	12.9 (mg/L)
D. bilirubin Simple (51 TN/46 FN) Severe (32 TP/39 FP)	97 71	41.03%	56.67%	45.07%	52.58%	0.17 (mg/dL)
TWEAK Simple (99 TN/16 FN) Severe (48 TP/5 FP)	115 53	75 %	95.19%	90.57%	86.09%	743 (pg/mL)

TP: True positive, FN: False negative, FP: False positive, TN: True negative, Sn: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value.

A correlation between the studied markers and the severity of appendicitis as recorded in operative and pathology reports was also analyzed. Serum TWEAK levels were significantly more sensitive for severity of appendicitis than other markers (Table 4).

DISCUSSION

Acute appendicitis is the most prevalent cause of abdominal pain and the most common reason for emergency abdominal surgery. It is most frequent between the ages of seven and 15 years old, although it can develop at any age, with a lifetime risk of about 7-8 percent (10). Acute appendicitis is classified into two types based on its severity: simple acute appendicitis (simple AA) and severe acute appendicitis (severe AA). Simple AA comprises both simple and suppurative appendicitis (without gangrene, perforation, and abscess formation). Gangrenous appendicitis and other acute appendicitis that can lead to abscesses and perforations are examples of severe AA.

Acute appendicitis is often diagnosed based on a clinical history and physical examination, which are supplemented by subsequent test data such as WBC and differential blood counts. Early and precise diagnosis is critical for effective treatment of acute appendicitis. However, the accurate diagnostic percentage ranges from 72% to 94%. The incidence of negative appendectomy varies between 15% and 34%. These figures demonstrate how difficult it is to make a diagnosis (11).

Standard blood tests such as white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP), bilirubin, alanine transaminase (ALT), and albumin have been used as markers for acute appendicitis, and novel blood markers such as procalcitonin, interleukin-6 (IL-6), serum amyloid-A (SAA), granulocyte colonystimulating factor (G-CSF), and calprotectin (12).

WBC, bilirubin, and CRP are often used indicators for the diagnosis of acute appendicitis, however the severity of acute appendicitis could not be effectively measured due to poor sensitivity and specificity for separating CAA from UAA (13). However, it is critical to categorize the severity of acute appendicitis. There is currently no way for properly predicting severity.

Modern imaging may improve diagnostic accuracy, but its usage may be restricted by availability, cost, and radiation exposure. Difficulties in diagnosing acute appendicitis have led to an ongoing search for new diagnostic indicators that may reduce radiation exposure and expenditures (3).

So yet, no biomarker has been proved to have sufficient diagnostic performance to be employed therapeutically in isolation. This would imply that future research should focus on the development of fresh unique diagnostic tests and their clinical value, rather than repeating earlier research into already examined biomarkers (14).

Kessler et al. reported a 69% elevation in the WBC count of appendicitis patients and a 56% elevation in non-appendicitis patients, with a sensitivity of 77% and a specificity of 63% at a level above 10.000 cells/lL (15). Allister et al. reported that the appendicitis patients had elevated WBC values that were greater than those of the control subjects (14.200 cells/lL vs. 10.600 cells/lL) (16). A meta-analysis by Kabir et al. has demonstrated that a WBC count in isolation is not a good marker to use for diagnosing appendicitis as it can be elevated in response to any inflammatory condition (17). Shogilev et al. describe multiple different cut-off values ranging from 9.4 to 14.6 (x10^9/L) with no clear recommendation on which one is best in the context of identifying acute appendicitis (18). Keohane et al. found that WBC count had the lowest sensitivity (75%) and specificity (63%) of the three blood results they examined (12). The broad range of results is evident in a review by Shogilev et al., which showed that elevated WBC has a sensitivity range between 62% and 87%, and specificity between 39% and 82% (18). Results from our study (sensitivity 87.1%, specificity 32.9%) fall comfortably

within this broad range and are similar to recent metaanalysis by Shogilev et al.

The limited diagnostic accuracy of high WBC is most likely related to the presence of the underlying broad inflammatory process found in acute appendicitis, as well as a variety of other inflammatory disorders (14).

As a result, we think that the WBC count has limited diagnostic usefulness in distinguishing appendicitis in individuals with pain in the right lower quadrant.

When it comes to appendicitis, CRP also plays a varying role in the literature. CRP is an acute phase protein that can be utilized as a marker and diagnostic tool in several inflammatory and disorder-related episodes. A meta-analysis exploring the diagnostic accuracy of CRP revealed a very wide range of sensitivity and specificity (47-74%, and 55-89%, respectively) (19,20). Other studies investigating the role of CRP in diagnosing AA have reported sensitivities ranging between 76.5% and 95.6%, specifities ranging between 26.1% and 77.7%, and PPV 95.6. 2 (19). CRP has a higher sensitivity but a poorer specificity when compared to other measures. In this investigation, CRP levels were within normal limits in several AA patients. This situation may be explained by the fact that CRP levels begin to rise 12-24 hours after the onset of symptoms (19,21). Kabir et al. indicated that CRP is better for detecting complicated or late-stage appendicitis as it is a lag indicator and is less useful for early-stage appendicitis (17). Other papers have also demonstrated that it is less useful for acute appendicitis but significant elevation is suggestive of abscess or perforation (12).

Jasper J. Atema et al. conducted a large multicentre retrospective review of five cohort studies of 1024 adult patients with clinically suspected AA who presented with a duration of symptoms ranging from two h to five days were included (22). They found 12 (11.8%) patients among those with normal IM had a final diagnosis of appendicitis. The conclusion was: No WCC count or CRP level can safely and sufficiently confirm or exclude the suspected diagnosis of acute appendicitis in patients who present with abdominal pain of five days or less in duration (22). Beltran et al. accessed high sensitivity for WBC counts and CRP levels (sensitivity, 0.9-1.0) to differentiate between patients with and without appendicitis, but low specificity (0.2-0.4) was observed (23).

Elevated CRP has shown a similar broad range of results, with sensitivity ranging between 57% and 91% and specificity 26% and 84% (24). The CRP figures for the sensitivity and specificity in our research were 87.1% and 23.1%.

The limited specificity of increased CRP in these data is likely related to the presence of the underlying widespread inflammatory process found with acute appendicitis, as well as a number of other inflammatory diseases. As a result, we feel the CRP test has limited diagnostic usefulness in the diagnosis of appendicitis.

Although some studies have found hyperbilirubinemia to be effective in diagnosing acute appendicitis, its clinical use remains debatable. Over the last decade, researchers have looked at the link between hyperbilirubinemia and appendicitis. Hyperbilirubinemia occurs in systemic infections caused by a variety of diseases, including general peritonitis and sepsis, and multiple processes underlying hyperbilirubinemia in systemic infection have been identified (25). Bilirubin was reported to have the highest sum of sensitivity (0.61) and specificity (0.61) with a threshold of 15 µmol/L by Kaser et al (26).

On the other hand, Abdelhalim et al. demonstrated that an elevated bilirubin has a specificity of 0.84 and positive predictive value of 0.94 for acute appendicitis, higher than both WBC and CRP. However, its sensitivity was low at only 0.44. When only cases of perforated appendicitis were considered, it was found that the specificity of an elevated bilirubin was only 0.63 and the PPV was 0.20. They argued that these findings contradict prior research that recommended for the use of serum bilirubin to diagnose acute appendicitis with perforation (27). They discovered that serum bilirubin was a poor predictor of these individuals and would not advocate its use in detecting them (27). Also Nevler et al. suggested that elevated serum bilirubin and ALT levels not purely specific for acute appendicitis (3). Results from our study (sensitivity 85.7%, specificity 36.8%) are similar to by Abdelhalim et al (27).

TNF-α was one of the first soluble protein factors to be characterized in the setting of septic illness. Other members of the TNF superfamily have recently been found to have a comparable function to TNF in the pathophysiology of viral or inflammatory disorders (28,29). TWEAK was discovered to cause apoptosis in a human cancer cell line. It has previously attracted attention as a critical regulator of inflammation and cell death in numerous cells and pathological situations, despite having a far greater tissue distribution than TNF. TWEAK occurs as a membrane-bound protein as well as a soluble variety that results from endoproteinase proteolytic cleavage. Both TWEAK-variants are biologically active after attaching to the Fibroblast growth factor-inducible 14, which serves as their genuine receptor. TWEAK serum concentrations have lately been characterized as changing in the setting of several inflammatory and cardiovascular disorders (28).

The current study is the first to look at TWEAK levels in acute appendicitis. TWEAK, WBC, CRP, and direct bilirubin levels were compared. When compared to the other biomarkers evaluated, TWEAK had a high sensitivity and specificity. TWEAK outperformed and outperformed all other markers in all groups. We discovered that serum TWEAK levels were associated to the degree of inflammation in acute appendicitis. With a sensitivity

of 95.2 percent and a specificity of 65 percent, our study completely investigated the diagnostic utility of TWEAK in patients with acute appendicitis, indicating the potential benefit in identifying acute appendicitis. Our results also showed that serum TWEAK was significantly higher in the severe AA group than in the simple AA group. ROC analysis showed that TWEAK had the largest AUC [0.987 (0.965-1.000)] for diagnosis severe AA, having cut-off value 743 pg/mL (sensitivity 75%, specificity 95.2%).

TWEAK concentrations were considerably greater in acute appendicitis patients compared to healthy persons, and plasma TWEAK levels indicated significant differences between severe AA and severe AA, indicating that this TWEAK has predictive value as a severity measure for the first time.

Despite certain limitations, our study had a relatively small cohort for acute appendicitis and illness severity, as well as being a single-center investigation.

There was no published evidence on the role of TWEAK in patients with acute appendicitis prior to the current study. TWEAK may not be a disease-specific marker, but its amplification in any clinical situation, as demonstrated in acute appendicitis in our study, may allow us to anticipate disease severity and hence prognosis. Current and future large-scale population research will aid in determining the utility of TWEAK as an acute appendicitis biomarker and its possible application in clinical practice.

CONCLUSION

In conclusion, increased serum TWEAK levels may be used to aid in the diagnosis of acute appendicitis as well as as prognostic indicators for the severity of appendicitis.

Ethics Committee Approval: The ethical approval for this study was obtained from Göztepe Training and Research Hospital, İstanbul Medeniyet University Institutional Ethics Committee (Date: 15.08.2018, Decision No: 2018/315).

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ORİJİNAL ÇALIŞMA-ÖZET
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Akut apandisit şiddetinin belirlenmesinde tümör nekroz faktörü benzeri zayıf apoptoz indükleyicisinin (TWEAK) serum düzeylerinin rolü

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ÖZET

Giriş ve Amaç: En yaygın akut karın nedenlerinden biri akut apandisittir (AA). Pek çok klinik araştırmanın gösterdiği gibi, deneyimli cerrahlar için bile klinik teşhis sıklıkla zordur. Bu çalışmanın amacı, akut apandisit teşhisi için serum TWEAK düzeylerinin kullanılıp kullanılamayacağını görmekti.

Gereç ve Yöntem: Haziran 2017-Mayıs 2019 tarihleri arasında AA tanısıyla ameliyat olan tüm hastalar çalışmaya dahil edildi. TWEAK, WBC, CRP ve bilirubin seviyeleri karşılaştırıldı.

Bulgular: WBC, CRP ve bilirubin seviyeleri patolojiyle karşılaştırıldı. AA hastalarında üç kan göstergesinin tümü önemli ölçüde arttı. Bununla birlikte, basit AA'lı hastalarla şiddetli AA'lı hastalar arasında üç kan göstergesinin düzeylerinde istatistiksel olarak anlamlı bir fark görülmedi. TWEAK plazma konsantrasyonları, şiddetli AA'lı hastalarda sağlıklı kontrol ve NAA gruplarına göre önemli ölçüde daha yüksekti. TWEAK seviyeleri, ciddi AA'lı hastalarda, basit AA'lı hastalara kıyasla anlamlı olarak daha yüksekti.

Sonuç: Yükselen serum TWEAK seviyeleri, akut apandisit tanısının yanı sıra apandisit şiddeti için prognostik gösterge olarak kullanılabilir.

Anahtar Kelimeler: Akut apandisit, enflamasyon, belirteç, apandisit şiddeti, tümör nekroz faktörü benzeri zayıf apoptoz indükleyicisi

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ORIGINAL ARTICLE
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Surgical outcomes of resected cystic neoplasms of pancreas: Experience from a tertiary care centre in India

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ABSTRACT

Objective: Cystic neoplasms of the pancreas form a rare heterogeneous group of pancreatic tumors with variable clinical and diagnostic characteristics. Its incidence has increased in recent years due to improvements in cross-sectional imaging methods and awareness amongst surgeons.

Material and Methods: This study aimed to study the demographic, clinical, imaging, and histopathologic characteristics, incidence of malignancy and outcome of surgical resection of pancreatic cystic neoplasms. Retrospective analysis of 91 patients who underwent surgical resection for cystic neoplasm of the pancreas between 2006 to 2017 at a tertiary care institute was done.

Results: There was a female preponderance in the study with a mean age of 47.2 years. Abdominal pain (46.1%) and jaundice (23.1%) were the most common symptoms. Computed tomography and endoultrasound (EUS) were the most commonly used imaging methods in the study and demonstrated good surgical correlation. Pancreaticoduodenectomy (37.1%) was the most commonly performed procedure followed by distal pancreaticosplenectomy (31.8%). Of the lesions, 9.8% were found malignant. Solid pseudopapillary epithelial neoplasm (SPEN) (37.3%) was the most common neoplasm followed by serous (21.9%), intraductal papillary mucinous neoplasm (IPMN) (15.3%) and mucinous neoplasm (14.3%). Preoperative radiological diagnostic correlation was found to be 75-100% implying the importance of imaging in cystic neoplasms of the pancreas. Morbidity and mortality in the study group were 28.5% and 2.1%, respectively.

Conclusion: Pancreatic cystic neoplasms were mostly benign with female preponderance and presented in the younger age group with prevalence of SPEN higher than IPMN in our subcontinent. These can be reliably diagnosed on preoperative cross-sectional imaging, and surgical resection is associated with favourable outcome and acceptable morbidity.

Keywords: Pancreatic cystic neoplasms, clinico-pathological co-relation, surgical resection

INTRODUCTION

Pancreatic cystic neoplasms (PCN) are a rare entity of pancreatic cystic diseases that are diagnosed less frequently as compared to epithelial neoplasms of pancreas. It is found to have a prevalence of 2.6% in patients undergoing abdominal CT and 13% in patients undergoing MRI for unrelated complaints (1,2). The reported incidence in the United States has been found to be one in 100 hospitalized patients (3).

PCNs constitute around 50% of cystic diseases of the pancreas, which is substantial, and includes a spectrum of benign, premalignant and malignant entities (4). Hence, the management also ranges from observation in benign cystic lesions up to surgical resection in malignant neoplasms. Most borderline premalignant lesions pose a therapeutic dilemma, wherein the risk of post-surgical morbidity is to be weighed against malignant transformation. The role of surgery becomes crucial because cystic neoplasms have a better prognosis after resection as compared to solid tumors (5).

WHO has classified PCNs as serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), solid pseudopapillary neoplasm (SPEN) and intraductal papillary mucinous neoplasm (IPMN). SCNs are not known to be malignant, whereas MCN, and IPMN have a high risk of malignant transformation. SPEN, on the other hand, has been found to be locally invasive in few cases (4).

Surgical resection has been the gold standard of management of PCN for more than a decade although the indications have changed dramatically. Increased incidence of cross-sectional imaging (CT/MRI) and advent of endoscopic ultrasound have positively contributed to increased detection rates of PCN and have also led to decreased incidence of unnecessary resections (6).

Although many earlier studies (mainly from the United States and China) (7,8) stating the prevalence, clinico-pathological features and surgical outcomes of PCN

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have been reported, data with respect to Indian subcontinent is sparse. Prolonged asymptomatic state and non-specific symptoms might be probable causes for delay in referral to dedicated tertiary care centres. Authors believe that this is the largest single centre study pertaining to PCNs as applicable to the Indian subcontinent. The present study was undertaken to study the demographics, clinical profile of cystic neoplasms of the pancreas, to identify variables associated with potentially malignant and malignant lesions and the outcomes of surgical resection in such lesions in a retrospective cohort study.

MATERIAL and METHODS

Ninety-one patients who underwent resection for suspected/proven pancreatic cystic lesions at a tertiary care centre between June 2006 to June 2017 were included in this retrospective cohort study after approval from institutional ethics committee and review board. Data was collected through the institutional database. The study included patients with radiologically suspected cystic neoplasms of the pancreas who underwent resection. Non-surgical patients were excluded.

CT scan was done as the first cross sectional radiological imaging for all patients. MRI/MRCP and endoscopic ultrasound (EUS) were done in selective cases. Cyst fluid CEA and serum CA 19-9 levels were done in cases where imaging could not clearly differentiate MCN from SCN.

Parameters that were recorded included age at presentation, sex, symptoms, radiological findings, location of tumor, type of surgery, surgical complications, histology, recurrence rate and mortality. Postoperative complications were graded according to the Clavien-Dindo classification (9). Grading of pancreatic complications was done according to the International Study Group of Pancreatic Surgery guidelines (10). Follow-up was done on outpatient basis for a minimum period of two years. Follow-up data was collected from the outpatient records and/or telephonic conversations.

The collected data was analysed using SPSS 19.0 software (SPSS, Chicago, Illinois, USA). As there were no control groups in this study, only descriptive measures were used. All patients undergoing surgery for PCN during the study period were taken as sample size. The results are reported as mean, median and percentage.

RESULTS

Surgical data from a high-volume tertiary care centre was studied over a period of eleven years (2006-2017) during which total pancreatic resections performed were 693. Out of these, 91 resections were performed for PCNs. Eighty one cases were histologically proven to be PCN, whereas 10 cases were found to be benign lesions (e.g. simple cyst, pseudocyst, neuroendocrine tumor (NET), hydatid cyst etc.).

SPEN was found to be the most common (n= 34; 37.3%), followed by SCN (n= 20; 21.9%), IPMN (n= 14; 15.3%) and MCN (n= 13; 14.3%). PCNs typically showed a female preponderance with SPEN showing the highest female to male ratio (33:1; 97%). IPMN and benign cysts showed a fairly uniform distribution between males and females. Median age of presentation was lowest for SPEN (29 y), followed by SCN (52 y), IPMN (56 y) and MCN (58 y) (Table 1).

Abdominal pain was the most common presenting feature occurring in 42 patients (46.1%) followed by jaundice seen in 21 patients (23.1%). Of the patients, 19.7% were detected incidentally and 10.9% of the patients presented with a mass (Table 1).

Pancreatic head and body were more common tumor locations compared to tail in this study (n= 37 and 36 vs 16) (Table 2).

Preoperative CT was performed as the first line cross sectional radiological imaging for all cases (Figures 1,2). MRCP was performed in 12 cases wherein CT indicated a diagnosis of IPMN. EUS was performed in a total of 47 cases. CT and EUS, as combined diagnostic modality, had good surgical correlation leading to high diagnostic accuracy (Table 2). Imaging features suggestive of SCN and MCN were well-demarcated multicystic lesions with or without mural nodules. IPMNs were characterized by the dilatation of the main pancreatic duct, branch duct or both. SPEN characteristically showed both solid and cystic components without local infiltration.

