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

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

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

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INSTRUCTIONS TO AUTHORS

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4. Agreement to be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

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

Manuscript Types

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

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

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

The details of the review process are below.

- All videos will be peer reviewed.
- All videos will be published on the journals official Web site.
- 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.

The following items must be provided:

- The file of the video written in Word format.
- A completed copy of the online broadcast consent form (form will be prepared and linked), together with completed copies of patient consent forms, if appropriate.
- All videos must contain an English narration.
- All videos should also be in the highest resolution possible, more details on accepted file types and resolution are available at this link (authors' video article submission guidelines; https://turkjsurg.com/video-article-guidelines).
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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.

Tables

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

Figures and Figure Legends

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

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

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

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

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

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

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

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FROM THE EDITOR'S DESK
Turk J Surg 2024; 40 (1): IX
10.47717/turkjsurg.2024.20240101

Dear Readers of the Turkish Journal of Surgery,

Welcome aboard the March 2024 issue of the Turkish Journal of Surgery, which is the first edition of the new year. Like every other issue, this one seeks to highlight the ever-evolving landscape of surgical sciences with profound insights and groundbreaking research findings.

In this issue, we focus on the demands of emergency surgery, a field where split-second decisions and precise maneuvers often determine the outcome. We are privileged to present two interesting articles on this critical area. The first looks at the intricate management of gunshot wounds to the abdomen and pelvis and addresses the complexities and challenges that such traumatic events (1). The second article focuses on surgical notes in emergency surgery and highlights the critical role of education in this documentation in emergency situations (2). These articles serve as a guide for professionals navigating the turbulent waters of emergency surgery.

In addition, our journal presents a number of noteworthy studies from the fields of pancreatic and breast cancer surgery. Büyükkasap et al. discuss the early diagnosis of failure of pancreatic anastomosis, which is known as the factor that most affects mortality in pancreatic surgery (3). On the other hand, Gündoğdu et al. focus on the complete pathologic response that can occur after neoadjuvant therapy in breast cancer (4). As advances in technology and surgical techniques continue to change the landscape of oncologic management, these articles offer valuable insights into the latest trends, innovations, and best practices in these specialties.

On this journey through the corridors of surgical knowledge, I would like to express my sincere gratitude to our esteemed authors whose dedication and scientific rigor have brought about these insightful contributions. My sincere thanks also go to our hard-working reviewers and editorial board members, whose expertise and judgment ensure the quality and integrity of our journal.

Here's to a year filled with growth, discovery, and endless possibilities!

Warm regards,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

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INTEGRATIVE REVIEW
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Integrating the new systemic treatment landscape and surgical therapy in hepatocellular carcinoma

Philipp K. Haber, Felix Krenzien, Kaya Sarıbeyoğlu, Johann Pratschke, Wenzel Schöning

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ABSTRACT

The treatment landscape of hepatocellular carcinoma has evolved rapidly within the last decade. Minimally-invasive techniques have reached a new level of safety, affording surgeons to pursue more aggressive treatment strategies to ultimately improve oncological outcomes. These procedures have been increasingly applied to treat patients with more progressed tumors and in select case even patients with advanced stage disease confined to the liver. Concomitantly, a dramatic increase in research into immunotherapy has altered the treatment paradigm in advanced disease stages, where the emerging treatment regimens can provide durable responses in a subset of the patient population for whom prognosis is dramatically improved. These treatments are now tested in early-stage disease to address the pressing unmet need of high recurrence rates after resection and in intermediate stage to complement the proven efficacy of intraarterial embolization in delaying progression. This review provides an in-depth discussion of these trends and describes how the treatment landscape has already changed and which impediments remain.

Keywords: Hepatocellular carcinoma, surgery, liver, chemotherapy, immunotherapy, systemic therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality globally. Despite improved screening programs and refined understanding of pathogenesis and risk factors, incidence rates are on the rise with ~1.000.000 new cases expected annually starting in 2025 (1,2). As a unique feature in clinical oncology, both staging and treatment allocation are dictated by the Barcelona Clinic Liver Cancer (BCLC) criteria that distinguish between very early (0), early (A), intermediate (B) and advanced stage disease (C) taking into account tumor morphometrics (size and number of nodules) as well as liver function and general health, accounted for by ECOG performance score (3). Historically, curative treatment approaches have been applied almost exclusively in patients with early or very early-stage disease. The underlying rationale for this notion, as advocated by guidelines, is to pursue ideal patient selection in order to ensure optimal outcomes (4,5). When rigorously applied, surgical resection for patients with early stage tumors can provide a median overall survival (mOS) of approximately five years although recurrence rates remain high at 50-70% within the same time period (6). Optimal candidates can be considered for liver transplantation (LT) which can improve outcomes further, providing five year mOS of ~70% while reducing recurrence rates to 10-20% after five years (7).

1st Trend: The Extension of Operative Indication

Improving the outcomes of patients with HCC has been the subject of substantial clinical and translational efforts involving several specialities in the treatment algorithm of this disease. Regarding surgical therapies, advances have been mostly based on a technical level. Refined surgical techniques and in particular minimally-invasive procedures have enabled clinicians to push the limits considerably in terms of extending indications. Patients with a higher risk profile, resections which entail a higher degree of difficulty and patients with more progressed tumors are nowadays amenable to resection (8-10). Several retrospective studies have validated this strategy as surgery has been able to provide improved outcomes compared to alternative treatments that these patients would have otherwise

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defaulted to (11-13). The benefits provided by these technical advances have encouraged surgeons to extend indications beyond early-stage disease and increasingly consider those patients with multinodular or even advanced stage disease for resection. Indeed, in patients with intermediate stage disease amenable to resection, surgical treatment conveyed a marked improvement in 1-,3- and 5- year survival rates compared to TACE (71%, 42%, and 33% vs. 54%, 24%, and 16%) as shown in a high-impact metaanalysis (14). Concerning patients with macrovascular invasion, emerging evidence, predominantly from Asia, have supported a role of liver resection in selected patients (15,16). A registry study from the US reporting outcomes of >11.000 patients has lead to similar results; resection -when feasible- is associated with a strong benefit in mOS compared to systemic therapy (21.4 vs. 8.1 months). Certainly these data should be interpreted cautiously given the evident selection bias (17). Even more recently, robotic surgery has been increasingly performed in hepatobiliary surgery and has been shown to be non-inferior to standard laparoscopy although longer learning curves have been reported (18-20). However, this approach has key innate advantages; first, it affords the operating surgeon increased stability. Second, with the improved instrumental flexibility, high stability, and tremor filtration, it is particularly effective in a narrow situs. Magnified 3-d vision further increases the precision of surgical maneuvers, which makes the robotic approach particularly effective in hilar dissection (Figure 1). Isolated resections of liver segment I, the caudate lobe, are traditionally procedures hardly amenable to laparoscopy, whereas the properties of the robotic platforms enable surgeons to conduct this challenging resection strictly minimally-invasively. Figure 1 shows preoperative imaging from a 61-year-old male with biopsy-proven HCC in CP A cirrhosis outside of Milan criteria. The patient subsequently underwent robotic-assisted Segment I resection at our center.

Overall, these minimally-invasive procedures have been demonstrated to elicit a major reduction in morbidity while retaining high-quality oncologic outcomes (21). A recent metaanalysis, reporting outcomes of 6812 patients, has substantiated these notions; laparoscopic resection for HCC was associated with a significantly reduced morbidity and 30 day mortality [odds ratio (OR) 0.42; 95% CI 0.34-0.52 and OR 0.32; 95% CI 0.16-0.66] while achieving similar rates in R0 resection (22). Moreover, a large French multicenter study has highlighted

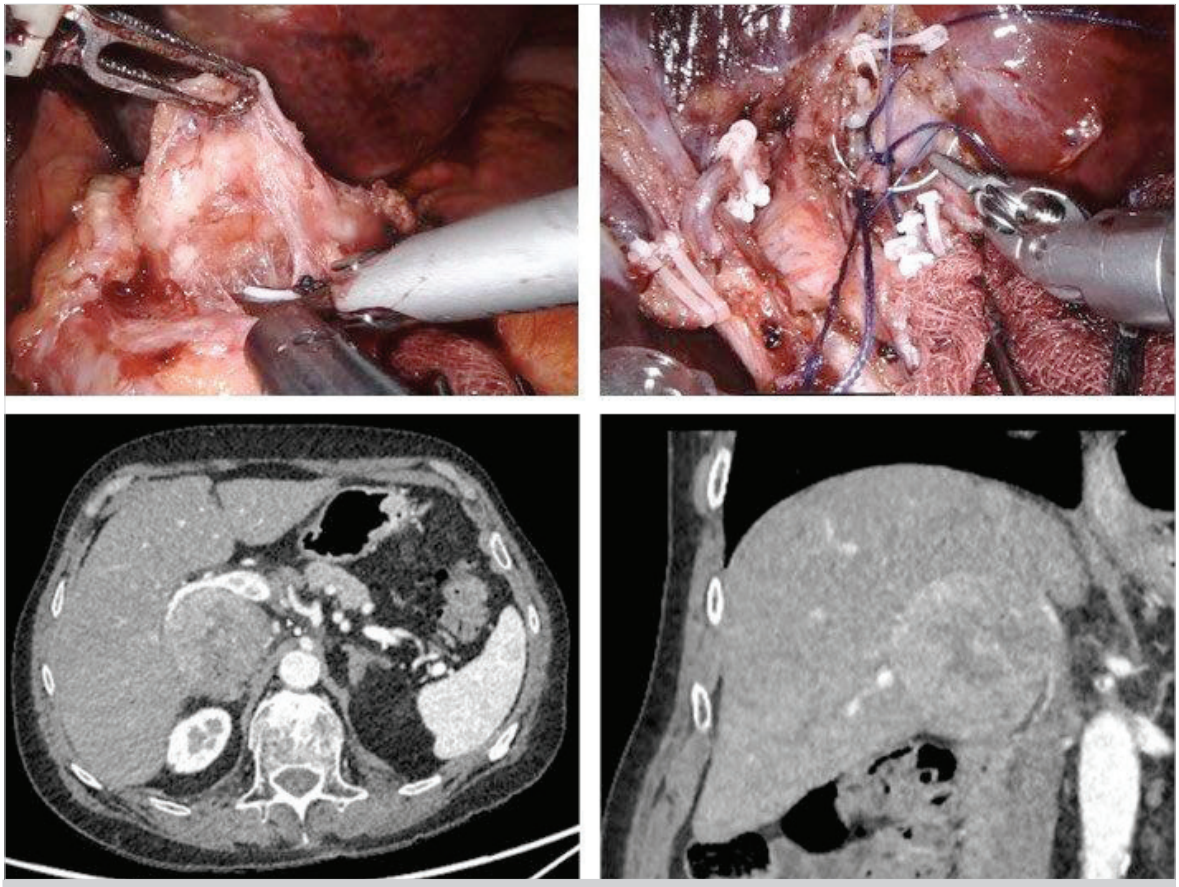

Figure 1. Top two panels: Hilar dissection using the robotic approach. Bottom two panels: Isolated biopsy-proven HCC in the caudate lobe prior to robotic-assisted segmentectomy.

the positive impact of laparoscopy on reducing the chance of post-hepatectomy liver failure (PHLF) (23).

These trends have been able to ameliorate the detrimental impact of organ scarcity on LT in HCC, where especially patients with compensated hepatic function are increasingly considered for resection as a definite treatment option. LT, on the other hand, is more and more reserved for patients where dismal liver function precludes resection or those where it offers a greater survival advantage compared to resection or intraarterial therapies.

Overall, this represents the first major trend in the clinical space; the extension of operative indication, heralded by technological advances and an improved understanding of morbidity risk. Excitingly, this trend is set to coalesce with the other major development in hepatocellular carcinoma; a fast-paced development of systemic therapy strategies.

2nd Trend: Extending Systemic Treatment Beyond Advanced Stage Disease

For the better part of the past two decades, the treatment of advanced stage HCC has been mostly limited to the use of receptor-tyrosine kinase inhibitors (TKI) that have been able to provide a modest survival benefit for a broad proportion of the patient population. In case of sorafenib, the first approved TKI, OS was extended by three months in both the SHARP and the AP trials (24,25). Likewise, lenvatinib, regorafenib and cabozantinib have provided similarly narrow benefits for patients (26-28). Within the past three years, however, treatment of advanced stage HCC has undergone a paradigm shift. As across cancer types, the use of immune checkpoint inhibitors (ICI) has revolutionized clinical care. Contrary to outcome patterns after TKI treatment, response patterns after ICI are highly heterogeneous; Indeed, only a proportion of the patient population exhibits radiological objective response (OR), where an outstanding survival advantage is achieved, whereas the majority of patients exhibit either stable disease or primary progressive disease (29). The size of the patient subset responding to ICI is variable across cancer type and guides whether single-agent ICI is a viable treatment option in a given field. In case of HCC, OR rates (ORR) are between 15-20% after single-agent anti-PD1 (30,31) but can be enhanced through combinatorial therapies; the combination of anti-PD-L1 atezolizumab and anti-VEGF bevacizumab has been demonstrated to elicit a mOS of beyond 19 months in patients with advanced stage and is now considered the standard of care (32). Dual ICI combination durvalumab and tremelimumab has also increased survival relative to sorafenib and represents an alternative in frontline (33). Further trials have investigated the viability of these combination treatments such as COSMIC312 and LEAP002 investigating cabozantinib + atezolizumab and lenvatinib + pembrolizumab, respectively (34,35). Although similar survival data was achieved, these trials have failed to meet their primary endpoint, in part due to unexpectedly well performing control arms. The central underpinning of the success of combination treatments has been the extension of the immune sensitive population through establishing a more ICI-conducive tumoral microenvironment by the auxiliary drug (36,37).

The treatment landscape of advanced HCC is thus proven to be highly dynamic at this point and efforts are shifting towards leveraging the established efficacy of these drugs in earlier disease stages to address major unmet needs that have prevailed for decades. In case of early stage disease, it is sought to reduce recurrence rates after resection or local percutaneous ablation which remain high at 50-70% after five years (38). Second, in intermediate stage disease, TACE is firmly established as the standard of care and has been virtually unchallenged in this position (39). Here ICIs have been increasingly tested as either standalone or complementary to TACE to prolong survival. To provide a better understanding of these trends the following sections will elucidate in more detail where these trends intersect, what the bottlenecks are and how the treatment landscape may change in the long run.

Reducing Recurrence Rates After Resection and Ablation

Adjuvancy

Reducing recurrence rates after resection and ablation remains a critically unmet need. The success of ICI-based systemic treatment in advanced stage HCC has imposed several investigations into its potential applications in earlier disease stages. The rationale behind this trend is that the efficacy of checkpoint inhibitors might be particularly pronounced in early-stage disease, where the tumor burden is still contained and malignant cells have acquired limited immune evasion mechanisms. As a cautionary tale, the same rationale has failed before, where the success of the TKI sorafenib has failed to elicit a meaningful benefit in an adjuvant setting and likewise brivanib which could not adjuvantly augment the efficacy of TACE (40,41). Interestingly, before the onset of checkpoint inhibitors, the only notable trial that reported a positive outcome in HCC that was designed for adjuvancy was a trial testing cellular immunotherapy by means of autologous cytokine-induced killer cells. The authors reported a significantly prolonged RFS although concerns regarding imbalanced study arms have hindered the adoption of these results by guidelines (42). The results, however, underscored the potential of immunotherapy to reduce recurrence rates following resection and ablation and may have contributed to the evolving treatment landscape of today.

The standard of care treatment for advanced HCC, anti-VEGF bevacizumab and anti-PD-L1 atezolizumab, convey a marked improvement in OS, PFS and objective response rates compared

to single-agent ICI and its success has prompted investigations in early disease stages to test its potential adjuvantly. Recently, results from IMbrave050 have been reported, where 668 patients were randomized to receive either active surveillance or atezolizumab + bevacizumab (43). At the first interim analysis, the primary endpoint of improving recurrence-free survival (RFS) was met, as treatment improved 12-month RFS from 65% to 78%. Expectedly, data for OS are immature at this point due to low frequency of events after a median follow-up of 17.4 months. Analysis of the Kaplan-Meier curves on RFS reveals a clear and early separation of the curves within the first year after treatment which leads to the reported 12-month RFS data. However, a convergence is observed in the subsequent period, when treatment is halted, which requires further long-term analysis. Given the trend, it remains unclear whether there will be any difference in two-year RFS, which would indicate the study regimen to delay early recurrence rather than preventing it in the first place. In HCC, recurrence within the first two years after resection are generally considered the results of remaining micrometastases whereas recurrence beyond that interval is regarded as a de-novo tumor, drawing into question the suggested duration of treatment. Given the high-crossover rate for those patients developing recurrence and the high rates of non-cancer specific mortality in HCC, it appears unlikely that a separation in OS curves will be observed in the future. Considering that RFS is unequivocally recommended as the primary endpoint for adjuvant trials in HCC, it is reasonable to assume that if a difference in RFS is maintained in follow-up analyses, atezolizumab and bevacizumab will be adopted by guidelines as the adjuvant treatment option of choice for those patients at high risk to develop recurrence. (As defined by the study protocol; 1 tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2 or Grade 3/4) (44). Further ongoing phase III RCTs testing adjuvant pembrolizumab (KEYNOTE-937), nivolumab (CHECKMATE 9DX), duvalumab ± bevacizumab (EMERALD 2) and toripalimab (JUPITER 04) are currently underway and will clarify the role of ICI in adjuvancy within the coming years.

Neoadjuvancy

The backbone of the current innovation in this setting is clearly based on checkpoint inhibitors. Strikingly, the application of these drugs to reduce recurrence rates might be most appropriate in a neoadjuvant setting: herein, the presence of the tumor can be leveraged as a priming load for antigen-presenting and ICI-boosted immune effector cells to convey antitumoral immunity and thus contain tumor growth or even induce necrosis prior to resection (Figure 2). This would render potential

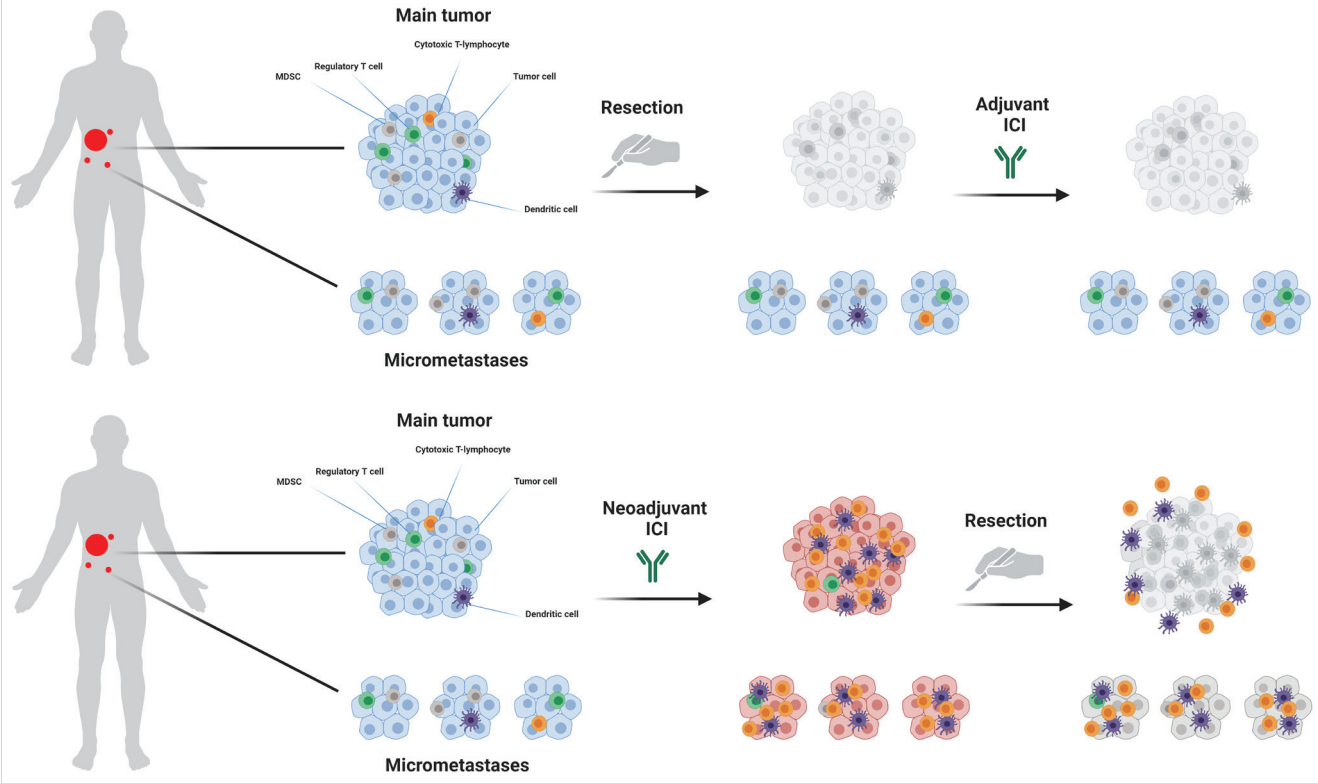

Figure 2. Adjuvant treatment with checkpoint-inhibitor based regimen might be less effective due to lacking induction of tumor-specific T cells and failure to eliminate micrometastasis leading to relapse (top panel). Neoadjuvant ICI, contrarily, may leverage the tumor as a priming load for effective antigen-presentation to induce effective immunosurveillance following resection.

micrometastases less viable following resection or ablation and empower T cells to conduct more effective immunosurveillance following resection. This hypothesis has been tested in tumors with more extensive history of ICI application such as melanoma where reports have found that neoadjuvant treatment leads to a more robust immune response with increased tumor-specific T cells (45). The neoadjuvant study design offers further advantages compared to a strictly adjuvant concept: investigators can assess response to treatment not just via imaging but also through histology, including the expansion of T cell infiltrates, tertiary lymphoid structures, which can be hubs of antitumoral immune response, and tumor cell viability. Pooled analysis from clinical trials in melanoma has shown that pathological assessment of response correlated with recurrence-free survival where patients with major pathological response (MPR= 70% tumor cell necrosis) having significantly longer RFS and disease-free survival (DFS) (46). Whether or not a patient displays MPR in the resection specimen may also guide clinical decision making regarding adjuvancy. In this scenario, patients with progression or only marginal tumor necrosis may not benefit from further postoperative treatment.

This would collaterally address a key caveat of ICI treatment, which is substantial heterogeneity in terms of response and the lack of clinically applicable biomarkers. From a research perspective, a neoadjuvant approach can also provide researchers with a unique opportunity to improve our grasp of the tumoral microenvironment and factors dictating response and resistance to treatment.

In HCC, neoadjuvancy is not yet integrated in routine clinical practice but very recently several high-quality studies have provided invaluable preliminary evidence of its feasibility. Kaseb et al. have reported a phase II study, where patients were randomized to receive either nivolumab (anti-PD1) every two weeks or nivolumab every four weeks + ipilimumab every six weeks (anti-CTLA4) for up to four doses prior to resection (47). Out of 20 patients undergoing resection, six had MPR in the specimen, with five of these patients developing complete tumor necrosis. The patients displaying MPR in turn, did not develop recurrence during the follow-up, whereas 50% of the remaining patients did, underscoring the potential of MPR as a surrogate endpoint in this clinical setting. Marron et al. have reported on the use of anti-PD1 agent cemiplimab in a further phase II study, where patients received two cycles of treatment for a total of six weeks prior to resection and eight further cycles following resection (48). The authors have found that 35% of patients had at least 50% of tumor cell necrosis and linked this with the rise of $CD8^+$ T cells from pre-treatment biopsies compared to the resection specimen. Transcriptomic analysis revealed several gene expression signatures related to Interferon-y signalling and active antigen presentation to be markedly enhanced among responding patients. In a further phase II trial, Xia et al. have reported on the perioperative use of apatinib (TKI) + camrelizumab (anti-PD1), which was able to elicit at least major pathological response in 4/18 patients (49). Nanostring-based transcriptome analysis also demonstrated inflammatory signalling and an intact antigen-presentation machinery to be enriched among responders.

More investigations in this field are currently underway (Table 1) with preliminary findings already reported that build on the available data from the published trials (50-52). With evidence building up and a refined grasp of predictors of response and resistance to ICI, the field is moving towards a point where biomarker-driven precision oncology in a neoadjuvant setting may be attainable in the mid-term.

Table 1. Selected phase II/III trials aimed at reducing recurrence rate in early stage HCC

Trial	Study Arm	Design	Primary Endpoint	High Recurrence Risk Only	Phase	Estimated Enrolment
PREVENT-2	Tislelizumab + Lenvatinib	Adjuvant	RFS	Yes	III	200
EMERALD-2	Duvalumab + Bevacizumab	Adjuvant	RFS	Yes	III	908
KEYNOTE-937	Pembrolizumab	Adjuvant	RFS	No	III	950
DaDaLi	Sintilimab + Bevacizumab	Adjuvant	RFS	Yes	III	246
SHR-1210-III-325	Camrelizumab + Rivoceranib	Adjuvant	RFS	Yes	III	687
JUPITER 04	Toripalimab	Adjuvant	RFS	No	III	402
CheckMate 9DX	Nivolumab	Adjuvant	RFS	Yes	III	545
JS001-020-Ib-HCC	Toripalimab + Lenvatinib	Neoadjuvant	MPR	No	II	40
NCT03916627	Cemiplimab	Neoadjuvant + adjuvant	MPR	No	II	73
NEOTOMA	Duvalumab + Tremelimumab	Neoadjuvant + adjuvant	Safety	No	II	28
NeoLeap-HCC	Pembrolizumab + Lenvatinib	Neoadjuvant + adjuvant	MPR	No	II	43
TALENT	Tislelizumab/Tislelizumab + Lenvatinib	Neoadjuvant + adjuvant	DFS	No	II	80

RFS: Recurrence-free survival, MPR: Major pathological response, DFS: Disease-free survival.

Enhancing The Efficacy of Intraarterial Therapies in Intermediate Stage

Transarterial chemoembolization is the stalwart treatment of intermediate stage HCC after it was established through a landmark metaanalysis by Llovet and Bruix in 2002 (39). Since then, however, little progress has been made, with the improvement in OS observed in the interval being mostly due to the success of post-progression therapies in the form of TKIs and ICI. Combination treatments trying to utilize the effectiveness of TKI together with TACE were futile and failed to show a meaningful survival benefit (53,54). Encouragingly, the onset of ICI is set to impact this disease stage as well. The rationale behind combining immunotherapy with intraarterial treatment appears sound; due to tumor cell necrosis evoked by TACE, a plethora of tumoral neoantigens are released that may be recognized by dendritic cells and thus function as a priming load for the immune system, which can then be boosted by ICI to exert antitumoral cyotoxicity. Moreover, locoregional treatments have been demonstrated to modulate immune properties within the tumor by repressing infiltrations of immunosuppressive T cells, particularly FOXP3 + regulatory T cells that have been implicated in immune evasion (55). The same rationale has been applied to earlier disease stages by combining radiofrequency ablation with ICI as well. Early experiences were published in 2017 when Duffy et al. reported feasibility through 32 patients receiving tremelimumab and undergoing either RFA or TACE. The combination interestingly provided higher response rates even outside the ablated zone supporting the notion that systemic treatment may augment locoregional strategies and vice versa. Further studies built on this premise and demonstrated that TACE + anti-PD1 may provide a survival benefit to either standalone treatment in intermediate and advanced stage, respectively (56,57). Similar results have been reported for transarterial radioembolization (TARE) which was able to elicit a response rate of 30.6% when combined with nivolumab compared to 20% as monotherapy (58). Recently, de la Torre et al. have reported on a phase II study also testing TARE + nivolumab in 42 patients, where an ORR of 41.5% was achieved and four patients were downstaged to subsequently undergo potentially curative liver resection.

Certainly, further evidence is needed to clarify the potential synergy between ICI and locoregional treatments. To this end, a recent press release has announced that the phase III EMERALD-1 study has met its primary endpoint of prolonging PFS in the interim analysis. In this trial 616 patients with unresectable HCC were randomized to receive either durvalumab + bevacizumab + TACE or TACE alone. Data regarding efficacy and safety are eagerly awaited as this combination could potentially represent a new standard of care for patients with intermediate stage HCC.

Several further trials testing TACE combined with single-agent ICI as well as doublets and triple therapies are currently ongoing with results expected within the next three years. A paradigm shift in the treatment of unresectable HCC would go beyond a simple change in the definitive treatment. Indeed, augmenting intraarterial strategies will likely have ramifications for patients on the waitlist for LT, where TACE is routinely applied as a bridging therapy to contain tumor growth. In this regard, preliminary evidence has been made available in recent years. Tabrizian et al. have reported on the feasibility of using ICI as a bridging therapy in a small series of nine patients from Mount Sinai (59). Herein, no rejections after LT were noted, a critical issue since ICI raise the risk of acute rejection when given after LT. Moreover, a third of patients developed at least 90% tumor necrosis following the bridging therapy. Clearly, several questions remain unanswered such as the timing of therapy with regard to LT and whether or not immunosuppressive regimens need to be adjusted accordingly.

Downsizing Through Systemic Therapy

Advanced stage disease remains the key domain of systemic treatment, where the application of checkpoint inhibitor-based combination treatment has driven a marked improvement in outcomes with tangible benefits for the patients. However, outcomes remain highly heterogeneous and a significant reduction in tumor burden as accounted for by the ORR is reached in approximately a third of patients, whereas the majority of patients exhibit stable disease and primary progression is observed in ~20% of the population (32). As a key feature of these novel treatments, response is sustained for a median duration of 18 months (60). In this interval, the reduction in tumor burden may open up therapeutic avenues with potentially curative treatments that the patients were previously not eligible for. For these select patients, the benefits conveyed by either resection or even transplantation is still attainable despite having previously advanced stage disease. Since approval of the current standard of care atezolizumab + bevacizumab or alternatively durvalumab and tremelimumab is relatively new, limited data is available on long term outcomes in patients achieving response and currently no consensus exists for pursuing potentially curative treatments in these patients. One small phase Ib study assessed the ability of cabozantinib and nivolumab to downsize irresectable non-metastatic HCC so that resection would be technically feasible and conducive from an oncologic perspective (61). A total of 15 patients were enrolled, most of whom had either multinodular disease or macrovascular invasion as initial contraindications towards surgery. Of those, 13 eventually underwent surgery, with one patient declining the procedure and one dropping out due to insufficient liver remnant function. 5/13 patients displayed MPR or complete pathologic response, whereas only

1/13 patients exhibited OR via imaging when using RECIST 1.1 criteria. This discrepancy underscores another disputed area in the field, where imaging criteria are simply morphometric readouts whereas histology workup can account for tumor cell viability and thereby provide a more granular picture of drug efficacy. This poses a challenge in clinical practice where routine serial biopsies after treatment are not available and recognizing a point in time where the tumor might be susceptible to anatomical targeting (i.e. ablation or resection) is thus entirely reliant on imaging. The biomarker analysis of the above-mentioned study highlighted the ability of the TKI cabozantinib to strengthen antitumor T cell responses, hence complementing the co-administered ICI nivolumab. Expectedly, the combination heavily enhanced the inflammatory infiltrate within the tumor in responding patients, where tumor cells accounted for ~30% of all cells within the specimen compared to 75% in non-responders. Despite these encouraging data, it has to be acknowledged that there is a paucity of trials exploring this highly important clinical setting and most evidence to date is derived from retrospective series. Zhang et al. reported about 224 patients receiving systemic treatment due to irresectable disease between 2019 and 2022. Twenty-six were deemed resectable after systemic treatment, for the most part featuring a TKI in combination with a checkpoint inhibitor as well as either TACE or hepatic artery infusion therapy (HAIC). Disease control in this patient population was 100%, with an ORR of 77% and all patients were still alive after a median follow up of 13 months (62). Further small series support the conclusion that for a proportion of patients with irresectable or advanced stage disease, ICI-based combo treatments may offer a path towards subsequent potentially curative treatments (63,64). It has to be mentioned that this path is currently very narrow and the vast majority of patients undergoing systemic treatment for advanced stage disease will at some point progress and receive 2nd and 3rd line therapy. However, given the improving grasp of determinants of response and resistance to systemic treatments in HCC, as well as the introduction of further drugs aimed at overcoming resistance, it is reasonable to hypothesize that this patient subset could expand in the coming years (65-68). For respective patients the line embedded in staging and treatment allocation that separates palliative and curative intent can hopefully blur through those trends.