Table 1. Patient demographics and clinical symptoms

	SCN	MCN	SPEN	IPMN	Miscellaneous	Total
Number of patients	20 (21.9%)	13 (14.3%)	34 (37.3%)	14 (15.3%)	10 (10.9%)	91
Median age (yrs)	52 (36-65)	58 (40-68)	29 (17-36)	56 (49-74)	43 (39-65)	
Sex (M:F)	5:15	2:11	1:33	6:8	4:6	
Incidental finding	6	2	4	3	3	18 (19.7%)
Abdominal pain	14	4	20	2	2	42 (46.1%)
Jaundice	6	1	4	8	2	21 (23.1%)
Mass		2	4	1	3	10 (10.9%)

SCN: Serous cystic neoplasm, MCN: Mucinous cystic neoplasm, SPEN: Solid pseudopapillary neoplasm, IPMN: Intraductal papillary mucinous neoplasm.

Table 2. Tumor characteristics and diagnostic correlation				
Type	**Head**	**Body/Neck**	**Tail**	**Size (cm), mean**
SCN	7	4	9	6.1 (3.1-13.2)
MCN Benign Malignant	 2 1	 4 3	 2 1	 7.1 (2.5-11.7) 7.5 (3.8-9.7)
SPEN	13	18	3	7 (2.9-12.4)
IPMN Non-invasive Invasive	 6 4	 4		 5.6 (2.7-10.6) 5.8 (4.1- 9)
Miscellaneous	4	2	4	6.2 (4-11.1)
Total	37	36	16	
Radiological and pathological correlation				
Type	**CECT (N)**	**MRI/MRCP (N)**	**EUS (N)**	**Correlation with surgical diagnosis (%)**
SCN	20		12	15/20 (75%)
MCN	13		9	10/13 (76.9%)
SPEN	34		10	32/34 (94%)
IPMN	14	12	8	14/14 (100%)
Miscellaneous	10		8	9/10 (90%)

CECT: Contrast enhanced CT, MRI: Magnetic resonance imaging, EUS: Endoultrasound.

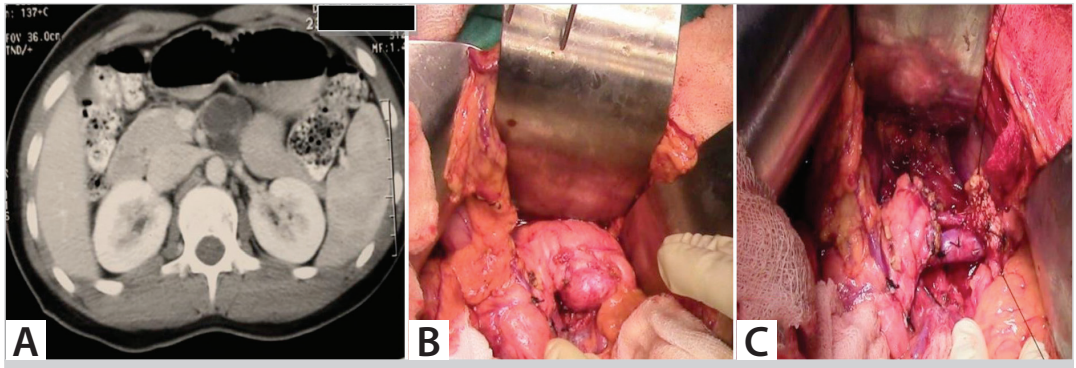

Figure 1. MCN. **A.** CECT showing a cystic lesion in body of pancreas. **B.** Intraoperative image of tumor and **C.** central pancreatectomy.

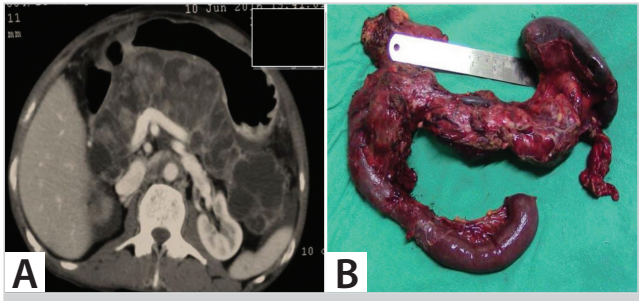

Figure 2. IPMN. **A.** CECT showing multiple cystic SOL involving the entire pancreas. **B.** Total pacreatectomy with splenectomy specimen.

EUS guided cyst fluid analysis/FNAC was done only in doubtful cases. It was found that elevated CEA levels correlated well with MCN. However, its absence did not rule out MCN. Elevated serum CA 19-9 and amylase levels were found to be poor predictors of cystic neoplasms (Table 3).

Indications for surgery included patients who were symptomatic and who fulfilled the criteria as per modified Fukuoka guidelines (11,12). Pancreatoduodenectomy (PD) was the most commonly performed surgical procedure (34; 37.3%), followed by distal pancreatectomy (DP, 29; 31.8%). Spleen preservation was done in nine cases (9.8%) that allowed a safe resection margin.

Table 3. Tumor marker characteristics

Type	Performed	Elevated cyst fluid amylase	Elevated cyst fluid CEA	Elevated serum CA19-9
SCN	10	-	4	3
MCN	7	-	5	3
SPEN	-			
IPMN	4	1	1	-
Miscellaneous	5	2	1	1

Table 4. Type of resection and complications

Type of resection	**n**				
Pancreatoduodenectomy (PD)	34				
PD with portal vein resection	1				
Distal pancreatosplenectomy (DPS)	29				
Spleen preserving distal pancreatectomy (SPDP)	9				
Central pancreatectomy	7				
Total pancreatectomy	2				
Enucleation	5				
Inoperable/palliative procedure/drainage	4				
Complications associated with type of procedure					
Type of resection	**POPF-A**	**POPF-B**	**POPF-C**	**PPH**	**DGE**
Pancreatoduodenectomy (PD)	9	4	2	2	9
PD with portal vein resection	-	-	-	-	-
Distal pancreatosplenectomy (DPS)	3	1	-	1	1
Spleen preserving distal pancreatectomy (SPDP)	2	-	-	-	-
Central Pancreatectomy	3	1	-	-	1
Total Pancreatectomy	-	-	-	-	-
Enucleation	-	-	-	-	-
Total (n)	17	6	2	3	11

POPF: Post-operative pancreatic fistula, PPH: Post-pancreatectomy hemorrhage, DGE: Delayed gastric emptying.

Central pancreatectomy was done in seven cases (7.6%) where adequate distal pancreas was preserved. Enucleation was performed in five (5.4%) cases where tumors were less than 3 cm, located away from the main pancreatic duct. PD with sleeve resection of the portal vein had to be performed in one case of malignant MCN with local infiltration of the portal vein. Total pancreatectomy was performed in two cases (2.2%) of IPMN that showed diffuse involvement of the pancreas (Table 4, Figures 1,2). Standard lymphadenectomy was performed as per ISGPS definition (13).

Assessment of the margin status on frozen section is crucial in IPMN resections. The authors routinely perform frozen section for margin status in IPMN. However, not so for other PCNs. There is an ongoing debate on the management of those patients with positive margins for benign IPMN with low-grade dysplasia. In our centre, such cases are not subjected to additional resections, whereas IPMN with high-grade dysplasia are treated with extended resections.

On histopathological evaluation, invasive lesions were found in nine cases (9.8%), out of which five were MCNs and four IPMNs (Table 2).

Postoperative pancreatic fistula was the most common complication encountered, type A was the most frequent (19%), followed by type B and C (6.5% and 2.1% respectively). Post pancreatectomy haemorrhage was reported in three cases and delayed gastric emptying occurred in 11 patients (Table 4).

Major complications were classified according to the Clavien-Dindo classification and included type B and C pancreatic fistula, post pancreatectomy haemorrhage and post-operative death within the first 30 days of hospitalisation. The authors found a total morbidity of 28.5%.

Table 5. Comparative analysis of large scale studies on PCN vs the present study

Characteristics	USA (31)	French (23)	China (20)	Our study
Institution	Single	Multi	Multi	Single
No of patients	1424	398 (396 PCNs)	2251	91
M:F ratio	1:2.3	1:6	1:2.4	1:4
Age at presentation (years)	63	54.5	47.5	47.6
Symptomatic (%)	51.5	57	-	80.3
Size (median in cm)	3	5.6	-	6.5
Location (%)				
Head	42	32.5	-	40.6
Body & Tail	58	67.5	-	59.4
Histology (%)				
SCN	23	32.6	30	21.9
MCN	11	28.5	16.2	14.3
SPEN	2	4.2	31.6	37.3
IPMN	27	10	22	15.3
Incidence of malignancy (%)	23	19.6	0.6-31.2	9.8
Morbidity (%)	35	-	-	28.5
Mortality (%)	0.7	2.7	-	2.1

Patients were followed up on outpatient basis for a minimum period of two years. Ten patients were lost to follow up, and 10 patients with benign cystic lesions on histopathology were excluded from follow-up. A total of 71 patients were followed up for a period ranging from two years to eight years (median follow-up of five years).

A total of two postoperative mortalities were reported (2.1%) due to pancreatic fistula leading to multi organ failure. One patient, who underwent total pancreatectomy for IPMN, died at home six months after surgery probably due to hypoglycaemic attack.

Recurrence was reported in two patients who underwent resection for MCN. The first patient presented with hepatic metastases and second one presented with loco-regional recurrence with encasement of hepatic artery and portal vein. Both patients were referred to the medical oncology department for palliative chemotherapy. Both patients died within six months of completion of chemotherapy.

DISCUSSION

Pancreatic cystic neoplasms have been a subject of keen academic interest since the past few years. Probable reasons for this are increased detection rate and change in surgical guidelines (11,12). Rate of surgical resection has increased in the past few years (7,14).

In the present study, SPEN was found to be the most commonly occurring PCN. This was in conformance with three other prior studies, one of which is from the author's institution (7,15,16) (Table 5). This could either mean increased surgical resections for SPEN due to symptomatic presentation and large size as found in our study, or might indicate a true increase in the prevalence of SPEN. Greater incidence of SPEN has been found in the Indian and Chinese population as compared to the western countries (17-20).

The prevalence of SCN has not changed significantly as they are largely considered to be benign. In the present study, major surgical indications for radiologically proven SCN were large symptomatic tumors and a diagnostic suspicion of other premalignant lesions. Mucinous tumors were reported in 14.3% of the patients that correlated with the Chinese experience (20). Surgical correlation was evident in 76.9% cases, which, however, did not affect the decision to resect as it was known to be premalignant. Prevalence of IPMN was found to be rather low (15%) as compared to data from the USA and China (17,20). This could indicate the confounding role of ethnic, genetic and racial factors. Furthermore, as a tertiary care referral centre, mostly symptomatic and large tumors were referred for further management to the study center. Additionally, PCNs on observation were not included in this study, which may have underestimated the actual prevalence of PCNs.

All PCNs except IPMN showed female preponderance similar to previous studies (20,21). A significantly higher rate of occurrence of MCN in females could be due to the possible role of human chorionic gonadotrophin (22). The mean age of presentation was found to be lesser in this study (47.1 y) as compared to the American literature (14,21). Increased prevalence of SPEN in this

study and symptomatic presentation overall could have led to earlier diagnosis. MCN and SPEN commonly occurred in the body as has been indicated in a previous study although the overall occurrence was similar in both the head and the body region (2). MCN and SPEN present with larger masses more frequently. The authors are of the opinion that tumors located in the body tend to develop symptoms later as compared to those located in the head region. A French study has also confirmed the above finding (23).

Abdominal pain was the most common presenting feature followed by jaundice and mass. About 19.7% of the cases were detected incidentally on cross sectional CT for unrelated complaints, which also meant that about 80% of the patients were symptomatic at presentation that may have contributed to earlier diagnosis and younger age at presentation.

A good diagnostic correlation with surgical diagnosis was observed in this study with CT and EUS. Ours being an academic centre, EUS and MRCP could be done liberally in conjunction with CT without cost constraints. Elevated cyst fluid CEA levels correlated well with MCN. Although CEA levels >192-200 ng/mL strongly indicate mucinous cysts, it does not distinguish between benign lesions and malignant ones (24). In addition, serum CA 19-9 levels >37 IU/mL is a strong predictor of invasive cancer in IPMN (25). It, however, lacks specificity. Hence, it is prudent to combine these tumor markers with EUS morphology (26). The overall incidence of malignancy was found to be 9.8% in this study, which was lower than previous studies (14,21). Authors believe that a comparatively smaller sample size may have resulted in this variation.

Type of surgery was guided by location and size of the tumor (27). A reported perioperative mortality of 2.1% has been noted in this study. A similar mortality rate has been reported by a Swiss study of 650 patients (28).

Recurrences are relatively uncommon in benign and borderline malignant PCNs; however, invasive lesions are reported to have recurrence rates similar to those of adenocarcinomas. Due to high recurrence rates and similar to conventional pancreatic ductal adenocarcinoma, a structured follow-up is recommended after surgery for all resected cystic lesions with high-grade dysplasia or invasive carcinoma (12). The risk of recurrence of non-invasive IPMN is much lower when compared to invasive IPMN and is estimated around 5-9% (29). The recurrence of non-invasive lesions is almost always non-invasive and occurs after a median of more than four years after resection (30).

The authors also compared their data from the present study to other previously published large studies on PCN (20,23,31). There were a few noteworthy features that were distinct to this study. For instance, the authors found a higher percentage of SPEN, a comparatively younger age at presentation and a lower incidence of invasive malignancy as compared to some of the prior publications. Demographic differences are noticed in the Indian population as compared to Western and Chinese population.

Although this is believed to be the largest single institution study on PCNs in India, it is not without flaws. A smaller sample size, exclusion of non-surgical cases on observation may have underestimated the true prevalence of this disease.

CONCLUSION

This study confirms that most cystic neoplasms of the pancreas are benign and can be reliably diagnosed with preoperative imaging in the form of CECT and EUS. Rate of surgical resection has increased due to improved detection on cross sectional imaging, and most patients can be offered surgery with acceptable morbidity. This study may act as a potential starting point for future studies with a more archetypal study population.

Ethics Committee Approval: This study was approved by NH Institutional Ethics Committee (Review letter no: 1911/2022, Date: 28.06.2022).

Informed Consent: Informed consent was obtained from the son of the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - DS; Design - NB; Supervision - NB; Data Collection and/or Processing - DS; Analysis and/or Interpretation - DS; Literature Review - NB; Writer- DS, NB; Critical Review - DS, NB.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Pankreasın cerrahi uygulanmış kistik neoplazilerinin sonuçları: Hindistan'daki üçüncü basamak bir bakım merkezinin deneyimi

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ÖZET

Giriş ve Amaç: Pankreasın kistik neoplazmaları, değişken klinik ve tanısal özelliklere sahip, nadir görülen, heterojen bir pankreatik tümör grubu oluşturur. Son yıllarda kesitsel görüntüleme yöntemlerindeki gelişmeler ve cerrahlar arasındaki farkındalık nedeniyle insidansı artmıştır. Bu çalışma, pankreas kistik neoplazmalarının demografik, klinik, görüntüleme ve histopatolojik özelliklerini, malignite insidansını ve cerrahi rezeksiyon sonuçlarını incelemeyi amaçladı.

Gereç ve Yöntem: 2006-2017 yılları arasında üçüncü basamak bir sağlık kuruluşunda pankreas kistik neoplazmı nedeniyle cerrahi rezeksiyon uygulanan 91 hastanın retrospektif analizi yapıldı.

Bulgular: Çalışmada yaş ortalaması 47,2 idi ve kadın ağırlıklıydı. Karın ağrısı (%46,1) ve sarılık (%23,1) en sık görülen semptomlardı. Bilgisayarlı tomografi ve endoskopik ultrason (EUS) çalışmada en sık kullanılan görüntüleme yöntemleriydi ve iyi bir cerrahi korelasyon gösterdi. Pankreatikoduodenektomi (%37,1) en sık uygulanan prosedürdü ve bunu %31,8 ile distal pankreatikosplenektomi izledi. Lezyonların %9,8'i malign bulundu. Solid psödopapiller epitelyal neoplazm (SPEN) (%37,3) en sık görülen neoplazmdı, bunu seröz (%21,9), intraduktal papiller müsinöz neoplazm (IPMN) (%15,3) ve müsinöz neoplazm (%14,3) izledi. Preoperatif radyolojik tanı korelasyonunun %75-100 olması pankreasın kistik neoplazmalarında görüntülemenin önemini göstermektedir. Çalışma grubunda morbidite ve mortalite sırasıyla %28,5 ve %2,1 idi.

Sonuç: Pankreatik kistik neoplazmalar çoğunlukla iyi huyluydu ve kadın ağırlıklıydı ve alt kıtamızda SPEN prevalansı IPMN'den daha yüksek olan genç yaş grubunda ortaya çıktı. Bunlar, preoperatif kesitsel görüntülemede güvenilir bir şekilde teşhis edilebilir ve cerrahi rezeksiyon, olumlu sonuç ve kabul edilebilir morbiditeyle ilişkilidir.

Anahtar Kelimeler: Pankreasın kistik neoplazileri, klinik-patolojik ilişki, cerrahi rezeksiyon

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ORIGINAL ARTICLE
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Frequency of axillary nodal complete pathological response of breast cancer patients in neoadjuvant chemotherapy setting: A cross-sectional study

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ABSTRACT

Objective: Pathological complete response (pCR) occurs in about 20-30% of patients undergoing systemic neoadjuvant therapy. This leads to the idea of sparing the patient the morbidity associated with axillary surgery. "Wait and watch" policy for cancers which achieve complete pathological response on neoadjuvant systemic therapy is a well-established practice in various cancers like the esophagus, rectum and larynx. This has led to organ preservation protocols being practiced worldwide for these cancers without affecting the overall survival of the patient. We believe patients undergoing a complete pathological response in the breast may be spared axillary surgery. Axillary surgery leads to morbidity and extra financial burden with no added advantage in survival.

Material and Methods: A total of 326 patients with breast cancer who had received neoadjuvant systemic chemotherapy from 2015 to 2020 were included in our retrospective study. Final histopathology of the breast and axillary surgery was noted to report the frequency of complete pathological response. The frequency of positive nodal disease with respect to stage, grade and type of cancer was measured.

Results: Among 326 patients, our study showed that 53% of patients with complete pathological response in breast also had complete response in the axilla compared to 43% with incomplete pathological response. No significant difference was found for age, menopausal status, initial tumor size when patients with complete pathological response were compared to non or partial responders. The rate of complete pathological response was higher in patients with clinically node negative patients after NACT, hormone negative, HER2 positive and triple negative population.

Conclusion: Our results indicated that 53% of the patients who developed complete pathological response in the breast underwent needless axillary procedure. Axillary surgery can be staged after the breast surgery if residual tumor is present on the histopathological specimen. In case of pCR, omission of axillary surgery can be considered. However, a larger population, multi-centric studies are needed for treatment guidelines.