CONCLUSION

Recent years have seen a steady improvement in outcomes for patients with HCC across disease stages. Two key developments have driven this trend; first is the refinement of anatomical approaches with new surgical techniques that enable to push the limits in terms of indications while maintaining acceptable safety outcomes. To this end, minimally-invasive resections have been adopted as the default treatment for early stage HCC by several high-volume centers globally, while liver transplantation, as a modality dependent upon a limited resource, is increasingly reserved to treat either younger patients or those with compromised hepatic function. Likewise, the therapeutic armamentarium of percutaneous ablative techniques has increased with techniques such as microwave ablation challenging radiofrequency ablation as the mainstay for very early-stage tumors and new modalities emerging to add layers of complexity to treatment allocation. The second major development has been the changing treatment paradigm in advanced stage fuelled by a drastic increase in both clinical and translational research. While further tyrosine kinase inhibitors have been established, the onset of checkpoint inhibitor-based immunotherapy has revolutionized systemic therapy. The ripple effects of new systemic treatment combinations are already seen in earlier disease stages, where their efficacy is utilized to reduce recurrence rates after resection or ablation and augment established intraarterial therapies to delay progression. Critically, these treatments have teased out a yet small patient population with progressed tumors that may undergo curative-intent treatment options after successful downsizing. Unfortunately, the near absence of clinically applicable predictive biomarkers to maximize the effectiveness of drug deployment remains a glaring unmet need. Likely, further development of synergistic combinations and their precision-oncology based application across disease stages will shape the trial landscape of this decade.

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BÜTÜNLEYİCİ DERLEME-ÖZET
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Hepatoselüler karsinomda yeni sistemik tedavi seçenekleri ve cerrahinin tedavi planına entegrasyonu

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ÖZET

Hepatoselüler karsinom tedavisi son on yılda hızlı bir şekilde gelişmiştir. Minimal invaziv teknikler güvenle uygulanmaya başlanmış ve cerrahların onkolojik başarıyı geliştirmek için daha agresif tedavi stratejileri izlemelerine olanak sağlamıştır. Bu ameliyatlar, ilerlemiş tümörleri olan hastaları ve hatta bazılarında karaciğerle sınırlı ileri evre hastalığı olan hastaları tedavi etmek için giderek daha fazla uygulanmaktadır. Buna paralel olarak, immünoterapi araştırmalarındaki dramatik gelişmeler, ortaya çıkan yeni tedavi rejimleriyle prognozu önemli ölçüde iyileştirmekte ve hasta popülasyonunun bazı alt kümelerinde kalıcı yanıtlar sağlayabilmektedir. Bu nedenle ileri hastalık evrelerindeki tedavi paradigması değiştirmektedir. Bu tedaviler erken evre hastalıkta, rezeksiyon sonrası yüksek nüks oranlarını önlemek, orta evrelerdeyse intraarteriyel embolizasyonun kanıtlanmış etkinliğini tamamlamak ve ilerlemeyi geciktirmek amacıyla denenmektedir. Bu derleme, bu trendlerin derinlemesine bir tartışmasını sunmakta ve günümüzde tedavi planlarının nasıl değiştiğini ve önümüzde hangi engellerin kaldığını açıklamaktadır.

Anahtar Kelimeler: Hepatoselüler karsinom, cerrahi, karaciğer, kemoterapi, immünoterapi, sistemik tedavi

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ORIGINAL ARTICLE
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Assessing the standard of emergency general surgical (EGS) operation notes in accordance with the Royal College of Surgeons guidelines

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ABSTRACT

Objective: Operation notes are important for care in surgical patients. The objectives of this study were to analyze the emergency general surgery (EGS) operation note documentation in accordance with the Royal College of Surgeons of England (RCSEng) guidelines and to assess the impact of creating awareness of the guidelines and effect of a new proforma.

Material and Methods: A retrospective review of 50 EGS operation notes was conducted between December 2019 and March 2020 and compared to RCSEng guidelines. Education was delivered on the importance of documentation in accordance with RCSEng guidelines. A new electronic proforma was introduced. A further 50 EGS operation notes were analysed between August 2020 and December 2020.

Results: One hundred operation notes were reviewed, and each given a score out of 19. Our interventions showed significant improvement to the average score (15.64 vs 17.96; p< 0.001). Within the second cycle, there was a statistically significance difference when comparing electronic to handwritten notes (18.55 vs 17.50; p= 0.001).

Conclusion: Implementation of the new proforma showed improvement in operation note documentation when compared to the RCSEng standard. Therefore, this study emphasizes the need for surgeons to familiarize themselves with the current guidelines.

Keywords: Emergency general surgery, operation notes, royal college of surgeons, audit, electronic operation notes

INTRODUCTION

Accurate documentation of an operation note is an essential tool for patient safety, post- operative care, and medico-legal evidence (1). Post-operative care instructions provide clear guidance for the wider team, whilst also acting as a reference point in future discussions about a patient's health (1). As a result, the importance of maintaining good documentation in an operation note cannot be underestimated (2).

Providing an accurate record of an operation is a duty of every surgeon (3). The General Medical Council (GMC) states that doctors must record work clearly, accurately, and legibly (3). The Royal College of Surgeons England (RCSEng 2022) states that surgeons must ensure that accurate, comprehensive, legible, and contemporaneous records are maintained of all their interactions with patients (4). Unfortunately, mistakes in documentation still occur in different medical specialties with clinical and medico-legal consequences (5). The National Confidential Enquiry into Patient Outcome and Deaths (NCEPOD) detailed that there were discrepancies between the standard of operation notes (6). In 2009, documentation was analyzed regarding patient care for those who died within four days of being admitted to the hospital in the NCEPOD report. A continuous finding was that poor documentation was consistently found in all aspects of patient management (7).

A prospective closed-loop audit was undertaken at a UK District General Hospital because it was noted that key information, outlined by the RCSEng guidelines, was lacking in many operation notes.

In our institution, current practice is to complete handwritten operation notes on a blank pink paper. Operation notes pertaining to emergency general surgery

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(EGS) were selected in this study as this is a high-risk proportion making up more than one-third of all general surgical admissions (8). These complex surgeries carry eight times high mortality compared to elective surgical admissions (9). Poor records can potentially have medico-legal ramifications as well as effecting patients care which is increasingly becoming more relevant in today's litigious climate (9).

Our primary aim was to assess the standard of EGS operation notes in accordance with the RCSEng guidelines at a single district general hospital. Our secondary aim was to evaluate the impact of the new electronic operation note proforma and raising awareness of the RCSEng guidelines on the standard documentation.

MATERIAL and METHODS

EGS operative notes were deemed as those operations conducted in the emergency theatres. The emergency team involves the general surgical team (consultant, registrar, and senior house officer), anesthetic team (consultant and registrar), scrub nurses and operating department practitioners (ODP). A record of EGS operations with patient hospital number was retrieved from hardcopy documentation kept in emergency theatres. Patient operative notes wereaccessible by the patient electronic system. Notes were examined by a single reviewer.

A retrospective 1st cycle audit of 50 consecutive EGS operative notes between December 2019 to March 2020 were carried out. Each operative note was examined against the RCSEng guidelines giving a score out of 19. A full checklist can be found in Table 1.

The findings were presented at our general surgical clinical governance meeting (CGM) with the audience including surgeons at all levels. The results were discussed in detail and areas of consistent deficiency were identified. Awareness was generated about the importance of good documentation and what RCSEng requires to be included in the operation notes. A new electronic operation note proforma was accepted by the senior clinical team. Prior to this point electronic medical records had not been used during emergency surgery.

The electronic proforma is a Microsoft word-based document which is accessible on the trusts shared drive. It provides pre-filled generic information such as time and date. In addition, it prompts surgeons to complete all sections of the proforma by filling in boxes. An example of the proforma can be found in Figure 1.

An action plan was agreed to conduct a re-audit following this intervention. Clinicians were given the option whether to complete operation notes against the RCSEng standards via a handwritten or electronic proforma. An option was given as not all senior consultants felt comfortable writing notes electronically. To complete handwritten proforma's, clinicians would simply print out the template from the trusts shared drive and fill in the proforma via hand.

Table 1. Table of the Royal College of Surgeons England good practice guidelines

	Royal College of Surgeons England good practice guidelines
1	Date
2	Time
3	Elective/emergency procedure
4	Operating surgeons
5	Theatre assistants
6	Theatre anesthetists
7	Operation procedure carried out
8	Incision
9	Operative diagnosis
10	Operative findings
11	Any problems/complications
12	Any extra procedure performed
13	Reason why it was performed
14	Details of tissue removed, added or altered
15	Identification of any prosthesis used
16	Details of closure technique
17	Anticipated blood loss
18	Detailed postoperative care instructions
19	Signature

Posters of the RCSEng guidelines were placed in emergency theatres reminding surgeons what should be detailed. The electronic version had to be approved by the IT team before the second cycle was conducted to ensure that the notes were being uploaded and filed correctly on the hospital system. The second audit cycle was conducted between August 2020 and December 2020 which included a mixture of handwritten and electronic operative notes.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 29.0. Mann-Whitney U test was used with statistical significance set at $p< 0.05$.

RESULTS

The first cycle was conducted between December 2019 to March 2020 where 50 EGS handwritten operation notes were reviewed. The average score against the RCS guidelines was 15.64/19 (82.31%). No record fulfilled all RCSEng criteria. The most common error was anticipated blood loss which was only documented in 2% of operation notes. Other common errors included name of theatre assistant (58%) and if the procedure was performed in an emergency/elective setting (20%).

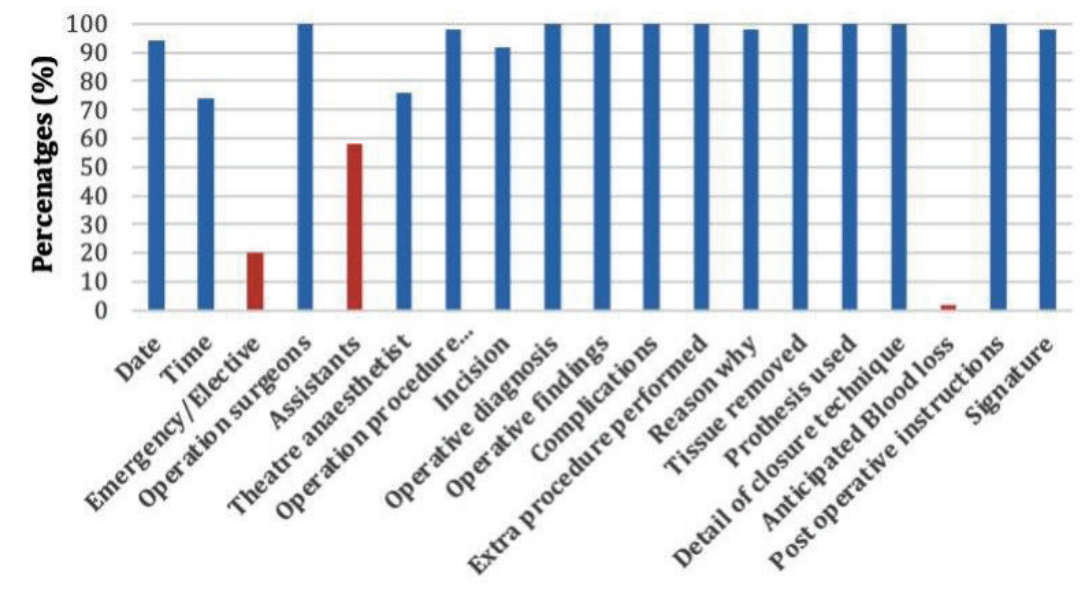


Figure 1. Chart illustrating the mean percentage compliance of each domain during cycle 1. The bars in red highlights those domains with a mean compliance <60%.

All notes audited in this first cycle included the name of operating surgeon, operative diagnosis, operative findings, any problems/complications, any extra-procedure performed/ reason why it was performed, details of tissue removed/added/ altered, identification of any prothesis used, details of closure technique and detailed postoperative care instructions. A graph of the first cycle results is shown in Figure 2.

The second cycle was conducted between August 2020 to December 2020 where a further 50 EGS operation notes were reviewed with an average compliance score of 17.96/19 (94.53%). The three most common areas missed in the first cycle showed significant improvement in the second cycle. Documentation of theatre assistants involved in the procedure (58% vs. 98%),anticipated blood loss (2% vs 62%) and specific mention of whether the operation was emergency/elective procedure (20% vs 86%). Figure 3 illustrates the improvements between the 1st and 2nd cycle in these three domains.

Twenty-six out of 50 operation notes analyzed in cycle two scored 19/19 (100%) when measured against the guidelines compared to zero out of 50 during the first cycle. Surprisingly, there was a small decline noted in categories such as time, tissue removed, prothesis used, details of closure technique and post-operative instructions post-intervention. Table 2 and Figure 4 illustrate the comparisons between the 1st and 2nd cycle for each domain.

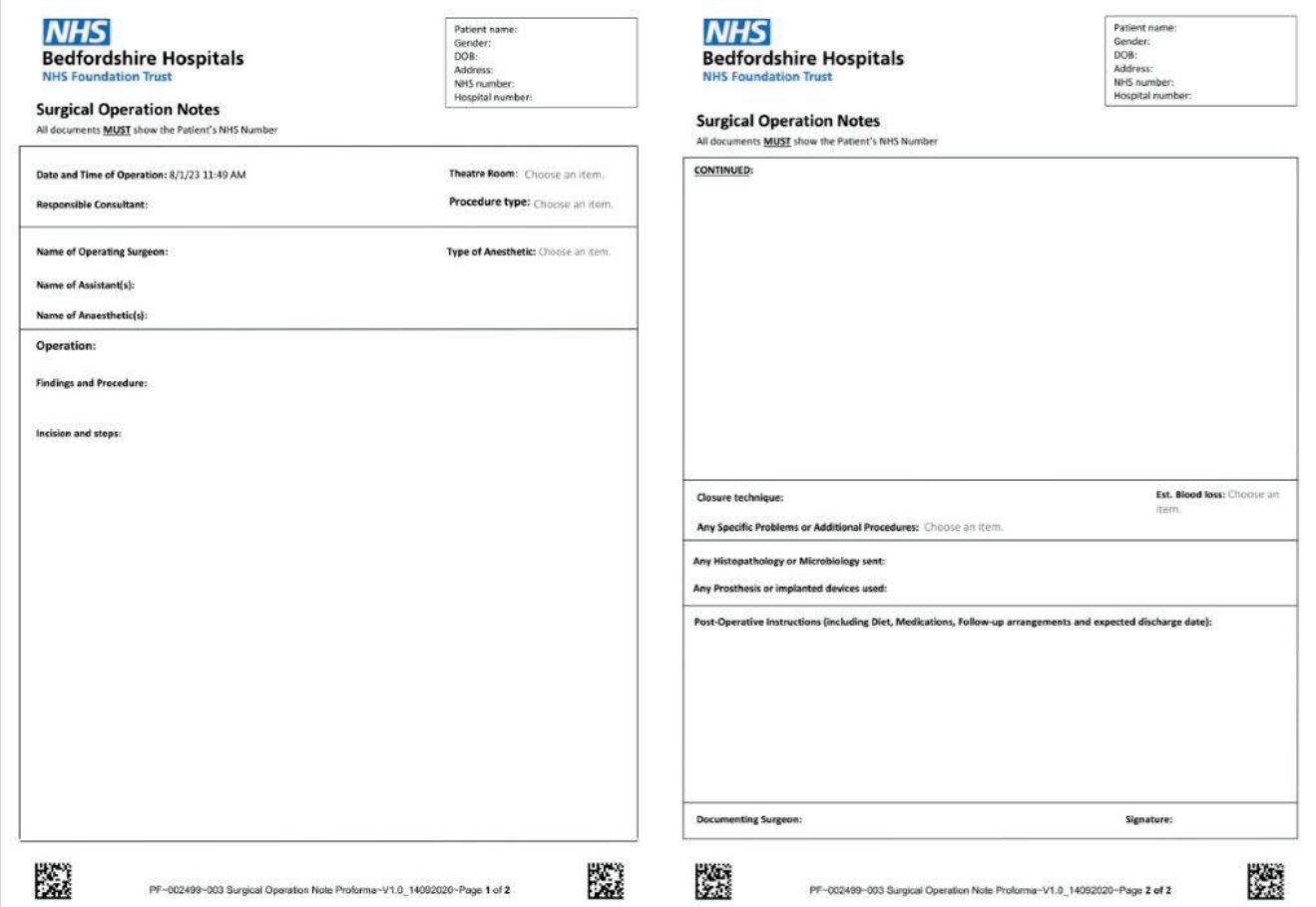
Within the re-audit, we compared the electronic operation notes (n= 22) with handwritten notes (n= 28). The mean score of electronic notes was 18.55/19 (97.61%) compared to 17.5/19 (92.11%) of handwritten notes, which was statistically significant (p= 0.001). Eighteen out of the 22 typed operation notes received 19/19 whilst this was only demonstrated in eight out of 28 handwritten notes. Figure 5 illustrates the comparison between handwritten and electronic documentation during the second cycle.

DISCUSSION

The accuracy of operation note documentation is extremely important for the delivery of care. The notes are not just vital for documenting intra-operative findings or communicating post- operative plans but also act as a legal record of an operation (10). In this closed loop audit, the first cycle demonstrated that 50 EGS operation notes had an average score of 15.64/19 (82.31%) when assessed against the RCSEng guidelines.

A previous study assessed the quality of operation notes and found that the RCSEng guidelines were not followed properly (11). During the second cycle, the intervention of raising awareness about the guidelines and creating a proforma was effective in improving the average score per operation note to 17.96/19 (94.53%). Electronic documentation when compared to handwritten documentation was far superior with the operation notes receiving an average score of 18.55/19 (97.61%) when measured with the guidelines.

The first cycle highlighted clear areas for improvement such as documenting anticipated blood loss (2%) and stating whether it is an emergency/elective procedure (20%).


NHS
Bedfordshire Hospitals
NHS Foundation Trust

Patient name:
Gender:
DOB:
Address:
NHS number:
Hospital number:

Surgical Operation Notes

All documents MUST show the Patient's NHS Number

Date and Time of Operation: 8/1/23 11:49 AM
Theatre Room: Choose an item.
Responsible Consultant:
Procedure type: Choose an item.

Name of Operating Surgeon:
Type of Anesthetic: Choose an item.
Name of Assistant(s):
Name of Anaesthetic(s):

Operation:

Findings and Procedure:

Incision and steps:

PF-002499-003 Surgical Operation Note Proforma-V1.0_14092020-Page 1 of 2

NHS
Bedfordshire Hospitals
NHS Foundation Trust

Patient name:
Gender:
DOB:
Address:
NHS number:
Hospital number:

Surgical Operation Notes

All documents MUST show the Patient's NHS Number

CONTINUED:

Closure technique:
Est. Blood loss: Choose an item.
Any Specific Problems or Additional Procedures: Choose an item.

Any Histopathology or Microbiology sent:
Any Prosthesis or implanted devices used:

Post-Operative Instructions (including Diet, Medications, Follow-up arrangements and expected discharge date):

Documenting Surgeon:
Signature:

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Figure 2. New electronic pro forma.

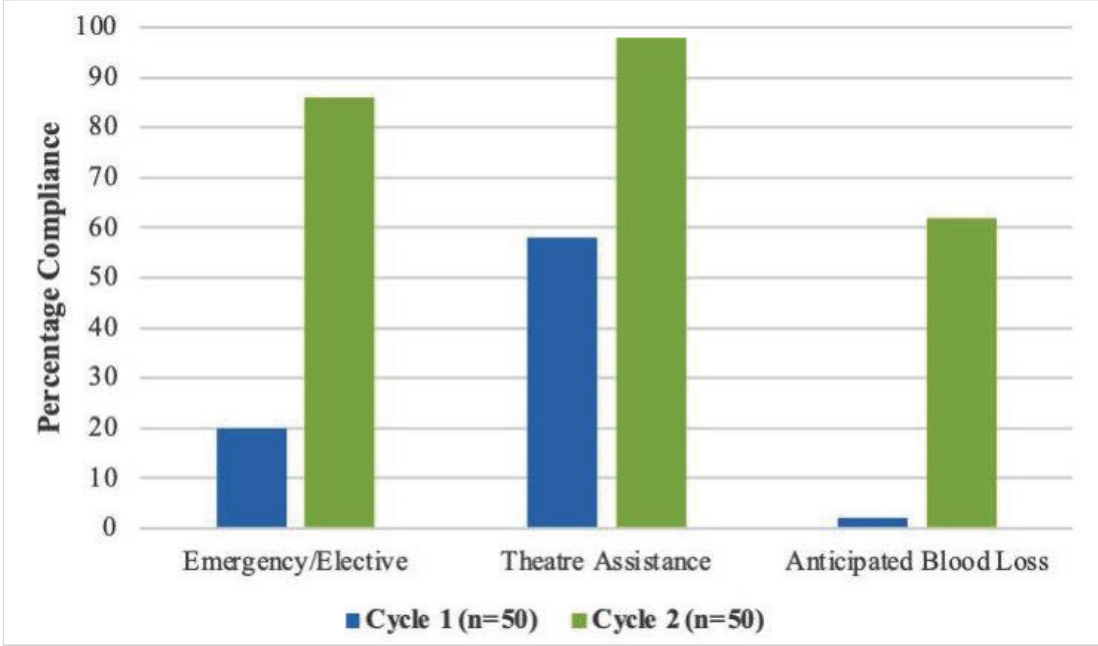

Figure 3. Chart comparing the results of both cycles for documentation of emergency or elective, theatre assistance and anticipated blood loss.

Table 2. Table of comparison of percentage compliance between 1st and 2nd audit cycles

Domains	1st cycle, %	2nd cycle, %
Date	94	100
Time	74	70
Emergency/elective	20	86
Operating surgeons	100	100
Theatre assistants	58	98
Theatre anesthetist	76	84
Operation procedure carried out	98	100
Incision	92	100
Operative diagnosis	100	100
Operative findings	100	100
Complications	100	100
Extra procedure performed	100	100
Reason why	98	98
Tissue removed	100	98
Prothesis used	100	98
Detail of closure technique	100	98
Anticipated blood loss	2	62
Post operative instructions	100	98
Signature	98	98

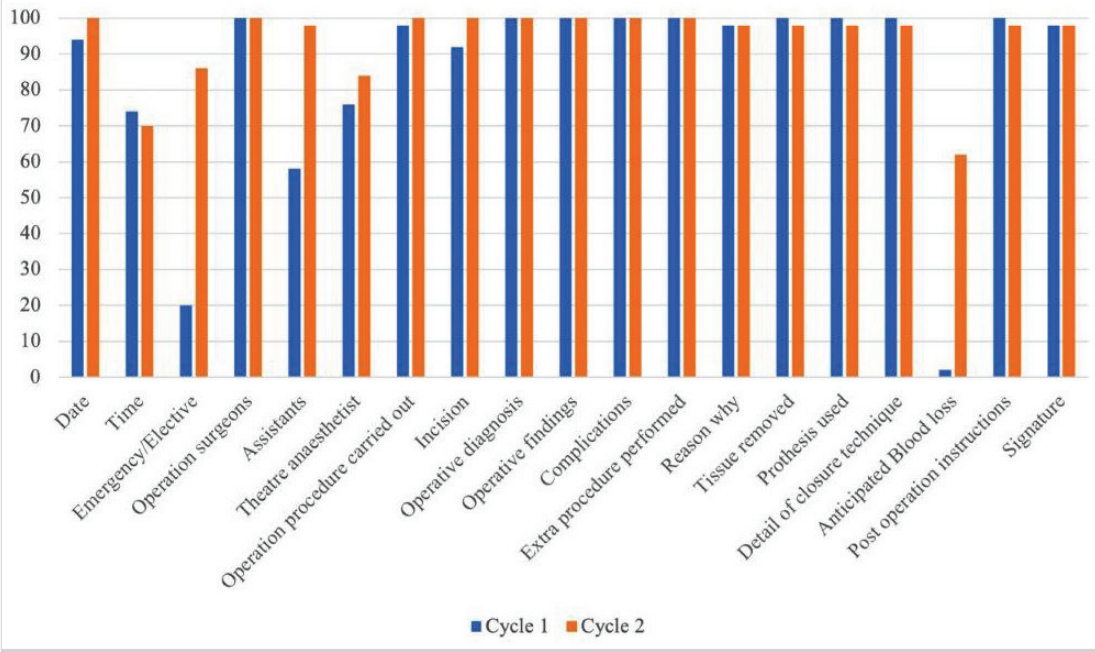

Figure 4. Percentage inclusion of specific criteria in audit round 1 and 2: Graphical representation.

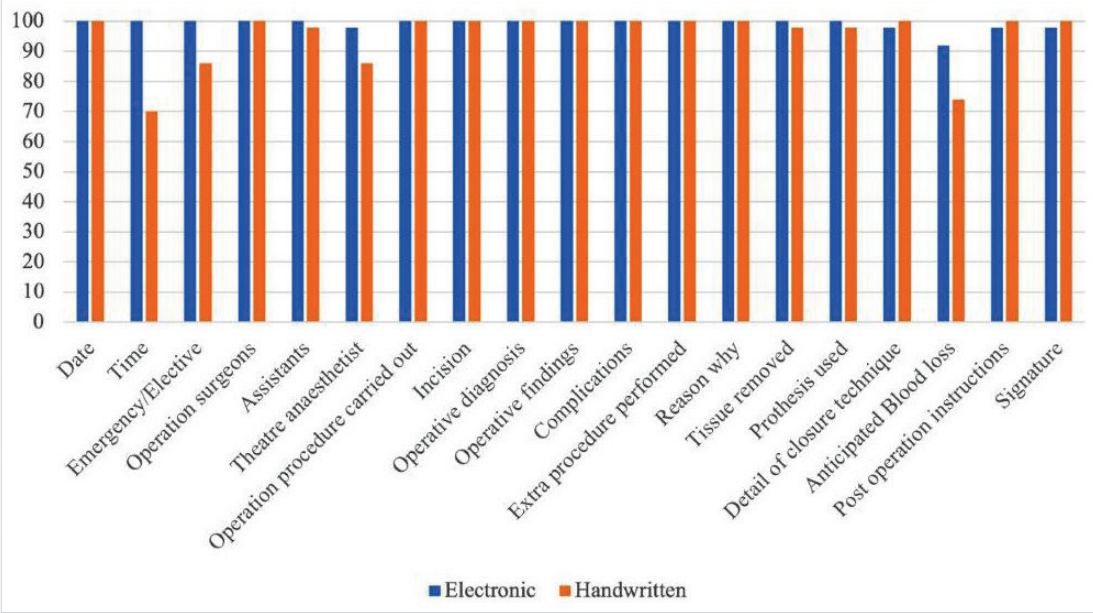

Figure 5. Percentage inclusion of specific criteria in cycle 2.
Electronic vs Handwritten: Graphical representation.

Following intervention, the second cycle showed significant improvement in documentation of anticipated blood loss (62%) and whether the procedure was emergency/elective (86%). These findings are comparable to a similar audit by Bozbıyık et al. in 2020 where their first cycle of 150 operation notes revealed 0% documentation rate for both anticipated blood loss and emergency/elective procedure. After the introduction of a proforma, the documentation rate for blood loss rose to 34% and for emergency/elective documentation rates increased to 28.67% (12). In comparison, our study reveals a much more significant impact of the proforma, albeit in a smaller sample study. A similar study focusing on improvements in pre- and post-intervention revealed significant improvement in documentation of estimated blood loss (2% to 73%, $p< 0.0001$) and elective or emergency procedure (1% to 83%, $p< 0.0001$) (13).

Documentation of estimated blood loss in our study and in literature fails to reach >90%. Visual estimation is the most used method for recording intraoperative blood loss and is generally performed poorly in the operating theatre (14). A systematic review by Tran et al. (2020) found that visual estimated blood loss was underestimated in 12 out of 13 studies (15). We believe there is poor compliance with documentation of estimated blood loss as many surgeons feel they only need to document it when there has been a significant amount of blood loss or because some are unaware of its inclusion in the operation notes.

It is known that the use of electronic databases and proformas are important to increase the quality of operation notes (16). The implementation of an electronic proforma was to help facilitate accurate documentation targeting the three main faults detected in the first cycle: Anticipated blood loss, assistants and emergency/elective procedure. This also eliminates the potential illegibility as incomplete and illegible hand-written notes often weaken a doctor's defense in court (17). Our findings show that electronic documentation was far more accurate compared to handwritten documentation in 17 out of the 19 domains. A full breakdown is found in Figure 5. In 2010, Barritt et al. demonstrated that computerized proformas can reduce differences between operation reports for the same procedure and facilitates reports tailored to the RCSEng guidelines (18). As a result, there is enough evidence to say that electronic documentation can be considered as gold standard; however, this option is still unfeasible for some hospitals (19). For these hospitals, aide-memoire sheet placed on the operation sheet or a poster in theatre has been shown to be effective (20,21).

A small negative impact of our interventions was noted between the 1st and 2nd cycle in five domains such as: Time (-4%), tissue removed (-2%), prothesis used (-2%), detail of closure technique (-2%) and post-operative instructions (-2%). It should be noted that the later four domains all had a 100% compliance rate during the 1st cycle, and it can be a challenge to maintain flawless standards even with the introduction of an intervention. Most mistakes were made in handwritten notes as 18 out of 22 typed notes had 100% compliance comparedto 8 out of 28 handwritten notes, further supporting the superiority of typed notes. Similar studies have noted a decrease in

compliance in different domains after an intervention. In 2022, Shah et al. noted a -4% reduction in compliance of signature despite a prompt box on their proforma. This supports the need to re-audits and amend our proforma if necessary. In addition, the use of electronic notes versus handwritten notes should be emphasized in future CGM.