Keywords: Neoadjuvant chemotherapy, axillary nodal response, breast cancer

INTRODUCTION

Pakistan has reported the highest incidence of breast cancer among Asian countries except Israel. According to a study, the projected incidence of breast cancer will rise to approximately from 23.1% in 2020 to 60.7% in 2025 (1,2). In Pakistan, one in every nine woman is at risk of developing breast cancer (3). The mortality rate in our country is one of the highest in South Asia owing to ignorance, lack of awareness and the dearth of a centralized screening program (3). Our breast cancer patients develop cancer at a comparatively younger age and present more frequently with an advanced stage cancer (4,5). Health prediction models point towards an increasing incidence in breast cancer worldwide including Pakistan (6,7). Breast cancer will be more prevalent in younger women, leading to more distress and affecting more families. Despite higher incidence of the disease, there are fewer facilities available countrywide to perform sentinel node biopsy, and hence, axillary dissection is still a standard procedure to address the axilla regardless of axillary nodal status in neoadjuvant setting resulting in additional morbidity of arm swelling and lymphedema.

Surgical management of the axilla in curable breast cancer has undergone a major paradigm shift in the last few decades. Historically, Halstead mastectomy was the

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biggest achievement endorsing the concept to address local disease aggressively which resulted in extensive mutilation and morbidity, afterwards in 1902, modified radical mastectomy emerged and was widely accepted endorsing the fact that breast cancer is a systemic disease and hence local treatment should not be aggressive in presence of effective adjuvant chemotherapy though carrying the risk of lymphedema and arm swelling (8-14).

In the late 20s, sentinel node biopsy became the preferred method for staging early breast cancer patients with clinically impalpable lymph nodes in the axilla (15-18). Trials like (NSABP-32, ALMANAC, Sentinella-GIVOM) proved SLNB was safe and effective in determining axillary metastasis and should be used instead of a formal axillary dissection in early breast cancer patients without clinically palpable nodes in the axilla (19-21). The ACOSOG Z0011 trial further established this by showing no benefit of ALND if one or two sentinel nodes were found positive for cancer in breast conservation setting (22). However, the use of sentinel lymph node biopsy after neoadjuvant treatment for breast cancer is not widely established. Higher false negative rate and lower detection rate after systemic therapy, as shown by the SENTINA trial and other studies, can be reduced with dual mapping and identification of at least three SLNs perioperatively.

Pathological complete response (pCR) occurs in about 20-30% of patients undergoing systemic neoadjuvant therapy. This leads to the idea of sparing the patient the morbidity associated with axillary surgery (23). A pCR is defined as no residual invasive disease in the breast and the axillary lymph nodes with rates varying according to the different breast cancer (BC) subtype. Hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative 7-16% hormone receptor-positive and HER2-positive 30-40%, hormone receptor-negative and HER2-positive 50-70%, triple-negative BC (TNBC) 25-33% (24).

"Wait and watch" policy for cancers which achieve complete pathological response on neoadjuvant systemic therapy is a well-established practice in various cancers like the esophagus, rectum and larynx (25). This has led to organ preservation protocols being practiced worldwide for these cancers without affecting the overall survival of the patient (25). We believe that patients undergoing complete pathological response in the breast may be spared an axillary surgery. Axillary surgery leads to morbidity and extra financial burden with no added advantage in survival as the patient is already cancer free after neoadjuvant chemotherapy.

This study will help us determine the subset of patients who can be spared an axillary surgery. In addition to saving the morbidity of an open procedure, this will lead to economic benefit for the patient and the society as a whole.

MATERIAL and METHODS

Between January 1st, 2015 to December 31st, 2020, the data of a total of 326 patients with diagnosed breast cancer and who underwent neoadjuvant chemotherapy followed by surgery was retrospectively included in this study. Tumor stage and immuno-histochemistry were recorded along with the final histopathology report of the breast and the axilla. All patients included in the study were above 18 years of age with diagnosed breast cancer, who underwent neoadjuvant chemotherapy. However, the patients who were operated on outside our hospital or whose histopathology specimen was reported and tested elsewhere and the patients who had incomplete medical records were excluded from the study. Sentinel node biopsy was performed by dual dye technique (radio-isotope and methylene blue dye), at least three sentinel nodes were retrieved in post neo-adjuvant patients. In case three nodes could not be found, the procedure was converted to formal axillary dissection to reduce false negative rate. In addition, if one or more sentinel nodes were positive for micro or macro metastasis, axillary dissection was performed.

The ethical exemption for this study was approved by the ethics review committee. Patients' personal information was deleted at the time of analysis and all responses were de-identified after data entry to maintain anonymization. No techniques were used to impetrate missing data so as to prevent bias in the study. Demographical and tumor related characteristics were calculated as descriptive. Chi-square test was used to compare the groups of achievers and non-achievers of complete pathological response with respect to patient's demographic and cancer related data and the patients who received negative axillary lymph node status over histopathology after axillary lymph node dissection (ALND). A logistic regression model was fitted to identify the predictors associated with complete pathological response and negative axillary lymph node status after ALND for the patients receiving NACT. The data was analyzed through SPSS software version. 22.0.

RESULTS

A total number of 326 accessible patients receiving NACT were included into the study. Mean age of the patients was 50.2 years. The median of abnormal breast lymph nodes prior to chemotherapy was one (SD= 0.897, R= 0-5) while the median of abnormal breast lymph nodes after chemotherapy was zero (SD= 0.792, R= 0-3). Median tumor size was 30 mm (SD= 12.6, R= 1-167). A total of 191 patients (65%) underwent core biopsy of the lymph nodes for metastasis, a median of three sentinel lymph nodes were removed (SD= 3, R= 0-4) among which a median of zero lymph nodes were positive on histopathology. Around half of the patients (53%) had a cancer clinical stage of T2N1, with most patients having grade II CA (73%) in the study.

Among the assayed cases, most patients had ER-/PR-/HER2+ status on histopathology (37.5%). Later, during follow-up, a total of 197 patients (67.5%) underwent axillary lymph node dissection, the positive lymph nodes on biopsy had a median of one (SD= 3.41, R= 0-20). Most patients (56.7%) underwent modified radical mastectomy. Baseline characteristics of the patients and tumors are described in Table 1.

Complete versus incomplete pathological response of the tumor and axillary lymph nodes in response to NACT were analyzed through univariate analysis and summarized in Table 2. A total of 104 patients (67.1%) achieved complete pathological response in the breast after NACT. It was observed that equivalent percentages of the patients with age group <50 and >50 achieved complete pathological response, which was statistically significant (<50 and >50= 30% and 70%; p= .001). Premenopausal women were observed to achieve pCR slightly higher than postmenopausal women (pre MP= 33.6%, post MP= 29.2%; p= 0.58), but the difference was not statically significant. Similarly, patients with clinical stage T0, T1 and T2 achieved pCR more than those with high clinical stage of T3 and T4, yet the difference was not significant (T0, T1, T2 and T3, T4 group= 31.3% and 25%; p= 0.48). The percentage of the patients with grade I, II and III achieving complete response was significantly comparable (grade I, II and III, group= 29% and 35%; p= 0.01). Patients with pre-treatment estrogen negative status achieved high pCR rate than patients with pre-treatment estrogen positive status (estrogen positive group= 17%, estrogen negative group= 43%; p= 0.001).

Potential predictors for complete pathological response were analyzed by fitting into a logistic regression model. Patients of age <50 years had very high odds of achieving pCR after NACT, but the result was insignificant (OR= 2.8; 1.07 CI, p= 0.30). Similarly, pre-menopausal women were very likely to achieve pCR after NACT (OR= 3.92; 1.83 CI, p= 0.18). Patients with grade I and II had fair chances of achieving pCR (OR= 1.4; .35 CI, p= 0.56). The patient group with estrogen negative status prior to treatment had very higher odds of achieving complete pathological response after NACT (OR= 4.5; 6.94 CI, p= 0.01). The details are summarized in Table 3. The patient group having negative lymph nodes post ALND achieved higher percentage of pCR than patients with positive lymph node status post ALND (negative LN and positive LN= 53% and 3%, p= 0.001) as illustrated in Figure 1.

A logistic regression model was fitted for analyzing the potential predictors of negative axillary lymph nodes status achievement after axillary lymph node dissection (ALND) in patients receiving NACT. The details are given in Table 4. The patients with initial tumor size >20 mm prior to NACT had high chances of achieving negative axillary nodal status on histopathology (OR= 1.6; .5, p= 0.48). The patient group with estrogen negative tumor had fair chances of achieving negative axillary response post NACT (OR= 1.3; .34 CI, p= 0.56).

DISCUSSION

After significant achievements in the de-escalation of breast surgery using neoadjuvant chemotherapy, there is growing interest in the de-escalation of axillary surgery. Our study reported that 67.1% of 326 post neoadjuvant patients achieved complete pathological response in the breast, and of these, 53% of the patients also had complete response in the axilla. In a recent study by Sanaz, it has been reported that 97% with breast pCR had a negative lymph node metastasis comparing to 71.6% without pCR (26). In another study at Samsung medical center, it has been evaluated that in a study of 1044 patients, 87% of patients with breast pCR have also achieved axillary pCR with overall 51% patients achieved pCR in total study (27). We reported clinically N0 status after neoadjuvant chemotherapy, and hormone receptor negative/HER2 positive tumors were most likely to achieve pCR in the axilla. Similar rates of pCR have been seen in a recently published study by Lim et al., where ~44% of HER2+ patients and ~37% of triple negative patients achieved pathological complete response (28). Our study also showed a positive relation between the receptor status and breast and axillary pCR with 41% patients with initial ER-status achieving pCR compared to 17.1% patients with ER+ tumors with 4.5 OR, 6.94 CI .01 p-value. For patients with both breast and axilla pCR response, when compared with subtypes according to receptor status, it was observed that in HER2+ patients, 64% and in triple negative group patients, 37.9% achieved pCR. Achieving breast pCR after neoadjuvant treatment has been linked with better survival outcomes (29). However, Kuerer et al. were the first to report relationship between breast and axillary complete response in 1998 which brought attention to possible de-escalation treatment strategies in this patient population (30). Our findings were also in line with the National Cancer Database (NCDB) analysis reporting complete response in 30.821 cT1-2N0-1 breast cancers for HER2-positive (*44%) and triple-negative (*37%) subtypes (31).

In another study, Tadros et al. have demonstrated a strong correlation between breast pCR and axilla pCR in their study. They have noted that breast pCR was higher in triple negative group with 37.5% compared to HER2+ group with 35.7%, and further they have concluded that 527 patients who achieved pCR with NST having HER2+ and triple negative breast cancer were all later found to have axillay pCR in the nodes (32). A similar study showed a strong correlation in achieving breast pCR with NST in patients with ER-, triple negative and ER+ HER2+ patients although they received low PCR rates in ER+ HER2- patients (33).

Table 1. Baseline characteristics of the patients and tumors and axillary node status	
Characteristics	**n (%)**
Age (mean), years	50.2
Menopausal status	
Pre-menopausal	148 (46.7)
Post-menopausal	146 (46.1)
Peri-menopausal	23 (7.3)
Number of abnormal lymph nodes pre-chemo	
No abnormal lymph node	59 (19)
1	156 (50.2)
2	63 (20.3)
3	32 (10.3)
5	1 (0.3)
Number of abnormal lymph nodes post-chemo	
No abnormal lymph node	214 (67.1)
1	45 (20.6)
2	34 (9.0)
3	25 (3.2)
Core biopsy of lymph nodes positive for metastasis	191(65)
Clinical stage	
T1N0	8 (4.8)
T1N1	17 (10.2)
T2N0	21 (12.7)
T2N1	88 (53.0)
T3N0	4 (2.4)
T3N1	20 (12.0)
T4N0	2 (1.2)
T4N1	6 (3.6)
Histology of invasive ductal CA	171 (96.6)
Grade	
I	10 (3.2)
II	228 (73.1)
III	74 (23.7)
Size of invasive focus	
Complete response	88 (31)
<1 cm	79 (27.8)
1-2 cm	47 (16.5)
>2 cm	69 (24.3)
4 cm	1 (0.4)
Receptor status	
ER-/PR-/HER2-	116 (37.5)
ER/PR/HER2+	51 (16.5)
ER/PR+ HER2-	99 (32)
ER/PR- HER2+	38 (12.3)

Table 1. Baseline characteristics of the patients and tumors and axillary node status (continue)	
Number of sentinel lymph nodes retrieved	
No sentinel lymph node retrieved	44 (28)
1	18(11.5)
2	13 (8.3)
>3	42 (26.8)
Number of lymph nodes positive on histopathology	
Complete response pathology	126 (68.1)
1	24 (13.0)
2	10 (5.4)
3	4 (2.2)
>3	19 (10.3)
Axillary lymph node dissection given	197 (67.5)
Nodes recovered in ALND	
None	76 (39)
<3	1 (0.5)
<10	8 (4.1)
<20	70 (35.9)
<30	35 (17.9)
<40	5 (2.6)
Positive lymph node biopsy	112 (90.3)
No. of positive nodes after ALND	
None	60 (48.8)
<3	32 (26.0)
<5	9 (7.3)
<10	16 (13.0)
<20	6 (4.9)
Type of surgery	
Mastectomy + SLNBx + AxLND	160 (56.7)
Mastectomy + SLNB	47 (16.7)
BCS + ALND	44 (15.6)
BCS + SLNB	31 (11.0)

SLNB: Sentinel lymph node biopsy, AxLND: Axillary lymph node dissection, BCS: Breast conserving surgery, ER: Estrogen receptor, PR: Progesterone receptor, SLN: Sentinel lymph node biopsy, BCS: Breast conserving surgery, ALND: Axillary lymph node dissection.

A large randomized prospective trial, ACSOG Z1071, has also reported similar responses to neoadjuvant therapy with regard to tumor biology. Seven hundred and one patients with cT1-T4, N1-N2 disease were recruited. Of triple negative tumors, 47% achieved complete pathological response, amongst these, 80% of patients also achieved complete response in the axilla (34-36).

As of now, surgical treatment remains gold standard for patients who have complete response in the breast. Although multiple trials like RESPONDER, NRG-BR005, MICRA trials are underway to identify group of patients with exceptional response to NAST identified with core needle biopsy of the tumor bed, these patients can avoid breast surgery. However, the current reported false negative rates by these studies are higher than the accepted threshold (37).

Retrospective data with a small cohort is one of the limitations of this study. Nevertheless, our results are in accordance with large randomized trials like ACSOG Z1071 supporting its applicability.

The idea that patients who achieve breast pCR can be spared of surgery leads to an exciting pathway of de-escalation in breast cancer treatment. Thus, identifying the group of patients who are more sensitive to NACT, refinement of techniques to reduce false negative rate of core needle biopsy of the tumor bed to

Table 2. Univariate analysis of patient and tumor characteristics and comparison between complete versus incomplete pathological response of primary tumor and axillary nodes after neoadjuvant chemotherapy

	Complete response		Incomplete response		
Characteristic	**No.**	**%**	**No.**	**%**	**p**
Total patients	104	67.1	51	32.9	
Patient's age (years)					
≤50	47	30.3	108	69.7	
>50	41	31.7	88	68.2	.00
Menopausal status					
Pre-menopausal	51	33.6	101	66.4	
Post-menopausal	37	29.2	94	71.8	.58
Clinical stage					
T0, T1 and T2	42	31.3	92	68.7	
T3 and T4	8	25	24	75	.48
Histopathological finding					
Ductal invasive CA	51	29.8	120	70.2	
Other	0	-	6	100	.11
Grade					
0	0	-	1	100	
I, II	61	29.3	147	70.7	
III, IV	26	35.1	48	64.9	.01
Receptor status					
Estrogen positive	23	17.2	111	82.8	.01
Estrogen negative	62	43.4	81	56.6	.00
HER2+	57	64.0	32	34.9	.01
Triple negative	44	37.9	72	62	.00

Table 3. Logistic regression analysis. Association of patient's demographics, estrogen receptor status and tumor characteristics with complete pathologic response

Characteristics	**OR**	**Wald 95% CI**	**p**
Age <50 years	2.8	1.07	.30
Pre-menopausal	3.92	1.83	.18
Tumor grade I, II	1.4	.35	.56
Estrogen negative	4.5	6.94	.01

OR: Odds ratio.

detect pCR will not only help to minimize breast surgery but also recognize selective patients who are more likely to achieve axillary pCR in association with the breast, and hence, the omission of axillary surgery can also be considered.

Ethics Committee Approval: This study was approved by Aga Khan University Ethics Review Committee (Decision no: 2021-6022-17743, Date: 05.05.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AAK; Design - SSD; Supervision - LV; Fundings - LV; Data Collection and/or Processing - AAK, SSD, AK; Analysis and/or Interpretation - UT; Literature Search - SJ; Writing Manuscript - SSD, AAK; Critical Reviews - LV.

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

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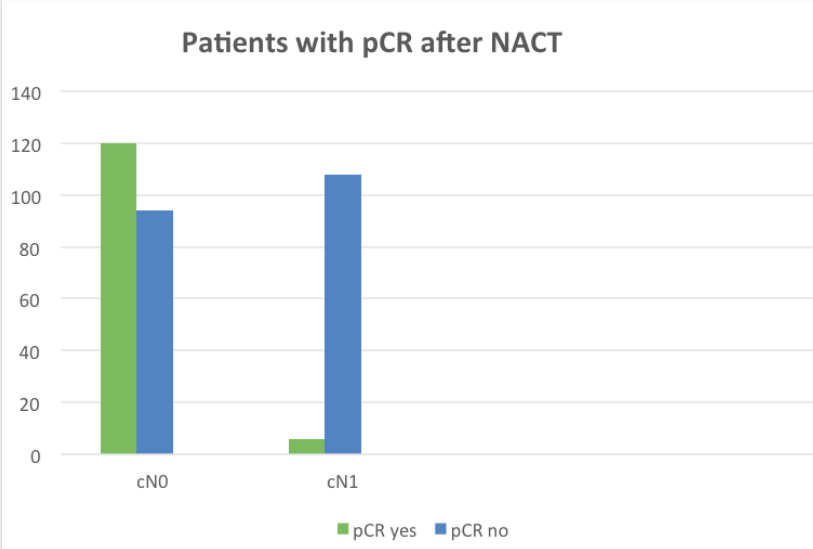

Figure 1. Illustrating the count of the achievers and non-achievers of complete pathological response among patient groups who were clinically node negative versus clinically node positive after NACT.

Table 4. Logistic regression analysis. Association of patient's demographics, estrogen receptor status and tumor characteristics with negative lymph nodes after axillary lymph node dissection

Characteristics	OR	Wald 95% CI	p
Initial tumor size >20 mm	1.6	.5	.48
Estrogen negative receptor status	1.3	.34	.56

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ORİJİNAL ÇALIŞMA-ÖZET
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Neoadjuvan kemoterapi ortamında meme kanseri hastalarında aksiller nodal tam patolojik yanıtın sıklığı: Kesitsel bir çalışma

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ÖZET

Giriş ve Amaç: Sistemik neoadjuvan tedavi gören hastaların yaklaşık %20-30'unda patolojik tam yanıt (pCR) oluşur. Bu da hastayı aksiller cerrahiyle ilişkili morbiditeden koruma fikrine yol açar. Neoadjuvan sistemik tedaviyle tam patolojik yanıt alınan kanserler için "bekle ve izle" politikası; özofagus, rektum ve larenks gibi çeşitli kanserlerde köklü bir uygulamadır. Hastanın genel sağkalımını etkilemeden bir memede tam bir patolojik yanıt geçiren hastaların aksiller cerrahiden kurtulabileceğine inanıyoruz. Aksiller cerrahi, morbiditeye ve ekstra mali yüke yol açarken sağkalımda herhangi bir ek avantaj sağlamaz.