Teaching on how to write accurate operation notes is limited. Borchert et al. have shown that there is little importance placed on how to write operation notes from medical school and surgical training programmes (22). There is no evidence of formal education on how to write an accurate and reliable operation note (18). We would advise local trusts introduce teaching on the importance and method of writing accurate medical notes.

Limitations

Type 2 error can occur due to our small sample size, and larger studies are required to validate our findings. However, when compared to similar studies, our sample size is comparable (23). Moreover, this study was only carried out across one surgical specialty and for consistency, further audits should be conducted across different surgical specialties. In addition, the RCSEng operation note guidelines cannot be applied to every specialty. For example, the use of prothesis is rare in a general surgical list but is more commonly used in a trauma and orthopaedic list. Knowing the distribution or breakdown of surgeries between cycles when assessing future standards of operation notes would be important as the accuracy of documentation can vary depending on the complexity of case. We therefore recommend the use of procedure-specific proformas can be introduced as they have been shown to improve standards for hemi-arthroplasty, laparoscopic cholecystectomy and in burns surgery (18).

CONCLUSION

In conclusion, this study shows that the quality of operative note taking improves when raising awareness amongst surgical staff. Furthermore, the use of an electronic proforma compared to handwritten is far superior. We recommend that all surgical departments should incorporate a simple electronic proforma. Continuous auditing and the introduction of an electronic version can ensure there is a high uniform standard of operative note recording.

Further studies will be needed to assess the effectiveness of making specific guidelines relating to different surgical specialties.

Ethics Committee Approval: The authors have received institutional permission to proceed with the study. Approval was provided in a letter uploaded to the Journal's official system on 21.12.2023.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 11-18

Acil genel cerrahi (EGS) ameliyat notlarının standardının *Royal College of Surgeons* kılavuzlarına uygun olarak değerlendirilmesi

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ÖZET

Giriş ve Amaç: Ameliyat notları cerrahi hastaların bakımı için önemlidir. Bu çalışmanın amacı, acil genel cerrahi (EGS) ameliyat notu dokümantasyonunu İngiltere *Royal College of Surgeons* (RCSEng) kılavuzlarına göre analiz etmek ve kılavuzlar hakkında farkındalık yaratmanın ve yeni bir proforma kullanımının etkisini değerlendirmektir.

Gereç ve Yöntem: Aralık 2019 ve Mart 2020 tarihleri arasında 50 EGS ameliyat notunun retrospektif incelemesi yapılmış ve RCSEng kılavuzlarıyla karşılaştırılmıştır. RCSEng kılavuzlarına uygun dokümantasyonun önemi konusunda eğitim verilmiştir. Yeni bir elektronik proforma tanıtılmıştır. Ağustos 2020 ile Aralık 2020 arasında 50 EGS operasyon notu daha analiz edilmiştir.

Bulgular: Yüz ameliyat notu incelendi ve her birine 19 üzerinden bir puan verildi. Müdahalelerimiz ortalama puanda önemli bir iyileşme göstermiştir (15,64'e karşı 17,96; p< 0,001). İkinci döngüde, elektronik ve el yazısı notlar karşılaştırıldığında istatistiksel olarak anlamlı bir fark vardı (18,55'e karşı 17,50; p= 0,001).

Sonuç: Yeni proforma uygulaması, RCSEng standardına kıyasla ameliyat notu dokümantasyonunda iyileşme göstermiştir. Bu nedenle, bu çalışma cerrahların mevcut kılavuzlara aşina olmaları gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Acil genel cerrahi, ameliyat notları, kraliyet cerrahlar koleji, denetim, elektronik ameliyat notları

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ORIGINAL ARTICLE
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Predictive value of drain fluid amylase level on postoperative day one after pancreatic resection for predicting postoperative pancreatic fistula

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ABSTRACT

Objective: The aim of this study was to evaluate the predictive value of the first postoperative day (POD1) drain fluid amylase in predicting pancreatic fistula formation following pancreaticoduodenectomy (PD).

Material and Methods: One-hundred and eighty-five prospective patients undergoing PD between April 2014 and April 2018 were studied retrospectively. Cut-off point to predict the development of POPF was determined by median values for drain fluid amylase of 1883 U/L. Patients were classified into two groups according to POD1 drain fluid amylase values: <1883 U/L (Group 1) and ≥1883 U/L (Group 2). Differences between the groups with clinically relevant POPF and without POPF were evaluated.

Results: The incidence of POPF was 17.2%. POD1 amylase level was the strongest predictor of POPF, with levels of higher than 1883 U/L demonstrating the best accuracy (87.5%), sensitivity (78.1%), specificity (89.5%), positive predictive value (60.9%), and negative predictive value (95.1%). One-hundred and forty-four patients (77.8%) had a POD1 drain amylase level of less than 1883 U/L, and POPF developed in only seven (3.7%) cases, whereas in patients with POD1 drain amylase level of 1883 U/L or higher (n= 41), the POPF rate was 31.4% [OR: 22.24, 95% CI (7.930–62.396), p< 0.001].

Conclusion: The cut-off point of POD1 drain fluid amylase level (1883 U/L) might predict the clinically relevant POPF with adequate sensitivity and specificity rates in patients undergoing pancreatic resection.

Keywords: Pancreaticoduodenectomy, amylases, postoperative complications, pancreatic fistula

INTRODUCTION

Despite the implementation of advancing techniques into postoperative management of the patients, complication rates after pancreatic resection remain high. Postoperative pancreatic fistula (POPF) is a common complication that threatens the patient's life after pancreaticoduodenectomy (PD). POPF can cause adverse consequences, including the development of intra-abdominal abscesses and intra-abdominal or intramucosal hemorrhage (1,2). For that reason, identifying high-risk patients for POPF in the perioperative period is critical for appropriate patient management planning.

The cut-off values were different among studies. Differences in the definition of POPF, differences in the surgical procedure, and retrospective studies prevent the establishment of the optimal cut-off value. From the viewpoint of the mechanism of POPF, the differences in surgical procedures do not affect fistula formation. A large-scale prospective trial is warranted to establish an optimal cut-off value that applies to any surgical procedure (3). However, there is not any consensus on POD1 drain fluid amylase cut-off value. Several studies have suggested that drainage fluid analyses contribute to predicting POPF, although there has long been a debate on the preventive and therapeutic implementation of abdominal drains after performing a pancreatic resection (4-10). The controversial results may be explained by the fact that any cohort of patients undergoing PD may not be homogeneous to determine the diagnostic and therapeutic implications of prophylactic abdominal drainage, in the absence of objective criteria to be used to determine the individual risks for developing POPF. Recently, the levels of amylase in the drainage fluid have received considerable attention, with researchers asking whether they can serve to predict PF or to decide the optimum time for drain removal.

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In several studies, predictive values (sensitivity, specificity, and positive and negative predictive values) were investigated and reported as strongly favorable for POPF (11,12). For this reason, we aimed to determine the optimal predictive value of POD1 drain fluid amylase level in estimating POPF after PD.

MATERIAL and METHODS

This study was performed after obtaining the permission of Gazi University Faculty of Medicine Clinical Research Ethics Committee (Decision Number: 425). Patients who had elective pancreaticoduodenectomy in the General Surgery Clinic of Gazi University Medical Faculty during the period from April 2014 to April 2018 participated in the study. All patients included in the study were operated by two experienced surgeons, performing more than 50 operations per year. Demographic data of the study patients and their intraoperative, pathological, and postoperative data were logged by the surgeons.

The standard PD as described in the literature was performed on all patients (13). In addition, the lymph nodes between the coeliac trunk and the superior mesenteric artery (triangular area) were retrieved, and the proximal jejunum was pulled up for P-J through the Treitz hole that occurred after duodenectomy. Pyloric preservation was not performed on any patients. An internal stent at the appropriate size was placed between the pancreatic duct and the jejunal opening in all patients, and external drainage was not performed. Two abdominal drains were placed around the P-J and hepaticojejunostomy. Blumgart anastomosis was performed on all patients as described; three or four transpancreatic U-sutures were placed approximately 1 cm distal to the transected edge of the pancreas going from front to back with suture. The seromuscular back wall of the jejunum was utilized, nearer the mesenteric edge, and 10 to 15 mm longitudinal seromuscular stitches were placed. The suturing then reverted to back to front through the pancreas completing the U. A duct-to-mucosa anastomosis was constructed with four to six stitches of polydioxanone 5-6/0 after creating a small opening (about 2-3 mm) in the jejunal loop. The transpancreatic U-sutures were then passed through the seromuscular layer of the anterior wall of the jejunal loop in the direction of the short axis. Each of the U method sutures was placed at a distance of 5 to 10 mm from the last. This procedure completely covered the pancreatic stump with jejunal serosa and protected the knots from cutting through the pancreatic tissue.

Resection and reconstruction of the superior mesenteric vein and portal vein were accepted as vessel resection. To prevent the development of stress ulcerations, proton pump inhibitors were administered to all patients. The parenchymal texture of the pancreas was determined as soft or hard by the surgeon by manually palpating the pancreatic remnant. After the operation, one drain was placed adjacent to the pancreaticojejunostomy and hepaticojejunostomy. The drain fluid amylase (DFA) levels on POD 1-, 3-, and -5 were recorded daily after the operation.

Postoperative pancreatic fistula was defined and classified according to the International Study Group for Pancreatic Surgery-2016 (14). The diagnosis of POPF was made if the amylase level of the drain fluid was three times higher than the serum amylase level on the 3rd postoperative day. This was regarded as biochemical leakage (BL). Grade B fistula was defined as fistula requiring any changes in the treatment (need for antibiotics, enteral or parenteral nutrition, percutaneous, endoscopic, or angiographic interventions) or fistula with abdominal drainage lasting longer than 21 days. Fistula-related organ failure, reoperation, or death was accepted as Grade C fistula. Grade B and C fistulas were defined as clinically relevant POPF (CR-POPF).

First, univariate and multivariate analyses were used to retrospectively investigate the relationship between patient and tumor characteristics, intraoperative, and postoperative features. Cut-off points to predict the development of POPF were determined by median values. Patients were classified into two groups according to POD1 drain fluid amylase level; those with a value <1883 U/L were named the low amylase group, and those with ≥1883 U/L were named the high amylase group. Patient and tumor characteristics were recorded, including age, sex, body mass index (BMI), pathological diagnosis (malignant or benign), operation time (min), estimated blood loss (mL), vascular resection performed/none, soft or hard pancreas parenchyma, main pancreatic duct size (mm), postoperative day one, two, and three drain fluid amylase levels, the median value of POD1 drain amylase value level (≥1883 U/L vs. <1883 U/L), Clavien-Dindo complication classification, and the re-operation rate.

The main pancreatic duct diameter was measured perioperatively by the surgeon who performed the operation. The morbidity rate in the postoperative period was determined by including all complications developing just after the surgery and throughout the postoperative period until the patient was discharged from the hospital. The Clavien-Dindo classification was used for complications (15). Delayed gastric emptying in the postoperative period was diagnosed by the International Study Group on Pancreatic Surgery.

Statistical Analysis

All data were summarized as mean ± standard deviation (SD). For univariate analysis, non-paired t-test and χ^2 test were used, and for multivariate analyses, logistic regression analysis was used. P-values <0.05 were considered statistically significant. Cut-off points to predict the development of POPF were determined by median values. Analysis of data and the

assessment of sensitivity, specificity, predictive values, and accuracy were performed with diagnostic formulas. SPSS program was used for statistical analysis.

RESULTS

Patient Characteristics

One-hundred and eighty-five patients undergoing PD were included in the study. Median age was 62 years (range= 24-85 years), and there were 104 male (56.2%) patients. Mean BMI of the patients was 26.3 ± 17.8 m^2/kg. Among the patients, 86 (46.5%) had comorbid factors; and 70 (37.8%) patients had ASA III/IV scores. Histopathological diagnosis was benign in 34 (18.4%) patients, and it was reported to be malignant in 81.6% of the patients. Ninety-nine (53.5%) patients were identified as having hard pancreatic parenchyma, and 86 (46.5%) patients had soft parenchyma. The main pancreatic duct diameter was <4 mm in 62 patients (33.5%), and 41 patients (22.2%) needed a blood transfusion during the operation. The postoperative pancreatic fistula rate was 17.3% (32). While the rate of POPF development was 25% (8) in patients with hard pancreatic parenchyma, it was 75% (24) in patients with soft pancreatic parenchyma. The postoperative pancreatic fistula was identified in 24 patients with soft and eight patients with hard pancreatic parenchyma. The main pancreatic duct diameter was less than 4 mm in 68% of patients with POPF (Table 1).

Using the median drain fluid amylase level (<1883 U/L vs. ≥1883 U/L) as a cut-off value.

Clinicopathological characteristics of the patients, intraoperative and postoperative features are presented in Tables 2, 3, and 4. Patients were divided into two groups: Patients with POD1 drain fluid amylase level lower than 1883 U/L (Group 1) and patients with POD1 drain fluid amylase ≥1883 U/L (Group 2). In 21.9% (n= 7) of the patients with POPF, POD1 drain fluid amylase levels were lower than 1883 U/L. Postoperative day one drain fluid amylase levels were higher than 1883 U/L in 78.1% (n= 25) of the patients who developed fistulas on POD1 (Table 2). There were more patients with hard pancreatic parenchyma (59.7% vs. 31.7%, p= 0.002) and ≥4 mm duct diameter (73% vs. 41%, p< 0.001) in Group 1 than Group 2. Patients with soft parenchyma were 46.5% (OR= 3.689, CI= 1.048-12.987) and more likely to form POPF compared to those patients with hard pancreatic parenchyma (p= 0.045). Patients with a small duct diameter (<4 mm) were 33.5% (OR= 3.732, CI= 1.333-10.447) and more likely to form POPF compared to those patients with a larger duct diameter (p= 0.012). It was determined that the need for blood transfusion was higher in Group 2 (36.6% vs. 18.1%, p= 0.012), and the results are shown in Table 3. Postoperative day one in Group 2 was related to a higher rate of overall morbidity that was significantly different (Table 4). There were no statistically significant differences between the groups in terms of demographic patients characteristics, ASA score, comorbidity, histopathological diagnosis, tumor location, vascular resection, estimated blood loss, internal stent replacement, operation time, or length of hospital stay (Tables 2, 3, and 4).

Predictors of PF

The multivariate analysis revealed that a POD1 drain fluid amylase level higher than 1883 U/L (OR= 22.24, 95% CI= 7.93-62.39), p= 0.0001), soft parenchyma (OR= 3.689, 95% CI= 1.04-12.98, p= 0.045), and <4 mm main pancreatic duct size (OR= 3.732, 95% CI= 1.33-10.44, p= 0.012) were the independent factors for POPF development, which is shown in Table 5.

Postoperative day one drain fluid amylase level was found to be the powerful predictor of POPF. The best accuracy (87.5%), sensitivity (78.1%), specificity (89.5%), positive predictive value (PPV) (60.9%), and negative predictive value (NPV) (95.1%) were found for POD1 drain fluid amylase level with 1883 U/L or higher (Table 6). The postoperative day one drain fluid amylase level was <1883 U/L in 144 patients (77.8%), and POPF was seen in seven patients (3.7%). The POPF incidence rate was 31.4% among 41 patients with ≥1883 U/L POD1 drain amylase level [OR= 22.24, 95% CI (7.930-62.396), p< 0.001].

DISCUSSION

Postoperative pancreatic fistula (POPF) formation following pancreatic surgery remains a challenge even in pancreatic centers with a high volume of patients. The reported incidence of POPF after PD ranges between 2% and 46% (16). Therefore, predicting the patients who will develop POPF might facilitate the management of this challenging complication and improve surgical outcomes. There are no clearly established tools to identify high-risk patients for developing POPF. The potential risk factors, such as soft parenchymal texture, narrow duct, intraoperative blood loss, and high BMI, have been suggested to be associated with POPF. But their predictive values are not adequate.

However, the early prediction of POPF remains controversial despite the availability of several various methods, proposed to estimate the development of POPF along with the associated risk factors. The precision of fistula according to the ISGPF in 2005 suggested that the drain fluid amylase level measured on postoperative day three or later and postoperative day one drain fluid amylase levels for diagnosis of POPF were not discussed in the ISGPF consensus meeting. This topic is controversial because there are conflicting results on using postoperative day one drain fluid amylase levels to predict the pancreatic fistula (10,17-22).

Table 1. Demographic, clinic, and operative characteristics of patients

	Total (n= 185)	POPF (n= 32)	No-POPF (n= 153)
Age, year			
<65	69 (37.3)	21 (65.6)	95 (62.1)
>65	116 (62.7)	11 (34.4)	58 (37.9)
Sex			
Male	104 (56.2)	19 (59.4)	85 (55.6)
Female	81 (43.8)	13 (40.6)	68 (44.4)
ASA Score			
I/II	115 (62.2)	21 (65.6)	94 (61.4)
III/IV	70 (37.8)	11 (34.4)	59 (38.6)
Comorbidity			
Yes	86 (46.5)	17 (53.1)	89 (45.1)
No	99 (53.5)	15 (46.9)	84 (54.9)
Pathologic Diagnosis			
Benign	34 (18.4)	3 (9.4)	31 (20.3)
Malign	151 (81.6)	29 (90.6)	122 (79.7)
Tumor Location			
Pancreas head	121 (65.4)	16 (50)	105 (68.6)
Distal choledoch	20 (10.8)	8 (25)	27 (17.6)
Ampulla tm	35 (18.9)	7 (21.9)	13 (8.5)
Duodenal tm	9 (4.9)	1 (3.2)	8 (5.2)
PJ Anastomosis Type			
Blumgart	144 (77.8)	23 (71.9)	135 (88.2)
Dunking	41 (22.2)	9 (28.1)	18 (11.8)
Pancreas Texture			
Soft	86 (46.5)	24 (75)	62 (40.5)
Hard	99 (53.5)	8 (25)	91 (59.5)
PD Diameter, mm			
≥4	123 (66.5)	10 (31.3)	113 (73.9)
<4	62 (33.5)	22 (68.7)	40 (26.1)
Blood Loss, mL			
≥400	46 (24.9)	10 (31.3)	36 (23.5)
<400	139 (25.1)	22 (68.7)	117 (76.5)
Blood Transfusion			
Yes	41 (22.2)	13 (40.6)	28 (18.3)
No	144 (77.8)	19 (59.4)	125 (81.7)
Operation Time, min			
≥240	137 (74.1)	27 (84.4)	110 (71.9)
<240	48 (25.9)	5 (15.6)	43 (28.1)
POD 1 Cut-off, U/L			
<1883	144 (77.8)	7 (21.9)	137 (89.5)
≥1883	41 (22.2)	25 (78.1)	16 (10.5)
POD 3 Cut-off, U/L			
<504	139 (75.1)	5 (15.6)	134 (87.6)
≥504	46 (24.9)	27 (84.4)	19 (12.4)
POD 5 Cut-off, U/L			
<98	142 (76.7)	4 (12.5)	138 (90.2)
≥98	43 (23.3)	28 (87.5)	15 (9.8)

Table 2. Comparison of the preoperative and demographic characteristics of the patients grouped according to the cut-off value of POD 1 drain amylase

		POD 1 Drain Amylase Cut-Off Value		
	All Patients (n= 185), %	**<1883 U/mL (n= 144)**	**≥1883 U/mL (n= 41)**	**p**
Age, year ≥65 <65	 69 (37.3) 116 (62.7)	 56 (38.9) 88 (61.1)	 13 (31.7) 28 (68.3)	0.402
Age, year, mean ± SD	60.0 ± 11.3	60.7 ± 11.3	57.5 ± 11.0	0.082
Sex Male Female	 104 (56.2) 81 (43.8)	 84 (58.3) 60 (41.7)	 20 (48.8) 21 (51.2)	0.359
BMI, m^2/kg	26.3 ± 17.8	27.8 ± 11.3	27.4 ± 3.4	**0.050**
ASA score I/II III/IV	 115 (62.2) 70 (37.8)	 87 (60.4) 57 (39.6)	 28 (68.3) 13 (31.7)	0.359
Comorbidity Yes No	 86 (46.5) 99 (53.5)	 76 (52.8) 68 (47.2)	 23 (56.1) 18 (43.9)	0.707
Pathologic Diagnosis Benign Malign	 34 (18.4) 151 (81.6)	 117 (81.3) 27 (18.8)	 34 (82.9) 7 (17.1)	0.807
Tumor Location Pancreas head Distal choledoch Ampulla tm Duodenal tm	 121 (65.4) 20 (10.8) 35 (18.9) 9 (4.9)	 99 (68.8) 25 (17.4) 14 (9.7) 6 (4.2)	 22 (53.7) 10 (24.4) 6 (14.6) 3 (7.3)	0.277

Table 3. Comparison of the intraoperative characteristics of the patients grouped according to the cut-off value of POD 1 drain amylase

		POD 1 Drain Amylase Cut-Off Value		
	All Patients (n= 185), %	**<1883 U/mL (n= 144), %**	**≥1883 U/mL (n= 41), %**	**p**
Pancreas Texture Soft Hard	 86 (46.5) 99 (53.5)	 58 (40.3) 86 (59.7)	 28 (68.3) 13 (31.7)	**0.002**
PJ Anastomosis Type Blumgart Dunking	 144 (77.8) 41 (22.2)	 127 (88.2) 17 (11.8)	 31 (75.6) 8 (24.4)	**0.017**
Vascular Resection Yes No	 16 (8.6) 169 (91.4)	 14 (9.7) 130 (90.3)	 2 (4.9) 39 (95.1)	0.330
Internal Stent No Yes	 156 (84.3) 29 (15.7)	 123 (85.4) 21 (14.6)	 33 (80.5) 8 (19.5)	0.444
PD Diameter, mm ≥4 <4	 123 (66.5) 62 (33.5)	 106 (73.6) 38 (26.4)	 17 (41.5) 24 (58.5)	**<0.001**
Operation Time, min ≥240 <240	 137 (74.1) 48 (25.9)	 106 (73.6) 38 (26.4)	 31 (75.6) 10 (24.4)	0.797
Blood Loss, mL ≥400 <400	 46 (24.9) 139 (25.1)	 33 (22.9) 111 (77.1)	 13 (31.7) 28 (68.3)	0.251
ES Transfusion Yes No	 41 (22.2) 144 (77.8)	 26 (18.1) 118 (81.9)	 15 (36.6) 26 (63.4)	**0.012**

Table 4. Comparison of the postoperative results of the patients grouped according to the cut-off value of POD 1 drain amylase

		POD 1 Drain Amylase Cut-Off Value		
	All Patients (n= 185), %	**<1883 U/mL (n= 144)**	**≥1883 U/mL (n= 41)**	**p**
POPF Yes No	 32 (17.3) 153 (82.7)	 7 (4.9) 137 (95.1)	 25 (61) 16 (39)	**<0.001**
POPF Grade Grade A Grade B Grade C	 19 (10.3) 10 (5.4) 3 (1.6)	 4 (2.8) 2 (1.4) 1 (0.6)	 15 (36.6) 8 (19.5) 2 (4.8)	0.216
DGE Yes No	 53 (28.6) 132 (71.4)	 37 (25.7) 107 (74.3)	 16 (39) 25 (61)	0.096
Bile Leakage Yes No	 6 (3.2) 179 (96.8)	 5 (3.5) 139 (96.5)	 1 (2.4) 40 (97.6)	0.742
Intraabd. Abses/Collection Yes No	 16 (8.6) 169 (91.4)	 12 (8.3) 132 (91.7)	 4 (9.8) 37 (90.2)	0.775
Intraabd. Haemoragia Yes No	 13 (7) 172 (93)	 9 (6.3) 135 (93.8)	 4 (9.8) 37 (90.2)	0.438
Other Complications Yes No	 11 (5.9) 174 (94.1)	 8 (5.6) 136 (94.4)	 3 (7.3) 38 (92.7)	0.674
LOH, day, median (range)	10 (5-96)	9.5 (5-96)	11 (5-55)	0.141
Morbidity Yes No	 81 (44.3) 104 (55.7)	 50 (34.7) 94 (65.3)	 32 (78) 9 (22)	**<0.001**

POD: Postoperative day, PD: Pancreaticoduodenectomy, POPF: Postoperative pancreatic fistula, DGE: Delayed gastric emptying, LOH: Length of hospital stay.

Table 5. Multivariate analysis of the predictors of POPF after PD

Variables	**n, %**	**OR (95% CI)**	**p**
Pancreatic Texture, Soft	86 (46.5)	3.689 (1.048-12.987)	**0.045**
Duct Diameter, <4 mm	62 (33.5)	3.732 (1.333-10.447)	**0.012**
Blood Transfusion, yes	41 (22.2)	0.488 (0.161-1.480)	0.205
POD 1 Amylase, ≥1883 U/mL	41 (22.2)	22.244 (7.930-62.396)	**<0.001**
POD 3 Amylase, ≥504 U/mL	46 (24.9)	4.802 (1.155-19.962)	**0.031**
POD 5 Amylase, ≥98 U/mL	43 (23.2)	22.468 (5.246-96.226)	**<0.001**

OR: Odds ratio, POD: Postoperative day, PD: Pancreaticoduodenectomy.

In our study, the cut-off value of postoperative day one drain fluid amylase level (1883 U/L) had 78.6% sensitivity, 89.5% specificity, and 87.5% accuracy rates for predicting POPF. A common point of the studies investigating this issue is that drain fluid amylase is very valuable in predicting the clinically relevant POPF on the POD1. However, in almost all studies, there is no consensus on what the cut-off value should be. When the cut-off value is 2365 U/L, 78% sensitivity, 80% specificity, 66% PPV, and 88% NPV have been reported (23). In another study, when the cut-off value was accepted as 350 U/L, the authors reported 79% specificity, 100% sensitivity, 41% PPV, and 100% NPV. Similarly, studies have reported that the cut-off values 4000 U/L and 5000 U/L are optimal for predicting the POPF (24,25). Our results are consistent with these trials, and we recommend that POD1 drain fluid amylase levels can be used in identifying high-risk patients to predict pancreatic fistula after PD.

Table 6. Predicted versus actual fistula formulation

		Actual		
		Fistula	**No-Fistula**	**Total**
Predicted	Fistula	25	16	41
	No-Fistula	7	137	144
	Total	32	153	185

Cut-off value 1883 U/L to maximize sensitivity (78.1%) and specificity (89.5%). Positive predictive value (PPV) 60.9%. Negative predictive value (NPV) 95.1%. False positive (FP) 21.9%. False negative (FN) 10.5%. accuracy 87.5%.

Yang Ji et al. reported that eight studies included in their meta-analysis provided published evidence indicating the predictive value of POD1 drain fluid amylase for developing POPF. Ansorge et al. investigated several clinical parameters for their predictive values for estimating the development of POPF and concluded that a POD1 drain fluid amylase level of 1322 U/L was the most clinically relevant parameter for predicting POPF (20).

Similarly, several studies have researched the significance of drain amylase levels for predicting POPF (8,11,26). El Nakeeb et al. investigated risk factors for POPF and recommended that a 1000 U/L cut-off value is best for predicting a clinically relevant pancreatic fistula (11). Facy et al. evaluated the levels of both lipase and amylase in the drain fluid in predicting POPF and found that the 500 U/L cut-off value of drain fluid amylase level was a good indicator for clinically relevant POPF (8). Kawai et al. retrospectively analyzed 1239 patients undergoing PD and demonstrated that a POD1 drain fluid amylase >4000 IU/L could predict POPF, based on a ROC curve analysis (18). The authors reported that this cut-off point was associated with a sensitivity of 62.2%, specificity of 89%, and accuracy of 84.8%. Another study reported that higher than 5000 U/L POD1 drain fluid amylase level is a significant predictive factor for POPF following distal pancreatectomy and PD (18). Similarly, another study reported that POD1 drain fluid amylase level higher than 5000 U/L is the best predictive marker for POPF, and they reported a sensitivity of 93% for PD and 100% for distal pancreatectomy (27). In another study that investigated whether POD1 drain fluid amylase could be used to estimate POPF following pancreatectomy, the authors reported that a low cut-off level of 100 U/L was associated with high sensitivity and NPV. Therefore, they recommended that early drain removal would be safe when drain amylase is lower than 100 U/L on the first postoperative day (19).

In our opinion, the wide range of proposed cut-off values depends on whether the drain amylase value is used to determine pancreatic fistula or patients who will not have a fistula. High cut-off values accurately predict those patients that will have a fistula, and low cut-off values predict those patients who will not have a fistula. Small differences in NPV for each cut-off value indicate that clinically relevant consequences of early drain removal should be reviewed from various aspects for the purposes of guiding management, rather than defining one POD1 drain amylase value as a cut-off. Therefore, the cut-off value may be different for each clinic.

In our opinion, it is important to determine the fistula or the patients who do not have a fistula. We believe that the cut-off value should then be determined according to the patient's fistula status. The comfort level of the surgeon should also be determined in selecting the cut-off point based on the small differences in NPV.

CONCLUSION

The cut-off point of POD1 drain fluid amylase level (1883 U/L) can help predict the clinically relevant POPF with adequate sensitivity and specificity rates in patients undergoing pancreatic resection. Multi-center, high-volume trials are now required to further investigate these findings.

Ethics Committee Approval: This study was approved by Gazi University Clinical Research Ethics Committee (Decision no: 425 Date: 06.07.2020).

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ORİJİNAL ÇALIŞMA-ÖZET
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Pankreas rezeksiyonu sonrası postoperatif birinci günde dren sıvısı amilaz düzeyinin postoperatif pankreatik fistülü öngörmedeki değeri

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, pankreatikoduodenektomi (PD) sonrası pankreatik fistül oluşumunu öngörmede ameliyat sonrası ilk gün (POD1) drenaj sıvısı amilazının öngörücü değerini değerlendirmektir.

Gereç ve Yöntem: Nisan 2014 ile Nisan 2018 tarihleri arasında PD geçiren 185 hasta retrospektif olarak incelendi. Hastalar POD1 drenaj sıvısı amilaz değerlerine göre iki gruba ayrıldı: <1883 U/L (Grup 1) ve ≥1883 U/L (Grup 2). Klinik olarak anlamlı POPF'lu ve POPF'suz gruplar arasındaki farklar değerlendirildi. 1883 U/L drenaj sıvısı amilazı için Pearson korelasyon katsayıları ve alıcı işlem karakteristikleri (ROC) eğrileri hesaplandı.