Gereç ve Yöntem: Retrospektif çalışmamıza 2015-2020 yılları arasında neoadjuvan sistemik kemoterapi alan toplam 326 meme kanserli hasta dahil edildi. Meme ve aksiller cerrahinin nihai histopatolojisinin, tam patolojik yanıtın sıklığını bildirdiği kaydedildi. Evre, derece ve kanser tipine göre pozitif nodal hastalık sıklığı ölçüldü.

Bulgular: Çalışmamız, üç yüz yirmi altı hasta arasında, memede tam patolojik yanıt olan %53 hastanın aksillada da tam yanıta sahip olduğunu, buna karşılık eksik patolojik yanıt olan %43 hastada olduğunu gösterdi. Tam patolojik yanıt veren hastalar, yanıt vermeyen veya kısmi yanıt verenlerle karşılaştırıldığında yaş, menopoz durumu, başlangıç tümör boyutu açısından anlamlı bir fark bulunmadı. NACT, hormon negatif, HER2 pozitif ve üçlü negatif popülasyondan sonra klinik olarak nod negatif hastalarda tam patolojik yanıt oranı daha yüksekti.

Sonuç: Sonuçlarımız, memede tam patolojik yanıt gelişen hastaların %53'üne gereksiz aksiller girişimi yapıldığını gösterdi. Histopatolojik örnekte rezidüel tümör varsa, meme cerrahisinden sonra aksiller cerrahi evrelendirilebilir. pCR durumunda, aksiller cerrahinin ihmal edilmesi düşünülebilir; ancak tedavi kılavuzları için daha geniş popülasyonlu, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Neoadjuvan kemoterapi, aksiller nodal yanıt, meme kanseri

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ORIGINAL ARTICLE
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Single vs. double drain in modified radical mastectomy: A randomized controlled trial

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ABSTRACT

Objective: It was aimed to test the hypothesis that the use of a double drain results in less seroma formation, duration of the hospital stay, surgical site infection (SSI), postoperative pain, hematoma, flap necrosis compared to a single drain in patients undergoing modified radical mastectomy.

Material and Methods: This parallel-group, single-institution randomized controlled trial was conducted at the department of surgery of our institute between April 2015 and July 2018. Women undergoing modified radical mastectomy were randomly allocated to either a single drain (n= 98) or double drain (n= 98).

Results: Both groups were comparable for baseline variables such as age, co-morbidity, BMI, and tumor characteristics. The variables of single drain yielded no better outcomes compared to double drain with estimated blood loss (101.67 ± 25.14 vs.101.67 ± 24.40, p> 0.001), drain volume (898.81 ± 116.42 vs 803.97 ± 103.22 mL, p> 0.001), duration of surgery in minutes (103.19 ± 15.96, 103.19 ± 15.93) and seroma formation (13.4% vs 6.1%, p= 0.082). However, single drain yielded less postoperative pain (mean 2.5 ± 0.70 vs 5.22 ± 5.10, p< 0.000). On multivariable Cox regression analysis, single drain was associated with a lower risk of significant postoperative pain [adjusted relative risk 0.14 (95% confidence interval (CI) 0.070-0.25)] and overall complications [adjusted relative risk 0.47, (95% CI 0.26-0.86)]. On multiple linear regression, the duration of drains in the single drain group was 0.01 days less than double drain (r2= 0.00, b= 0.388, p> 0.001).

Conclusion: The use of a single drain significantly reduces postoperative discomfort and pain while demonstrating similar morbidity to the patient with two drains. We thus recommend preferential use of a single drain in modified radical mastectomy (NCT02411617).

Keywords: Modified radical mastectomy, seroma, postoperative pain, single drain

INTRODUCTION

Despite increasing trends toward breast conservation surgery, modified radical mastectomy (MRM) remains the most commonly performed surgical procedure for breast cancer (1). The complications following MRM include seroma, wound infection, hematoma, postoperative pain, flap necrosis, and prolonged axillary drainage (2). Operative morbidity associated with MRM is between 30 and 50%, which is attributed to large raw surface after mastectomy (1). Seroma is one of the most common complications after MRM, which has been reported to occur in 85% of cases (reference). It mainly delays wound healing, causes wound dehiscence, infections, and results in a longer hospital stay (3,4).

The use of drains during MRM remains one of the most investigated and at the same time, controversial of all techniques aimed at reducing the rate of seroma formation (4-7). It is believed that closed suction drainage in MRM accelerates wound healing and decreases overall complications (7,8). However, confusion exists regarding optimal suction pressure, the number of drains, duration of drainage, and in fact whether the drain should be used at all following MRM (4,9,10). There are few good-quality studies comparing the use of single and multiple drains in breast cancer surgery (7,8). In a previous study assessing single drain versus double drain, no significant difference has been observed in seroma formation (30.4% vs. 36.4%), total drain volume (244.80 ± 95.31 vs. 283.80 ± 111.75 mL) and drain days (9.25 ± 2.16 vs. 9.89 ± 0.54) (4). However, many surgeons still do not prefer single drain because they think that it increases seroma formation. The reason for using seroma formation as a priority in the study is based on the reports

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of common occurrence after breast surgery and since the study aimed to show that seroma was less related to both single and double drain thus proving the previous studies' results. Hypothesis of the study is:

H_0 single drain ≠ single drain

H_A single drain = double drain

Our study was initiated to compare the use of a single drain with two drains following MRM in a controlled, randomized prospective setting. Previously conducted studies have not led surgeons to a consensus regarding the number of drains mainly because of study limitations, including single-arm study, nonrandomized design, and randomized study with inadequate sample size and presence of confounders (2,4,6,10). We thus planned this randomized controlled trial to determine whether a single drain has a role in reducing operative morbidity compared to two drains. This study aimed to evaluate the effect of the number of drains primarily on seroma formation rate followed by postoperative pain, flap necrosis, wound infection, hematoma, and hospital stay during the immediate postoperative period after MRM for breast cancer.

MATERIAL and METHODS

Study Design

We conducted this randomized controlled trial at the department of surgery of our institute from April 2015 to July 2018. Being a tertiary care hospital, breast diseases are managed in an integrated and evidence-based manner. Every breast cancer case is thoroughly discussed in weekly breast tumor board meetings comprising a breast surgeon, medical oncologist, radiation oncologist, histopathologists, radiologist, and a specialist nurse to formulate an individualized management strategy for each patient. Cancer staging is performed according to the American Joint Committee on Cancer staging system.

Subject Selection and Randomization

We included all women who underwent MRM for biopsy-proven carcinoma of the breast. Those who refused surgery and had immediate reconstruction were excluded from the study. Selected patients who consented to surgery were included, and a statistician placed them in a computer-generated randomization sequence. The sequence was communicated to the surgeon only once the patient was in the operating room.

Surgical Procedure

All procedures were performed by a single surgeon who had more than five years of experience in breast surgery. Skin incision was made with a conventional scalpel, and flaps were raised. Breast tissue was reflected off the pectoralis major muscle with electrocautery, and the medial and lateral borders of the pectoralis minor muscle were defined. The pectoralis minor was retracted, and a standard level II axillary clearance was performed in all patients. Venous branches and lymphatics in the axilla were clipped and ligated. Hemostasis was secured followed by the placement of either one drain in the axilla or two drains, with one in the axilla and the other placed under the flaps according to randomization. Staplers were used to approximate the wound edges. Postoperative treatment was uniform throughout the study in keeping with clinical pathways.

Enrollment Criteria

Establishing inclusion and exclusion criteria for study participants is a standard, required practice when designing high-quality research protocols. As we set the inclusion criteria, we also set the exclusion criteria. Common exclusion criteria include characteristics of eligible individuals that make them highly likely to be lost to follow-up, miss scheduled appointments to collect data, provide inaccurate data, have comorbidities that could bias the results of the study, or increase their risk for adverse events (most relevant in studies testing interventions).

Follow-Up

All patients were given intravenous paracetamol six-hourly to control pain in the immediate postoperative period. Most of our patients were discharged with drains on the first postoperative day. A follow-up visit was scheduled in the outpatient clinic with further instructions to report back immediately if the drain bottle filled up, lost vacuum, or peri drain leak was encountered. A card was given at the time of discharge to every patient to be able to record drain volume at home daily at a specific time after placing the bottle on a flat surface. In this study, out of 221 participants, 25 patients were lost to follow-up and were excluded from the study. The drains were removed on follow-up once the volume was less than 30 mL per 24 hours.

Outcome Variables

Outcome variables were seroma formation, duration of hospital stay, wound infection, postoperative pain, and flap necrosis. Seroma was defined as the presence of fluid collection beneath the skin flaps after the removal of the drains to cause patient discomfort within 30 days of surgery. Superficial skin infection (SSI) was assessed as per U.S. Centers for Disease Control and Prevention criteria. SSI was defined as an infection of the skin and subcutaneous tissue that occurred within 30 postoperative days along with at least one of the following criteria: (1) purulent drainage from the superficial incision, (2) organisms (other than *Staphylococcus epidermidis*) isolated from an aseptically obtained culture of fluid or tissue from the superficial incision, (3) at least one of the given signs or symptoms of infection (i.e. pain or tenderness, localized swelling, redness, heat or superficial incision deliberately opened by the surgeon with culture-

positive pus or tissue) and diagnosis of SSI by the surgeon or attending physician (4). Postoperative pain was evaluated 24 hours after surgery by a nurse using a visual analog score ranging from 0 to 10 (minimum to maximum pain), a visual analog scale score of C4 was labeled as significant pain.

Sample Size

World Health Organization software was used to calculate sample size for different outcome variables, the highest sample size was formulated for total drain days reported in a previous study. A sample size of 96 participants in each group was calculated for the mean of total drain days for single drain versus double drain with standard deviation of 1-2 days at 5% level of significance (one sided) and 80% power. An ideal set of 141 people were required for this analysis where 71 patients in each group would have been sufficient for the analysis. According to Andrede (2020), in quantitative studies, a sample that is larger than necessary will be better representative of the population and will hence provide more accurate results. It prevents type II error.

Our study sample included a total of 196 patients in which only two cases had missing data and eventually resulted in 96 participants in each group.

RESULTS

In each intervention group, 96 patients were recruited consecutively (Figure 1). Two patients were excluded from each group

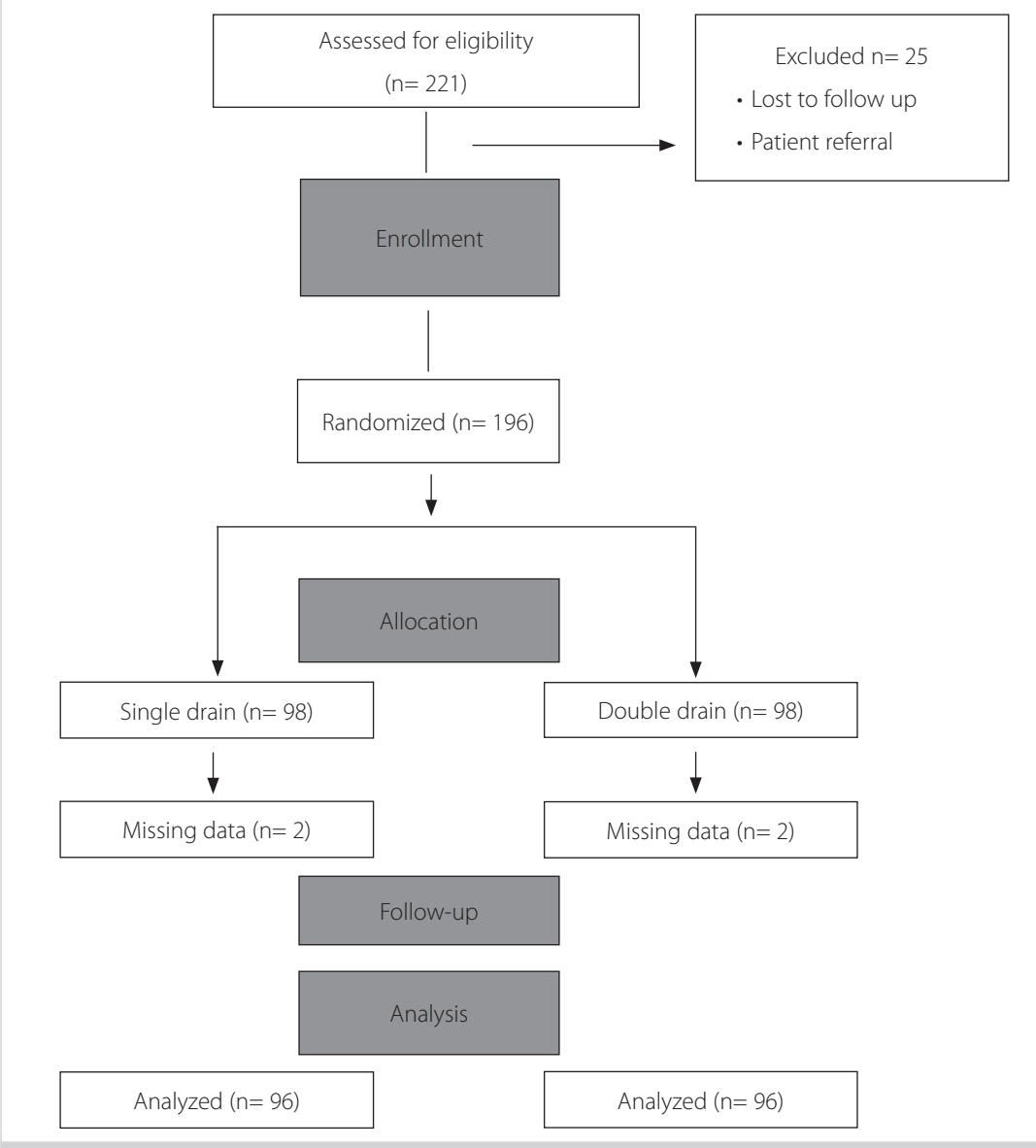

Figure 1. Consort flow diagram of the participants.

due to missing data. Both groups were comparable in terms of baseline variables with a mean age of 55.13 ± 9.0 and 55.37 ± 8.4 years, respectively (Table 1). Further analysis showed that double drain did not yield better outcomes (Table 2) compared to single drain, with estimated blood loss (101.67 ± 24.402 vs. 101.24 ± 25.15, p= 0.90), drain volume (803.97 ± 103.22 vs. 898.81 ± 116.42, p= 0.743), drain days (7.62 ± 2.44 vs. 7.14 ± 2.53, p= 0.145), seroma formation (6.1% vs. 13.4%, p= 0.08), operative time (103.19 ± 15.96 vs. 103.97 ± 15.93 min, p= 0.49), and SSI (3 vs. 4%, p= 0.570). Double drain was not better than

Table 1. Baseline variables between single vs. double drain groups

Variable	Single drain (n= 96)	Double drain (n= 96)	p
Age	55.13 ± 9.0	55.37 ± 8.4	0.848[a]
BMI	23.21 ± 3.5	23.21 ± 3.2	0.988[a]
Comorbidities			
DM	20 (20.4%)	16 (16.3%)	0.290[b]
HTN	13 (13.4%)	17 (17.3%)	0.276
Smoking	0	0	0.636[b]
Breast weight (grams)	818.80 ± 168.91	826.14 ± 162.24	0.757[a]
Clinical TNM stage			
I	4 (4.1%)	5 (5.1%)	
II	49 (50.0%)	59 (60.2%)	
III	45 (45.9%)	34 (34.7%)	0.277[b]
Clinical T stage			
I	4 (4.1%)	5 (5.1%)	
II	31 (31.6)	46 (46.9%)	
III	45 (45.9%)	46.9 (35.5%)	
IV	18 (18.4%)	13 (13.3%)	0.147[b]
Clinical N stage			
N1	33 (33.7%)	46 (46.9%)	
N2	52 (53.1%)	41 (41.8%)	
N3	13 (13.3%)	11 (11.2%)	0.165[b]
No. of nymph nodes			
Retrieved	15.43 ± 4.11	16.23 ± 4.01	0.172[a]
Neoadjuvant therapy	32 (33%)	37 (37.4%)	0.521[b]
Menopause	62 (63.9%)	63 (63.6%)	0.967[b]
Receptor status			
ER positive	58 (59.8%)	58 (58.6%)	0.863[b]
PR positive	58 (59.8%)	56 (56.6%)	0.570[b]
Her-2/neu positive	41 (42.3%)	32 (32.3%)	0.150[b]
Histology			
Ductal carcinoma	90 (92.8%)	95 (96%)	0.334[b]
Lobular	7 (7.2%)	4 (4%)	0.370[b]
Tumor grade			
I	28 (28.9%)	17 (17.2%)	
II	46 (47.2%)	46 (46.7%)	
III	23 (23.7%)	36 (36.4%)	0.063[b]

[a]t-test.
[b]X^2 test.
[c]Mann-Whitney U test.

Table 2. Comparison of outcome variables between single and double drain groups

Outcome	Single drain (n= 96)	Double drain (n= 96)	p
Seroma	13 (13.4%)	6 (6.1%)	0.082[b]
Number of puncture	0.103 ± 0.39	0.04 ± 0.244	0.182[a]
Total volume drained	898.81 ± 116.42	803.97 ± 103.22	0.743[a]
Duration of drain	7.62 ± 2.44	7.14 ± 2.53	0.145
Hospital stay	1.04 ± 0.198	1.05 ± 0.221	0.735[a]
Wound infection	3 (3.1%)	4 (4%)	0.570[b]
Hematoma	1 (1%)	1 (1%)	0.988[b]
Flap necrosis	0 (0%)	1 (1%)	0.321[b]
Pain	2.5 ± 0.70	5.22 ± 5.10	0.001[c]
Blood loss	101.24 ± 25.14	101.67 ± 24.40	0.904[a]

[a]t-test.
[b]X^2 test.
[c]Mann-Whitney U test.

Table 3. Univariate and multivariable regression analysis for significant postoperative pain

Covariate	Univariate CRR (95% CI)	Multivariate ARR (95% CI)
Intervention		
Single	**1**	**1**
Double	0.14 (0.08-0.25)	0.14 (0.07-0.25)
Age up to 50	1	1
C51	0.96 (0.63-1.46)	0.99 (0.65-1.51)
Weight of specimen		
Up to 850 g	1	1
C851 g	1.22 (0.82-1.84)	1.28 (0.84-1.89)
Neoadjuvant therapy		
No	1	1
Yes	0.83 (0.56-1.24)	0.74 (0.50-1.11)
BMI		
Normal	1	1
Overweight	1.40 (0.92-2.13)	1.41 (0.91-2.12)
Obese	1.02 (0.41-2.51)	0.88 (0.35-2.18)

CRR: Crude relative risk, CI: Confidence interval, ARR: Adjusted relative risk.

single drain for overall complications. Mean postoperative pain was significantly less in single drain as compared to double drain (2.5 ± 0.70 vs. 5.22 ± 5.10, p< 0.000).

DISCUSSION

In this randomized controlled trial, we assessed the use of double drain versus single drain in patients undergoing MRM and found that the outcomes of double drain had not significantly altered the results in its favor compared to single drain. Single drain significantly reduced postoperative discomfort (postoperative pain) without increasing drain volume, drain duration, and overall complications (seroma, flap necrosis, and SSI) to the patient.

The use of drains in MRM is one of the most investigated techniques aiming to reduce seroma formation (11,12). Seroma is the most common complication seen after mastectomy and axillary surgery with an incidence of 3-85%, which ultimately leads to wound problems such as impaired healing, dehiscence and infections (13). There are still controversies regarding the number of drains, duration of drainage, and whether these drains should be at all used in breast cancer surgery (7,9,11).

Table 4. Univariate and multivariable regression analysis for overall complications

Covariate	Univariate CRR (95 % CI)	Multivariate ARR (95 % CI)
Intervention		
Single	1	1
Double	0.46 (0.17-1.21)	0.46 (0.17-1.22)
Neoadjuvant therapy		
No	1	1
Yes	1.17 (0.44-3.09)	1.14 (0.43-3.02)
BMI		
Normal	1	1
Overweight	0.77 (0.25-2.34)	0.74 (0.24-2.26)
Obese	1.03 (0.13-7.47)	1.00 (0.13-7.60)

CRR: Crude relative risk, ARR: Adjusted relative risk, CI: Confidence Interval.

Previously conducted studies have not shown that double drains yield better outcomes than a single drain (4,14). Additionally, single drain placement in MRM surgery results in less postoperative pain (15,16). In order to increase internal validity, we controlled the confounders at the design phase by restricting the inclusion criteria to a single procedure, i.e. MRM. A few variables that may affect the outcomes are the weight of the mastectomy specimen, age, BMI, and preoperative chemotherapy. All of these variables were comparable between the groups at baseline, making possible a valid comparison of outcomes between both groups.

This study has several limitations. Because the decision of putting the number of drains was communicated at the time of surgery, it was not possible to blind the surgeons or assessors from the intervention. So as to reduce reviewer's bias, different people were involved at various phases of the study, including randomization, pain score evaluation, and assessment of wound-related outcomes. All surgeries were performed by a single operating surgeon to overcome operator-dependent bias. The sample size was calculated for drain volume and drain days, which was not powered enough to compare other individual outcomes, such as seroma, SSI, and hematoma. Therefore, we compared overall and individual complications between the two groups including the proportion of patients with any of the above-mentioned complications. Because of certain uncontrollable factors, such as evaporation, suction usage, and irrigation, EBL measurement always carries a non-differential misclassification bias. Ideally, measurement of pre- and postoperative hemoglobin and hematocrit should support estimation of blood loss during surgery.

Seroma and other wound-related complications cause undue patient anxiety, require multiple hospital visits, and delay any required adjuvant chemotherapy (17,18). Every attempt should be made to decrease the morbidity associated with MRM, which enticed researchers to identify the association of the number of the drain with seroma and other complications. Earlier studies have found that the use of multiple drains is an effective way of reducing the incidence of seroma and associated complications (19). However, it is associated with long hospital stay and significant postoperative pain (15). With equal morbidity reported for either of the modality, inclination to place the second drain has been dwindling. Terrell et al., in their study, have found that the rate of seroma formation is equal in both single and two-drain groups (20,21). Similarly, a comparison study authored by Kapoor et al. has not found any significant difference in seroma and other complications between one and two drain groups in MRM (22). Another research by Puttawibul et al. have opined that the single drain group did not differ significantly from two drains when it came to the incidence of seroma formation, aspirated fluid volumes, and other related complications. The study by Hashemi et al. has concluded that the single, most important determinant of seroma formation is the type of breast cancer surgery and the number of lymph nodes retrieved, both of which were controlled in our study thanks to proper selection criteria and randomization (4).

On the other hand, controversies exist whether decreasing the number of drains decreases patients' pain and hospital stay without an associated increase in the risk of seroma after mastectomies. Guneri et al., in their randomized controlled trial, have found that the use of two drains in MRM is associated with less seroma formation while having similar pain and hospital stay as a single drain (14). The sample size in the study was small and they also included patients with sentinel lymph node biopsy. Moreover, the surgeries were performed by more than one surgeon, including residents, and thereby incorporating a learning curve as a possible confounder in the trial, which in the end, limited the authors from drawing a definite conclusion.

Our trial proves the benefit of the single drain in pain control after overcoming the above-stated limitations. We also found significant reductions in pain between the two groups. Moreover, these findings can also be attributed to a larger sample size of our study compared to other studies.

The results of this randomized trial can be generalized especially in developing countries where this disease usually presents at an advanced stage and mastectomy is the preferred method of surgical treatment.

CONCLUSION

The use of single drain after MRM results in less pain although the morbidity is equal to that of double drain. We recommend the use of single drain in MRM.

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Ethics Committee Approval: This study was approved by Memon Medical Institute Hospital Ethics Committee (Decision no: ERC-07-2013 MMIH, Date: 17.05.2014).

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Author Contributions: Concept - SK, MK; Design - SK; Supervision - SK; Data Collection and/or Processing - SK, MK; Analysis and/or Interpretation - SK, AW; Literature Review - MK, AW; Writer- SK, MK, AW; Critical Review - SK, MK.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 145-152

Modifiye radikal mastektomide tek ve çift dren karşılaştırması: Randomize kontrollü bir çalışma

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ÖZET

Giriş ve Amaç: Modifiye radikal mastektomi uygulanan hastalarda çift dren kullanımının tek drene göre daha az seroma oluşumu, hastanede kalış süresi, cerrahi alan enfeksiyonu (CAE), postoperatif ağrı, hematom, flep nekrozuyla sonuçlandığı hipotezinin test edilmesi amaçlandı.

Gereç ve Yöntem: Bu paralel gruplu, tek kurumlu, randomize kontrollü çalışma, Nisan 2015 ile Temmuz 2018 tarihleri arasında enstitümüzün cerrahi bölümünde gerçekleştirildi. Modifiye radikal mastektomi uygulanan kadınlar rastgele olarak tek dren (n= 98) veya çift dren (n= 98) olarak gruplara ayrıldı.

Bulgular: Her iki grup yaş, eşlik eden hastalık, VKİ ve tümör özellikleri gibi temel değişkenler açısından karşılaştırılabilirdi. Tahmini kan kaybı (101,67 ± 25,14'e karşı 101,67 ± 24,40, p> 0,001), dren hacmi (898,81 ± 116,42'ye karşı 803,97 ± 103,22 mL, p> 0,001), dakika olarak cerrahi süre ve seroma oluşumu (%13,4'e karşı %6,1, p= 0,082) gibi tek dren değişkenleri çift drene kıyasla daha iyi sonuç vermedi (103,19 ± 15,96, 103,19 ± 15,93). Ancak, tek dren daha az postoperatif ağrıyla sonuçlandı (ortalama 2,5 ± 0,70'e karşı 5,22 ± 5,10, p< 0,000). Çok değişkenli Cox regresyon analizinde, tek dren, postoperative ağrı açısından daha düşük risk [düzeltilmiş bağıl risk 0,14 (%95 güven aralığı (CI) 0,070-0,25)] ve daha düşük genel komplikasyonlar [düzeltilmiş bağıl risk 0,47 ile ilişkilendirildi (%95 CI 0,26-0,86)]. Çoklu lineer regresyonda tek drenli grupta dren süresi çift drenli gruptan 0,01 gün daha azdı (r2= 0,00, b= 0,388, p> 0,001).

Sonuç: Tek dren kullanımı ameliyat sonrası rahatsızlık ve ağrıyı önemli ölçüde azaltırken iki dren kullanan hastalarla benzer morbidite gösterir. Bu nedenle, modifiye radikal mastektomide (NCT02411617) tek drenin tercihli kullanımını öneriyoruz.

Anahtar Kelimeler: Modifiye radikal mastektomi, seroma, postoperatif ağrı, tek dren

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ORIGINAL ARTICLE
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Surgery versus no surgery in stage IV gallbladder carcinoma: A propensity score-matched analysis

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ABSTRACT

Objective: Patients with stage IV gallbladder cancer (GBC) have a dismal prognosis. Mostly, they are not amenable to surgical treatment. However, in some of them, a potentially curative surgical resection is possible. There is paucity of the literature comparing survival of patients with surgically resectable stage IV GBC to the patients with unresectable stage IV GBC.

Material and Methods: This retrospective study was conducted on patients with AJCC stage IV GBC who were managed by a surgical unit at a tertiary care center from May 2009 to March 2021. Patients were grouped into either surgery group (cases) or no surgery group (control). Cases were compared to controls for demographic characteristics, clinical parameters, and survival rates. A comparison was made in both unmatched and matched (propensity score matching 1:1 with covariates age, gender, ECOG, chemotherapy, and TNM staging) groups.

Results: The total number of patients with stage IV GBS was 120, out of that, 29 were cases, and 91 were controls. After matching, each group had 28 cases (28 + 28= 56). Post-matching AJCC stage, chemotherapy, and other parameters were equally distributed between the groups (p= 1.00). However, cases had more patients with N2 metastasis (p< 0.001), and controls had more patients with distant metastasis (p< 0.001). Cases vs. controls, overall survival before matching was 22 vs. seven months (p= 0.001) and after matching was 22 vs. 11 months (p= 0.005).

Conclusion: Patients with stage IV GBC amenable to potentially curative surgical resection (R0) have significantly better survival than patients with non-surgical treatment. Therefore, it may be more appropriate to classify these group differently.

Keywords: Carcinoma gallbladder, stage IV, surgery

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract cancer; more than nine per 100.000 Indian women are affected by this cancer every year (1). Overall prognosis of patients with GBC is poor due to delayed presentation and aggressive nature of the disease (2). However, in less than 10% patients, the disease is limited to the gallbladder (3). These early stage gallbladder cancers are those tumours that are limited to the gallbladder without significant lymph node involvement: stage I and stage II (4). Since stage I tumours are difficult to diagnose preoperatively, most are discovered incidentally. They represent a proportion of gallbladder cancer that could be easily cured. A simple cholecystectomy is sufficient for pT1a (mucosal tumour) while a radical resection is indicated for pT1b (muscularis layer involvement) and T2 (stage II) tumours (5). Most stage IV (AJCC VII) patients are beyond surgical resection, so palliative care is offered (2,6). There are some patients who presents with a resectable GBC but classified under stage IV B GBC due to extensive lymph nodes metastasis. Kondo et al. have reported that surgical resection is unlikely to benefit the patients with extensive LN metastasis (N2 stage) (7). However, other authors have reported survival benefit of surgical resection in such patients (8,9). Recently, Chen et al. (2019) have also reported survival benefit in patients with advanced GBC provided that R0 resection has been achieved (9). In view of conflicting literature, we compared the survival outcome of patients with surgically resectable stage IV GBC to those with non-surgical treatment.

MATERIAL and METHODS

This retrospective case-control study was done from a prospectively maintained database of a single unit at a tertiary care centre. A total of 124 patients diagnosed with stage IV gallbladder cancer (as per AJCC 8th edition) were treated from May

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2009-March 2021. One hundred and twenty patients were included in the final analysis after excluding the patients with in-hospital mortality (n= 4).

The following data were collected for all patients from our prospectively maintained records: sex, age, performance status, comorbidities, clinical features, CEA and CA 19-9 levels, primary tumour characteristics (location, T category, lymph nodal status, locoregional involvement, distant metastasis and histological grade according to the 8th edition of the AJCC staging manual), details on chemotherapy, biliary drainage and surgery-associated variables (type of procedure, duration, blood loss, postoperative complications). Complications were graded based on Clavien-Dindo classification (10).

Cases (surgery group, n= 29): Patients with surgically resectable GBC who were diagnosed as stage IV GBC following histopathological examination.

Controls (no surgery group, n= 91): Patients either had inoperable GBC at initial presentation or were no amenable to surgical resection following staging laparoscopy or laparotomy.

These two groups were compared for their baseline demographic characteristics, clinical parameters, and survival rates. Propensity score matching was done between these groups, one to one nearest neighbor match with covariates: age, sex, ECOG, chemotherapy, and TNM staging. The comparisons were made between both unmatched and matched groups (Figure 1).

Patient Management Protocol

All patients with suspected or diagnosed GBC were evaluated clinically which was followed by CBC, LFT, RFT, INR, tumour markers, ultrasonography (USG) of the abdomen and contrast enhanced computed tomography (CECT) of the chest and abdomen. Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) were utilized selectively. Patients with suspicion of M1 disease underwent guided biopsy and cases with confirmed metastatic GBC were considered for chemotherapy and palliative care. Patients with possible involvement of the bile duct were confirmed with MRCP, and after confirmation, all such patients were referred for preoperative/palliative biliary drainage. Patients with deemed resectable disease would undergo staging laparoscopy. Any suspicious metastatic deposits were sent for frozen histopathological examination (HPE). On negative HPE, curative resection was performed. On positive HPE, palliative procedures such as gastrojejunostomy, colo-colic bypass, or segment 3 bypass were performed depending on the symptoms.

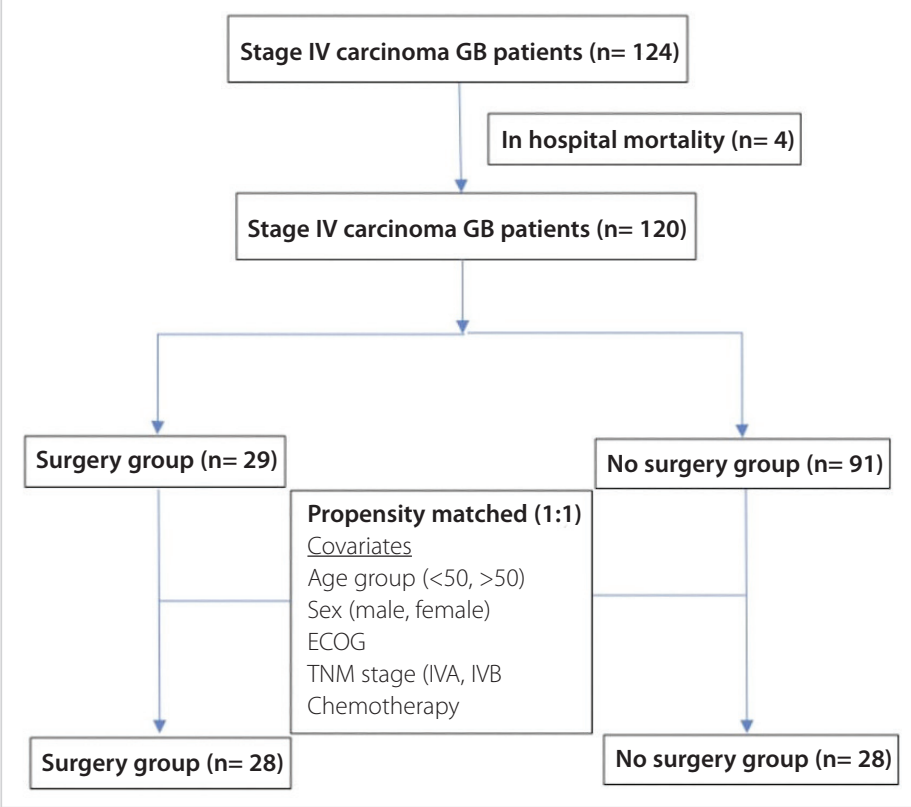

Figure 1. Flow diagram of patient selection.

Surgical Procedure

Standard procedure was a segment 4b, 5 resection (anatomic bi-segmentectomy or extended wedge resection), en-bloc cholecystectomy, and LN dissection along with stations 8, 12 and 13 (11). Frozen section for cystic duct margin was sent and if positive CBD excision was done. CBD excision was also routinely done in all cases if there was visible evidence of infiltration. Those with vascular or extensive liver infiltration were treated with extended right hepatectomy/major liver resections. Also, patients with obvious infiltration of adjacent organs underwent multi-visceral resections like duodenal sleeve/duodenectomy, colonic sleeve/segmental colonic resections, partial pancreatic head resection, and distal gastrectomy.

Follow-up

Patients received palliative or adjuvant chemotherapy after medical oncologists, surgeons and patients' informed consent. They were followed up every three months with physical examination, CEA and CA 19-9, and abdominal ultrasonography during the first year, followed by every six months after that. CECT abdomen was done yearly. Recurrences were identified either clinically or using radiological imaging. If patients could not turn up to the OPD, their status was traced telephonically.

Statistical Analysis

Data analysis was done using the SPSS version 28.0 (IBM Corp., Somers, NY, USA). Parametric numerical data were represented as mean (± standard deviation). Non-parametric numerical data are expressed as median (interquartile range). Categorical and ordinal data were represented as percentages. Parametric numerical data were compared with Student's t-test. Non-parametric numerical data were compared with Mann-Whitney U test. Chi-square test and Fisher's exact test compared categorical and ordinal data. Survival analysis was done using the Kaplan-Meier method and compared with a log-rank test. MedCalc version 20.011 (MedCalc Software Ltd. Ostend, Belgium; https://www.medcalc.org;2021) was used to obtain survival analysis graphs. A p value of ≤0.05 (two-sided) was considered statistically significant.

RESULTS

A total of 124 patients (cases= 33; controls= 91) with stage IV GBC patients were treated during the 12-year period. There were four postoperative deaths in the surgery group. Hence, 120 patients (cases= 29, controls= 91) were included for survival analysis in the unmatched population. After propensity score matching, 28 patients in each group were included for the analysis. Baseline clinical and demographic profiles were similar in both unmatched and matched populations, except poor performance status patients were statistically significantly higher in the control group. Baseline CEA and Ca 19.9 levels were significantly higher in the control group of unmatched and matched populations (Table 1). The control group has significantly more patients with an advanced T stage and M1 disease than cases of unmatched and matched population. Cases have significantly more N2 stages than controls. However, TNM staging was similar between the groups. The most common site of M1 disease was the liver, followed by the peritoneum and supraclavicular lymph node. There was a significant overall survival benefit in cases over the control groups (unmatched: 22 months vs. seven months, $p< 0.0001$; matched: 22 months vs. 11 months, $p= 0.005$) (Figure 2). Overall survival of the patients with stage IV B disease was significant in the cases than the control group (unmatched 14 vs. six months, $p< 0.0001$; matched 14 vs. three months, $p= 0.015$) (Figure 3). In the surgical group, median recurrence-free survival was nine months. The type of procedures performed in the surgery group is listed in Table 2. There were two (6.8%) R1 resections in the surgery group. Both had wedge resection, and the liver margin was positive. A patient in the surgical group had peritoneal nodule; frozen histological examination showed no malignancy and final examination showed malignancy. In the control group, 39 patients were explored; eight patients underwent palliative gastrojejunostomy; segment 3-bypass, colonic resection and anastomosis, and palliative ileo-transverse anastomosis were done in one patient each. Adjuvant chemotherapy, palliative chemotherapy was received in 69% of cases and 51.6% of controls of unmatched group respectively. After matching, 67.9% cases and controls received chemotherapy.