Bulgular: POPF insidansı %17,2 idi. POD1 amilaz düzeyi postoperatif pankreatik fistülünün (POPF) en güçlü öngörücüsü olmuş, 1883 U/L'den yüksek düzeyler en iyi doğruluğu (%87,5), duyarlılığı (%78,1), özgüllüğü (%89,5), pozitif öngörü değerini (%60,9) ve negatif öngörü değerini (%95,1) göstermiştir. Yüz kırk dört hastanın (%77,8) POD1 drenaj amilaz düzeyi 1883 U/L'den düşüktü ve sadece yedi (%3,7) vakada POPF gelişirken, POD1 drenaj amilaz düzeyi 1883 U/L veya daha yüksek olan hastalarda (n= 41) POPF oranı %31,4'tü [OR: 22,24, %95 CI (7,930-62,396), p< 0,001].

Sonuç: POD1 drenaj sıvısı amilaz düzeyinin (1883 U/L) kesme noktası, pankreas rezeksiyonu yapılan hastalarda klinik olarak ilgili POPF'yi yeterli duyarlılık ve özgüllük oranlarıyla öngörebilir.

Anahtar Kelimeler: Pankreatikoduodenektomi, amilaz, postoperatif komplikasyonlar, pankreas fistülü

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ORIGINAL ARTICLE
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Effect of silver colloid dressing over conventional dressings in diabetic foot ulcer: A prospective study

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ABSTRACT

Objective: Topical silver treatments and silver dressings are increasingly being utilized for the local treatment of wounds; nevertheless, the evidence for their usefulness is unclear. The aim of this study was to investigate the impact of conventional dressings and silver colloid dressing on diabetic foot ulcers (DFU) with and without compression therapy.

Material and Methods: This prospective, double-blind experiment included 50 patients with non-ischemic DFUs, split into two groups of 25 patients each. The study was conducted for a period of six months. The primary endpoint was to evaluate the entire epithelialization (total healing) of all ulcers on the study leg.

Results: The ulcer area significantly decreased in the colloidal silver group (67.77 ± 17.82%) compared to the conventional saline group (21.70 ± 23.52%). When compared to the conventional group, the colloidal silver group required considerably fewer days to reach the endpoint (23.15 ± 8.15 days vs. 48.35 ± 18.07 days), and by day 14, ulcer area reduction (from 100%) was greater (48% in the silver group vs. 89.69% in the conventional group).

Conclusion: In managing DFUs, unstructured hydrogel wound dressings using silver colloids based on ionic silver are more effective than regular saline dressings since they heal wounds more quickly in fewer days while also drastically reducing ulcer areas over time.

Keywords: Diabetic foot ulcer, silver colloid dressing, bandaging, dressing therapy

INTRODUCTION

A diabetic foot ulcer (DFU) refers to a chronic, non-healing wound or sore that occurs on the leg or foot of an individual with diabetes. DFUs are frequently observed as a complication of diabetes, especially in those with inadequate blood glucose management or long-standing diabetes. Diabetic foot ulcers (Figure 1,2) can develop due to a combination of factors, including peripheral neuropathy (nerve damage), peripheral arterial disease (reduced blood flow), impaired wound healing, and due to increased susceptibility to infection (1).

An ulcer is defined as a break in the continuity of the covering epithelium. Foot ulcers can occur in both acute and chronic forms, and they can be attributed to various factors such as venous or arterial insufficiency, diabetes, burns, trauma, chronic pressure, or surgical interventions. The use of antiseptic agents may reduce the bacterial load but it may simultaneously hamper the fibroblast and other viable tissues (2).

Many forms of dressing are available including hydrocolloid dressings, foam dressings, paraffin dressings, and polyurethane dressings. Hydrocolloid dressings are a type of wound dressing that can be used for various types of wounds, including those in diabetic legs. These dressings are made of a gel-like material that contains hydro active particles, such as gelatine or sodium carboxy-methyl cellulose, which absorb wound exudates (fluid) and create a moist environment for the wound. Foam dressings are designed to absorb exudates from the wound while maintaining a cozy environment. They are made of soft, flexible materials that contain small open cells. The dressings have a non-adherent outer layer that helps prevent sticking to the wound bed. Paraffin dressings, also known as paraffin gauze dressings, are a type of wound dressing that consists of fine mesh gauze impregnated with paraffin wax. Paraffin dressings are commonly used in the

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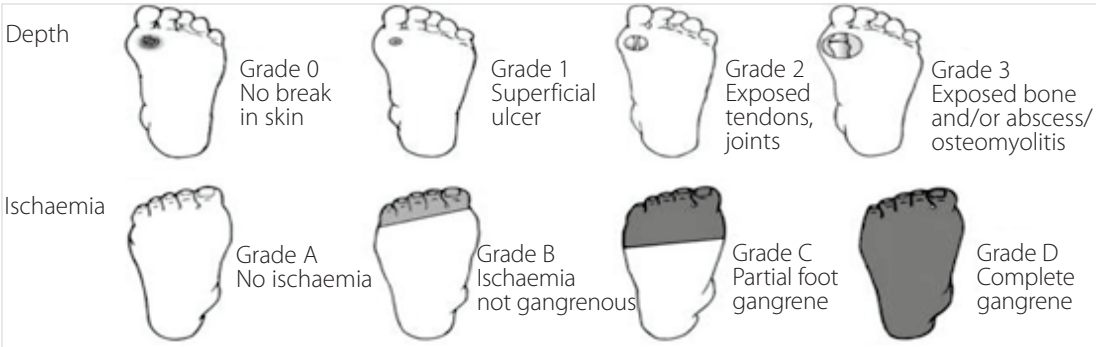


Figure 1. Diabetic foot ulcers-foot & ankle-orthobullets.

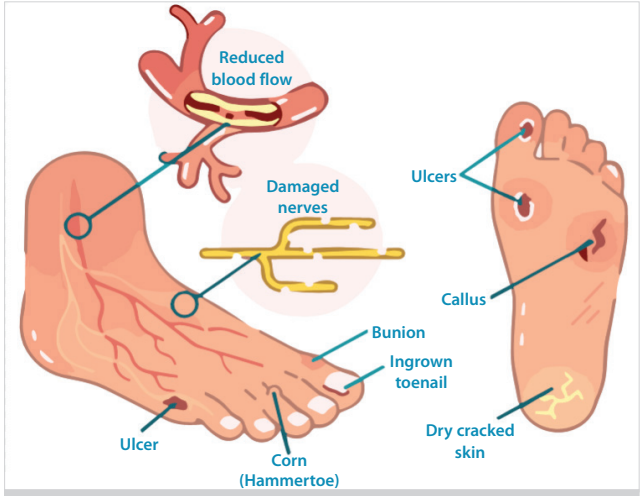


Figure 2. Diabetic foot.

management of burns, particularly superficial burns, and can also be used for other types of wounds. Polyurethane dressings are a type of wound dressing that is commonly used in the management of various types of wounds. These dressings are made of a thin, flexible, and transparent film or foam that is composed of polyurethane (3-6).

Beginning around 1000 BC, the Greeks and Romans utilized silver as a cleanser, antibiotic, and therapy for illnesses (7). Even though silver has a very low potential for toxin formation and only very rarely leads to microbial resistance, in vitro studies have demonstrated the effectiveness of silver-based dressings in battling pathogenic germs. So, the use of silver colloid in diabetic and venous ulcers acts as a very effective tool in wound management. With the increasing surface area to volume ratios accompanied by decreased toxicity to the tissues, the advent of nanotechnology has enabled the development of nano-silver particles that has a huge role in accelerated wound healing (8,9) (Figure 3,4).

The study aimed to assess and compare silver colloidal dressings with conventional dressings for the treatment of DFUs.

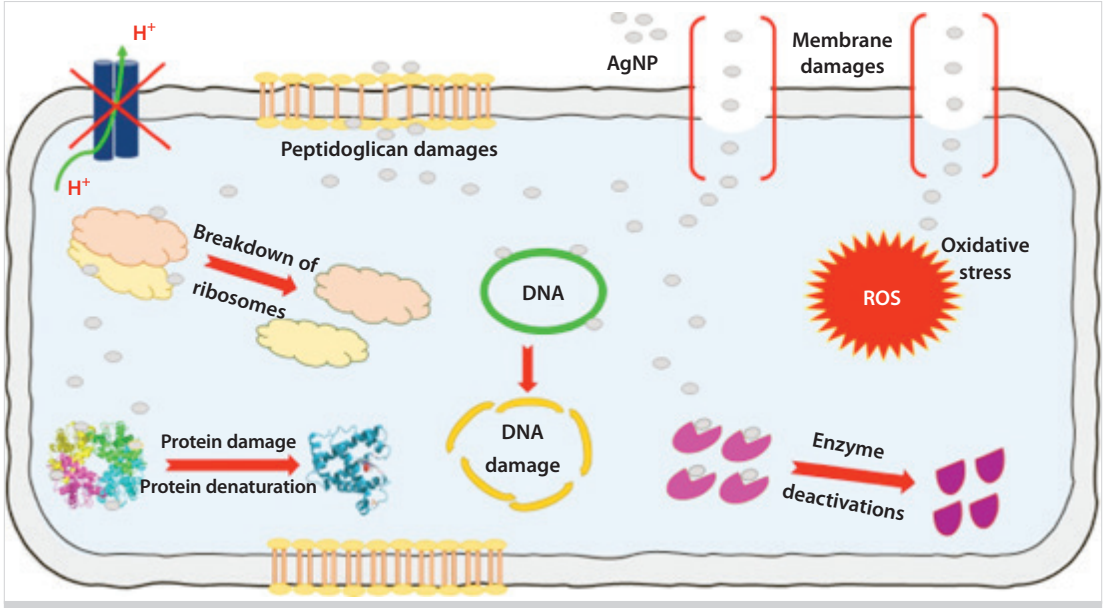


Figure 3. Silver-and silver nanoparticle-containing wound dressings for wound healing.

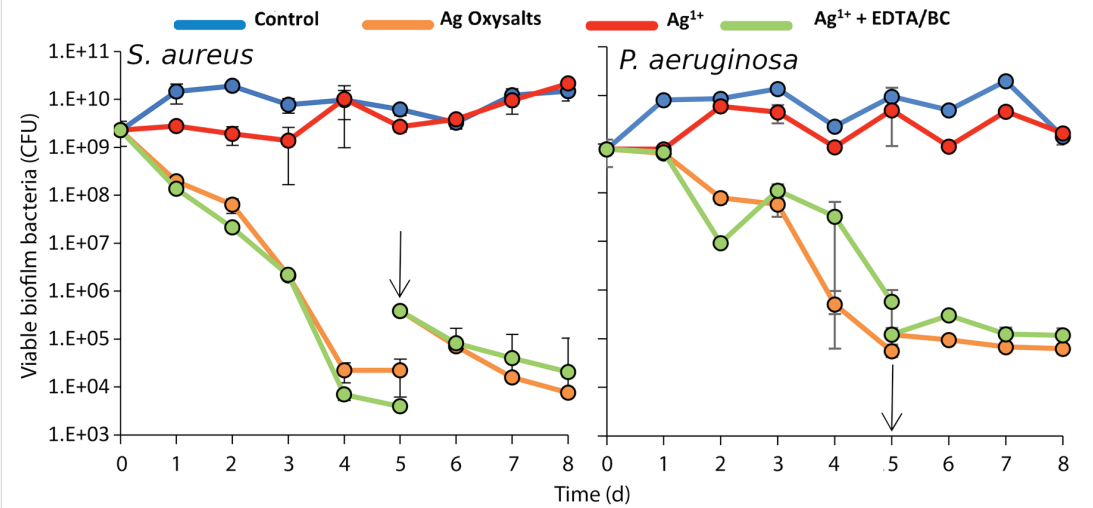


Figure 4. Silver oxynitrate-based dressings' anti-biofilm properties and facilitation of healing.

MATERIAL and METHODS

The study involved a total of 50 patients who had provided their consent to participate. It was a prospective study conducted at the Department of General Surgery in Indira Gandhi Institute of Medical Sciences Hospital. The study was conducted for a period of six months and was approved by the Institution Ethics Committee.

Simple random sampling was employed for the individuals in the study. Fifty patients were divided equally into two groups, group A and group B, with 25 patients in each group. The first 25 patients received conventional wound dressing as per standard practice, belonging to group A. The next 25 patients received silver colloid dressing, belonging to group B. The purpose of this division was to compare the outcomes of the two different dressing methods.

The patients were followed up for a period of six months to assess the effectiveness of the respective dressings. Data was collected and analysed to evaluate factors such as wound healing, infection control, and overall management of DFUs. This study design helped provide valuable insights into the potential benefits of silver colloid dressing compared to conventional dressing for DFUs.

Patient Criteria

The study included all adult patients who had a DFU with an area of at least 2 cm^2. These ulcers fell under Wagner grades I and II, indicating relatively superficial ulcers with no significant infection or tissue involvement. The ulcers had a minimum duration of 30 days, indicating chronic wounds that had not led within a reasonable timeframe. Specific criteria were used to exclude certain patients from participating in the study. These exclusion criteria were as follows - 1) patients with foot ulcers caused by other underlying conditions such as paraplegia, varicose veins, or other coexisting diseases, 2) patients with conditions or factors such as vasculitis, carcinoma, immune system disorders, treatment with corticosteroids, connective tissue disease, chemotherapy, immune suppressive agents, radiation therapy, uncontrolled diabetes, or osteomyelitis that can prevent a wound from healing, 3) patients known to have hypersensitivity or allergic reactions to colloidal silver gel, the substance being studied, 4) patients who had tested positive for COVID-19, indicating an active infection and patients who had tested positive for specific antibodies (seropositive), indicating a previous COVID-19 infection.

Statistical Analysis

Chi-square test was employed in the statistical analysis of the gathered data. The software used for data analysis was SPSS version 1.0.0.1406. The statistical program helped analyse and interpret the data obtained from the study, providing valuable insights into the effectiveness of the compared treatment methods.

RESULTS

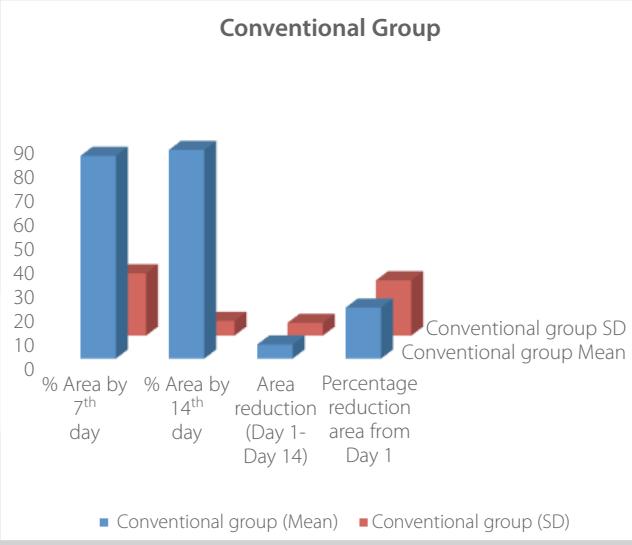
In the study, participants' average ages ranged from 57.6 years for group A to 62.4 years for group B. Although no particular numbers were given, both groups had a higher proportion of male patients (Table 1). The division of ulcers according to their cause (spontaneous or post-traumatic) was compared between group A and group B. While considering the number of dressings needed, the average for group B was 11.5, which was much less than the average of group A which was found to be 24.04, and this difference was found to be statistically significant ($p< 0.05$).

In group A, 40% of the participants required repeated dressings, which indicates that a substantial portion of this group needed dressings multiple times during the study period. While

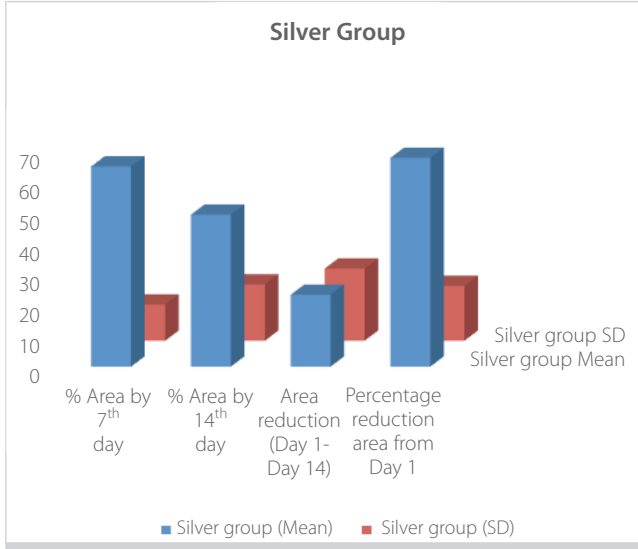
Table 1. The quantity of dressings needed in each group

	Silver group		Conventional group	
Number	Count	Column n %	Count	Column n %
1.0	25	100%	15	60%
2.0	0	.0%	5	20%
3.0	0	.0%	4	16%
5.0	0	.0%	1	4%
p= 0.02, Chi-square test				
	Mean	**SD**	**Mean**	**SD**
Area by 7th day, %	65.00	11.78	86.19	26.47
Area by 14th day, %	49.34	18.29	88.68	6.28
Area reduction (day 1-day 14)	23.34	23.46	6.05	5.48
Percentage reduction area from day 1	67.77	17.82	21.70	23.52

comparing group B to group A, significant reductions in ulcer areas were observed. Group B showed reductions of 65% ± 11.78% on day seven, 86.19 ± 26.47% on day seven, and 49.34 ± 18.29% on day 14 compared to group A. These reductions indicate that the ulcers in group B decreased in size more rapidly compared to group A. By day 14, when compared to group A, the mean area reduction in group B was a little larger. The ulcer area reduced to 23.34 ± 23.46 cm^2 in group B, while in group A, it reduced to 6.05 ± 5.48 cm^2. The difference in mean area reduction was found to be statistically significant ($p< 0.05$). The study also reported that the percentage reduction in ulcer area was higher in group B (67.77 ± 17.82%) compared to group A (21.70 ± 23.52%). These percentages indicate the relative reduction in ulcer area compared to the initial size (Graphic 1,2).



Graphic 1. Silver group.



Graphic 2. Conventional group.

Furthermore, when compared to group A, the total days to reach the study's endpoint were significantly lower in group B. Group B reached the endpoint in an average of 23.15 ± 8.15 days, while group A took an average of 48.35 ± 18.07 days. This difference in the time taken to reach the endpoint was found to be statistically significant, although the specific statistical test used was not mentioned.

DISCUSSION

Diabetes has many complications, one of which is DFUs, which can have serious consequences if not properly managed. They typically occur as a result of reduced blood flow, nerve damage, and impaired wound healing associated with diabetes. Nearly 70% of patients with DFUs require surgical procedures, and 40% of the patients end up needing a cutaway (5,7,10). Given the high occurrence of DFUs, which impose a substantial

burden of morbidity on individuals with diabetes and the extensive understanding of the disease process in diabetic patients, the inquiry arises as to whether the current standard of care for DFUs, which involves conventional dressings, should be re-evaluated in light of the various modern biological dressings that are now accessible (10-13).

Alluvial silver acts as ions of the silver depot and has a sustained local antibacterial effect, as well as sufficient water for the absorption of excess exudates, avoidance of microbial settlement, and relatively painless bandage removal, and all contribute to the creation of this environment. Ionic silver ions have been created as the active component in alluvial silver-based dressings as a result of nanotechnology's use of silver's wound-healing abilities. These bioactive dressings have been successfully developed and are now widely available in various countries. By harnessing the potential of nanotechnology, these dressings offer enhanced wound healing capabilities and have emerged as a valuable tool in promoting effective wound management. It is believed to have broad-spectrum antimicrobial activity, which means it can potentially help in reducing the risk of infection in diabetic foot ulcers (14-16).

As per our study, various criteria have been practiced while the effectiveness of traditional dressings and ionic silver-based dressings for DFU therapy. According to the study on day seven, the ulcer in the colloidal silver dressing group was significantly reduced to 65% (compared to the initial area of 100%) and the colloid silver dressing group's area of the ulcer was dramatically reduced to 49.34% by day 14 (compared to the conventional dressing's 88.68%). The colloidal silver dressing group had a considerably shorter duration reaching the endpoint, which was endogenous closure or an ulcer suitable for parted weight skin grafting when compared to the conventional dressing group.

Compared to more traditional topical silver treatments (Figure 5), colloidal silver dressing has essentially no or very little systemic toxicity. There is some evidence suggesting that colloidal silver may have anti-inflammatory properties and can promote wound healing by reducing inflammation and stimulating tissue repair (17). This is because smaller particles have more surface area and elute silver ions from the body at a rate that is far lower than what is necessary to cause systemic poisoning. According to studies, a topical adjuvant used in wound care is frequently ineffective against microbe-produced biofilms, which are generally resistant to removal with silver (18,19).

Preparations based on silver particles serve as a reservoir for silver ions, ensuring long-term maintenance of the ideal silver ion concentration. This sustained and optimal concentration allows for the delivery of silver ions, which possess anti-biofilm properties, at levels exceeding 30 ppm while avoiding systemic effects by staying below 60 ppm. By achieving this balance, the use of colloidal silver-based preparations promotes the desired therapeutic effects without causing harm to the body. As a result, the ultimate purpose of each dressing is to produce an environment that is favourable for wound healing.

Studies have demonstrated the efficacy of silver against microbial biofilms, which are typically resistant to standard wound care treatments. By acting as a depot for silver ions, colloidal silver-based dressings maintain an optimal concentration of silver ions, creating a favourable environment for wound healing (11). It is important to note that the choice between colloidal silver dressings and conventional dressings for DFU should be made based on individual patient factors, wound characteristics, and healthcare professionals' recommendations. The goal is to select the most appropriate dressing that optimizes wound healing, reduces the risk of infection, and addresses specific patient needs.

Currently, the most frequent kind of long-lasting, on-healing foot ulcers found in clinical practices have not generally acknowledged the standard of care for treatment. These ulcers pose a significant burden of morbidity among diabetic

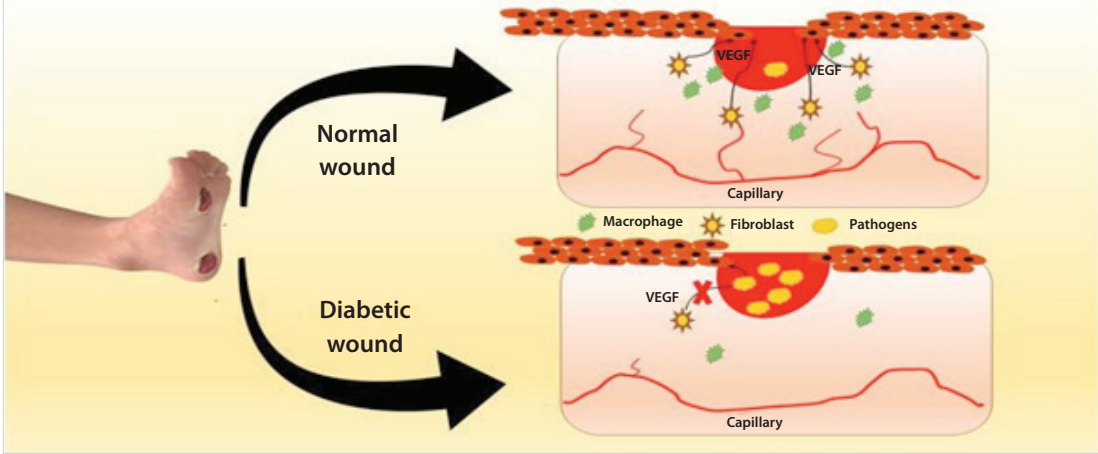


Figure 5. Advanced and promising technology for treating diabetic wounds is silver nanoparticles.

patients, with approximately 40% of patients eventually requiring amputation and 70% of patients requiring surgical intervention (20).

Given the prevalence and severity of DFUs, it is essential to evaluate whether conventional dressings are still reasonable as the standard of care, especially considering the availability of modern biological dressings. Despite being a well-known adjunct in wound healing, the use of silver has primarily been focused on burn wounds rather than DFUs. However, advancements in nanotechnology have led to the development of these based dressings with ionic ions as the present ingredient, which has shown promise in wound healing (11,20).

The study of Sharma et al., has demonstrated a noteworthy reduction in the ulcer in the area in the colloidal silver dressing group, with a reduction of 66% (compared to the initial area of 100%) on day seven. In comparison, the conventional dressing group has shown a reduction of 85.18% on day seven. Furthermore, on day 14, the colloidal silver dressing group has exhibited a significant reduction to 48% of the initial ulcer area, while the conventional dressing group has shown a reduction to 89.69%. The size of the wound decreased at a faster rate in silver colloid dressing than in conventional diabetic foot dressing (5).

According to Gupta V et al., dressings with nanocrystalline silver ions have emerged as an economical option for managing diabetic foot ulcers. These dressings contain tiny silver particles that release silver ions, which have antimicrobial properties. By using nanocrystalline silver dressings, the period of hospitalization for patients with diabetic foot ulcers can be reduced, resulting in a decreased burden on the healthcare system. Antimicrobial properties of nanocrystalline silver ions help prevent and treat infections in diabetic foot ulcers, which can lead to faster healing and improved outcomes for patients. Additionally, by reducing the need for prolonged hospital stays, nanocrystalline silver ion dressings can help to optimize healthcare resources and reduce healthcare costs. The cost-effectiveness of nanocrystalline silver ion dressings lies in their ability to promote wound healing and prevent complications, which can ultimately reduce the overall treatment costs associated with ulcers in diabetic feet. By reducing the healing time and minimizing the risk of infections, these dressings can potentially lead to shorter hospital stays, fewer healthcare visits, and lower expenses for patients and the healthcare system as a whole. Overall, the utilization of nanocrystalline silver ion dressings in the treatment of diabetic foot ulcers offers a cost-effective approach that not only improves patient outcomes but also eases the burden on healthcare resources (10).

Additionally, the final objective, which could be a suitable ulcer for split-thickness skin grafting or spontaneous closure, was reached by the colloidal silver dressing group much more quickly than the standard dressing group. The colloidal silver group also required fewer dressings overall until reaching the endpoint. Although the length of hospitalization did not show a statistically significant difference, it is worth noting that this factor may be influenced by various patient-related factors and is not the sole determinant of the dressing material's efficacy (12).

Ionic dressings are more effective than traditional dressings for healing these foot ulcers, according to the results of our study. These dressings promote faster wound healing, require fewer dressings overall, and provide a conducive environment for wound recovery. Ionic silver-based dressings should be strongly explored for implementation as the level of treatment for treating this ulcer due to its cost-effectiveness and improved results (21). As a result, we infer from our research that ionic silver-based dressings are unquestionably a superior method of treating DFUs and also a financially viable option for patients. As a result, we strongly advise that their adoption as the standard of care for the management of diabetic foot ulcers be strongly considered.

It is important to note that without specific details about the study, such as the study design, sample size, methodology, and any potential limitations, it is difficult to assess the overall quality and generalizability of the findings.

CONCLUSION

Silver-based dressings have a faster rate of wound healing. This was shown by the granulation tissue's early development, the treatment's effectiveness after two weeks, a decline in the percentage of slough and discharge, and a real reduction in the percentage of ulcer area. Additionally, the patients in our trial group who received ionic silver-based dressings reached the end point sooner and either had an ulcer that had spontaneously closed or was ready for a split-thickness skin graft. Also, patients in the colloidal silver group required significantly fewer dressings overall compared to the patients in the conventional group.

Ethics Committee Approval: This study was approved by the Indira Gandhi Institute (Decision no: 495/IEC/IGIMS/2022, Date: 01.04.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AR, VB; Design - YT; Supervision - VB; Fundings - VB, YT; Materials - AR, SS; Data Collection and/or Processing - AR, YT; Analysis and/or Interpretation - SS; Literature Search - AR; Writing Manuscript - AR; Critical Reviews - SS, AR.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 28-35

Diyabetik ayak ülserinde gümüş kolloid pansumanın geleneksel pansumanlar karşısında etkisi: Prospektif bir çalışma

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ÖZET

Giriş ve Amaç: Topikal gümüş tedavileri ve gümüş pansumanlar yaraların lokal tedavisi için giderek daha fazla kullanılmaktadır ancak bunların yararlılığına ilişkin kanıtlar net değildir. Bu çalışmada, kompresyon tedavisi uygulanan ve uygulanmayan diyabetik ayak ülserleri (DFU) üzerinde geleneksel pansumanların ve gümüş kolloid pansumanın etkisi araştırılmıştır.

Gereç ve Yöntem: Bu prospektif, çift kör deney, her biri 25 hastadan oluşan iki gruba ayrılmış, iskemik olmayan DFU'lu 50 hastayı içermektedir. Çalışma altı aylık bir süre boyunca yürütülmüştür. Birincil sonlanım noktası, çalışma bacağındaki tüm ülserlerin tüm epitelizasyonunu (toplam iyileşme) değerlendirmekti.

Bulgular: Ülser alanı kolloidal gümüş grubunda (%67,77 ± 17,82) konvansiyonel serum fizyolojik grubuna (%21,70 ± 23,52) kıyasla önemli ölçüde azalmıştır. Geleneksel grupla karşılaştırıldığında, kolloidal gümüş grubunun son noktaya ulaşması için önemli ölçüde daha az gün gerekmiştir (23,15 ± 8,15 güne karşılık 48,35 ± 18,07 gün) ve 14. günde ülser alanındaki küçülme (%100'den geriye) daha fazla olmuştur (gümüş grubunda %48'e karşı geleneksel grupta %89,69).

Sonuç: DFU'ların yönetiminde, iyonik gümüş bazlı gümüş kolloidler kullanan yapılandırılmamış hidrojel yara örtüleri, yaraları daha az günde daha hızlı iyileştirdiği ve zaman içinde ülser alanlarını önemli ölçüde azalttığı için normal serum fizyolojik içeren yara örtülerinden daha etkilidir.

Anahtar Kelimeler: Diyabetik ayak ülseri, gümüş kolloid pansuman, bandajlama, pansuman tedavisi

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ORIGINAL ARTICLE
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Abdominal versus pelvic gunshot injuries in terms of postoperative outcomes: A cohort representing the experience of 406 cases in seven years

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ABSTRACT

Objective: Gunshot injuries have become a significant problem globally. This study aimed to assess the differences between abdominal versus pelvic gunshot injuries in terms of postoperative outcomes to determine which type of injury is more lethal.

Material and Methods: This was a cohort study carried out to compare patients who had abdominal versus pelvic gunshot injuries, to analyse the differences in the impact of the anatomical site of injury on morbidity, mortality, and disabilities in all patients who had been admitted to the hospital due to torso gunshot injuries from February 2011 to December 2018.

Results: During the study period, 406 patients suffered from torso gunshot injuries. 391 were males and 15 were females; 343 (84.4%) patients had abdominal gunshot wounds, which were considered the first group, while in the second group, there were 63 (15.6%) patients who had pelvic gunshot wounds In the first group, 328 (95.6%) patients required urgent explorative laparotomy, complications were observed in 83 (24.2%) patients, while re-operations were reported in 51 (14.9%) patients and 11 (3.2%) patients had permanent functional disabilities, and 46 (13.4%) patients passed away. In the second group, all patients were treated with urgent explorative laparotomy, 17 (27%) patients suffered from complications, re-operation occurred in 13 (20.6%) patients, permeant functional disability occurred in 17 (27%) patients, and mortality was seen in 16 (25.4%) patients.