DISCUSSION

The treatment of advanced GBC is still not yet clearly defined. Most GBC patients are diagnosed at an advanced stage despite improved diagnostic modalities. Many of the patients in clinical practice present to us in an advanced stage (12). The prognosis of these patients is poor even after radical resection (13-15). Even studies have suggested that patients with stage IV are unlikely to benefit from surgical resection (16,17). But in recent years, many studies have supported the more aggressive surgical treatment of patients with advanced GBC (18,19).

The reported survival of stage IV GBC patients is 3-4% (13,14). The AJCC TNM staging defines stage IV GBC as the presence of either T4 stage, N2 stage, or M1 disease. However, the N2 stage of AJCC 8th edition differs from the 7th edition by having lymph node positivity rather than lymph node station. This change was brought based on population-based studies (20). The designation of N2 stage beside metastatic disease (M1) in stage IVB implies prognosis N2 stage and M1 are similar (21). The latter precludes surgical resection and the former deserves a resection if the tumour is resectable. This study was attempted to evaluate the survival difference in the two groups.

Table 1. Clinical, demographic, pathological and follow-up profile of the two groups

	Before matching			After matching		
Variables	**Surgery (n= 29)**	**No surgery (n= 91)**	**p**	**Surgery (n= 28)**	**No surgery (n= 28)**	**p**
Age (years)*	50 (45-60)	50 (45-60)	0.629	50 (45-60)	50 (44-63)	0.680
Female**	18 (62.1)	58 (63.7)	0.871	18 (64.3)	14 (56.0)	0.846
ECOG 1/2/3**	3/23/3	5/40/46	0.000#	2/23/3	3/21/4	0.805
Comorbidities**	5 (17.2)	9 (9.9)	0.283	4 (14.3)	1 (3.6)	0.160
Clinical features**						
Pain	24 (82.8)	69 (75.8)	0.436	23 (82.1)	21 (75.0)	0.515
Jaundice	5 (17.2)	23 (25.3)	0.373	5 (17.9)	7 (25.0)	0.515
Abdominal lump	6 (20.7)	27 (29.7)	0.346	6 (21.4)	6 (21.4)	1.000
Stent/PTBD	9 (31.0)	33 (36.3)	0.607	9 (32.1)	8 (28.6)	0.771
IGBC	7 (24.1)	11 (12.1)	0.114	7 (25.0)	2 (7.1)	0.069
GOO	3 (10.3)	10 (11.0)	0.923	3 (10.7)	3 (10.7)	1.000
Biochemical parameters*						
Hemoglobin, gm/dL	10.5 (10.0-11.9)	10.2 (9.6-10.6)	0.022#	10.7 (10.1-11.9)	10.2 (9.7-11.4)	0.243
TLC, cells/m^3	9.0 (7.2-11.6)	7.8 (6.4-9.7)	0.017#	8.7 (7.2-11.9)	7.1 (5.8-8.9)	0.015#
Platelets, cells/	2.30 (1.96-2.40)	2.30 (1.60-3.08)	0.663	2.26 (1.94-2.40)	2.15 (1.75-3.06)	0.718
Creatinine, mg/dL	0.8 (0.6-0.9)	0.9 (0.7-1.0)	0.138	0.8 (0.6-0.9)	0.8 (0.7-0.9)	0.624
Bilirubin, mg/dL	0.9 (0.5-1.4)	1.1 (0.7-7.0)	0.013#	0.8 (0.5-1.6)	0.9 (0.7-6.7)	0.194
Albumin, gm/dL	3.4 (3.1-3.8)	3.4 (3.1-3.8)	0.725	3.4 (3.1-3.8)	3.4 (3.1-3.8)	0.818
CA 19.9, IU/mL	34.0 (18.4-62.0)	87.0 (55.2-208.0)	0.000#	37.0 (18.5-62.0)	107.0 (62.0-437.0)	0.002#
CEA	2.3 (1.2-6.0)	4.3 (2.3-7.3)	0.011#	2.4 (1.3-6.0)	4.5 (2.2-10.6)	0.028#
T stage**						
T2	9 (31.0)	4 (4.4)		09 (32.1)	02 (7.1)	
T3	18 (62.1)	48 (52.7)	<0.001#	17 (60.7)	16 (57.1)	0.007#
T4	2 (6.9)	39 (42.9)		02 (7.1)	10 (35.7)	
N stage**						
N0/Unknown	1 (3.4)	84 (92.3)		1 (6.9)	25 (89.3)	
N1	1 (3.4)	2 (2.2)	<0.001#	1 (3.6)	0 (00)	<0.001#
N2	27 (93.1)	5 (5.5)		26 (92.9)	3 (10.7)	
Metastases**	1 (03.4)	72 (79.1)	<0.001#	1 (3.6)	26 (92.9)	
TNM stage**						
Stage IV A	3 (10.3)	19 (20.9)	0.202	2 (7.1)	2 (7.1)	1.000
Stage IV B	26 (89.7)	72 (79.1)		26 (92.9)	26 (92.9)	
Site of mets						
IAC LN	0 (0)	11 (12.1)		0 (0)	4 (14.3)	
Liver	0 (0)	24 (26.4)		0 (0)	8 (28.6)	
Peritoneal nodule	1 (3.4)	14 (15.4)		1 (3.6)	6 (21.4)	
Omental	0 (0)	4 (4.4)		0 (0)	2 (07.1)	

Table 1. Clinical, demographic, pathological and follow-up profile of the two groups (continue)

Variables	Before matching			After matching		
	Surgery (n= 29)	No surgery (n= 91)	p	Surgery (n= 28)	No surgery (n= 28)	p
SCLN	0 (0)	6 (6.6)	0.897	0 (0)	02 (07.1)	0.813
Malignant ascites	0 (0)	3 (3.3)		-	-	
Krukenberg	0 (0)	2 (2.2)		-	-	
Port site	0 (0)	1 (1.1)		0 (0)	01 (03.6)	
Pulmonary	0 (0)	1 (1.1)		-	-	
Unknown	0 (0)	6 (6.6)		0 (0)	03 (10.7)	
CBD involvement	10 (34.5)	42 (46.5)	0.269	10 (35.7)	12 (42.9)	0.584
PV/HA involvement	3 (10.3)	25 (27.5)	0.040#	3 (10.7)	4 (14.3)	0.565
Pancreas involvement	1 (3.4)	3 (3.3)	0.968	1 (3.6)	2 (7.1)	0.553
Duodenal involvement	6 (20.7)	31 (34.1)	0.174	6 (21.4)	8 (28.6)	0.537
Stomach involvement	1 (3.4)	8 (8.8)	0.341	1 (3.6)	1 (3.6)	1.000
Colon involvement	1 (3.4)	13 (14.3)	0.113	1 (3.6)	2 (7.1)	0.553
Adjuvant/Palliative chemo-therapy	20 (69.0)	47 (51.6)	0.102	19 (67.9)	19 (67.9)	1.000
Partial chemotherapy	8 (27.6)	11 (12.1)	0.046#	8 (28.6)	4 (14.30)	0.193
Overall survival in months, Median (95% CI)	22 (16-24)	7 (6-10)	<0.0001#	22 (16-24)	11 (7-15)	0.005#
Recurrence free survival in months, median (95% CI)	9 (7-15)			9 (7-15)		

BMI: Body mass index, ASA: American Society of Anesthesiologists, TLC: Total leukocyte count, CEA: Carcinoma embryonic antigen, IAC LN: Inter aortocaval lymph node, SCLN: Supraclavicular lymph node, CBD: Common bile duct, PV: Portal vein, HA: Hepatic artery.
*Values expressed in median (inter quartile range).
**Expressed in n (%).
#p value significant.

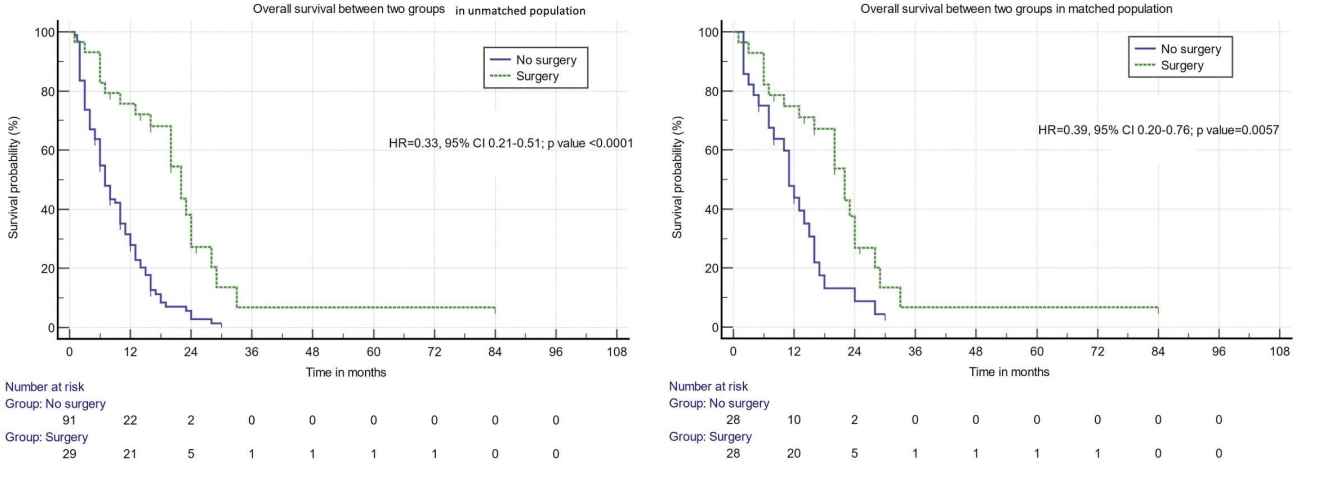

Figure 2. Overall survival between the two groups in unmatched and matched population.

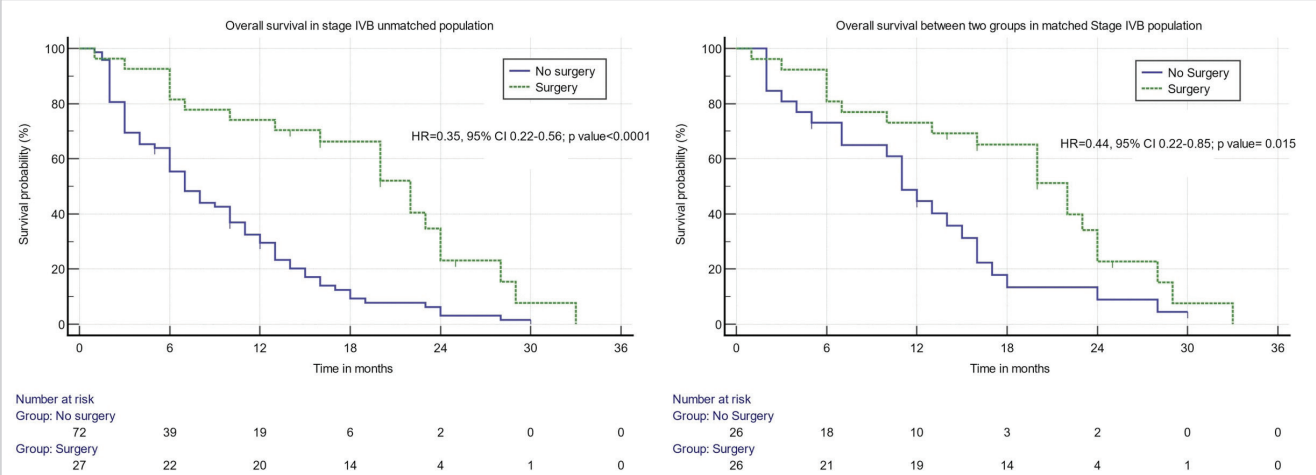

Figure 3. Overall survival between the two groups of stage IV B in unmatched and matched population.

Table 2. Clinical data of the surgical group (n= 29)

Type of procedure	**n (%)**
Extended cholecystectomy-wedge resection (ECW)	13 (44.8)
Alone	7 (24.1)
Plus, duodenal sleeve resection	1 (0.03)
Plus, segmental colon resection plus distal gastrectomy	1 (0.03)
Plus, CBD excision	1 (0.03)
Plus, colonic resection	1 (0.03)
Plus, resection of IVC wall	1 (0.03)
Plus, pancreatico duodenectomy	1 (0.03)
Extended cholecystectomy-S4b + S5 resection	11 (37.9)
Alone	6 (20.0)
Plus, CBD excision	4 (13.7)
Plus, segmental colonic resection of sleeve resection of duodenum	1 (0.03)
Completion cholecystectomy	2 (06.8)
Extended right hepatectomy	1 (03.4)
Extended cholecystectomy-S4, S5, S6 resection plus distal gastrectomy plus CBD excision	1 (03.4)
Extended cholecystectomy-S4, S5, S6 resection plus CBD excision	1 (03.4)
Surgery duration in minutes, median (IQR)	300 (240-410)
Blood loss in mL, median (IQR)	200 (190-300)
Complications	
Bile leak	4 (13.7)
Duodenal leak	1 (0.03)
SSI	6 (20.0)
Paralytic ileus	2 (0.06)

The role of surgery in N2 stage patients were studied with conflicting results. A review by Fong Y et al. in 2001 did not support surgery in N2 stage patients (22). Wakabayshi et al. in 2004 and Chijiiwa et al. in 2007 had shown no benefit for N2 stage patients (15,23). A study by Birnbaum et al. showed that surgery can be offered to N2 stage patients (24). A review by Koerkampet al. in 2014 states that the presence of distant metastases, nodal metastases beyond hepatoduodenal

ligament, and T4 tumours are unlikely to benefit from surgical resection (17). However, Chen et al. have shown that R0 resection has significant superior survival in stage IVA GBC and stage IVB GBC without distant metastases (9). A similar result was seen in the present study.

As per the recent AJCC 8th edition, N2 stage can be confirmed by the presence of more than three lymph nodes metastases, which can usually be detected by postoperative histopathological examination. There were a few N2 patients of the control group in the present study. The diagnosis of the N2 stage was made based on the malignant features of nodes, i.e., loss of hilar structure, matting, circular shape, size >10 mm, and heterogenous internal architecture based on imaging. However, these patients, too, had distant metastases. Interestingly, a study from Japan has suggested confirming N2 disease (>4 regional nodes) by intraoperative frozen section before performing major resections (21).

Chen et al. and Kang et al. could obtain R0 resection in 17% and 15% of stage IV GBC patients, respectively (9,19). In our study, 32/124 (25%) had R0 resection. To achieve such R0 resection, we had less threshold for multi-visceral resection. Surgeons refrain from multi-visceral resection because of significant morbidity and mortality. There were four (12%) postoperative deaths in the present study, and one patient each had Clavien-Dindo grade 3 and grade 4 complications among 33 patients in the surgery group. Stage IV GBC patients in the surgery group were majorly due to the N2 stage. There was a survival benefit in patients who had curative resection in the present study. This suggests that the presence of the N2 stage did not preclude curative resection and had better survival than the patient's distant metastases, which precluded curative resection. However, Kang et al. have shown that the removal site of metastases along with primary in limited metastases to liver and peritoneum had better survival than palliative surgery alone (19).

The AJCC system has some stages with heterogenous groups with different long-term outcomes, especially in advanced stages of GBC (25). Median survival was 22 months in patients who underwent surgery with curative intent for stage IV GBC vs. 11 months in patients not treated by curative surgical intervention. Stage IVB includes patients with N2 stage or M1 disease; the former is a potentially resectable group and the latter does not deserve resection. A similar result has been shown by a study that some patients with N2 disease were able to undergo R0 resection, in which regional lymph nodes are routinely removed during radical GBC resection and had longer survival times than patients with M1 disease (20). The study results may prompt us to say that patients with stage IV amenable to R0 resection may be placed differently in the AJCC classification system. However, this needs to be validated with larger sample studies.

Thus, gallbladder cancer patients with adjacent organ involvement and significant nodal disease still benefit from radical resection. With new improvements in multimodality management like neoadjuvant and adjuvant chemotherapy protocols, the combination of surgery and CT may improve the survival rate of patients with advanced GBC.

There were a few limitations in the study. The retrospective nature of the study introduces selection bias. Although matching the groups with factors affecting the survival was attempted to reduce such bias, it cannot remove the effect of unknown confounders of survival. Tumour markers of the control group were significantly higher than those of the cases, suggesting a higher tumour burden in the control group.

CONCLUSION

Patients with surgically resectable stage IV GBC have significantly better survival than patients with unresectable stage IV GBC. Thus, in stage IV GBC without M1 disease, R0 resection should be the goal whenever possible, and N2 nodal metastasis does not preclude a curative resection.

Ethics Committee Approval: This study was approved by Maulana Azad Medical College and Associated Hospital Institutional Ethics Committee (Decision no: 427, Date: 14.11.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - HN, PN, SK; Design - SK, PN; Supervision - HN; Fundings - HN; Data Collection and/or Processing - PN, SK; Analysis and/or Interpretation - PN, SK; Literature Search - PN; Writing Manuscript - PN, SK; Critical Reviews - HN.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 153-161

Evre IV safra kesesi karsinomlarında cerrahi tedaviye karşın cerrahi olmayan tedavi: Skor-eşleştirilmiş eğilim analizi

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ÖZET

Giriş ve Amaç: Dördüncü evre safra kesesi kanseri (GBC) olan hastaların prognozu kötüdür. Çoğunlukla cerrahi tedaviye uygun değildirler. Ancak bazılarında potansiyel küratif cerrahi rezeksiyon mümkündür. Cerrahi olarak rezeke edilebilir evre IV GBC'li hastaların sağkalımını, rezeke edilemeyen evre IV GBC'li hastalarla karşılaştıran çok az literatür vardır.

Gereç ve Yöntem: Bu retrospektif çalışma, Mayıs 2009'dan Mart 2021'e kadar üçüncü basamak bir merkezdeki cerrahi birim tarafından tedavi edilen AJCC evre IV GBC'li hastalar üzerinde gerçekleştirildi. Hastalar, ameliyat grubu (olgular) veya ameliyatsız grubu (kontroller) olarak gruplandırıldı. Olgular, demografik özellikler, klinik parametreler ve hayatta kalma oranları açısından kontrollerle karşılaştırıldı. Hem eşleşmeyen hem de eşleştirilmiş (ortak değişkenler yaş, cinsiyet, ECOG, kemoterapi ve TNM evrelemesiyle 1:1 eşleşen eğilim skoru) gruplarında bir karşılaştırma yapıldı.

Bulgular: Evre IV GBC'li toplam hasta sayısı 120 idi, bunun 29›u vaka ve 91'i kontroldü. Eşleştirmeden sonra her grupta 28 vaka vardı (28 + 28= 56). Eşleştirme sonrası AJCC evresi, kemoterapi ve diğer parametreler gruplar arasında eşit olarak dağıldı (p= 1,00). Ancak olgularda N2 metastazı olan hasta sayısı daha fazlaydı (p< 0,001), kontrol grubunda uzak metastazı olan hasta sayısı daha fazlaydı (p< 0,001). Olgular ve kontroller, eşleştirmeden önceki genel sağkalım 22'ye karşı yedi aydı (p= 0,001) ve eşleştirmeden sonra 22'ye karşı 11 aydı (p= 0,005).