Conclusion: Our clinical experience has shown that mortality rates and long-term disability occur at a higher rate in pelvic gunshot injuries therefore early senior surgeon input is mandatory for the potential poor outcome to be minimized.

Keywords: Gunshot, abdominal wound, pelvic wound, torso injury

INTRODUCTION

In recent years, gunshot injuries have started to be considered common emergency cases, and many studies have documented that it is becoming a significant problem globally (1,2). Due to the widespread availability of weapons in the Libyan community during the last ten years, the incidence of firearm-related violence has dramatically increased (3).

The effect of a gunshot injury depends on missile calibre, velocity, and trajectory. The high velocity of a bullet can cause both penetration to an organ, as well as a blast injury to nearby organs, in addition to thermal injuries; therefore, higher mortality rates occur due to the greater energy transmitted to tissues (4). Torso gunshot injuries can cause significant bleeding, and subsequently septic consequences according to the nature of the injured organs, which may both lead to a significant rate of morbidity and mortality; and therefore, early diagnosis and early surgical intervention of an injured patient are essential to improve outcomes. Urgent explorative laparotomy has been the definitive traditional care for torso gunshot injuries; while recently with the more understood mechanism of injuries and with the advent of the new diagnostic and therapeutic modalities, non-operative management has become increasingly gaining acceptance for the selected cases (5,6).

The human trunk is formed by the abdominal and pelvic cavity, whereas there is no true separation between both cavities. The abdominal cavity contains many solid rich vascular organs, which significantly bleed when injured, as well as hollow organs that are responsible for septic complications after injury, while the

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pelvic cavity is the narrow overcrowded space inside the pelvic bones, which is divided into the lesser and greater pelvis, contains the reproductive organs, the lower part of the urinary tract, rectum, and major pelvic blood vessels protected by the pelvic bone, the superior edge of the pelvic bone considered the border between the abdominal and pelvic cavity. The diaphragm forms the superior border of the abdomen while the inferior border of the pelvic cavity is the pelvic diaphragm. The vertebral column and strong posterior abdominal wall muscles support the trunk posteriorly, while the remaining part is covered by an anterior lateral abdominal wall muscle. The retroperitoneum is located behind the peritoneal layer of the abdominal and pelvic cavity and contains the pancreas, urinary tract organs, and the major blood vessels.

The aim of the current study was to assess and analyse the differences between abdominal versus pelvic gunshot injuries in terms of short-term postoperative complications, long-term disabilities, and the mortality rates to determine which type of injury is more lethal and needs aggressive resuscitative measures.

MATERIAL and METHODS

A cohort study of 406 patients was conducted to compare patients who had abdominal gunshot injuries (the first group) and the second group of patients, who were those with pelvic gunshot injuries, to analyse the differences in the impact between abdominal versus pelvic gunshot injuries, on short-term post-operative complications, which is considered the primary end point. Moreover, there are long-term disabilities and mortality rates, which are considered the secondary end point of the study to determine which type of injury is more lethal and needs aggressive resuscitative measures in all consecutive, non-selected patients, who were resuscitated by a trauma team following the protocols of the Advanced Trauma Life Support of the American College of Surgeons, and had undergone urgent explorative laparotomy in our department, during the time period from February 17, 2011, to December 31, 2018. Table 1 demonstrates the baseline characteristics of the patients in both groups included in the study.

Patient data such as age, sex, past medical history, injured anatomical area, vital signs upon admission, blood transfusions, concomitant organs injuries, the grade of organs injury, injury severity score, methods of diagnosis, types of surgical procedures, postoperative complications, the indication of re-operation, procedures in the re-operation, length of hospital stay, long-term functional disability, and mortality rates of patients were all collected and prospectively reviewed. The data were collected and entered to the database, in which all documents and records were updated over the course of the study through medical staff reports.

According to intraoperative findings, which determined whether the injured organs were in the abdomen or pelvis, the patients were classified into one of the two study groups, while the small bowel was treated as an abdominal organ because of its mesentery and the fact that the majority of it is located inside the abdomen, as well the true pelvis is occupied by the rectum, the urinary bladder and reproductive organs in the normal anatomical state. On the other hand, all cases of gunshot wounds with intrathoracic organ injuries that required thoracoabdominal exploration, patients with injuries to the abdominal and pelvic organs, and patients with multiple gunshot wounds to other areas, such as the head and extremities, were excluded because they might present more challenging circumstances. Similarly, all cases of non-penetrating gunshot wounds were excluded.

Table 1. Baseline characteristics of the patients in both groups included in the study

Basic Characteristic	Abdominal Gunshot Wounds	Pelvic Gunshot Wounds	p value
Mean age (Years)	29	27.4	0.685
Body mass index (Mean)	22.7	21.4	0.732
Male: Female ratio (No)	25:1	30:1	0.812
History of cigarette smoking (No, %)	305 (88.9%)	51 (80.9%)	0.076
History of hypertension (No, %)	2 (0.58%)	1 (1.5%)	0.392
History of diabetes mellitus (No, %)	4 (1.1%)	1 (1.5%)	0.780
History inflammatory bowel disease (No, %)	2 (0.58%)	1 (1.5%)	0.392
Multi injured organs (No, %)	183 (53.5%)	43 (68.2%)	0.028
Shock on admission (No, %)	190 (55.4%)	44 (69.8%)	0.032
Blood transfusion (No, %)	219 (63.8%)	51 (80.9%)	0.008
Therapeutic laparotomies	296 (86.2%)	60 (95.2%)	0.047
Negative laparotomies	32 (9.3%)	3 (4.7%)	0.235
Total cases (No)	343	63	

In statistical analysis, all continuous variables were expressed as mean ± standard deviation (SD) to evaluate the distribution of data, and the categorical data were expressed as frequency and percentage. Comparisons between the groups were made using the $\chi 2$ test or Fisher's exact test for categorical variables as appropriate. Statistical analyses were performed using the SPSS v21 statistical software, and p values of less than 0.05 were considered statistically significant. We also conducted both unadjusted and adjusted logistic regression analyses to determine variables associated with a statistically significant study result. Initially, univariable analyses were conducted to identify factors (i.e. shock, postoperative complications, multi-organ injury, therapeutic laparotomy, and postoperative bleeding) associated with a significant study result. In adjusted analysis, we evaluated the risk of mortality and disability after abdominal and pelvic gunshot injury in a multivariable logistic regression model.

In addition, informed consent was obtained as the hospital is a teaching university hospital, and thus, written informed consents are routinely signed and from all admitted patients or legally authorised representatives during the hospital stay and before the studies, for all research to use patients' data and to be published in academic activities and researches, and ethics approval was also received, as this study was approved by the Al-Jalaa teaching hospital, Benghazi University Institutional Review Board (IRB).

RESULTS

During the study period, 406 urgent explorative laparotomies were conducted for patients who suffered from torso gunshot injuries, and Table 2 shows details of the actual operative interventions performed in both groups. There were 391 (96.3%) male and 15 (3.7%) female patients. Mean age was 28.7 years while standard deviation was 9.0 (range= 18-70 years). Three hundred and forty-three (84.4%) patients who had abdominal gunshot injuries were considered the first group in the study, while in the second group, there were 63 (15.6%) patients who had pelvic gunshot injuries.

In the first group, there were 183 (53.5%) patients who had multi organ injuries, while 117 (34%) patients suffered from a single organ injury. One hundred and ninety (55.4%) patients were in shock at the time of admission. Three hundred and twenty-eight (95.6%) patients required urgent explorative laparotomies, 32 (9.3%) of them had no intra-abdominal organ injuries which were considered negative laparotomy, two (0.6%) patients were treated with delay explorative laparotomy, and 15 (4.3%) patients were treated conservatively. Post-operative complications were observed in 83 (24.2%) patients, and Table 3 shows a comparison of postoperative complications in both groups, while Table 4 shows the rest of the complications in each group separately. Re-operations were reported in 51 (14.9%) patients and 11 (3.2%) patients who had post-operative long term permanent functional disability (Table 5); meanwhile, 46 (13.4%) patients passed away in the post-operative period.

In the second group, 43 (68.3%) patients sustained multi organ injuries, while 17 (27%) patients had single organ injuries; 43 (68.3%) patients were hemodynamically unstable at time of admission. All patients in this group were treated with urgent explorative laparotomy, and three of them (4.7%) had a negative laparotomy. Seventeen (27%) patients suffered from post-operative complications in this group (Tables 3,4), while re-operation occurred in 13 (20.6%) patients. Post-operative permanent functional disability was significantly clear throughout the long-term follow-up in 17 (27%) patients (Table 5), and mortality in this group of patients occurred in 16 (25.4%) patients. Further, a significant statistical difference was determined between the abdominal gunshot and pelvic gunshot injured patients with respect to both long-term disability and mortality (p= 0.015 and p= 0.0001, respectively), while there was also a non-significant difference in short-term postoperative complications, as well as re-operation rates (p= 0.637 and p= 0.248, respectively).

After adjustment for potential confounders, the risk of mortality was 1.5 times higher after pelvic gunshot injury than after abdominal gunshot injury. As compared to postoperative complications, shock, multi-organ injury, and postoperative bleeding were associated with an increased risk of death. The risk did not differ significantly for therapeutic laparotomy. Moreover, there is a much higher risk of long-term postoperative disability related to pelvic gunshot injuries. After relevant confounders were adjusted for, pelvic gunshot injuries were found to have a 13 times higher risk of postoperative disability than abdominal gunshot injuries. Kidney, pelvic nerve plexus, anal canal, and spinal cord injury were related to a higher risk of disability. On another side, post-operative bleeding and therapeutic laparotomy both carried a similar level of risk.

DISCUSSION

Gunshot injuries represent a unique surgical and public health challenge worldwide. Many studies have documented that gunshot injuries are a common surgical condition and have become a significant problem globally (1,2). Correspondingly, incidences have dramatically increased in the last ten years in Libya (3). Until now, there has been controversy in the management of gunshot injuries despite the huge number of research in medical institutes around the world. Military gunshot wounds are high energy penetrating injuries, and the nature of the penetration depends upon the trajectory of the missiles and the amount of energy that is transmitted through the affected tissue, which leads to an unpredictable wide variation in the severity of the injuries, while additional tissue damage may occur due to the cavitation wave of gas and fluid of surrounding tissue or from the fragmentation of the bullet and adjacent bone.

Table 2. Types and numbers of performed operative procedures in both groups

Abdominal Gunshot Wound Group				
	Organ	**Procedure**	**No**	**Percent %**
1	Diaphragm	Diaphragm primary repair with chest tube insertion	32	9.3%
2	Spleen	Splenectomy	33	9.6%
3	Stomach	Gastric wall primary repair	42	12.2%
4	Duodenum	Duodenal primary repair	8	2.3%
5	Liver	Topical liver parenchymal hemostasis Liver parenchymal primary repair Direct blood vessel ligation Perihepatic packing Non-anatomic liver resection	19 29 17 24 4	24.1%
6	Gall bladder	Cholecystectomy	12	3.4%
7	Pancreas	Pancreatic debridement Distal pancreatectomy	12 3	4.3%
8	Small bowel	Small bowel primary repair Small bowel resection & anastomosis	90 38	37.3%
9	Large bowel	Ascending colon primary repair Ileocecal resection Right hemicolectomy Transverse colon primary repair Transverse colon resection & anastomosis Transvers loop colostomy Descending colon primary repair Sigmoid colon primary repair Sigmoid colon resection and anastomosis Sigmoid loop colostomy Hartmann operation	16 2 40 44 9 13 8 14 2 10 11	49.2%
10	Kidney	Kidney primary repair Nephrectomy	6 21	7.8%
11	Ureter	Ureter primary repair Ureter anastomosis with DJ stent	2 5	2%
12	Blood vessels	Aorta primary repair IVC primary repair Superior mesenteric artery primary repair Inferior mesenteric artery ligation Inferior epigastric artery ligation	1 5 3 1 2	3.3%
	Pelvic Gunshot Wound Group			
	Organ	**Procedure**	**No**	**Percent %**
1	Rectum	Rectal primary repair with proximal loop colostomy Rectal primary repair	19 9	44.4%
2	Urinary bladder	Urinary bladder primary repair	24	38%
3	Urethra	Urethral primary repair with supra pubic catheter insertion	5	7.9%
4	Anal canal	Anal canal debridement with proximal loop colostomy	7	11%
5	Blood vessels	External iliac artery primary repair External iliac artery graft placement External iliac artery end-to-end anastomosis External iliac vein ligation Internal iliac artery primary repair Internal iliac artery ligation Internal iliac vein ligation	3 2 1 3 1 2 1	20.1%

Table 3. A comparison of postoperative complications in both groups

Postoperative Complication	Abdominal Gunshot Wound	Pelvic Gunshot Wound	p value
Postoperative bleeding	32 (9.3%)	13 (20.6%)	0.008
Wound infection	24 (6.9%)	5 (7.9%)	0.790
Incisional hernia	23 (6.7%)	1 (1.5%)	0.113
Postoperative abscess	12 (3.4%)	3 (4.7%)	0.625
Septic shock	9 (2.6%)	3 (4.7%)	0.357
Pneumonia	9 (2.6%)	2 (3.1%)	0.804
Postoperative ileus	6 (1.7%)	2 (3.1%)	0.454
Acute renal failure	3 (0.8%)	2 (3.1%)	0.128
Mortality	46 (13.4%)	16 (25.3%)	0.015

Table 4. The rest of the complications in each group separately

Abdominal Gunshot Wound Group		
Postoperative Complication	**No of Cases**	**%**
Anastomosis leak	12	3.4%
Burst abdomen	7	2%
Biliary leak	5	1.4%
Atelectasis	4	1.1%
Missile tract infection	3	0.8%
Pancreatic fistula	3	0.8%
Gangrenous colon	2	0.5%
Missed colon injury	2	0.5%
Acute respiratory distress syndrome	2	0.5%
Small bowel fistula	2	0.5%
Colostomy abscess	2	0.5%
Gastro-cutaneous fistula	1	0.2%
Postoperative gastric leak	1	0.2%
Aspiration pneumonia	1	0.2%
Colonic fistula	1	0.2%
Duodenal fistula	1	0.2%
Erosion of superior mesenteric artery	1	0.2%
Pulmonary embolism	1	0.2%
Fistula after colostomy closure	1	0.2%
Pelvic Gunshot Wound Group		
Recto-cutaneous fistula	3	4.7%
Urinary tract infection	2	3.1%
Colostomy necrosis	1	1.5%
Urine leak	1	1.5%
Disseminated intravascular coagulation	1	1.5%
Deep venous thrombosis	1	1.5%
Pleural effusion	1	1.5%

Table 5. Type of long-term disability in abdomen and pelvic gunshot injuries

No	Injury Mechanism	Disability	No (%)
First Group (Abdominal Gunshot Wounds)			
1	Complete spinal cord injury	Paraplegia	5 (1.4%)
2	Shattered kidney	Single kidney	4 (1.1%)
3	Destructive small bowel injury	Short bowel syndrome	1 (0.3%)
4	Massive bleeding	Myocardial infarction	1 (0.3%)
Second Group (Pelvic Gunshot Wounds)			
1	Anal canal injury	Anal incontinence	7 (11%)
2	Urethral injury	Urethral stricture	3 (4.7%)
3	Pelvic nerve plexus injury	Foot drops Sexual erectile dysfunction Retrograde ejaculation Neurogenic bladder	4 (6.3%) 2 (3.1%) 2 (3.1%) 1 (1.5%)
4	Fracture head of femur	Total hip replacement	1 (1.5%)

Abdominal and pelvic gunshot injuries most commonly lead to the rupture of solid organs, lacerations of hollow organs, and eviscerations of abdominal contents. Ruptured solid organs can cause considerable bleeding with an immediate sign of abdominal distension and hemodynamic instability and shock, with mortality due to the persistent bleeding that can be prevented or reduced by the identification of the early signs of shock with simultaneous administration of resuscitative measures. Meanwhile, in the case of hollow organ lacerations, the abdomen may also bleed although they also lead to peritonitis in short periods, or later with septic complications as intra-abdominal abscesses.

The rate of stomach injuries in gunshot wounds has recently increased to 10-15%, with the surgical treatment ranging from the simple primary repair of the wall to gastro-enterostomy or partial gastric resection according to the grade of the gastric injury (7). Moreover, as the stomach is a rich blood supply organ, the simple repair of its wall has a high success rate. Injuries to the stomach often have concomitant injuries to adjacent organs which lead to increased morbidity and mortality. In our study, 12% of patients had gastric injuries, all of which were treated by primary repair, and 87.8% of them had multi-organ injuries. Due to a missing injury, one patient developed a postoperative gastric leak while another patient had high output gastro-cutaneous fistula after the repair.

In addition, small bowel injuries occur in more than 40% of gunshot abdominal wounds (8), in our study, it was 37%, its principles of treatment are by primary repair or resection with re-anastomosis, according to the grade of damage. The colon is the second most frequently injured organ in gunshot patients (8), which has a significant septic complications risk (15-50%) (9); the state of shock and blood transfusion are considered predictive risks for these complications (10). Despite all recent developments in trauma surgery, some controversies persist in the treatment of colorectal injuries (11). In the current study, it was not possible to observe any advantages of the diversion over the primary repair in hemodynamically stable patients. Therefore, to reduce the risk of psychological trauma, complications of colostomy, unnecessary repeated hospitalisation, a decrease of economic costs, and complications of stoma revision operations, it is necessary to consider that the primary repair of penetrating colon injuries is an acceptable alternative method of treatment over colostomy, which represents our conclusion from two previous studies based on the management of colonic gunshot wounds in our department (8,10).

The liver is the third most frequently injured organ in gunshot abdomen wounds (8), in which 14% of liver injured patients require urgent surgical treatment (12). Control of the bleeding with conserving liver parenchyma is the main goal of surgery, the techniques ranging from topical haemostasis, primary repair of parenchyma, and the balloon tamponed technique in case of bleeding of the deep missile tract through the liver tissue. In high-grade injuries, the direct ligation of bleeding vessels is required, and liver packing is used in damage control surgery which leads to lower mortality rates (13); while hepatic resection is reserved for severe injuries only. In our case, topical liver tissue haemostasis, whether thermal or chemical, was performed in 22% of patients with liver injuries, liver tissue primary repair in 35.2%, direct blood vessel ligation in 21%, perihepatic packing in 29.5% of the patients as part of damage control surgery, and non-anatomic liver resection in 4.2% of the patients. Postoperative liver-related complications, which occurred in 21% of the patients, such as intraoperative and postoperative bleeding, biliary leak, and hepatic abscess, all are considered the most common complications in all surgical techniques (14). Many studies have suggested that the

selective non-operative management of gunshot liver injuries is safely feasible to reduce the incidence of unnecessary laparotomy (15).

Gall bladder injuries are considered rare cases, and our rate was 3.4%; the vast majority are of a penetrated form, and mortality in these cases is induced by the severity of their associated injuries (16). Regardless of injury type, immediate cholecystectomy remains the preferred form of treatment (17). Separately, the spleen is most frequently injured in blunt, rather than penetrating trauma, and penetrating splenic injury is more commonly due to gunshots and not stabbings, and it is associated with intra-abdominal as well as thoracic injuries (18). Urgent splenectomy is still the standard life-saving procedure with low morbidity and mortality, and recently a significant percent of splenic injuries has been managed non-operatively in selected patients (19).

Retroperitoneal injuries are common in patients who have abdominal gunshot wounds, with incidence ranging from 20-33% (20). The most commonly injured organs in the retroperitoneal space are as follows; the colon, kidneys, duodenum, and then the pancreas (21); meanwhile, the mortality rates for retroperitoneal injuries depend upon the zone of injury. Pancreatic and duodenal injuries are uncommon (22) due to their anatomical background as a small target surrounded by vital organs, with more than 90% of pancreatic and duodenal injuries associated with injuries to the adjacent major blood vessels (23). Additionally, blurred injury signs lead to delays in diagnoses and treatment, which end with significant morbidity and mortality (24). The pancreatic and duodenal injuries in our study were 4% and 2.3%, respectively. After debridement and distal pancreatectomy, pancreatic fistulas occurred in 21.5% of cases, with a mortality rate of 42.8% primarily attributable to massive bleeding. In contrast, duodenal fistulas occurred in 25% of cases following simple repair and gasto-jejunostomy, with one patient suffering a paraplegic spinal cord injury.

Major blood vessels injuries in torso gunshot wounds are uncommon with high mortality rates despite perioperative resuscitation and damage-control strategies, which do not substantially result in a reduction (25). Hemodynamic instability with abdominal distention is a clinical sign of vascular injuries. During trauma laparotomies, the proximal control of aortic injuries can occur with an aortic cross-clamp, sponge stick, or manual compression, while the primary repair remains feasible (26). Injury to the superior mesenteric artery carries significant morbidity due to small bowel ischemia; and therefore, patients do not tolerate superior mesenteric artery ligation (27). Comparatively, inferior vena cava injuries remain highly lethal, which have a high mortality rate. Even though the primary suturing was the most common method of repair, some literature has concluded that ligation of the inferior vena cava is an acceptable damage control technique (28). Only once did we observe aortic damage that required re-exploration to treat postoperative bleeding, while inferior vena cava injury was seen in 1.4% of abdominal gunshot wounds, and bleeding was the primary cause of death in 60% of the cases.

Kidneys are the most injured organs in the urinary tract (29). This can cause bleeding or urine extravasation, while selective observation and/or various operative techniques can offer high renal salvage rates following gunshot injuries (30). Nine percent of our patients experienced renal damage as a result of a penetrating injury. Sixteen percent of them underwent non-operative management, 19.3% underwent primary parenchymal repair, while nephrectomy was necessary for 64.5% of the patients due to high-grade injury.

Despite the last upgrade of highly sophisticated diagnostic modalities, gunshot pelvic wounds are still a big challenge to trauma surgeons, which represent a potentially life-threatening condition. A high-energy penetrating trauma increases the likelihood of pelvic bone fractures with the risk of profuse bleeding, which also cause concomitant pelvic viscera injuries. Furthermore, life-threatening bleeding can occur from the presacral venous plexus in 80-90% of cases, while arterial bleeding can stem from the iliac arteries (31). Nerve injury in pelvic gunshots can be due to the penetrating effect of the bullet through the pelvic cavity at the time of trauma or due to surgical manipulation at the time of laparotomy, which may occur in 50% of cases, and manifest with pain, paraesthesia, sensory deficit, and motor weaknesses, which is often permanent (32).

The vast majority of penetrating rectal injuries are caused by pelvic gunshots (33), with rectum bleeding considered a clinical diagnostic sign. In hemodynamically stable patients, computer tomography imaging and rigid sigmoidoscopy can confirm the diagnosis. Some international literature has considered the anatomical site of penetrating rectal injury as a predictive risk factor for post-operative complications (34). Accordingly, Lavenson and Cohen have described the principles of treating rectal injuries by the primary repair, proximal colon diversion, presacral drainage, and distal rectal washout (35), In our study, 44.4% of patients with pelvic gunshot wounds had rectal injuries with a morbidity of 25%. On the other hand, anal canal injuries from gunshots are rare and have not yet received enough research (36). The best way to treat anal injuries, however, is still up for debate. Some research suggested tissue debridement and faecal diversion, followed by delayed sphincter repair, but other studies found early sphincter repair is superior (37). Eleven percent of our patients suffered from gunshot wounds to the anal canal, and they all ended up permanently disabled with anal incontinence.

About 25% of all urinary bladder injuries are caused by gunshot wounds, and these wounds are frequently accompanied by rectal injuries (38). In 50% of cases, haematuria is present, which provides a high index of suspicion of the diagnosis (39). In our study, urinary bladder injury occurred in 38% of the patients with pelvic gunshot wounds, all of whom were treated by primary wall repair, and 7.9% of the patients experienced urethral injury treated by urethral primary repair with supra pubic catheter insertion, 60% of whom developed ureteral strictures.

In this study, we identified the presence of shock, multi-organ injury, post-operative bleeding, and injured area as significant risk factors for mortality in patients with gunshot injuries. We also found an overall Odd's ratio of 1.5 for the effect of a pelvic injury on the rate of mortality. However, establishing sufficient ambulance services, blood banks and regional trauma centres decreased mortality rates to 9.5% in the 1990s. Delayed admission time, insufficient blood support, and the high rate of large intestine injuries affected the post-operative infectious complications and the death incidence. Risk factors related to postoperative infections for abdominal gunshot injuries are uncontrolled shock, duration of surgery, transfusion requirement, and the number of injured organs (40). Whereas previous studies have shown that in military and civilian torso gunshot wounds, the mortality rate rises with the number of intraabdominal organs injured (41). Like others, we demonstrated a positive correlation between the number of organs injured and mortality. However, the number of organs injured does not accurately quantify the overall severity of the injury. For example, a patient with an isolated 3 cm superficial hepatic laceration is not as severely injured as another with extensive hepatic parenchyma destruction, but both have one organ injured (41).

Since penetrating wounds are a common cause of vascular injuries, emergency exploration for these wounds is gaining high importance, and since the percentage of complications in penetrating injuries is related to the amount of energy transferred through the tissue, and neurovascular injury is considered its complications (42), vascular examination on the part of the clinician in gunshot injuries is very important (40). In studies in which the mortality rate for pelvic fracture patients in shock is reported, the rate varies from 21 to 50 percent (43,44). However, in a well-controlled prospective cohort study carried out at a level I trauma centre, 54% of trauma patients who presented in shock died (blood pressure less than or equal to 90 mmHg). Thus, it appears that for pelvic fracture patients who arrive in the emergency room in shock, the chances of survival are roughly 50 percent (45). However, by using multivariable analyses, we observed that the most important factor was the presence of shock with (Odd's ratio 5.85).

On the other hand, although permanent effects can be anticipated, the long-term impact of gun violence, particularly in terms of physical function and occupational handicap, is still poorly understood (46-48). For instance, difficulty with daily activities and chronic pain that remained for up to two years after injury among patients treated for gunshot wounds has been under investigation in recent research (46). However, we sought to examine the effect of abdominal and pelvic gunshot injury on long-term disability. We investigated several possible risk factors such as spinal cord, kidney, anal canal, pelvic nerve, and urinary bladder injuries. The researchers reported that particular damage patterns were associated with persistent disabilities. For instance, neurological impairment was linked to chronic pain (49). Studies on long-term functional outcomes provide analysis without considering the cause of late disability. The severity of the initial anatomic soft tissue injury pattern may not be accurately determined by looking back at files to locate past complaints and observations.

Urogenital injuries can be associated with erectile dysfunction and urinary incontinence, and urethral strictures have been reported in 31% to 69% of complete urethral transactions (50). Due to the high energy necessary for pelvic bony fracture, 60 to 90% of patients presenting bone fracture have urinary bladder injury, while 6-8% of patients with bladder injury will have pelvic fracture (51). Also, as a result of gunshot wounds, traumatic nerve laceration is more common than was previously thought, and delaying treatment for patients who have partial or total nerve lacerations could lead to worse clinical results and higher morbidity (52). Most injuries to the spinal cord after a gunshot result in complete paraplegia.

In the presence of multiple war hotspots internationally, gunshot injuries need to be studied in detail, as gunshot injuries differ in their salient features and outcome based on the anatomical area. Our multivariate analysis reveals that the kidney and the pelvic nerve injury are the most important factors for long-term disability in this study. In simple terms, the complicated nature of anatomical features of the pelvis has a clear impact on the difficulty in controlling haemorrhage as well as increasing the risk of permanent disability. Therefore, trauma surgeons need to be aware of these differences and prepare accordingly. Moreover, a specialized triage system could be set up to minimize the time spent by injured people waiting for the proper specialist. More investigations are required to compare these phenomena in other conflicts and circumstances because there have not been many studies comparing the impact of this injury in these anatomical locations on the features of the injured patient.

CONCLUSION

Our clinical experience has shown that mortality rates and long-term disability occur at a higher rate in pelvic gunshot injuries

when compared to abdominal gunshot wounds therefore early senior surgeon input is mandatory for the potential poor outcome to be minimized.

Ethics Committee Approval: This study was approved by Benghazi University Al-Jalaa Teaching Hospital Ethics Committee (Decision no: 361/2022, Date: 10.12.2023).

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ORİJİNAL ÇALIŞMA-ÖZET
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Postoperatif sonuçlar açısından karın ve pelvik ateşli silah yaralanmalarının karşılaştırılması: Yedi yılda 406 vakanın deneyimini temsil eden bir kohort

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ÖZET

Giriş ve Amaç: Ateşli silah yaralanmaları tüm dünyada önemli bir sorun haline gelmiştir. Bu çalışmanın amacı, hangi yaralanma tipinin daha ölümcül olduğunu belirlemek için abdominel ve pelvik ateşli silah yaralanmaları arasındaki farkları postoperatif sonuçlar açısından değerlendirmektir.

Gereç ve Yöntem: Bu çalışma, abdominel ve pelvik ateşli silah yaralanması olan hastaları karşılaştırmak ve Şubat 2011 ile Aralık 2018 tarihleri arasında ateşli silah yaralanması nedeniyle hastaneye başvuran tüm hastalarda yaralanmanın anatomik bölgesinin morbidite, mortalite ve sakatlıklar üzerine etkisindeki farklılıkları analiz etmek için yapılan bir kohort çalışmasıdır.

Bulgular: Çalışma döneminde 406 hasta, gövde ateşli silah yaralanması geçirdi. Hastaların 391'i erkek, 15'i kadındı; 343 (%84,4) hastada abdominel ateşli silah yaralanması vardı ve bunlar birinci grup olarak kabul edilirken, ikinci grupta pelvik ateşli silah yaralanması olan 63 (%15,6) hasta vardı. Birinci grupta 328 (%95,6) hastaya acil eksploratif laparotomi gerekmiş, 83 (%24,2) hastada komplikasyon görülmüş, 51 (%14,9) hastada tekrar ameliyat yapılmış, 11 (%3,2) hastada kalıcı fonksiyonel yetersizlik görülmüş ve 46 (%13,4) hasta hayatını kaybetmiştir. İkinci grupta, tüm hastalar acil eksploratif laparotomi ile tedavi edilmiş, 17 (%27) hastada komplikasyon görülmüş, 13 (%20,6) hastada tekrar ameliyat olmuş, 17 (%27) hastada kalıcı fonksiyonel sakatlık oluşmuş ve 16 (%25,4) hastada mortalite görülmüştür.

Sonuç: Klinik deneyimlerimiz, pelvik ateşli silah yaralanmalarında mortalite oranlarının ve uzun süreli sakatlığın daha yüksek olduğunu göstermiştir, bu nedenle potansiyel kötü sonuçların en aza indirilmesi için erken kıdemli cerrah müdahalesi zorunludur.

Anahtar Kelimeler: Ateşli silah, karın yaralanması, pelvik yara, gövde yaralanması

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ORIGINAL ARTICLE
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Liver resection versus ablation in geriatric populations - Does one method impart improved in-hospital mortality?

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ABSTRACT

Objective: This study aimed to compare surgical resection versus ablation for managing liver malignancies in patients 65 and older.

Material and Methods: Cases with liver tumors were extracted from the NSQIP database for patients aged ≥65 years. Following propensity score matching, multivariate Cox regression was used for 30-day morbidity and mortality for liver resection and ablation.

Results: Following a propensity score matching, 1048 patients were 1:1 matched for comorbid conditions. Patients stayed in the hospital three days longer after resection (p< 0.001). Mortality was lower after ablation (p= 0.013). This difference was more prominent in patients with primary liver tumors (p= 0.008). Group A had a 10-fold lower risk of developing an abdominal abscess, a fourfold decrease in hospital-associated pneumonia (p= 0.001) and reintubation, a 10-fold reduction in bleeding requiring transfusion (p< 0.001), and a three-fold decrease in risk of developing sepsis (p< 0.001).

Conclusion: Despite being a generally sicker patient population with worse underlying liver function, ablative techniques were associated with a lower risk of adverse outcomes when compared to more aggressive resection of primary malignant tumors of the liver.

Keywords: Liver cancer, resection, ablation, complications

INTRODUCTION

There has been a marked increase in the percentage of the geriatric population in the United States. Over the next few decades, we expect nearly a quarter of the US population to be 65 years or older (1). Since this is the largest growing population subset, we must be equipped and ready to address the unique challenges the elderly population provides to the field of surgery. Physiologic reserve decreases with aging as the frailty level increases (2). There has been a significant concentration on preoperative optimization and "prehab" to address this need; however, little has been done to address different surgical options catering to the aging patient (3).

With the advancement in screening and imaging, there is an increasing number of patients with primary and secondary liver malignancies. With a higher number of liver tumors diagnosed, more patients require treatment. Under ideal circumstances, the treatment of choice for liver malignancies remains as resection (4). Most of the studies regarding liver ablation have been for secondary liver malignancies. Data demonstrate that overall survival is comparable. However, local recurrence rates are variable (5,6). Early complication rates in the literature are low for ablation (0-27%), with more recent literature citing the rate around 7% (7).

This study aimed to analyze the outcomes of liver resection and ablation for liver malignancies in patients aged 65 years or older. We hypothesized that elderly patients undergoing resection would have higher complication rates and 30-day mortality.

MATERIAL and METHODS

Data were obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). ACS NSQIP is a national database that provides preoperative risk factors, operative data, and 30-day outcomes.

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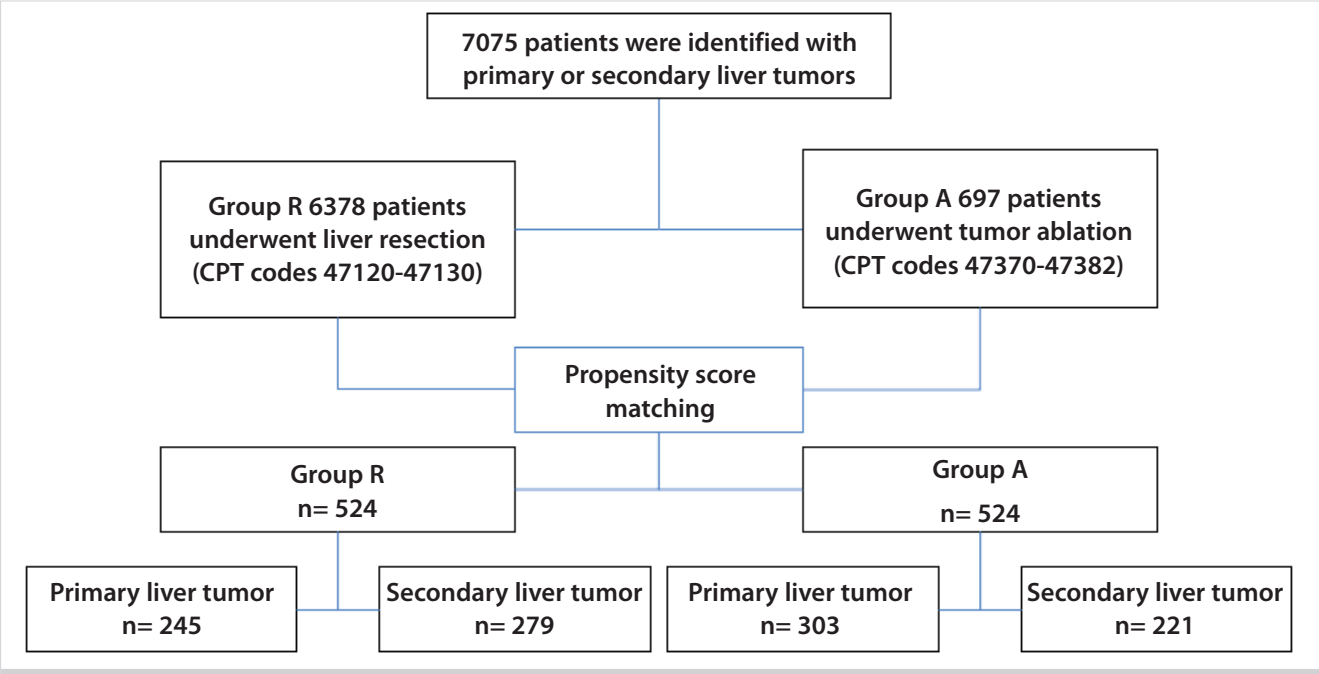

Figure 1. Flow diagram depicting the study cohorts.

The ACS NSQIP database was queried for patients aged 65 years and greater who had liver resection (Group R) or ablation (Group A) between 2008 and 2016 (Figure 1). These patients were identified using the International Classification of Diagnosis (ICD) and Current Procedural Terminology (CPT) codes (Group R: 47120-47130 and Group A: 47370-47382). Patients were excluded if there was missing information for diagnosis, length of stay, in-hospital, and 30-day mortality rates.

Data were collected for American Society of Anesthesiologists (ASA) classification, the number of units of packed red blood cells given intraoperatively, operating time (measured in minutes), length of hospital stay (measured in days), postoperative wound infection, organ space/surgical site infection, pulmonary complications, renal complications, cardiovascular complications, the frequency of returning to the operating room, readmission, 30-day, and in-hospital mortality rates. ASA classification is in accordance with the American Society of Anesthesiologists (8). Definitions of the data obtained are described in detail elsewhere (9).

Statistical Analysis and Data Management

Data were maintained on a spreadsheet (Excel, Microsoft®, Redmond, WA, USA) and analyzed using SPSS for Mac OS version 28.0 (IBM Inc. Chicago, IL). Mean data were presented with 95% confidence intervals where appropriate unless otherwise noted. We analyzed anthropometric and presurgical comorbid data and compared the two groups of patients based on their treatment modalities using Chi-square or Fisher's exact tests. We also utilized Chi-square tests to compare postoperative complications between the different interventions. The null hypotheses were rejected with a 95% confidence interval. Logistic regression models were also constructed to calculate the propensity scores. Data from groups R and A were matched by a 1:1 ratio using propensity score matching (PSM). We selected the variables based on their respective scores with a caliber of 0.1 decimal. The variables chosen for PSM included the chronic use of steroids, weight loss >10%, ascites, bleeding disorders and ASA physical status. Multivariate Cox proportional hazards regression was used for time-to-event analyses, and data are presented as odds/hazard ratio with confidence interval. A subgroup analysis was then carried out of primary versus secondary liver tumors (Figure 1).

RESULTS

Seven thousand seventy-five patients underwent surgical treatment for liver malignancy between 2008 and 2016, liver resection was performed in 6378 (Group R; 90%), and 697 (10%) underwent tumor ablation (Group A). Patient demographics were comparable between the two groups, apart from weight loss >10%, BMI, presence of ascites, bleeding disorders and prior use of corticosteroids (Table 1). One thousand forty-eight patients were included in the matched propensity analysis: 524 for each operative intervention modality. The prevalence of preoperative comorbid conditions was comparable between the two groups after the PSM. Preoperative comorbidities are also seen in Table 1 both before and after PSM.

Table 1. Patient demographics, clinical information, co-morbid diseases before and after propensity score matching. Asterisks indicate the variables included in propensity score matching

		Before Propensity Score Matching			After Propensity Score Matching		
Category		**Resection (n= 6378)**	**Ablation (n= 697)**	**P-value**	**Resection (n= 524)**	**Ablation (n= 524)**	**P-value**
Age (year)		72 ± 5	72 ± 5	0.437	72 ± 5	72 ± 6	0.068
Sex	Male	3744 (59%)	324 (61%)	0.270	302 (58%)	321 (61%)	0.257
	Female	2633 (41%)	205 (39%)		221 (42%)	202 (39%)	
Height (cm)		168 ± 10	168 ± 10	0.223	--	--	--
Weight (kg)		79 ± 18	81 ± 18	0.008	--	--	--
Body mass index		27.8 ± 5.6	28.3 ± 5.4	0.064	27.8 ± 5.7	28.3 ± 5.4	0.137
Caucasian race		4565 (72%)	398 (72%)	0.342	379 (72%)	364 (70%)	0.341
ASA II/III/IV*		953/4834/567	57/413/57	0.014	57/408/56	57/408/56	0.999
Diabetes mellitus		1599 (25%)	159 (25%)	0.999	159 (30%)	159 (30%)	0.999
COPD		348 (5.5%)	27 (5.1%)	0.842	39 (7.4%)	26 (5%)	0.842
Active smoking		685 (11%)	68 (13%)	0.147	57 (11%)	67 (13%)	0.398
Dyspnea		495 (7.8%)	50 (7.2%)	0.611	50 (9.5%)	36 (6.9%)	0.143
Dependent functional status		83 (1.3%)	7 (1.0%)	0.645	10 (1.9%)	6 (1.1%)	0.328
Ascites*		41 (0.6%)	22 (4.2%)	<0.001	24 (4.6%)	22 (4.2%)	0.786
Hypertension		4235 (66%)	343 (65%)	0.444	361 (69%)	338 (65%)	0.149
End-stage renal failure		17 (0.3%)	0 (0.0%)	0.636	--	--	--
Prior steroid use*		206 (3.2%)	26 (3.7%)	0.045	25 (4.8%)	25 (4.8%)	0.999
Weight loss >10%*		291 (4.6%)	14 (2.6%)	0.036	13 (2.5%)	13 (2.5%)	0.999
Bleeding disorder*		274 (4%)	69 (10%)	<0.001	57 (11%)	57 (11%)	0.999
Prior sepsis		439 (6.8%)	64 (9.2%)	<0.001	--	--	--

Table 2. Preoperative laboratory data (Mean ± Standard Deviation) before propensity score matching. These variables were not included in the matching, and they were fundamentally different between the two treatment modalities

Preoperative Labs	**Resection (n= 524)**	**Ablation (n= 524)**	**P-value**
Bilirubin (mg/dL)	0.74 ± 0.85	0.86 ± 0.64	0.009
Aspartate aminotransferase (unit/L)	37 ± 39	41 ± 32	0.003
Alkaline phosphatase (units/L)	114 ± 88	108 ± 57	0.016
Albumin (gram/dL)	3.9 ± 0.5	3.7 ± 0.6	<0.001
Hematocrit (percent)	38.6 ± 5.2	38.6 ± 4.9	0.771
White blood cells (counts/nL)	7.12 ± 3.34	5.73 ± 2.04	<0.001
Platelets (counts /nL)	218 ± 84	163 ± 74	<0.001
Prothrombin time (seconds)	12.3 ± 2.2	12.7 ± 2.1	0.173
International normalized ratio	1.05 ± 0.18	1.12 ± 0.22	<0.001
Sodium (mmol/L)	139.2 ± 3.1	138.8 ± 3.2	0.008
Creatinine (mg/dL)	0.98 ± 0.48	1.0 ± 0.56	0.390

In univariate analysis of the matched patients, preoperative laboratory data was notable for having higher bilirubin (0.86 ± 0.64 vs. 0.74 ± 0.85 mg/dL, p= 0.01), INR (1.12 ± 0.22 vs. 1.05 ± 0.18, p< 0.001), AST (41 ± 32 vs. 37 ± 39 units/L, p= 0.003) but lower platelets (163 ± 74 vs. 218 ± 84 counts/nL, p< 0.001) and albumin (3.7 ± 0.6 vs. 3.9 ± 0.5 gm/dL, p< 0.001) in Group A when compared to the patients in Group R (Table 2). Preoperative laboratory values were not included for PSM since these values were fundamentally different and any attempt to match for these variables revealed no matched subjects between groups R and A.

Table 3. The occurrence of postoperative complications in patients undergoing surgical resection versus ablation for liver tumors after propensity score matching in 1048 patients. The odds ratios were calculated based on the risk of a particular complication after liver ablation compared to liver resection

Preoperative Labs	Resection (R) (n= 524)	Ablation (A) (n= 524)	Odds Ratios 95% Confidence	P-value
Predicted risk of mortality (percent)	3.26 ± 3.67	1.64 ± 1.84	---	<0.001
Predicted risk of morbidity (percent)	23.7 ± 10.3	8.4 ± 5.8	---	<0.001
Operative duration of procedure (minutes)	226 ± 119	134 ± 82	---	<0.001
Total length of hospital stay (days)	7.9 ± 6.6	3.1 ± 4.5	---	<0.001
Any post-procedural morbidity	176 (33.6%)	38 (7.3%)	0.16 (0.11-0.23)	<0.001
Wound dehiscence/infection	22 (4.2%)	7 (1.3%)	0.31 (0.13-0.73)	0.007
Abdominal abscess formation	26 (5.0%)	3 (0.6%)	0.11 (0.03-0.37)	<0.001
Hospital-associated pneumonia	27 (5.2%)	7 (1.3%)	0.25 (0.11-0.58)	0.001
Re-insertion of endotracheal tube	17 (3.2%)	6 (1.1%)	0.35 (0.14-0.88)	0.033
Venous thromboembolism	14 (2.7%)	7 (1.3%)	0.49 (0.20-1.23)	0.130
Acute kidney injury	12 (2.3%)	5 (1.0%)	0.41 (0.14-1.18)	0.140
Urinary tract infections	16 (3.1%)	7 (1.3%)	0.43 (0.18-1.05)	0.090
Cerebrovascular event/stroke	4 (0.8%)	1 (0.2%)	0.25 (0.03-1.01)	0.374
Major adverse cardiac event	16 (3.1%)	3 (0.6%)	0.18 (0.05-0.63)	0.004
Major bleeding requiring transfusion	112 (21.4%)	14 (2.7%)	0.10 (0.06-0.18)	<0.001
Sepsis with or without shock	25 (4.9%)	7 (1.3%)	0.27 (0.12-0.63)	0.003
Death within 30 days	15 (2.9%)	5 (1.0%)	0.33 (0.12-0.91)	0.039

Postoperative Morbidities and Adverse Events

Postoperative occurrence of adverse events was analyzed in 1048 patients following PSM (Table 3). One hundred and seventy-six patients (33.6%) in Group R developed post-procedural complications, slightly higher than the risk of morbidity of 23.7 ± 10.3% predicted by the ACS risk calculator. In contrast, only 38 (7.3%) patients had reported post-procedural adverse events in Group A, which was on par with the 8.4 ± 5.8% risk calculated by ACS. Overall, there was a six-fold decrease in the risk of a postprocedural adverse event in Group A compared to group R [0.16 (0.11-0.23); p< 0.001]. Patients in Group A were three times less likely to have dehiscence or deep wound infections [0.31 (0.13-0.73); p= 0.007] and fourfold less likely to develop hospital-associated pneumonia [0.25 (0.11-0.58); p< 0.001]. Similarly, the frequencies of major adverse cardiac events (potentially fatal cardiac dysrhythmias, ST elevation myocardial infarction and/or cardiogenic shock) were 5.5-fold lower in Group A compared to those in Group R [0.18 (0.05-0.63); p= 0.004]. Postoperative bleeding was noted in 21.4% of patients in Group R, whereas only 2.7% of patients in Group A developed significant bleeding requiring transfusion (p< 0.001). Postoperative sepsis with or without shock was reported four times less in Group A than in Group R [0.27 (0.12-0.63); p= 0.003]. There were no differences in the prevalence of venous thromboembolism (VTE), acute kidney injury (AKI), urinary tract infection (UTI) or cerebrovascular event (CVE) between the two groups.

Post-procedural death and in-hospital mortality

The unmatched analysis demonstrated improved 30-day survival for geriatric patients with a primary liver tumor who had undergone ablation versus those who had undergone resection (p= 0.043). The mortality rates following tumor ablation and surgical resection were comparable to those predicted by the ACS calculator (Table 3). Cox regression analysis of the matched patients revealed a lower risk of in-hospital mortality in Group A than in Group R [0.33 (0.13-0.83); p= 0.013] (Figure 2A). Subgroup analysis of the matched data further indicated that the risk of in-hospital mortality was much lower after tumor ablation than resection in those with primary hepatic malignancy diagnosis (Figure 2B; p= 0.008). The survival benefit was insignificant among patients with secondary metastatic liver lesions (Figure 2C; p= 0.391).

DISCUSSION

This is the first study comparing liver ablations and resections in a geriatric population. With an aging population, it is essential to garner a better knowledge of how best to treat this patient population and optimize their outcomes. Hepatocellular carcinoma is increasing in incidence and prevalence (10). Considering the average age of diagnosis is 65 years old for HCC, treatment discussion of resection versus ablation is becoming more common. Secondary liver malignancies are also seen more frequently in our aging population.

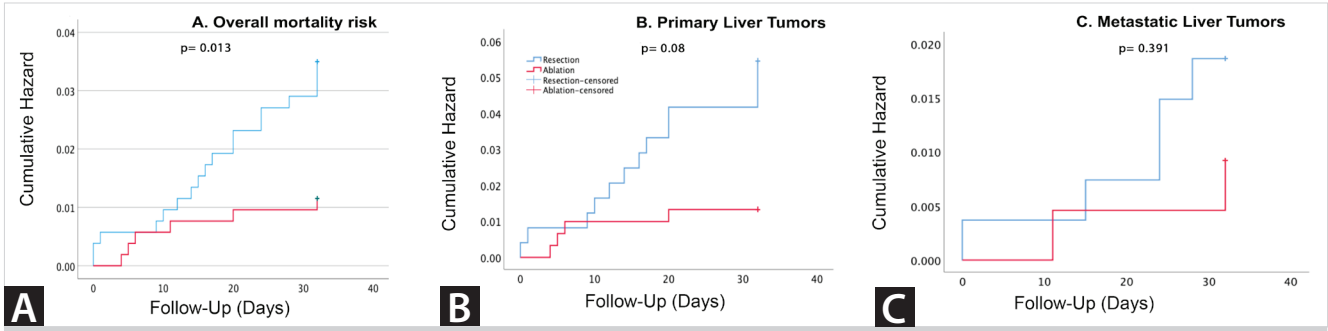

Figure 2. Kaplan-Meier analysis for 30-day mortality of the patients comparing liver ablation and surgical resection. The upper panel **(A)** shows the hazard risk of all patients. The middle panel **(B)** demonstrates the hazard risk between the two treatment groups in the subgroup of patients with primary liver tumors. In contrast, the lower panel **(C)** shows the risk in the subgroup of patients with secondary metastatic tumors of the liver.

There was no difference in sex or age between patients who underwent ablation or resection. However, patients who ultimately had a liver ablation had a higher BMI and a higher number of comorbidities. Preoperative laboratory data for liver enzymes, bilirubin, sodium, and INR portrayed a worse underlying liver function for ablation patients than for resection patients. Despite more comorbidities, obesity, and worse underlying liver function, liver ablation patients had fewer postoperative complications and death rates within 30 days than patients undergoing resection. While ablation patients had lower platelet counts and higher INR, they were less likely to bleed postoperatively than patients treated with resection.

Dedinska and colleagues have demonstrated an improved five-year survival for patients below 65 years of age undergoing liver resection (4). They attribute this difference mainly to the higher prevalence of benign tumors although the scant presence of age-related changes in physiology may have also been a factor. In multivariate analysis, however, they did not find malignancy as a significant risk factor for adverse outcomes. Interestingly, a subset of patients underwent radiofrequency ablation, and their data demonstrated that geriatric patients with ablation had the worst survival.

A single-institution study has compared younger versus older patients undergoing liver resections. There were no differences in severe complications or length of stay, but elderly patients were more likely to be discharged to a rehab facility (11). Another study has looked at age as a risk factor for complications for all abdominal operations for a site-wide database. They have found an increase in postoperative complications and 90-day morbidity in patients of advanced age (2).

Prior studies have compared outcomes following ablation versus resection, but they do not seem limited to elderly patients. A well-conducted meta-analysis has demonstrated that patients with early-stage HCC undergoing liver resection had significantly better long-term disease-free and overall survival (12). These patients likely represent a different patient population from ours, given that they analyzed early-stage HCC. Like our study, they demonstrate that underlying liver disease significantly predicts postoperative outcomes. Another recent meta-analysis has shown no difference in overall survival but lower recurrence-free survival in patients with liver ablation (13). However, patients in this study ranged in mean/median age from 47-71 years. Most were included with preserved liver function (Childs-Pugh class A or B) and single tumors up to 5 cm. The patient population was predominantly Asian. Only one of the included studies was conducted in Europe and non in North America. Post-treatment complications were significantly lower, and the length of stay was significantly shorter in the ablation group. Minimally invasive resection and ablation were compared in a small subset of patients for survival and complications showing similar overall survival and fewer complications in the ablation group. Another report has compared ablations and resections in patients with colorectal metastasis. This study has shown that T4 status, lymph node positivity, and tumor diameter greater than 3 cm portended poorer disease-free survival in the ablation group (14).

There are several limitations to our study. Although these data are derived from the NSQIP database, providing excellent power, there are significant limitations associated with the NSQIP database itself. We cannot separate minimally invasive and open surgeries, and it is possible that more ablations were done laparoscopically than resections, especially in patients with underlying liver disease. Given that these liver resections and ablations were performed for malignant tumors, data on oncologically important variables (clinical stage, margins recurrence-free survival, etc.) would strengthen our findings. We could not examine local recurrence rates, believed to be higher in ablation patients. However, local recurrences have not been demonstrated to translate into worse overall survival in ablation patients but into worse recurrence-free survival more subsequent interventions. We are limited to 30-day mortality and cannot report on long-term survival.

Additionally, there was a fundamental difference between the treatment groups, which could not be adjusted even with PSM. Due to the retrospective nature of this study, group allocation was based on the patient's physical condition and the risk of a given procedure at the time of treatment. Any further attempt to expand the PSM to include the laboratory values results in no matched patients between the two groups. Although patients were even more fragile in group A than in group R, the survival benefit and lower risk postoperative complication compel the choice of tumor ablation in treating liver lesions <5 cm in diameter in severely ill patients.

CONCLUSION

Patients undergoing liver ablation had more comorbidities, worse underlying liver function and lower in-hospital mortality. For primary liver malignancies, resection had a significantly worse 30-day survival. Underlying liver disease is an essential determinant of postoperative complications, and special consideration should be given to liver function when choosing between surgical treatment modalities for elderly patients.

Ethics Committee Approval: The research utilized a retrospective cohort study design, drawing data from the American College of Surgeons National Surgical Quality Improvement Program, which is open to the public and the participating institutions. The study uses unidentified information and it was exempted from Institutional Review Board regulation.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - CG, NN; Design - CR, NN; Supervision - , CG, SS; Fundings - SS, NN; Data Collection and/or Processing - GS, NN; Analysis and/or Interpretation - CR, CG, NN; Writing Manuscript - CR, CG, NN; Critical Reviews - CG, SS, NN.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 47-53

Geriyatrik hastalarda ablasyon ile karaciğer rezeksiyonunun karşılaştırması - yöntemlerden biri hastane içi mortaliteyi iyileştirir mi?

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı karaciğer malignitelerinin tedavisinde 65 yaş ve üzeri hastalarda cerrahi rezeksiyon ile ablasyonu karşılaştırmaktı.

Gereç ve Yöntem: Karaciğer tümörlü vakalar NSQIP veri tabanından 65 yaş üstü hastalar olarak alındı. Eğilim skoru eşleştirmesinin ardından, karaciğer rezeksiyonu ve ablasyonu için 30 günlük morbidite ve mortalite için çok değişkenli Cox regresyonu kullanıldı.

Bulgular: Eğilim skoru eşleştirmesinin ardından, 1048 hasta komorbid durumlar için 1:1 eşleştirildi. Hastalar rezeksiyondan sonra üç gün daha uzun süre hastanede kaldı (p< 0,001). Ablasyon sonrasında mortalite daha düşüktü (p= 0,013). Bu fark primer karaciğer tümörü olan hastalarda daha belirgindi (p= 0,008). Grup A'da abdominal apse gelişme riski 10 kat, hastane ilişkili pnömoni (p= 0,001) ve yeniden entübasyon riski dört kat, transfüzyon gerektiren kanama riski 10 kat (p< 0,001) ve sepsis gelişme riski üç kat (p< 0,001) daha düşüktü.

Sonuç: Genel olarak daha hasta ve altta yatan karaciğer fonksiyonu daha kötü olan bir hasta popülasyonu olmasına rağmen ablatif teknikler karaciğerin primer malin tümörlerinin daha agresif rezeksiyonu ile karşılaştırıldığında daha düşük komplikasyon riski ile ilişkilendirilmiştir.

Anahtar Kelimeler: Karaciğer kanseri, rezeksiyon, ablasyon, komplikasyonlar

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ORIGINAL ARTICLE
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The role of C-reactive protein/albumin ratio and prognostic nutritional index in the diagnosis of complicated acute appendicitis

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ABSTRACT

Objective: C-reactive protein (CRP) levels increase and albumin levels decrease in patients with inflammation. CRP/albumin ratio (CAR) is a new inflammation-associated prognostic indicator. The prognostic nutritional index (PNI) was described as a simple and neutral indicator of adverse outcomes not only in chronic diseases but also in acute conditions. The aim of this study was to investigate the clinical significance of the CAR and PNI value in differentiating complicated acute appendicitis (AA).

Material and Methods: We retrospectively examined the medical records of 187 patients with AA. Patients were divided into two groups according to pathological results [non-complicated (n= 161) and complicated (n= 26)]. Demographic, clinical, laboratory, and pathological data were examined and compared between the groups. Logistic regression analyses were performed to determine the independent predictors for complicated AA.

Results: Median age of the study group was 32 (23-41) years, and most of the patients were males (n= 101, 54%). Patients in the complicated AA group were significantly older compared to the patients in the non-complicated AA group [38 (32-49.5) years vs. 30 (22-41) years, p= 0.002]. The complicated AA group had significantly higher CAR level compared to the non-complicated AA group (p= 0.001). The length of hospital stay was significantly longer in the complicated AA group compared to the non-complicated AA group [2.5 (2-4.25) days vs. 1 (1-2) days, p< 0.001]. Other variables (including PNI) did not significantly differ between the groups. In univariate logistic regression analysis, only age was found to be a significant variable (OR= 1.045, 95% CI= 1.016-10.74, p= 0.002), but in multiple variate logistic regression analysis, no variable was found to be significant in predicting complicated AA.

Conclusion: We concluded that CAR and PNI value are not independent predictors of complicated AA.

Keywords: Appendectomy, nutrition, lymphocyte, CAR, PNI

INTRODUCTION

Acute appendicitis (AA) is one of the most common causes of acute abdomen. The lifetime incidence of AA is about 7%, and the risk of being complicated with perforation is between 17% and 20% (1). It is extremely important to determine both AA and its complications. Delay in diagnosis can lead to negative outcomes and make the surgery more challenging. For patients with delayed diagnosis, readmission rate, postoperative complications, and the length of hospital stay increase (2).

Imaging methods, especially ultrasonography and computed tomography, are used in the diagnosis of AA and its complications. Since these require special equipment and an experienced radiologist, simpler diagnostic methods are needed (3). Preoperative diagnosis of AA can be made effectively and quickly with inexpensive laboratory tests plus clinical findings and physical examination (4).

However, specific biomarkers are needed to differentiate between complicated and non-complicated AA.

Prognostic nutritional index (PNI), is calculated by serum albumin level and peripheral leukocyte count (5). It is an independent adverse prognostic risk factor for critically ill patients, both in the short and long term (6). Also, it has been reported that the C-reactive protein (CRP)/albumin ratio (CAR) is useful in predicting the prognosis and mortality risk of patients with AA (7).

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In this study, we aimed to explore the correlations between complicated AA and CAR and PNI.

MATERIAL and METHODS

The local ethics committee approval was obtained for the study (2021/2097). Two hundred and thirty-two patients had undergone appendectomy in two years (January 2017-January 2019). We determined the inclusion criteria as follows; age> 18 years and primary diagnosis of AA.

Exclusion criteria were defined as elective appendectomy, normal pathological result, mucocele, mesenteric cyst, and appendectomies that were performed for another procedure (e.g. laparoscopic colon resection or gynecological surgery). Finally, one hundred and eighty-seven patients were included in the study. Age, sex, the length of the complaints (hour), laboratory data [white blood cell (WBC) (10^3/uL), mean platelet volume (MPV) (fL), platelet distribution width (PDW) (fL), platelet (Plt) count (10^3/uL), platelet/lymphocyte ratio (PLR), red cell distribution width (RDW) (fL), CAR, PNI, radiological data [appendix diameter (mm)], length of hospital stay (day), and pathological data were analyzed retrospectively.

We divided the study group into two subgroups according to the pathological results; the non-complicated AA group (n= 161) and the complicated AA group (n= 26). While detecting plastron, perforation, or gangrene in the pathology or operation was defined as complicated AA, detecting edema, suppuration, or inflammation was defined as non-complicated AA. Blood samples were obtained within one hour of admission. AA diagnosis was done and the decision to operate was made via patients' clinical condition, physical examination, laboratory tests, and imaging methods. For all patients, ultrasonography was performed while computed tomography was used selectively. PNI was calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3) (5). The appendix diameter was defined as the largest diameter measured on ultrasonography.

Written informed consent was obtained from the patients before surgery. All operations were performed laparoscopically.

Statistical Analysis

We used the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) for statistical analyses. The Shapiro-Wilk test was performed to determine the normality of the distribution of numerical variables. Numerical variables were defined as median (interquartile range) and were compared with the Mann-Whitney U test. Categorical variables were defined as frequency (percentage) and were analyzed by using the Chi-square tests. Univariate logistic regression analysis followed by multiple variate logistic regression analysis containing the variables which had a p< 0.1 in the univariate logistic regression analysis was performed to determine the independent predictors of complicated AA. The results were given as odds ratio (OR), 95% confidence interval (CI), and p values. A two-sided p-value of less than 0.05 was considered significant.

RESULTS

Table 1 shows the demographic, clinical, laboratory, and pathological data of the whole study group and subgroups. Median age of the study group was 32 (23-41) years, and most of the patients were males (n= 101, 54%). The patients in the complicated AA group were significantly older compared to the patients in the non- complicated AA group [38 (32-49.5) years vs. 30 (22-41) years, p= 0.002]. There was no significant difference between the groups in terms of sex, the length of symptoms, WBC count, MPV value, PDW value, Plt count, , PLR, RDW value, PNI, and preoperatively measured appendix diameter.