Sonuç: Potansiyel olarak küratif cerrahi rezeksiyona (R0) uygun evre IV GBC'li hastalar, cerrahi olmayan tedavi alan hastalara göre önemli ölçüde daha iyi hayatta kalma oranına sahiptir. Bu nedenle bu grupları farklı şekilde sınıflandırmak daha uygun olabilir.

Anahtar Kelimeler: Karsinom, safra kesesi, evre IV, cerrahi

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ORIGINAL ARTICLE
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Acute pancreatitis: It can be the first sign of silent gallstones

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ABSTRACT

Objective: The management of asymptomatic cholelithiasis is controversial. Silent gallstones are generally assumed to cause complications after at least one episode of biliary colic. The ratio of those silent stones that had initially caused, -or were diagnosed as the etiological agent of- acute pancreatitis has not been reported in the literature yet. Our study was designed to investigate the ratio of asymptomatic cholelithiasis in acute biliary pancreatitis cases.

Material and Methods: One hundred and seventy-one patients of 305 cases, who were followed up with the diagnosis of acute biliary pancreatitis, were identified retrospectively. Demographic specifications, laboratory findings and clinical progressions of the patients were inspected. Clinical histories were detailed by phone calls. Gallstones were radiologically detected in 85 out of 171 cases. Those patients were divided as symptomatic and asymptomatic. Clinical findings and follow-ups were evaluated by "Chi-square" test.

Results: In the study group, 80% of the patients were asymptomatic (n= 68) and 16.47% of the patients (n= 14) had complicated pancreatitis. Regarding the severity of the clinical course, being symptomatic or not was not identified as a significant factor (p= 0.108). In regard of creating symptoms, the size of the stone was not significant (p= 0.561) and obtained no prediction about the clinical severity of the pancreatitis (p= 0.728).

Conclusion: Asymptomatic cholelithiasis patients had a major percentage in acute biliary pancreatitis cases. The "wait and see" approach should be re-evaluated for silent gallstones in prospective trials.

Keywords: Acute biliary pancreatitis, asymptomatic cholelithiasis, silent gallstones

INTRODUCTION

The management of asymptomatic gallbladder stones is still a matter of debate. Gallstones that are noticed during routine abdominal ultrasonography performed for other reasons and that do not cause any symptoms and/or complications associated with gallstones are called asymptomatic gallstones. Although dyspeptic complaints are thought to be due to gallstones in the absence of typical biliary symptoms, this issue is controversial (1,2).

Since the occurrence of gallbladder stones in the population is clearly higher than the rate of cholecystectomy cases, the management of asymptomatic disease needs even further analysis (1,3).

In a study focusing on the natural course of the gallstones, no remarkable complications have been noted in any of the patients enrolled in the study before the occurrence of typical symptoms of gallstone disease (GSD) (4).

On the other hand, it has been previously reported that 10-year cumulative complication rate for asymptomatic and symptomatic patients are 3% and 7%, respectively (5). This latter study has shown that silent gallstones might not stay uneventful in the long term.

Acute biliary pancreatitis (ABP) is one of the most severe complications of GSD.

There are numerous factors that determine the clinical severity of pancreatitis. Recognizing and differentiating these clinically and therapeutically important factors significantly affect the morbidity and mortality of this disease (6-10). Although most of the patients with ABP have self-limiting mild disease with excellent prognosis, severe ABP with multi-organ failure might occur in 10-15% of the patients and bears a considerable risk for mortality (11).

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In this study, we aimed to investigate the incidence and role of asymptomatic gallstones in ABP, and clinical features of patients with asymptomatic gallstone who had been diagnosed with ABP. At the same time, the effect of the gallstone size on the development of symptoms and whether stone size or the presence of symptoms are related to the severity of pancreatitis were also examined.

MATERIAL and METHODS

Study Design

Eighty-five eligible cases according to the inclusion criteria out of 326 patients admitted to the outpatient clinic of the surgical emergency unit in İstanbul University Cerrahpaşa Medical Faculty between January 2005-March 2013 and had been diagnosed with acute pancreatitis were included in this retrospective study (Figure 1).

Demographic features, laboratory findings and clinical outcomes of the patients were collected from the patients' files. Medical histories of the patients were detailed by telephone interviews.

Exclusion Criteria

Patients who had been diagnosed with acute pancreatitis due to other causes rather than acute biliary pancreatitis, and whose detailed histories were not accessible from the patient file archive system or who did not response to phone calls, and patients with no radiologically proven gallstones, deceased patients, patients with performed ERCP, patients who had undergone cholecystectomy and patients with pancreas cancer history were excluded.

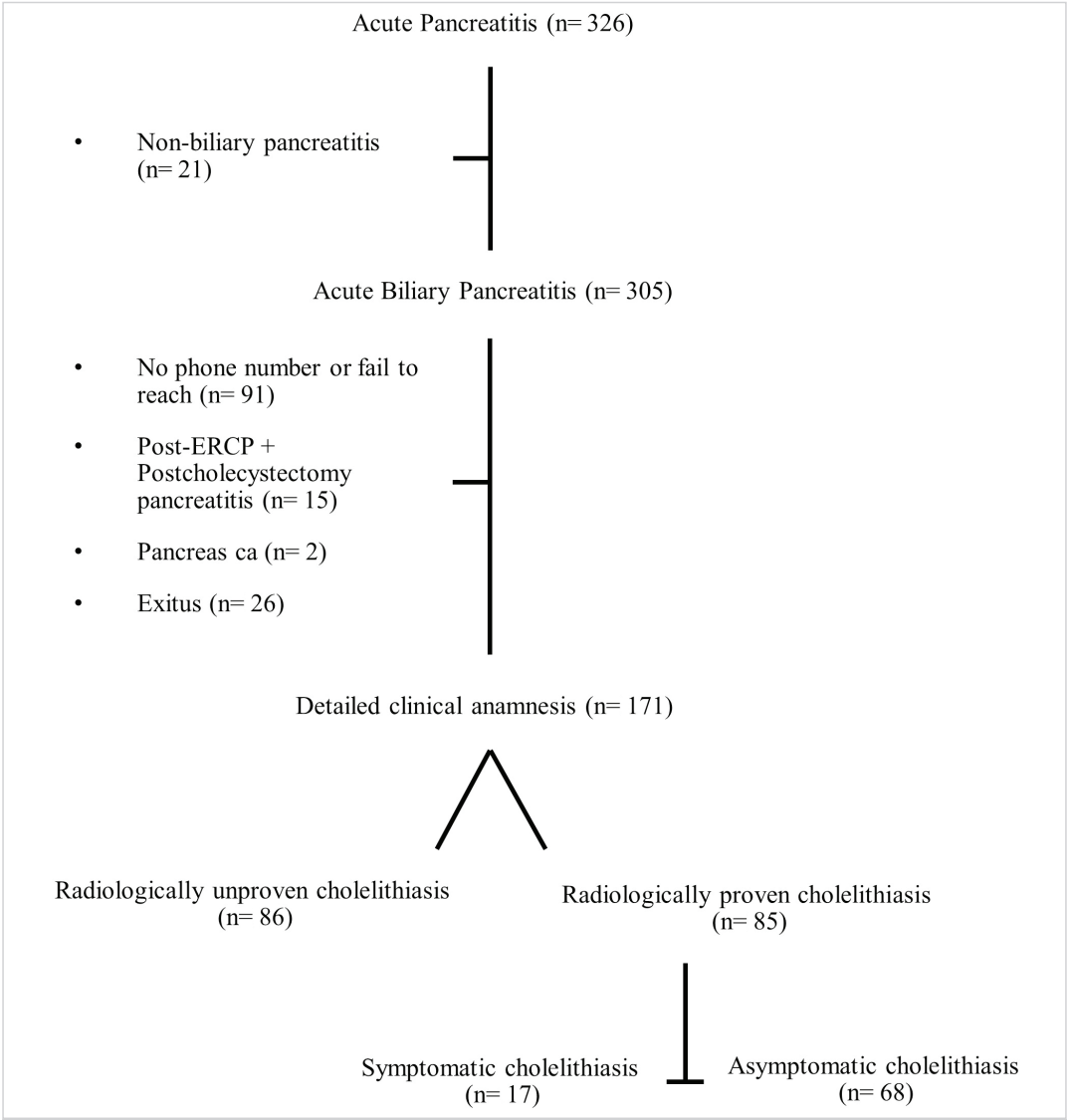

Figure 1. The chart that represents the categorization of the patients.
*Patients who fulfilled the inclusion criteria.

Inclusion Criteria

Eighty-five patients with radiologically proven cholelithiasis were included in this study and divided into two groups; Group 1: symptomatic cholelithiasis (n= 17), Group 2: asymptomatic cholelithiasis (n= 68) (Figure 1).

Statistical Analysis

Chi-square test was employed to analyze clinical findings and follow-ups of those two groups using IBM SPSS Statistics 20 for Windows (Illinois, USA).

RESULTS

Acute biliary pancreatitis was the first clinical presentation in 68 patients. Seventeen patients (20%) out of 85 declared to have symptoms of biliary colic prior to acute biliary pancreatitis, but the remaining 68 patients (%80) did not define any biliary symptoms prior to their admission to the emergency unit (Figure 1).

There were 85 patients (45 females, 40 males) with radiologically documented cholelithiasis. Mean age was 55.02 ± 17 years and 50.93 ± 16.70 years for female and male patients, respectively, and there was no significant difference (p= 0.275). Mean duration of complaints was four days, and hospitalization duration was eight. Median follow-up time was 34 months. In forty-six patients who had comorbidities, the leading cause was "cardiac complications" (Table 1).

Regarding patients with radiologically proven cholelithiasis, rate of comorbidity was higher in symptomatic cases (p< 0.05) (Table 2).

Fourteen patients (16%) were reported to have complicated pancreatitis according to the modified Atlanta classification, and lack or existence of symptoms has no significant effect on the severity of pancreatitis (p> 0.05) (Table 3).

Detected gallstones were grouped according to their diameters as follows: <1 cm and ≥1 cm. There was no significant correlation between the diameter of the gallstones and the occurrence of complicated pancreatitis (p> 0.05) (Table 4).

Table 1. Clinical and demographic characteristics of the study population (n= 85)

Clinical and demographic characteristics of the patients	
	Value
Mean age (years) (n= 85)	53
Mean age (female, years) (n= 45, 52%)	55
Mean age (male, years) (n= 40, 48%)	51
Mean duration of hospitalization (days)	8.88
Mean duration of complaints (days)	4
Median value of follow-up time (months)	34
Smoking (number of patients)	15 (17.64%)
List of reported comorbidities* (n= 46)	
	Number of patients
Metabolic diseases	13 (15.29%)
Cardiac diseases	31 (36.47%)
Neurological diseases	3 (3.52%)
Gastrointestinal diseases	8 (9.41%)
Respiratory diseases	5 (5.88%)
Other	6 (7.05%)

*Patients with one or more comorbidities and who were radiologically proven to have gallstones.

Table 2. The relationship of comorbidities and symptom status (n= 85)

	Number of patients without comorbidities	**Number of patients with comorbidities**	**p**
Symptomatic patients (n= 17, 20%)	3	14	<0.05
Asymptomatic patients (n= 68, 80%)	33	35	

Table 3. Clinical classification of pancreatitis according to symptomatic status of patients before pancreatitis (n= 85)

	Symptomatic patients	**Asymptomatic patients**	**p**
Complicated pancreatitis*	5	9	>0.05
Non-complicated pancreatitis*	12	59	

*Clinical classification of pancreatitis according to modified Atlanta classification.

Table 4. Effect of gallstone diameter on clinical classification (n= 85)

	Gallstone diameter <1 cm	**Gallstone diameter >1 cm**	**p**
Complicated pancreatitis*	9	5	>0.05
Non-complicated pancreatitis*	49	22	

*According to modified Atlanta classification.

Table 5. Relation between gallstone diameter and symptom status of the patients (n= 85)

	Gallstone diameter <1 cm	Gallstone diameter >1 cm	p
Symptomatic patients	11	6	>0.05
Asymptomatic patients	47	21	

Table 6. Detailed anamnesis findings

	Symptomatic patients (n= 17)	Asymptomatic patients (n= 68)	p
Patients who were diagnosed with cholelithiasis	13 (76%)	7 (10%)	<0.05
How was the patient diagnosed for cholelithiasis?	12 R 1 C	7 In	N/A
Patients who are aware of risks of cholelithiasis	9	None	N/S
Doctor recommendations for the management of cholelithiasis	8 Op	3 Op	N/S
	4 P	1 P	N/S
	1 F	3 F	N/S

C: On checkup, F: Clinical follow-up, In: Incidentally, Op: Operation, P: Leaved to patient's decision, R: Radiological.

Regarding symptomatic status of the patients, no significant difference was observed (p> 0.05) between the two groups according to gallstone size: gallstone diameter <1 cm (n= 58), gallstone diameter >1 cm (n= 27) (Table 5).

While detailing the patients' history, we recognized that sixty-one patients from the asymptomatic group and four patients from the symptomatic group were reported to be aware of cholelithiasis just after the diagnosis of pancreatitis. Only nine of them were aware of the clinical risks of cholelithiasis such as cholecystitis and pancreatitis (Table 6).

Recommendations by the physicians, in each group of patients, were as follows: to operate, to follow-up, leaving to patient's decision (Table 6).

DISCUSSION

This study demonstrated that pancreatitis was the first sign to clinically emerge in 68 patients (80%) with silent gallstones and revealed that asymptomatic gallstones play a significant role in ABP and they do not have a milder clinical course.

There is no prospective study in the literature that can offer a definitive therapeutic approach to asymptomatic gallstones. The literature on silent stones argues that clinical follow-up is sufficient (1,4,5,12). This leaves surgeons in a dilemma in terms of treatment approach for gallbladder stones that have never created symptoms. This study showed that the majority of our acute biliary pancreatitis cases were not previously aware that they had gallbladder stones. Innocent gallstones were discussed in studies which also include cost effectiveness data as a secondary goal. All those reality mentioned before have raised the idea that silent gallstones should be clinically re-questioned; to operate or not (13). Knowing the incidence of asymptomatic cholelithiasis in acute biliary pancreatitis cases can make us reevaluate the decision to follow-up.

The clinical significance of asymptomatic gallstones is controversial. It has been reported that in patients with gallstones, the lifelong likelihood of having symptomatic GSD is 10-25% (12). It is evident that most of the gallbladder stones remain "silent" during early decades of life but they may cause severe symptoms or complications in 40% of the patients older than forty years (14). Once ABP occurs, the management might be challenging, and therefore, it is crucial to elucidate the risk factors that lead to ABP. This difficulty to assess the risk factors which may lead to complicated pancreatitis have led clinicians to search for some predictive values such as gallstone size and functional tests (7-10,15-22). While investigating the importance of silent gallstones in acute pancreatitis, we addressed the clinical progression of the cases together with these predictive values and focused on gallstones in this manner.

Few prospective studies have investigated the natural course of gallstones in the literature (23-25). Festi et al. have reported the results of their eight-year long prospective study on GSD (24). In this study, cholecystectomy rate has been found relatively high in asymptomatic cases (%41.3), thus it was not achievable to monitor potential long-term complications of silent GSD. Moreover, it was not evident how many complications had taken place in asymptomatic patients.

In another study, researchers investigated the patients whose GSD had been initially diagnosed with life-threatening complications or death related to the disease. Out of thirty mortality patients, only 20% had biliary colic pain and other symptoms, while the remaining 80% had no symptoms

associated with cholelithiasis. These surprising results reveal that silent GSD does not mean predictably a mild clinical course (26).

The results of our study showed that concomitant disease rate was higher in symptomatic GSD patients. Or vice versa, one may think that patients with concomitant disease may have higher rate of symptoms in comparison to asymptomatic patients.

In patients with acute biliary pancreatitis, we identified cardiac diseases as the most common comorbidity. Co-occurrence of pancreatitis and cardiac disease suggests cardiac problems in cholelithiasis as a risk factor for biliary pancreatitis. It is necessary to be aware that patients with asymptomatic cholelithiasis accompanying cardiac problems may carry a higher risk for biliary event.

In the literature, asymptomatic patients were previously classified as low-risk (gallstone diameter larger than 3 mm or smaller than 20 mm and no concomitant serious disease) and high-risk groups (gallstone diameter smaller than 3 mm or larger than 20 mm; biliary sludge) (12). In our study, we found that the gallstone size had no effect on the course of pancreatitis.

Moreover, it has been reported that there is no previous biliary colic pain in half of the patients with pancreatitis (27), which does not support the results of some other studies reporting that at least a biliary colic pain bout is expected before the manifestation of biliary complications (2,12).

The results of this study showed that asymptomatic gallstones can emerge with acute pancreatitis, which is one of the most important biliary complications, with a substantially high incidence. It also showed that the size of the gallstone is not important in terms of symptom development, and once pancreatitis occurs, the clinical course is not milder in asymptomatic patients compared to symptomatic ones.

According to detailed anamnesis data, most of the cholelithiasis patients in the symptomatic group had been diagnosed before admission. It was found that about half of them had not been aware of the clinical risks of cholelithiasis. A similar situation revealed that there is no biliary risk information among the cases diagnosed incidentally with cholelithiasis in the asymptomatic group. In both groups, there were uncertainties in doctor's evaluations, where the decisions of follow-up and surgery were left to the patient's own decision. This indicates that in clinical practice surgeons have difficulty in making definitive treatment decisions in cases of cholelithiasis.

CONCLUSION

In conclusion, according to the results obtained in this study, asymptomatic GSD may result in acute pancreatitis with a noteworthy incidence, and severity of pancreatitis in asymptomatic patients is similar to symptomatic cases. Also, the size of the gallstone is not a good predictor for the existence of biliary symptoms or to assess the severity of pancreatitis. Asymptomatic cholelithiasis patients have a major percentage in acute biliary pancreatitis cases. The "wait and see" approach for silent gallstones might be supported with prospective studies to build up a structured treatment algorithm.

The main limitation of this retrospective study is the way of data collection. Anamnesis detailing was completed with telephone interviews, which relied on patient's subjective memories about the incident. Retrospective design was chosen to analyze the unbiased approach of the clinicians about silent gallstones and ABP. On the other hand, this limitation provided us to see the if gallstone size really matters and to assess if silent gallstones were as innocent when left without adequate surgical intervention.

Ethics Committee Approval: This study was approved by İstanbul University Cerrahpaşa Faculty of Medicine Deanery Clinical Research Ethics Committee (Decision no: B.30.2.İST.0.30.90.00/29620, Date: 02.10.2013).

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (2): 162-168

Akut pankreatit: Sessiz safra taşlarının ilk bulgusu olabilir

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ÖZET

Giriş ve Amaç: Asemptomatik kolelitiyazisin tedavisi tartışmalıdır. Sessiz safra kesesi taşlarının genellikle en az bir biliyer kolik atağından sonra komplikasyonlara neden olduğu varsayılır. Başlangıçta akut pankreatite neden olan veya etiyolojik etken olarak teşhis edilen sessiz taşların oranı literatürde henüz bildirilmemiştir. Çalışmamız akut biliyer pankreatit olgularında asemptomatik kolelitiyazis oranını araştırmak için tasarlanmıştır.