The complicated AA group had significantly higher CAR level compared to the non-complicated AA group (p= 0.001), and also we found prolonged hospital stay in the complicated AA group compared to the non-complicated AA group and this difference was statistically significant [2.5 (2-4.25) days vs. 1 (1-2) days, p< 0.001]. The most common pathology was AA (n= 134, 71.7%) followed by suppurative appendicitis (n= 27, 14.4%) in the whole study group. The most common pathology of complicated AA was perforated appendicitis (n= 23, 88.5%).

In Table 2, the results of univariate and multiple variate logistic regression analyses of predictors for complicated AA were given. In univariate logistic regression analysis only age was found to be a significant variable (OR= 1.045, 95% CI= 1.016-10.74, p= 0.002), but in multiple variate logistic regression analysis, no variable was found to be significant in predicting complicated AA.

DISCUSSION

In this study, although CAR was higher in the complicated AA group, we found that both CAR and PNI were not independent predictors of complicated AA. Besides, the other variables that were examined in the study were not able to predict complicated AA significantly.

Complicated AA accounts for 20-30% of all AA (1). Complicated AA causes an increase in postoperative complications and financial burden, delay in recovery, and longer stay in hospital. It is important to diagnose complicated AA early to prevent these undesirable situations (8).

Although many other diagnostic tools are available, the patient's clinical condition and physical examination are the cornerstones of diagnosing AA. In addition, laboratory tests are guiding in the diagnosis of AA (9). Previously serum bilirubin value, neutrophil-lymphocyte ratio, WBC value, CRP value, MPV value, RDW value, PLR value, and immature granulocytes were examined to predict

Table 1. Demographic. clinical. laboratory. and pathological data of the whole study group and subgroups

	Study Group (n= 187)	Non-complicated Acute Appendicitis Group (n= 161)	Complicated Acute Appendicitis Group (n= 26)	p
Sex (male)	101 (54)	85 (52.8)	16 (61.5)	0.407
Age (year)	32 (23-41)	30 (22-41)	38 (32-49.5)	**0.002**
Length of symptoms (hour)	24 (12-48)	24 (12-48)	24 (17-48)	0.363
WBC (10^3/uL)	12.6 (10.2-16)	12.5 (10.15-16)	12.95 (11.73-16.6)	0.606
MPV (fL)	10.2 (9.5-10.9)	10.2 (9.4-10.9)	10.5 (9.6-11.2)	0.226
PDW (fL)	12.3 (11.1-14.9)	12.3 (10.95-14.95)	12.25 (11.4-14.18)	0.900
Plt (10^3/uL)	241 (204-286)	248 (203-286)	240 (206.75-271.5)	0.711
PLR	122.07 (91.79-179.78)	118.75 (87.14-177.46)	134.16 (107.63-201.9)	0.168
RDW (fL)	12.9 (12.3-13.65)	12.8 (12.4-13.8)	12.95 (12.3-13.53)	0.932
CRP/albumin ratio	0.53 (0.11-1.57)	0.41 (0.09-1.22)	1.62 (0.42-3.54)	**0.001**
PNI	39.02 (37-42.01)	40.01 (37.01-42.01)	39.01 (34.76-40.26)	0.076
Appendix diameter on USG (mm)	9 (8-11)	9 (8-10)	9.5 (7.75-11)	0.805
Length of hospital stay (day)	2 (1-2)	1 (1-2)	2.5 (2-4.25)	**<0.001**
Pathology				**<0.001**
• Acute appendicitis	134 (71.7)	134 (83.2)	-	
• Suppurative appendicitis	27 (14.4)	27 (16.8)	-	
• Plastrone appendicitis	1 (0.5)	-	1 (3.8)	
• Perforated appendicitis	23 (12.3)	-	23 (88.5)	
• Gangrenous appendicitis	2 (1.1)	-	2 (7.7)	

Significant P values are given as bold.
WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, Plt: Platelets, PLR: Platelet/lymphocyte ratio, RDW: Red cell distribution width, CRP: C-reactive protein, PNI: Prognostic nutritional index, USG: Ultrasonography.

complicated AA (1,3,8,10-12). Haghi et al. have reported that MPV and RDW could be used to diagnose perforated AA (11). Liu et al. have concluded in their meta-analysis that PLR could be used to distinguish between perforated and non-perforated AA. In this study, no relationship was found between complicated AA and WBC value, MPV value, RDW value, and PLR value (13).

CRP is an acute-phase protein that increases with the severity of the inflammation (1). CAR is a highly sensitive indicator of the severity of the inflammation and of the progression of diseases (14). A higher CAR indicates a more serious inflammatory condition due to the positive correlation of CRP and negative correlation of albumin with inflammation (15). There are many studies about the relationship between CAR and poor prognosis (16,17). Additionally, İbrahim et al. have stated that the higher preoperative CAR is a significant predictor for prolonged length of hospital stay, longer duration of operation, and cause of postoperative fever (18). In our study, we found significantly higher CAR in the complicated AA group compared to the non-complicated AA group in intergroup comparisons. However, CAR was not found to be an independent predictor of complicated AA in logistic regression analyses. This may be due to the limited number of patients in the study. PNI is calculated by albumin level and lymphocyte count, which are often used in clinical practice. This index provides information about the nutritional and immunological status of patients (19). The clinical findings of AA occur due to visceral and parietal peritoneum sensitivity with increased inflammation. When inflammation increases, negative acute phase indicators, like serum albumin levels, decrease (20). PNI provides a prediction of adverse outcomes in acute diseases as well as chronic diseases (21). In their study about PNI in patients with aortic dissection, Keskin et al. (6) have found that the intensity of the inflammatory reaction was associated with the decrease in albumin level. As a result, they argued that the albumin level would be low in high risk patients. Unlike the results of that study, a relationship was not found between PNI value and complicated AA in our study.

This study has some limitations. The first is its retrospective design. The second is the limited number of included patients and the limited data. Third, no examination of the relationships between CRP value, CAR, and PNI value with prognosis and postoperative complications.

CONCLUSION

CAR and PNI value are not independent predictors of complicated AA.

Table 2. Univariate and multiple variate analyses of the predictors for complicated acute appendicitis

	Univariate Analysis				Multiple Variate Analysis			
		95% CI				95% CI		
	OR	Lower	Upper	p	OR	Lower	Upper	p
Sex (male)	1.431	0.612	3.342	0.408	-	-	-	-
Age (year)	1.045	1.016	1.074	**0.002**	1.028	0.986	1.072	0.192
Length of symptoms (hour)	1.014	0.998	1.029	0.081	1.013	0.997	1.029	0.111
WBC (10^3/uL)	1.031	0.935	1.137	0.537	-	-	-	-
MPV (fL)	1.203	0.857	1.687	0.285	-	-	-	-
PDW (fL)	0.977	0.826	1.155	0.787	-	-	-	-
Plt (10^3/uL)	0.997	0.991	1.003	0.386	-	-	-	-
PLR	1.001	0.998	1.005	0.514	-	-	-	-
RDW (fl)	0.976	0.842	1.132	0.749	-	-	-	-
CRP/albumin ratio	1.005	0.960	1.052	0.821	-	-	-	-
PNI	0.942	0.866	1.024	0.160	-	-	-	-
Appendix diameter on USG (mm)	0.984	0.898	1.077	0.719	-	-	-	-

Significant P values are given as bold.

OR: Odds ratio, CI: Confidence interval, WBC: White blood cell, MPV: Mean platelet volume, PDW: Platelet distribution width, Plt: Platelets, PLR: Platelet/lymphocyte ratio, RDW: Red cell distribution width, CRP: C-reactive protein, PNI: Prognostic nutritional index, USG: Ultrasonography.

Ethics Committee Approval: This study was approved İnönü University Health Sciences Non-invasive Clinical Research Ethics Committee (Decision date: 18.05.2021, No: 2021/2097).

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Author Contributions: Concept - AZ; Design - AZ, YMB; Supervision - KS; Data Collection and/or Processing - MZÖ; Analysis and/or Interpretation - YMB; Literature Search - AZ; Writing Manuscript - AZ, YMB, KS; Critical Reviews - KS, MZÖ.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 54-58

Komplike akut apandisit tanısında C-reaktif protein/albümin oranı ve prognostik beslenme endeksinin rolü

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ÖZET

Giriş ve Amaç: Enflamasyonu olan hastalarda C-reaktif protein (CRP) düzeyleri artarken albümin düzeyleri azalır. CRP/albümin oranı (CAR), enflamasyonla ilişkili yeni bir prognostik göstergedir. Prognostik beslenme endeksi (PNI), yalnızca kronik hastalıklarda değil aynı zamanda akut durumlarda da olumsuz sonuçların basit ve nötr bir göstergesi olarak tanımlanmıştır. Bu çalışmanın amacı komplike akut apandisiti ayırt etmede CAR ve PNI değerinin klinik önemini araştırmaktır.

Gereç ve Yöntem: 187 akut apandisit hastasının tıbbi kayıtları retrospektif olarak incelendi. Hastalar patoloji sonuçlarına göre komplike olmayan (n= 161) ve komplike olan (n= 26) olmak üzere iki gruba ayrıldı. Her iki grup arasında demografik ve klinik veriler, laboratuvar bulguları ve patoloji sonuçları karşılaştırıldı. Komplike akut apandisitin bağımsız belirleyicilerini belirlemek için lojistik regresyon analizleri yapıldı.

Bulgular: Çalışma grubunun ortanca yaşı 32 (23-41) yıl olup, hastaların çoğunluğu erkekti (n= 101, %54). Komplike akut apandisit grubundaki hastalar, komplike olmayan akut apandisit grubuna göre anlamlı derecede daha yaşlıydı [38 (32-49,5) yaş ve 30 (22-41) yaş, p= 0,002]. Komplike akut apandisit grubunun CAR düzeyi komplike olmayan akut apandisit grubuna göre anlamlı derecede yüksekti (p= 0,001). Hastanede kalış süresi komplike akut apandisit grubunda komplike olmayan akut apandisit grubuna göre anlamlı olarak daha uzundu [2,5 (2-4,25) güne karşı 1 (1-2) gün, p< 0,001]. Diğer değişkenler (PNI dahil) gruplar arasında anlamlı farklılık göstermedi. Tek değişkenli lojistik regresyon analizinde sadece komplike akut apandisit tanısında yaş anlamlı değişken olarak bulunurken (OR= 1,045, %95 CI= 1,016-10,74, p= 0,002), çok değişkenli lojistik regresyon analizinde ise anlamlı bir değişken bulunamadı.

Sonuç: CAR ve PNI değerinin komplike akut apandisitin bağımsız belirleyicileri olmadığı sonucuna vardık.

Anahtar Kelimeler: Apendektomi, beslenme, lenfosit, CAR, PNI

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ORIGINAL ARTICLE
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Colorectal cancer screening; colonoscopy and biopsy results in people undergoing colonoscopy due to positive fecal occult blood test

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ABSTRACT

Objective: Screening programs are important for the early detection of colorectal cancer, which is one of the causes of high morbidity and mortality. In this study, we investigated the colonoscopy results, the incidence of adenoma and cancer, and the relationship between test results and cancer in individuals with a positive fecal occult blood test for colorectal cancer screening.

Material and Methods: Within the scope of the colorectal cancer screening program, colonoscopy was requested for individuals aged 50-70 years who applied to our outpatient clinic with a positive fecal occult blood test. The results were collected and analyzed.

Results: The results of the colonoscopy could be obtained in only 237 (56.43%) of the 420 patients who were referred for a colonoscopy because of a positive fecal occult blood test. Colonoscopy results were normal in 15 (6.33%), benign anal disease in 64 (27%), benign colonic disease in 12 (5.06%) and polyp + adenocarcinoma in 146 (61.61%). Pathology results were benign polyp in 37 (15.61%), adenomatous polyp in 86 (36.29%) and adenocarcinoma in 23 (9.71%). Quantitative test results were higher in the adenomatous polyp + adenocarcinoma group and statistically significant (p= 0.03).

Conclusion: Individuals with positive fecal occult blood tests, especially those with high quantitative test results, should be encouraged to have a colonoscopy, and they should be warned about the high probability of adenomatous polyps and colorectal cancer.

Keywords: Colorectal cancer screening, fecal occult blood test, immunochemical test, colonoscopy

INTRODUCTION

Colorectal cancer (CRC) remains a major health problem worldwide due to its high incidence and high mortality rates. According to the Global Cancer Observatory, CRC is the 4th most common and 3rd most fatal cancer worldwide. CRCs develop slowly and are usually advanced when they become symptomatic. If these cancers can be diagnosed at an early stage, the chances of a cure can be high. Early diagnosis is only possible through screening programs. Screening increases the likelihood of detecting early-stage cancer or precancerous lesions. Studies have shown that colorectal cancer-related deaths are significantly reduced with screening programs (1,2).

A fecal occult blood test (FOBT) is one of the methods used for CRC screening. Despite its disadvantages such as being affected by medication and food intake and not being able to show the bleeding focus, it ranks first in screening programs since it is easily applicable and inexpensive. In this study, we aimed to investigate the colonoscopy results, the incidence of adenoma and cancer, and whether there is a correlation between FOBT results and cancer in patients with positive FOBT performed in primary health care centers and admitted to our hospital for colonoscopy.

MATERIAL and METHODS

This prospective study was designed for patients who applied to the General Surgery Outpatient Clinic of Ümraniye Training and Research Hospital, University of Health Sciences for colonoscopy due to positive FOBT performed in a primary health center between July 2019 and January 2023. The ethics committee of our institution approved the study (28.06.2019/12832). In line with the ethics principles of the Declaration of Helsinki, the identity and health information of the patients were protected by observing confidentiality and privacy.

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As part of the national CRC screening program, asymptomatic people aged 50-70 years were asked to undergo FOBT at primary health care centers. Initially, a quantitative test based on immunochemical immunoassay with numerical results was used as a screening test, and a result above 100 ng/ml was considered positive. Later, a qualitative test based on the rapid chromatographic immunoassay method was used, which gives positive/negative results. Patients with positive FOBT were referred to more advanced centers for colonoscopy. Patients who applied to our outpatient clinic, for this reason, were included in the study. Patients who underwent colonoscopy for colorectal or anal complaints, patients with inflammatory bowel disease, and/or gastrointestinal system tumors were excluded.

Colonoscopy was ordered for patients who applied to our outpatient clinic for colonoscopy due to positive FOBT. The results of colonoscopy performed in our institution were checked through the hospital information system and the results of colonoscopy performed in an external center were checked through the national database. Patients were recorded in an excel file.

Colonoscopy results were grouped as normal, benign anal disease (hemorrhoids, anal fissure, etc.), benign colonic disease (diverticulum, angiodysplasia, etc.), and polyp + adenocarcinoma. Pathology results in patients in the polyp and adenocarcinoma group who underwent biopsy were divided into subgroups as a benign polyp (hyperplastic polyp), low-grade tubular adenoma, high-grade tubular adenoma, low-grade tubulovillous adenoma, high-grade tubulovillous adenoma, low-grade villous adenoma, high-grade villous adenoma and adenocarcinoma. In the presence of more than one lesion or pathological result in the same patient, the more malignant one was considered to avoid confusion (Figure 1).

Demographic characteristics of the patients, colonoscopy results, pathology results in those who underwent biopsy due to polyps or masses, and whether there was a correlation between the results of FOBT and pathology results were investigated, and the data were analyzed.

Statistical Analysis

Statistical analyses were performed online using the GraphPad QuickCalcs program. Continuous variables were expressed as mean ± standard deviation (SD), and categorical data were expressed as count and percentage. The Fisher's exact, Chi-square, and student's t-test were used to analyze group comparisons. The difference was considered statistically significant if $p< 0.05$.

RESULTS

During the study period, colonoscopy was requested for 420 patients. However, the results were available in 237 (56.43%) patients, and these patients were included in the study. Of these 237 patients, 112 (47.26%) were females and 125 (52.74%) were males with a mean age of 59.69 years.

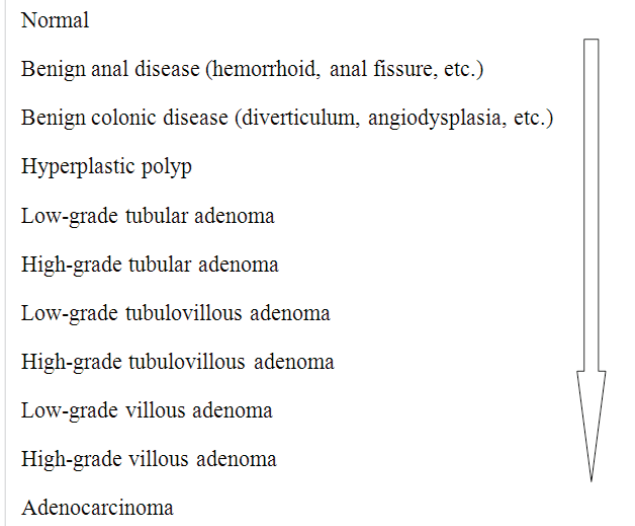

Figure 1. Ranking of lesions detected in colonoscopy and pathology from benign to more malignant.

Of the 237 patients with available colonoscopy, colonoscopy results were reported as normal in 15 (6.33%), benign anal disease in 64 (27%), benign colonic disease in 12 (5.06%) and polyp + adenocarcinoma in 146 (61.61%) (Table 1).

The pathology results of the biopsied polyp and adenocarcinoma group were as follows: 37 (25.34%) benign polyp, 64 (43.84%) low-grade tubular adenoma, 6 (4.11%) high-grade tubular adenoma, 3 (2.06%) low-grade tubulovillous adenoma, 13 (8.90%) high-grade tubulovillous adenoma and 23 (15.75%) adenocarcinoma (Table 1). The rates of these lesions in the total study population were 15.61%, 27%, 2.53%, 1.27%, 5.49%, and 9.71%, respectively.

There were 73 patients who underwent quantitative immunochemical testing and colonoscopy. In the subgroup analysis of this group of patients, there was no statistically significant difference in terms of gender ($p= 0.64$). There was no statistically significant difference between polyp + adenocarcinoma and normal + benign anal and colonic disease ($p= 0.13$). There was no statistically significant difference between hyperplastic polyp and adenomatous polyp + adenocarcinoma ($p= 0.22$). There was no statistically significant difference between adenomatous polyp and adenocarcinoma ($p= 0.38$). The FOBT result was higher in patients with adenocarcinoma, and the difference was statistically significant ($p= 0.04$). In the adenomatous polyp+adenocarcinoma group, the FOBT results were higher and the difference was statistically significant ($p= 0.03$) compared to the other benign disease group, including hyperplastic polyp (Table 2).

Table 1. Demographic characteristics, colonoscopy, and pathology results of the study population

	Total (n= 237)		Quantitative (n= 73)		Qualitative (n= 164)	
	n	**%**	**n**	**%**	**n**	**%**
Sex						
Female	112	47.26	22	30.14	90	54.88
Male	125	52.74	51	69.86	74	45.12
Colonoscopy Result						
Normal	15	6.33	2	2.74	13	7.93
Benign anal disease	64	27	22	30.14	42	25.61
Benign colonic disease	12	5.06	4	5.48	8	4.88
Polyp + Adenocarcinoma	146	61.61	45	61.64	101	61.58
Pathology Result						
Hyperplastic polyp	37	25.34	10	22.22	27	26.73
Low-grade tubular adenoma	64	43.84	17	37.78	47	46.54
High-grade tubular adenoma	6	4.11	1	2.22	5	4.95
Low-grade tubulovillous adenoma	3	2.06	1	2.22	2	1.98
High-grade tubulovillous adenoma	13	8.90	5	11.11	8	7.92
Low-grade villous adenoma	-	-	-	-	-	-
High-grade villous adenoma	-	-	-	-	-	-
Adenocarcinoma	23	15.75	11	24.45	12	11.88

Table 2. Association of colonoscopy and pathology results with quantitative test results

	Quantitative ICT (Mean ± SD)	**p**
Sex		
Female	3849.73 ± 8896.23	0.64
Male	2817.27 ± 8538.13	
Normal + Benign anal and colonic disease	1207.21 ± 3225.85	0.13
Polyp + Adenocarcinoma	4323.84 ± 10525.67	
HP	684.40 ± 1223.18	0.22
AP + Adenocarcinoma	5363.69 ± 11746.06	
AP	4158.58 ± 11893.64	0.38
Adenocarcinoma	7993.00 ± 11517.50	
Normal + Benign anal and colonic disease + HP	1069.63 ± 2830.55	0.03
AP + Adenocarcinoma	5363.69 ± 11746.06	
Normal + Benign anal and colonic disease + HP +AP	2265.35 ± 7778.01	0.04
Adenocarcinoma	7993.00 ± 11517.50	

ICT: Immunochemical test, SD: Standart deviation, HP: Hyperplastic polyp, AP: Adenomatous polyp.

DISCUSSION

Colorectal cancers are common cancers worldwide and cause increased morbidity and mortality in the late stage. They grow slowly and are often advanced when they become symptomatic. They usually occur in old age and the majority develop from an adenoma. It takes approximately 8-10 years to develop cancer from an adenoma. Therefore, if it is detected in the pre-malignant stage and diagnosed early, it is a treatable disease. Early diagnosis will reduce morbidity and mortality as well as treatment costs (3-5).

Screening programs are important to detect early-stage colorectal cancer in the asymptomatic period. Different methods such as fecal occult blood test, fecal DNA test,

sigmoidoscopy, colonoscopy, double contrast barium enema, CT colonography, and capsule endoscopy are used for screening. Countries that screen for colorectal cancer use one of these methods as the primary screening test to the extent of their means. In our country, as in most countries, individuals between the ages of 50 and 70 are screened by performing a colonoscopy every 10 years and a FOBT every two years. Although colonoscopy is superior to other tests because it allows direct detection of the lesion and biopsy, it is an invasive method. Despite its disadvantages such as not being able to distinguish between upper and lower gastrointestinal bleeding and being affected by many factors in the diet, FOBT is used in the first place in screening programs in many countries because it is easily applicable and cost-effective (1,6-8).

Guaiac and immunochemical methods are used for the detection of fecal occult blood. Since the guaiac method is a test based on determining the peroxidase-like activity of the heme group, it is affected by all molecules and foods with peroxidase activity. Therefore, foods with peroxidase activity such as turnips, radishes, cabbage, cauliflower, broccoli, apples, bananas, red meat, and iron therapy should be stopped a few days before the test is performed. The immunochemical test is more specific than the guaiac test since it screens only human hemoglobin (9-13). Although it is more expensive, it reduces the need for unnecessary colonoscopies because it has a lower false positive rate and is therefore cost-effective. These tests are divided into two as quantitative and qualitative. The quantitative immunochemical test measures the hemoglobin concentration in the stool sample with an automatic device and gives a numerical value. In qualitative immunochemical testing, the results are based on visual inspection. If hemoglobin is present in the stool, a colored band appears on the test strip. The positivity rate of the qualitative immunochemical test is higher, but the quantitative immunochemical test is superior in detecting cancer (14-16). Although there was no statistically significant difference in this study, adenocarcinoma was detected in 15.07% of patients with positive quantitative test results and in 7.32% of patients with positive qualitative test results (p= 0.09).

In studies, different cut-off values ranging from 25-200 have been used for quantitative immunochemical testing, and sensitivity and specificity have been found to be 25%-100% and 20%-97%, respectively (17-19). In a meta-analysis by Meklin et al. pooled sensitivity and specificity have been calculated as 86% and 85%, respectively (6). When the cut-off value is low, the rate of unnecessary colonoscopy increases, whereas when it is high, the risk of failing to detect malignancy arises. While the high cut-off values are used in populations with limited opportunities to perform a colonoscopy, the lower cut-off values are used in populations with adequate opportunities. In our study, we accepted the cut-off value for FOBT positivity as 100 ng/mL and requested colonoscopy in the next step for individuals with a result above this. The quantitative test result was statistically significantly higher in patients with adenomatous polyps and adenocarcinoma compared to the others (p= 0.03).

It is observed that the rate of colonoscopy is low in patients who were asked to undergo colonoscopy due to positive FOBT (19-21). In a study conducted by Mayir et al. 42.3% of patients who were requested a colonoscopy because of positive FOBT had a colonoscopy and a malignant polyp was found in one patient (0.8%) (22). In a screening study conducted by Nakazato et al. which included FOBT and colonoscopy, the rate of colonoscopy was 20.36% and cancer was found in 15 (1.79%) of 840 patients with positive FOBT (7). In our study, the rate of colonoscopy was 56.3%, adenomatous polyps were found in 36.29% of them, and adenocarcinoma in 9.71%.

Limitations of the Manuscript

The number of individuals screened for colorectal cancer with FOBT and therefore, the positive rate of the test is unknown. The study was not comprehensive and included only individuals who applied to our outpatient clinic for colonoscopy. Therefore, the number of patients included in the study was low. The immunochemical tests used in the study were not the same in all patients, some were quantitative and some were qualitative. Since colonoscopy was performed in different centers rather than in a single center, it may have caused different evaluations due to the person performing it.

CONCLUSION

Early diagnosis and treatment of colorectal cancer, one of the major causes of morbidity and mortality, is an important issue. Early diagnosis is only possible with screening programs. Although colonoscopy is the gold standard today, it is not always possible to perform it widely. FOBT is one of the leading screening programs and reduces the need for colonoscopy because it is easy to perform and inexpensive. However, it is observed that the rate of colonoscopy in patients with positive FOBT is low. Here, primary healthcare providers and physicians who order colonoscopies have an important responsibility. Individuals with positive FOBT, especially those with high quantitative test results, should be encouraged to undergo a colonoscopy and should be warned about the high probability of colorectal cancer.

Ethics Committee Approval: This study was approved by Ümraniye Training and Research Hospital Clinical Research Ethics Committee (Date: 28.06.2019, Decision no: 12832).

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Kolorektal kanser taraması; gaitada pozitif gizli kan testi nedeniyle kolonoskopi yapılan kişilerde kolonoskopi ve biyopsi sonuçları

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ÖZET

Giriş ve Amaç: Yüksek morbidite ve mortalite nedenlerinden biri olan kolorektal kanserlerin erken dönemde tespit edilebilmesi için tarama programları önemlidir. Bu çalışmada, kolorektal kanser taraması için yapılan gaitada gizli kan testi pozitif olan bireylerin kolonoskopi sonuçları, adenom ve kanser ensidansı, test sonuçları ile kanser arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Kolorektal kanser tarama programı kapsamında dışkıda gizli kan testi pozitif çıkan ve polikliniğimize başvuran 50-70 yaş arası bireylere kolonoskopi yapılması istendi. Sonuçlar toplandı ve analiz edildi.

Bulgular: Gaitada gizli kan testi pozitifliği nedeniyle kolonoskopi için yönlendirilen 420 hastanın sadece 237'sinde (%56,43) kolonoskopi sonucu elde edilebildi. Kolonoskopi sonucu 15 (%6,33) hastada normal, 64 (%27) hastada benign anal hastalık, 12 (%5,06) hastada benign kolonik hastalık ve 146 (%61,61) hastada polip + adenokarsinom şeklindeydi. Patoloji sonuçları 37'sinde (%15,61) benign polip, 86'sında (%36,29) adenomatöz polip ve 23'ünde (%9,71) adenokarsinom şeklindeydi. Kantitatif test sonuçları adenomatöz polip + adenokarsinom grubunda daha yüksekti ve istatistiksel olarak anlamlıydı (p= 0.03).

Sonuç: Gaitada gizli kan testi pozitif olan bireyler, özellikle de kantitatif test sonuçları yüksek olanlar, kolonoskopi yaptırmaya teşvik edilmeli ve adenomatöz polip ve kolorektal kanser olasılığının yüksek olduğu konusunda uyarılmalıdır.

Anahtar Kelimeler: Kolorektal kanser taraması, gaitada gizli kan testi, immünokimyasal test, kolonoskopi

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A prospective case-control study of disability, quality of life, and functional impairment of shoulder movements after latissimus dorsi myocutaneous flap reconstruction in breast cancer patients

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ABSTRACT

Objective: Dysfunction of shoulder movements could be a limiting factor to the use of Latissimus dorsi (LD) flap. This study aimed to assess the impact of LD flap reconstruction on shoulder dysfunction and the quality of life.

Material and Methods: This study comprised 28 early breast cancer cases who underwent breast conserving surgery (BCS) with LD flap and 40 controls. Subjective and objective assessments were done a year later.

Results: Mild and moderate disability were found in 85.71% and 14.3% cases vs. 100% and 0% controls (p= 0.316) respectively. Physical and emotional functioning were 84.29 ± 5.61 and 66.67 ± 6.05 in cases vs. 86.67 ± 8.38 and 70.0 ± 6.84 in controls (p= 0.36, 0.23) respectively. Pain score in cases was 23.8 ± 15.6 vs. 12.17 ± 8.4 in controls (p= 0.018). LD muscle strength in extension was 4.39 ± 0.35 in cases vs. 4.88 ± 0.22 in controls (p< 0.001), 4.43 ± 0.18 for adduction in cases vs. 4.65 ± 0.24 in controls (p= 0.006). ROM of shoulder in flexion was 151.61 ± 4.86° in cases and 153.88 ± 2.36° in controls (p= 0.08), 40.36 ± 3.52° in cases vs. 49.13 ± 1.86° in controls for extension (p< 0.001), in abduction it was 150.54 ± 3.69° in cases vs. 150.00 ± 0.00° in controls (p= 0.518), in adduction was 30.89 ± 4.0° in cases vs. 38.13 ± 1.11° in controls (p< 0.001), in external rotation was 73.57 ± 3.63° in cases vs. 77.63 ± 2.36° in controls (p< 0.001), and internal rotation was 69.46 ± 3.56° in cases vs. 79.00 ± 1.26° in controls (p< 0.001).

Conclusion: We conclude that functional impairment should not be a determining factor for LD flap in breast reconstruction surgery.

Keywords: Latissimus dorsi, flap reconstruction, quality of life, shoulder dysfunction, breast conserving surgery

INTRODUCTION

A wide range of options are available for breast reconstruction after breast conserving surgery (BCS) and may include autogenous flaps like transversus rectus abdominis flap, latissimus dorsi (LD) flap, gluteal and thoraco-epigastric flap or alloplastic reconstructions including implants and combination procedures. LD flap is the most used and most versatile flap which can withstand radiation, can be mobilized to fill any quadrant of the breast and the technique is relatively easy to learn (1).

The LD muscle is primarily used in extension, adduction, and internal rotation. Routine activities like pulling a door, walking upstairs, getting up from sitting position with the help of arms are dependent on LD (2). The use of LD flap may impair the above-mentioned shoulder functions, which could be a limitation of its use in reconstruction surgery.

In this study, we evaluated the functional impairment after LD flap breast reconstruction on patient's shoulder movements and QOL using the disabilities of the arm, shoulder and hand (DASH) questionnaire and The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaire and assessed the range of motion of the shoulder and muscle strength as part of the objective assessment.