Gereç ve Yöntem: Akut biliyer pankreatit tanısıyla takip edilen 305 olgunun 171'i geriye dönük olarak belirlendi. Hastaların demografik özellikleri, laboratuvar bulguları ve klinik ilerlemeleri incelendi. Klinik geçmişler telefon görüşmeleriyle detaylandırıldı. Yüz yetmiş bir vakanın 85'inde safra kesesi taşları radyolojik olarak tespit edildi. Bu hastalar semptomatik ve asemptomatik olarak ayrıldı. Klinik bulgular ve takipler "Ki-kare" testiyle değerlendirildi.

Bulgular: Çalışma grubunda hastaların %80'i asemptomatikti (n= 68) ve hastaların %16,47'sinde (n= 14) komplike pankreatit vardı. Klinik gidişatın şiddetine göre semptomatik olup olmaması anlamlı bir faktör olarak belirlenmedi (p= 0,108). Semptom oluşturma açısından taşın boyutu önemli değildi (p= 0,561) ve pankreatitin klinik şiddeti hakkında herhangi bir öngörü elde edilmedi (p= 0,728).

Sonuç: Asemptomatik kolelitiyazis hastaları, akut biliyer pankreatit vakalarında majör bir yüzdeye sahipti. İleriye dönük çalışmalarda sessiz safra taşları için "bekle ve gör" yaklaşımı yeniden değerlendirilmelidir.

Anahtar Kelimeler: Akut biliyer pankreatit, asemptomatik kolelitiyazis, sessiz safrataşı

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CASE REPORT
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Synchronous pancreas and gallbladder cancer with concomitant alopecia totalis

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ABSTRACT

A 55-year-old female presented with history of pain in the right hypochondrium along with complete loss of facial and scalp hair over last two months. On evaluation, she was found to have locally advanced, synchronous malignancies of the gallbladder and head of the pancreas. Synchronous malignancy of gallbladder and pancreas is in itself very rare and less than 10 such cases have been reported in the world literature. Alopecia totalis has been classically associated with various autoimmune disorders. However, alopecia totalis as a presenting feature of any abdominal malignancy has never been reported in the medical literature. The present report describes a rare association of synchronous pancreatobiliary malignancies with strange clinical presentation.

Keywords: Alopecia totalis, synchronous, pancreatobiliary, malignancy

INTRODUCTION

Synchronous dual malignancy of gallbladder and pancreas is extremely rare and only a handful of cases have been reported till date (1). The usual manifestations of pancreatobiliary malignancy include pain, jaundice, anorexia, cholangitis and duodenal obstruction. Intraabdominal malignancy presenting with alopecia has never been reported in the medical literature so far. Alopecia totalis (AT) affects 1.7% of general population and is characterized by severe loss of scalp as well as facial hair. The exact etiology remains unknown, but immunological factor has been implicated in most of the cases (2,3). We describe a rare case of synchronous dual pancreatobiliary malignancy with odd presentation of alopecia totalis. To the best of our knowledge, this is the first report describing concomitant alopecia totalis in the background of abdominal malignancy in humans.

CASE REPORT

A 55-year-old lady presented with complaints of abdominal pain and total loss of scalp and facial hair since two months. She also had long-standing history of dyspepsia and post-prandial abdominal bloating. She was primarily evaluated at another hospital one year back and was diagnosed to have chronic calculus cholecystitis on abdominal ultrasound examination. She was advised to undergo cholecystectomy. However, her symptoms resolved with medications and she was lost to follow up. Over last two months she developed mild to moderate intensity, non-colicky pain in her right hypochondrium, requiring oral analgesics. She also has been suffering from anorexia and weight loss of five kg since last three months. She described rapid hair fall starting two months back and resulting in complete loss of facial and scalp hair over a short duration of 20 days (Figure 1).

General examination of the patient was non-contributory and abdominal palpation revealed a vague, non-tender gallbladder mass. There was total loss of scalp and facial hair though the skin appeared normal. There was no sign of any fungal infection or cutaneous metastasis.

Her laboratory tests revealed a normal complete blood count and normal liver function except a mildly elevated alkaline phosphatase level (340 IU/L). Her kidney function and thyroid profile were also within normal range. A computed to-

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Figure 1. A. Front view of patient's face showing total loss of facial and scalp hair. **B.** Lateral view of the patient with alopecia totalis.

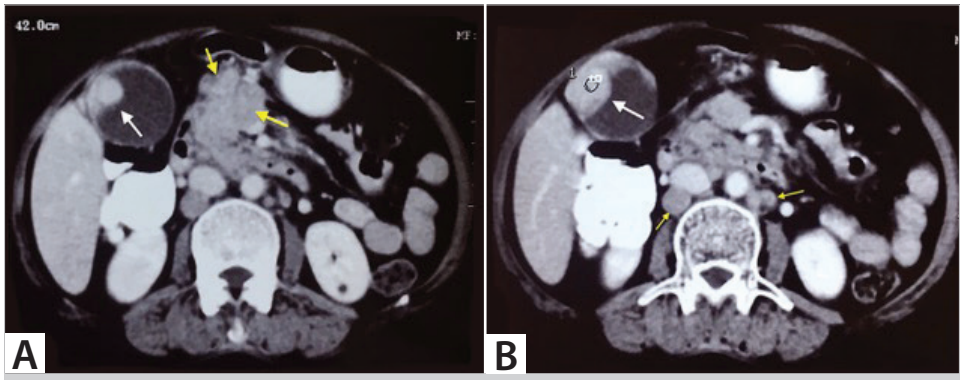

Figure 2. Computed tomography showing: **A.** Enhancing tumors in the gallbladder (white arrow) and head of the pancreas (yellow arrows), **B.** Gallbladder mass (white arrow) with enlarged paraaortic, aortocaval and retrocaval lymph nodes (yellow arrows).

mography (CT) scan of her abdomen was done, which showed an ill-defined, heterogeneously enhancing growth in the body of gallbladder and other bulky mass in the head of pancreas. Multiple paraaortic, aortocaval and retrocaval lymph nodes were enlarged. The lymph nodal mass was seen encasing the coeliac trunk, common hepatic artery, superior mesenteric vein and portal vein (Figure 2). Percutaneous fine needle aspiration cytology done separately from gallbladder and pancreatic head mass was consistent with adenocarcinoma.

In view of locally advanced nature of malignancy, she was planned to undergo palliative therapy. Her disease progressed despite receiving palliative chemotherapy and she died of advanced malignancy three months after diagnosis. Alopecia persisted till the end of her life.

DISCUSSION

Synchronous malignancy of gallbladder and pancreas is of extreme rarity. To the best of our knowledge, less than ten cases have been reported worldwide (1). This is the first case of this rare synchronous malignancy from India. Incidence of gallbladder malignancy in north Indian population is among highest in the world. Chronic calculus cholecystitis is a well-known risk factor for development of gallbladder malignancy. Our patient also had long-standing cholecystitis, which might have led to malignant transformation in the gallbladder. However, there was no identifiable risk factor for development of pancreatic malignancy in our patient. Congenital conditions like choledochal cysts and abnormal pancreaticobiliary duct junction (APBDJ) that are associated with pancreatobiliary carcinogenesis, were not present in our patient (4,5). Genetic analysis to look for mutations predisposing to pancreatic malignancies was not done in our patient.

The usual presentations of pancreatobiliary malignancy include abdominal pain, jaundice, anorexia and weight loss (4). However, AT has never been reported as a presenting feature of any abdominal malignancy. Alopecia is usually associated with autoimmune conditions such as thyroid disease, lupus, pernicious anemia and ulcerative colitis (5). However, our patient didn't have any active autoimmune disease. She was non-diabetic and her thyroid function tests were normal. There was no history of chronic liver or kidney disease. Her complete blood counts and mean corpuscular volume were within normal range, excluding pernicious anemia as the cause for hair loss.

In some patients, alopecia can have familial causes as well. However, there was no history of alopecia totalis in any of her first- or second-degree female relatives. Excruciating pain associated with malignancy can also result in alopecia in some cases. But it is an unlikely cause for hair loss in our patient as the intensity of pain was mild to moderate only and was well controlled with analgesics. The AT in our patient may be only attributed to paraneoplastic syndrome associated with gallbladder malignancy. Few cases of severe alopecia have been reported in patients with lymphoma, but there is no report of AT as a presenting complains in any intraabdominal malignancy (6-8). The mechanism behind this paraneoplastic process is not yet fully understood. The prognosis of AT is usually poor the chance of full hair regrowth is known to be less than 10%. As our patient was planned to undergo chemotherapy for malignancy, no specific treatment was given for hair regrowth (9).

The management of pancreatobiliary malignancy depends on the stage of the tumor (4). Complete surgical resection remains the most effective option for patients with localized disease (5, 10). However, most patients already have advanced malignancy at the time of diagnosis, and such patients are managed with palliative or investigational therapy.

CONCLUSION

We report the first case of AT in a patient of locally advanced synchronous dual pancreatobiliary malignancy. Though the exact etiology remains unknown, paraneoplastic phenomenon might have led to rapid and complete hair loss in our patient.

Peer-review: Externally peer-reviewed.

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

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OLGU SUNUMU-ÖZET
Turk J Surg 2023; 39 (2): 169-172

Eşlik eden alopesi totalisi ile birlikte senkron pankreas ve safra kesesi kanseri

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ÖZET

Elli beş yaşında kadın hasta, son iki aydaki tam fasiyal ve kafa derisi kıllarının kaybının yanı sıra sağ hipokondrium ağrısı şikayetiyle başvurdu. Değerlendirmede, safra kesesinin lokal ilerlemiş, senkronize malignitesi ve pankreas başı olduğu tespit edildi. Safra kesesi ve pankreasın eş zamanlı malignitesi kendi başına çok nadirdir ve dünya literatüründe bu gibi 10 vakadan daha az rapor edilmiştir. Alopesi, çeşitli otoimmün bozukluklarla klasik olarak ilişkilendirilmiştir. Bununla birlikte, herhangi bir abdominal malignitenin bir sunum özelliği olarak alopesi totalisi, tıbbi literatürde hiç bildirilmemiştir. Bu raporda, senkronize pankreatobiliyer malignitelerin ilginç bir ilişkisi tanımlanmaktadır.

Anahtar Kelimeler: Alopesi, senkron, pankreatobiliyer, malignite

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CASE REPORT
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Breast hematoma with active bleeding due to seat belt injury

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ABSTRACT

Breast emergencies are not frequent but play an important part in routine breast imaging applications. Diagnosis and identification of seat belt injury in emergency department are essential for patient management and early treatment of advanced cases. Herein we reported imaging findings of a patient who had prominent swollen at her left breast accompanying tissue edema and painful palpable mass formed by active bleeding hematoma as a result of seat belt injury due to a car accident. Radiologic examinations revealed hematoma in the breast accompanying active bleeding.

Keywords: Breast, computed tomography, hematoma, seat belt injury

INTRODUCTION

Breast emergencies are not frequent but play an important part in routine breast imaging applications. Emergencies are acute situations including inflammatory pathologies (mastitis and abscess), complications of interventional procedures (post-biopsy hemorrhage-hematoma, milk fistula), wire localization complications, trauma including hematoma, pseudoaneurysm and seat belt injury (1). As these pathologies require urgent treatments, it is very important to recognize imaging and clinical findings (1). Seat belt injuries have characteristic findings and there is a group of different organ injuries. It is important to know the mechanism and clinical findings of seat belt injury in breast in order to patient evaluation and management. In this case report, we are presenting a case of breast hematoma in a woman due to seat belt injury.

CASE REPORT

A 38-year-old female patient admitted to the emergency department of our hospital due to car accident. During the accident she was in the car, at the front, next to the driver. Clinical examination showed prominent swollen at her left breast accompanying tissue edema and painful palpable mass extending from upper inner quadrant to lower-outer quadrant with cutaneous bruising in overlying skin of whole breast. In the laboratory analyses, white blood cells were elevated (14.9 mm^3), hemoglobin and hematocrit values were in normal limits but near to the lowest levels (12.2 g/dL and 36.7%). Coagulation parameters were normal. The patient was redirected to radiology department for intravenous enhanced thoraco-abdominal computed tomography (CT) examination. Patient follow-up was realized by breast ultrasonography (US) in the hospitalization duration.

In CT examination, there was diffuse skin and subcutaneous tissue thickness accompanying prominent edema in the whole left breast. There was a multilobulated nodular lesion extending from upper inner quadrant to lower-outer quadrant of left breast with the largest dimension of 15 cm (Figure 1A) including a hyperdense area due contrast material extravasation as a result of active arterial bleeding (Figure 1B). There was no enhancement in the nodular lesion and diagnosed as hematoma. The source active bleeding was one of the branches of lateral mammarian artery, which is a branch of lateral thoracic artery (Figure 1C). US evaluation verified

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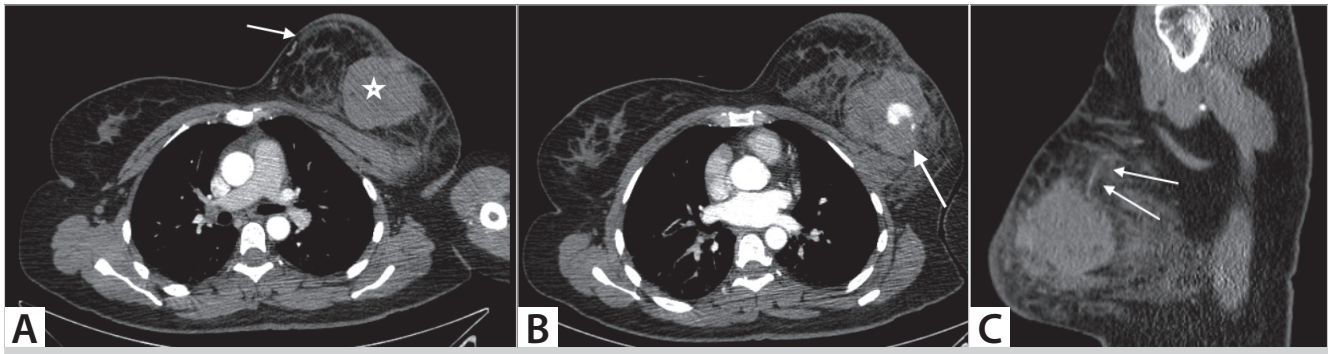

Figure 1. (A,B). Axial and **(C)** Sagittal intravenous enhanced CT images. **(A)** There is a multilobulated nodular lesion compatible with hematoma extending from upper inner quadrant to lower-outer quadrant of left breast (star). Additionally, the breast parenchyma is heterogeneous with diffuse skin and subcutaneous tissue thickness (arrow). **(B)** Hyperdense area at the central part of hematoma reveals contrast material extravasation due to active bleeding. **(C)** There is a thin enhancing arterial structure extending into the hematoma (arrows). This artery is compatible with one of lateral mammarian artery branch, which is originated from lateral thoracic artery is the source of active bleeding.

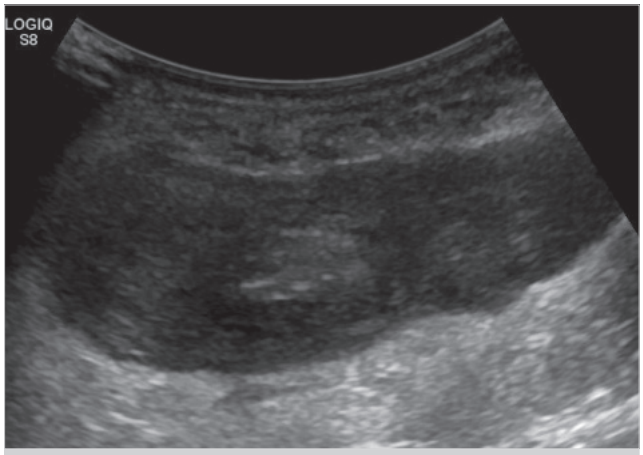

Figure 2. US image reveals hypoechoic heterogeneous nodular lesion including hypo-anechoic areas compatible with breast hematoma. Convex probe was used because of large size of breast and hematoma.

and revealed the hematoma (Figure 2). Compressed bandage was applied and the patient put in follow-up procedure.

DISCUSSION

Injuries formed by the harness of seat belt have characteristic findings and these findings form seat belt syndrome. In this syndrome, there is a group of injuries including, breasts and chest wall soft tissue injuries, fractures of clavicle, sternum, rib and spine. Additionally mesenteric injury and organ perforation especially organs with hollow are seen (2). There are multiple different variables affecting the injury. These variables are the type of seat belt, presence of air bag, the speed of the vehicle, age and the position of the patient (2). In a car accident, if the car is a left-hand drive, the passenger sitting next to the driver usually has injury at the upper inner quadrant of right breast and lower inner quadrant of left breast (3).

These patients represent with painful swollen breast including hematoma accompanying scar and bruising at the overlying skin and injuries at the line of seat belt (2,4).

In radiologic evaluation, mammography (MG) reveals increased linear density and additional skin thickening in the acute phase and fat necrosis afterwards (3). In US examination, there are non-specific findings including hypoechoic heterogeneous areas including hypo-anechoic fluid collections with debris compatible hematoma at different age and acute hemorrhage (3). There are band-shaped enhancement at the site of injury in magnetic resonance imaging. This site is hyperintense on T2 weighted and STIR images. After formation of fat necrosis, central fat elements are surrounded by rim enhancement and oil cysts can be seen (5).

In the management, primarily, a professional fitted bra is provided and symptomatic medication including non-steroidal and narcotics are applied for pain. If there is a breast deformation, breast reconstruction can be considered. Rarely breast avulsion and massive hemorrhage can be seen and in these cases emergent surgical procedures are applied (2).

In cases which can be put in follow-up procedure, physical evaluation and radiologic follow-up including MG 3-6 months after the injury (2).

CONCLUSION

Breast emergencies, especially seat belt injuries are very rare. Diagnosis of this entity is important in management and follow-up procedures. Identification of seat belt injury in emergency department is essential for patient management and early treatment of advanced cases.

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Author Contributions: Concept - IBA, SÖA; Design - IBA; Supervision - AİS, PB; Materials - SÖA; Data Collection and/or Processing - IBA; Analysis and/or Interpretation - AİS, PB; Literature Search - IBA; Writing Manuscript - IBA; Critical Reviews - PB.

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OLGU SUNUMU-ÖZET
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Emniyet kemeri yaralanmasına bağlı aktif kanama içeren meme hematomu

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ÖZET

Meme acilleri sık değildir ancak rutin meme görüntüleme uygulamalarında önemli bir role sahiptir. Acil serviste ağır olgularda emniyet kemeri yaralanmasının saptanması ve tanısı hastanın değerlendirilmesi ve erken tedavisinde önemlidir. Bu olgu sunumunda trafik kazası nedeniyle emniyet kemeri yaralanması sonucunda sol memesinde dokuda ödem ve aktif kanayan hematoma bağlı ağrılı palpabl kütlenin eşlik ettiği belirgin boyut artışıyla başvuran hastaya ait görüntüleme bulgularının sunulması amaçlanmıştır.

Anahtar Kelimeler: Bilgisayarlı tomografi, emniyet kemeri yaralanması, hematom, meme

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