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MATERIAL and METHODS

This prospective case-control study was conducted in a tertiary care centre in India from September 2019 to August 2020. The study population consisted of 68 patients with early breast cancer (Stage I-IIIa) who underwent primary surgery. Twenty-eight patients who underwent BCS + LD flap reconstruction was enrolled as cases and 40 controls underwent BCS or modified radical mastectomy (MRM) without flap reconstruction. All patients in our study had undergone axillary dissection during the respective surgeries. Also, all patients went through a course of radiotherapy and chemotherapy post-surgery. Patients who received neoadjuvant chemotherapy with metastatic disease or pre-existing shoulder deformities were excluded.

Postoperatively, all patients (cases and controls) were advised arm strengthening by exercise and shoulder physiotherapy. The exercise schedule was set as follows, by the physical medicine and rehabilitation physician, as per institutional protocols:

Days 1-7 (immediately post-surgery): Deep breathing, pump it ups, shoulder shrugs and circles, shoulder blade squeeze, and arm lifts.

After drain removal till six weeks post-surgery: Wand exercises, winging, wall climbing, side bends, and snow angels.

After six weeks post-surgery (advance exercises): Strengthening exercises with light weights (500 g to 1 kg) and regular aerobic exercises.

A re-evaluation of cases and controls was done one year after the surgery.

QOL and subjective domains were assessed using DASH and the EORTC QOL-C30 questionnaire. The bilateral shoulders' range of motion (ROM) were assessed in six primary movements of LD viz. flexion, extension, abduction, adduction, external and internal rotation, which was done by physical medicine and rehabilitation specialists using goniometry and the Oxford scale.

The DASH questionnaire has been developed by the American Academy of Orthopaedic Surgeons in collaboration with other organisations (3). It includes thirty items to grade the functional impairment of upper limbs of patients. The first 21 items evaluate the patient's ability to perform certain activities, which come into use in daily living, in the preceding week. The next five items evaluate symptoms like pain, numbness and weakness, whereas the last four items evaluate the effect of pain and weakness on the patient's social activity. Dominance of the upper limb or the side affected in surgery does not alter the DASH score, because the upper limb works as a unit and the DASH is a functional measure of that working unit. It has been validated in multiple studies (4). Scoring of each question ranges from 1 to 5, where one represents no disability and five represents inability to perform the activity. The score is calculated by utilizing the DASH formula. Score of zero represents no functional impairment while a score of 100 represents very severe impairment.

DASH score is calculated using the following equation:

$$\text{DASH disability score} = \left[\frac{(\text{sum of n responses})}{\text{n}} - 1\right] \times 25$$

(Where, n= number of completed response)

These scores were then categorized into groups as:

- 0%- No disability
- 0-20%- Minimal disability
- 21-40%- Mild disability
- 41-60%- Moderate disability
- 61-80%- Severe disability
- 81-100%-Very severe disability

The EORTC (European Organization for Research and Treatment of Cancer) questionnaire is an organized and validated system for evaluating the health-related Quality of Life (QoL) of cancer patients (5). The EORTC QOL-C30 is composed of nine multi-item scales, which include five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea or vomiting), a global Quality of Life (QoL) scale and six single-item measures. Every multi-item scale includes a different set of items, and no item occurs in more than one scale. All scales and single-item measures range in score from 0-100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high QoL. But a high score for a symptom scale or item represents a high level of symptomatology. Estimating the average of the items that contribute to the scale, will give us the raw score. Linear transformation is used to standardise the raw score, so that scores range from 0 to 100. A higher score represents a higher level of functioning or a higher level of symptoms.

The range of motion (ROM) of the shoulder joint was evaluated by goniometry with no passive support given to the arm. The endpoint of assessment of each shoulder movement was the point where pain or soft tissue tightness started and the patient was unable to move her shoulder. All these ROMs were compared with the normal reference ranges (as per the American Academy of Orthopedic Surgeons) (6).

Bilateral LD muscle strength at the shoulder joint was measured using the Oxford scale for all patients by evaluating extension and adduction (7). These movements involve grading the muscle strength at the shoulder joint, and the point where

compensatory movement of shoulder and/ or trunk occurred was considered as the endpoint.

Statistical Analysis

Data analysis was done using MS Excel (Microsoft Corporation, Seattle, WA) and SPSS v22 (IBM, USinc). Simple descriptive analysis was performed to express the data in terms of percentage and mean ± standard deviation. The groups (cases and controls) were compared using the unpaired t test (for parametric variables), and a p-value of <0.05 was considered significant.

All procedures were followed according to the ethical standards of human experimentation and the Helsinki declaration (rev. 2013). Ethics approval was obtained from the Institutional Ethics Committee.

RESULTS

In our study, mean age of the cases was 43.86 ± 7.82 years (range= 35-53 years), whereas that of the control was 47.85 ± 8.56 years (range= 35-64 years) (p= 0.176). Both cases and controls were matched for the stage of the disease, with stage II being the most common stage at presentation in both groups [26 cases (92.8%) vs. 26 controls (65%) (p= 0.23)] (Table 1).

On DASH scoring, the disability experienced by the cases and the controls was found to be comparable (p= 0.32). In cases, the disability scores varied from mild (85.71%) to moderate (14.79%) while all patients in the control group had mild disability scores. Absence of disability, minimal, severe or very severe disability score was not found in either of the groups (Table 2).

Table 1. TNM distribution (AJCC-7) of patients in case and control groups

		Case		Control		
Stage	**Grading**	**n**	**%**	**n**	**%**	**p-value**
0	TisN0M0	0	0.00	0	0.00	
IA	T1NOM0	0	0.00	2	5.00	0.380
IB	T0N1miM0	0	0.00	0	0.00	-
	T1N1miM0	0	0.00	0	0.00	
IIA	T0N1M0	0	0.00	2	5.00	0.380
	T1N1M0	0	0.00	2	5.00	0.380
	T2N0M0	6	20.00	10	25.00	0.727
IIB	T2N1M0	18	60.00	14	35.00	0.26
	T3N0M0	2	6.67	0	0.00	0.380
IIIA	T0N2M0	0	0.00	2	5.00	0.380
	T1N2M0	0	0.00	2	5.00	0.380
	T2N2M0	0	0.00	2	5.00	0.380
	T3N1M0	2	6.67	2	5.00	0.834
	T3N2M0	0	0.00	2	5.00	0.834
IIIB	T4NOM0	0	0.00	0	0.00	-
	T4N1M0	0	0.00	0	0.00	-
	T4N2M0	0	0.00	0	0.00	-

Table 2. Comparison of DASH score in the patients (cases vs control)

	Cases n= 14		Control n= 20		
Disability	**n**	**%**	**n**	**%**	**p-value**
No (0%)	0	0.00%	0	0.00%	0.316
Minimal (1-20%)	0	0.00%	0	0.00%	
Mild (21-40%	24	85.71%	40	100.00%	
Moderate (41-60%)	4	14.29%	0	0.00%	
Severe (61-80%)	0	0.00%	0	0.00%	
Very severe (81-100%)	0	0.00%	0	0.00%	

Using EORTC QLQ-C30, the mean global health score was 73.21 ± 9.90 in cases vs. 75.83 ± 10.4 in controls (p= 0.316).

Amongst various parameters of the functional domain, no role function showed a measurable difference between the two groups. Mean physical functioning/QoL was 84.29 ± 5.61 in cases vs. 86.67 ± 8.38 in control (p= 0.36). Mean role functioning/QoL in cases was 79.76 ± 14.88 and 86.67 ± 11.6 in controls (p= 0.14). Mean emotional functioning/QoL in cases was 66.67 ± 6.05 vs. 70.0 ± 6.84 in control (p= 0.24). Mean cognitive functioning/QoL in cases was 100.0 ± 0.0 and in control was 96.67 ± 6.84 (p= 0.08). Mean social functioning in cases was 68.38 ± 6.05 vs. 70.17 ± 7.40 in controls (p= 0.31) (Table 3).

On assessment of symptomatology, the patients in the case group experienced worse pain (23.81 ± 15.63) vs. 12.17 ± 8.4 in controls (p= 0.018) and other symptoms like fatigue scored greater in control group (cases 29.4 ± 9.4 vs. controls 33.3 ± 0.0; p= 0.06), whereas insomnia scores (cases 23.8 ± 15.6 vs. controls 28.3 ± 4.7; p=0.22) and dyspnoea assessment scores (cases 9.5 ± 5.6 vs. controls 8.3 ± 14.8; p= 0.82) were comparable in both the groups. GI symptoms like constipation (case 26.2 ± 14.2 vs. controls 16.7 ± 17.1; p= 0.097) and vomiting (case 1.2 ± 4.5 vs. controls 5.0 ± 9.5; p= 0.17), appetite loss (case 7.1 ± 14.2 vs. control 8.3 ± 14.9; p= 0.81), diarrhoea (case 4.8 ± 12.1 vs. control 10.0 ± 15.7; p= 0.30). Financial difficulties (case 64.3 ± 15.9 vs. control 66.7 ± 0.00; p= 0.5) were comparable in both the groups (Table 4).

An objective assessment of muscle strength was done in primary movements like extension and adduction by using the Oxford scale. Mean muscle strength in extension movement in cases was 4.39 ± 0.35 and in controls was 4.88 ± 0.22 (p< 0.001), and in case of adduction, it was 4.43 ± 0.18 in cases and 4.65 ± 0.24 in controls (p= 0.006) (Table 5).

The range of motion (ROM) of the shoulder joint was compared in each movement. Mean ROM in flexion was 151.61 ± 4.86° in cases and 153.88 ± 2.36° in controls (p= 0.080); in extension it was 40.36 ± 3.52° in cases and 49.13 ± 1.86° in controls (p< 0.001); in abduction it was 150.54 ± 3.69° in cases and 150.00 ± 0.00° in controls (p= 0.518); in adduction it was 30.89 ± 4.00° in cases and 38.13 ± 1.11° in controls (p< 0.001); in external rotation it was 73.57 ± 3.63° in cases and 77.63 ± 2.36° in controls (p< 0.001); and in internal rotation it was 69.46 ± 3.56° in cases and 79.00 ± 1.26° in controls (p< 0.001). Flexion and abduction were two movements that remained equally restricted among the groups. The cases experienced greater restrictions in extension, adduction, external and internal rotation (Table 6).

Table 3. Comparison of functional score in the patients (cases vs control)

	Cases	Controls	
	Mean ± SD	**Mean ± SD**	**p-value**
Physical functioning	84.29 ± 5.61	86.67 ± 8.38	0.361
Role functioning	79.76 ± 14.88	86.67 ± 11.6	0.138
Emotional functioning	66.67 ± 6.05	70.00 ± 6.84	0.235
Cognitive functioning	100.00 ± 0.0	96.67 ± 6.84	0.079
Social functioning	68.38 ± 6.0	70.17 ± 7.4	0.309

Table 4. Comparisons of symptom score/items in the patients (cases vs control)

	Cases	Control	
	Mean ± SD	**Mean ± SD**	**p-value**
Fatigue	29.37 ± 9.35	33.33 ± 0.00	0.065
Nausea and vomiting	1.19 ± 4.45	5.00 ± 9.52	0.174
Pain	23.81 ± 15.63	12.17 ± 8.4	0.018
Dyspnoea	9.52 ± 15.63	8.33 ± 14.81	0.823
Insomnia	23.81 ± 15.63	28.33 ± 4.67	0.229
Appetite loss	7.14 ± 14.19	8.33 ± 14.81	0.816
Constipation	26.19 ± 14.19	16.67 ± 17.10	0.097
Diarrhea	4.76 ± 12.10	10.00 ± 15.67	0.302
Financial difficulties	64.29 ± 15.82	66.67 ± 0.00	0.502

Table 5. Comparisons of latissimus dorsi muscle strength in terms of its primary motion (cases and control)

	Cases	Control	
	Mean ± SD	**Mean ± SD**	**p-value**
Overall			
Extension	4.39 ± 0.35	4.88 ± 0.22	<0.001
Adduction	4.43 ± 0.18	4.65 ± 0.24	0.006
Right Latissimus dorsi			
Extension	4.21 ± 0.80	4.80 ± 0.41	0.009
Adduction	4.21 ± 0.58	4.65 ± 0.49	0.024
Left Latissimus dorsi			
Extension	4.57 ± 0.76	4.95 ± 0.22	0.042
Adduction	4.64 ± 0.63	4.65 ± 0.49	0.971

Table 6. Comparison of range of motion of the shoulder joint in the patients (cases vs controls)

	Cases	Control	
	Mean ± SD	**Mean ± SD**	**p-value**
Overall			
Flexion	151.61 ± 4.86°	153.88 ± 2.36°	0.080
Extension	40.36 ± 3.52°	49.13 ± 1.86°	<0.001
Abduction	150.54 ± 3.69°	150.00 ± 0.00°	0.518
Adduction	30.89 ± 4.00°	38.13 ± 1.11°	<0.001
External rotation	73.57 ± 3.63°	77.63 ± 2.36°	<0.001
Internal rotation	69.46 ± 3.56°	79.00 ± 1.26°	<0.001
Right Shoulder Joint			
Flexion	150.36 ± 4.58°	152.25 ± 4.13°	0.218
Extension	37.86 ± 3.78°	49.75 ± 1.12°	<0.001
Abduction	150.71 ± 5.50°	150.00 ± 0.00°	0.563
Adduction	28.21 ± 2.49°	37.50 ± 2.56°	<0.001
External rotation	75.36 ± 5.35°	76.50 ± 3.66°	0.465
Internal rotation	68.21 ± 4.64°	79.25 ± 1.83°	<0.001
Left Shoulder Joint			
Flexion	152.86 ± 6.42°	155.50 ± 5.10°	0.191
Extension	42.86 ± 7.26°	48.50 ± 3.28°	0.004
Abduction	150.04 ± 3.08°	150.00 ± 0.00°	0.605
Adduction	33.57 ± 7.70°	38.75 ± 2.22°	0.007
External rotation	71.79 ± 4.64°	78.75 ± 2.75°	<0.001
Internal rotation	70.71 ± 4.32°	78.75 ± 2.22°	<0.001

DISCUSSION

In our study, most of the patients who were treated for breast cancer with BCS and LD flap reconstruction were younger with a mean age of <60 years. The disability scores in both groups were comparable with the majority of the patients having mild to moderate functional impairment. In our study, good quality of life was noted in both groups. Similarly, other functional domains, such as role functioning, emotional functioning, cognitive functioning and social functioning were also found comparable in both groups. Though cases experienced worse pain, other symptoms were similar in either of the groups. Extension and adduction strength were inferior in patients with

LD reconstruction. Flexion and abduction remained equally restricted. The cases had more restrictions in extension, adduction, external and internal rotation.

The age of patients in our study group is similar to that of the study conducted by de Oliveira et al. (8). Majority of women of age >55 years do not prefer extensive procedures like breast reconstruction with LD flap which is a finding also observed by Reddy et al. in a study conducted among Indian women, comparing various treatment options for breast cancer in different age groups. They concluded that breast conservation was less preferred by the elderly, because of barriers like significant comorbidities, restricted physical mobility, and financial considerations (9).

No minimal or severe functional impairment was noted in any of our patients. In a study by Garusi et al., two of the three cases had no to minimal disability. They also stated that in the group of patients who did not practice sports, the median disability score was 18.7, as compared to 7.5 in patients who play sports with LD involvement (10). The higher disability score in our study is probably because most of the women do not practice sports activities nor perform active exercises regularly. Also, poorer follow-up to physiotherapy could also explain the higher score.

To objectively classify the patients in our study, we adopted the division used by Imran et al. in their cross-sectional study on breast cancer patients using the EORTC QLQ-C 30 questionnaire and divided the patients into two groups according to their scores. Patients who scored <33.3% for global health status had poor quality of life and who scored ≥66.7% had good quality of life. A similar division was used for functional scales and symptom scales, a score of <33.3% had a lower level of symptomatology, while patients with a score ≥66.7% had a higher level of symptomatology (11).

In our study, good quality of life was noted in both groups. de Gournay et al., in their retrospective study, have found that there was no significant difference in the quality of life between cases and controls, a finding similar to our study (12).

Extension and adduction strength was lesser in patients with LD reconstruction, though it did not translate to decrease in motion at the shoulder joint. Our results are in agreement with those in the study by Eyjolfsdottir et al., who documented reduced muscle strength in extension and adduction movements using the pulley and weight method in patients with LD flap reconstruction one year after surgery, as compared to their preoperative values (13).

Range of motion of the shoulder joint was compared in each movement of LD, and we found that flexion and abduction were two movements that remained equally restricted among the groups. The cases experienced greater restrictions in extension, adduction, external and internal rotation, although the range of motion remained within normal limits as per the guidelines of American Academy of Orthopedic Surgeons (AAOS) (6).

The study done by Garusi et al. has also assessed the range of motion at the shoulder joint in cases after one year and found that the shoulder joint recovery was >80% in all the movements, using the contralateral latissimus dorsi as a control (10). The range of motion is affected the most in abduction followed by flexion, internal or external rotation, and extension.

The reason for this difference is probably because, in the study of Garusi et al., reconstruction surgery in many patients was done after mastectomy, as compared to our cases where breast conservative surgery was done. Also, since the latissimus dorsi does not actively participate in abduction and flexion, the limitations in these movements may be contributed by other factors (10).

Limitations

The sample size of our study is small, considering the fact that ours is a resource crunch setting in a middle-income country, where most patients belong to the lower economic strata of the society, and not many patients choose for BCS, instead they prefer to go for MRM. Same is the reason why we had to include patients undergoing MRM in the control group. However, the effect that the difference in the types of surgical procedures would have on the shoulder function and kinesiology is far less when compared to that due to LD Flap reconstruction. Hence, this difference won't make any significant difference to the results of our study.

CONCLUSION

Patients with LD flap reconstruction do not have a major disability in performing day-to-day activities or a negative impact on shoulder function after a year of their respective surgeries. They have a good quality of life, and functional domains such as role functioning, emotional functioning, cognitive functioning and social functioning and symptoms are similar. Active exercises and physiotherapy post-surgery may however improve the functional impairment and recovery post -surgery.

Ethics Committee Approval: This study was approved by the King George's Medical University U.P. Institutional Ethics Committee (Decision no: 1728/Ethics/19, Date: 11.11.2019).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 65-72

Meme kanseri hastalarında latissimus dorsi miyokutanöz flep rekonstrüksiyonu sonrası omuz hareketlerinin fonksiyonel bozukluğu, yaşam kalitesi ve engellilik üzerine prospektif bir vaka kontrol çalışması

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ÖZET

Giriş ve Amaç: Omuz hareketlerindeki disfonksiyon latissimus dorsi (LD) flebinin kullanımını sınırlayıcı bir faktör olabilir. Bu çalışmanın amacı, LD flep rekonstrüksiyonunun omuz disfonksiyonu ve yaşam kalitesi üzerine etkisini değerlendirmekti.

Gereç ve Yöntem: Bu çalışmaya LD flep ile meme koruyucu cerrahi (MKC) uygulanan 28 erken evre meme kanseri olgusu ve 40 kontrol olgusu dahil edildi. Bir yıl sonra subjektif ve objektif değerlendirmeler yapıldı.

Bulgular: Hafif ve orta derecede engellilik sırasıyla %85,71 ve %14,3 olguda, %100 ve %0 kontrol grubunda saptandı (p= 0,316). Fiziksel ve duygusal işlevsellik olgularda sırasıyla 84,29 ± 5,61 ve 66,67 ± 6,05 iken kontrollerde 86,67 ± 8,38 ve 70,0 ± 6,84 idi (p= 0,36, 0,23). Olgularda ağrı skoru 23,8 ± 15,6 iken kontrollerde 12,17 ± 8,4 idi (p= 0,018). LD kas gücü ekstansiyonda olgularda 4,39 ± 0,35 iken kontrollerde 4,88 ± 0,22 (p< 0,001), addüksiyonda olgularda 4,43 ± 0,18 iken kontrollerde 4,65 ± 0,24 idi (p= 0,006). Omuzun hareket açıklığı fleksiyonda olgularda 151,61 ± 4,86° iken kontrollerde 153,88 ± 2,36° (p= 0,08), ekstansiyonda olgularda 40,36 ± 3,52° iken kontrollerde 49,13 ± 1,86° (p< 0,001), abdüksiyonda olgularda 150,54 ± 3,69° iken kontrollerde 150,00 ± 0,00° (p= 0,518), addüksiyonda olgularda 30,89 ± 4,0°'ye karşı kontrollerde 38,13 ± 1,11° (p< 0,001), dış rotasyonda olgularda 73,57 ± 3,63°'ye karşı kontrollerde 77,63 ± 2,36° (p< 0,001) ve iç rotasyonda olgularda 69,46 ± 3,56°'ye karşı kontrollerde 79,00 ± 1,26° idi (p< 0,001).

Sonuç: Meme rekonstrüksiyonu cerrahisinde fonksiyonel bozukluğun LD flep için belirleyici bir faktör olmaması gerektiği sonucuna vardık.

Anahtar Kelimeler: Latissimus dorsi, flep rekonstrüksiyonu, yaşam kalitesi, omuz disfonksiyonu, meme koruyucu cerrahi

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ORIGINAL ARTICLE
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Pathological complete response and associated factors in breast cancer after neoadjuvant chemotherapy: A retrospective study

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ABSTRACT

Objective: This study aimed to determine clinical and pathological factors that identify a pathological complete response (pCR) in breast cancer patients undergoing neoadjuvant chemotherapy (NAC).

Material and Methods: A retrospective, single-center study was conducted in women over the age of 18 who had been diagnosed with pathologically confirmed invasive breast cancer and who had received NAC between July 2016 and October 2021. Patient demographics, clinical, radiological, treatment, and pathological data were reviewed from the electronic hospital records. The primary outcome of interest was pCR, defined as the absence of residual invasive breast cancer in both the breast and axillary lymph nodes. Multivariable logistic regression analysis was used to identify factors associated with pCR.

Results: A total of 119 patients were included in the analysis. The distribution of age was 54.5 ± 11.5 years. pCR was observed in 33 (27.7%) patients. pCR for breast tissue was observed in 43 (36.1%) patients. There was no statistically significant relation between the clinical stage and pCR. Age, age at first labor, extent of disease in the breast, NAC completeness, clinical tumor size (cT) stage, clinical lymph node (cN) stage, and molecular subtype were analyzed in a multivariable model. Analysis showed that molecular subtype was the only independent factor related to pCR. pCR rates across molecular subtypes were: 8.7% in luminal-A, 10.8% in luminal-B, 54.5% in human epidermal growth factor receptor 2 (HER-2)-positive, 42.4% in luminal-B (HER-2 positive) and 46.7% in triple-negative. There was no statistically significant difference between luminal-A and luminal-B subgroups (odds ratio 1.15, 95% confidence interval, 0.19-9.35, p= 0.881). Despite the limited number of patients in HER2-positive and triple-negative groups, both demonstrated statistically significant higher odds compared to reference group.

Conclusion: The presented study underscores the relevance of molecular subtypes in determining the response to neoadjuvant chemotherapy in breast cancer patients. Particularly HER2-positive and triple-negative subtypes may demonstrate more favorable response rates.

Keywords: Breast cancer, neoadjuvant chemotherapy, pathological complete response, molecular subtypes

INTRODUCTION

Several treatment options including chemotherapy, hormone therapy, radiation therapy, and surgery are used in the treatment of breast cancer (1,2). However, the efficacy of these treatments can vary significantly from patient to patient, highlighting the necessity for personalized treatment strategies. Important variables such as age, genetic composition, and individual characteristics are critical to the treatment's success (3-5). Modern treatment regimens may include a combination of several treatment strategies (6). By considering these individual factors, healthcare professionals work to create treatment plans that are customized to meet the specific needs of each patient. Such personalized approaches are crucial in improving the survival rates of breast cancer patients (7).

Several parameters need to be evaluated during the initial treatment planning phase (8). In recent years, tumor molecular subtypes have emerged as one of the most extensively researched factors in this regard. Molecular subtyping provides valuable insights into the heterogeneity of breast cancer, enabling healthcare professionals to better understand the underlying biology and tailor treatment strategies accordingly. By categorizing breast cancer into distinct molecular subtypes, such as luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)-positive tumors, and triple-negative breast cancer (TNBC), clinicians can identify specific characteristics and response patterns to different therapies (5,8,9).

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This information aids in the selection of appropriate treatment modalities based on the molecular profile of the tumor.

The aim of the study was to evaluate the clinical and pathological factors contributing to achieving a pathological complete response (pCR) for breast cancer patients who received neoadjuvant chemotherapy (NAC). By doing this, the research aimed at increasing our understanding of the underlying factors, which might significantly improve our ability to predict which patients would benefit from NAC the most.

MATERIAL and METHODS

The study was designed as a single-center, observational study and included the retrospective analysis of all female patients over the age of 18 diagnosed with invasive breast cancer that was pathologically confirmed and who received NAC between July 2016 and October 2021 at Karadeniz Technical University, Faculty of Medicine, Farabi Hospital.

The study was approved by the ethics committee of the university. Exclusion criteria were defined as metastatic disease at the time of diagnosis, previous treatment for breast cancer, and inability to access patient data after neoadjuvant therapy.

Electronic hospital records were reviewed for patient demographics, clinical data, radiological data, treatment data and pathological data. The TNM Classification System of the Union for International Cancer Control (8^{th} edition) was used for pathological analysis (10). Subsequently, clinical results were verified by radiological evaluations to improve diagnosis accuracy. In order to assess the effectiveness of treatment, treatment data such as details about chemotherapy protocols and surgical procedures was categorized. In order to reduce data missingness, patients were contacted and invited to the hospital.

pCR was defined as the absence of residual invasive breast cancer in histopathological samples from both the breast and axillary lymph nodes (ypT0/ypTis-ypN0) (11). Systemic treatment was given by evaluating the analyzed clinical and biological factors according to factors such as age, pre-NAC clinical tumor size (cT) stage, clinical lymph node (cN) stage and histopathological molecular subtype. Systemically, cyclophosphamide, anthracycline and taxane treatments were administered to patients with HER2 expression, trastuzumab and/or pertuzumab treatment, and patients with TNBC were treated with carboplatin according to the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines. Lesions were marked with clips before systemic treatment. The patients were analyzed in two groups according to their NAC treatment response as non-pCR and pCR.

Estrogen receptor (ER), progesterone receptor (PR) and HER2 status were assessed using immunohistochemistry (IHC) analysis. Positivity for ER and PR status was defined as expression in >1% of tumor cells. ER positive and PR positive tumors were classified as luminal type A or B according to their Ki-67 proliferation index < or ≥14. HER2 expression was determined by IHC or fluorescent in situ hybridization (FISH), depending on the situation. The molecular subtypes were classified as luminal-A, luminal-B, luminal-B (HER2-positive), HER2-positive, and triple-negative. As a surgical method, breast-conserving surgery (BCS) or mastectomy was performed according to the results of multicentricity, patient preference and pathological data. As axillary surgical procedure, sentinel lymph node biopsy (SLNB) was performed in case of cN0, with axillary lymph node dissection (ALND) applied if there was a SLNB positivity; for cN positive cases axillary surgical methods (SLNB or ALND) were preferred based on the surgeon's choice.

Statistical Analysis

Open-source statistical programming language R software (Vienna, Austria) was used to analyze the data. In the presentation of numerical data, mean ± standard deviation or median (Q1-Q3) was used according to distribution. Categorical data were presented as n (%). T- test or Mann-Whitney U test was used for numerical data when comparing the two groups. Chi-square or Fisher tests were used to evaluate categorical data. Logistic regression test was used to examine the factors related with pCR (uni-and multivariable). Beyond parameters with a p-value below 0.10 in univariable analysis, clinically important factors were added into the multivariable analysis. When parameters were correlated with each other or used in the definition of a factor, the most important one among them was included in the model. The effect sizes were expressed as odds ratio (OR) with the corresponding 95% confidence interval (CI) and p value. P value <0.05 was considered statistically significant.

RESULTS

The current study included 119 female patients diagnosed with breast cancer, with a mean age of 54.5 ± 11.5 years. In 64 (%53.8) patients, the tumor was located in left breast, and the most common locations in the breast were the outer and upper quadrants. A total of 62 (%52.1) patients were in the premenopausal period.

pCR was observed in 33 (27.7%) patients. pCR for breast was 43 (36.1%) patients and for axilla 58 (48.7%) patients (Figure 1). Among all patients, 51 (42.9%) did not show pCR neither in the breast nor axilla. For 10 (8.4%) patients, there was pCR in the breast but not in the axilla. Demographics and clinical characteristics of patients were presented in Table 1. There was not a statistically significant difference between pCR and non-pCR groups in terms of demographics and personal history.

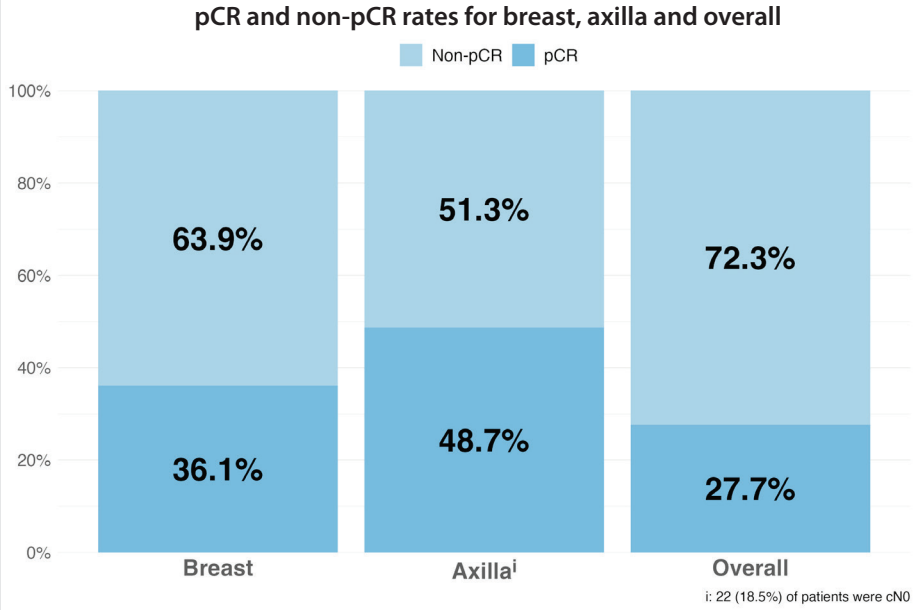

Figure 1. pCR and non-pCR rates for the breast, axilla and overall.

Table 1. Demographics and clinical characteristics of the patients

Variable		All Patients (n= 119)	pCR (n= 33)	Non-pCR (n= 86)	p
Age		54.5 ± 11.5	54.2 ± 10.3	54.6 ± 11.9	0.872
BMI		29.3 (24.9-34)	30.9 (24.3-34.9)	29.1 (25-33.9)	0.684
Smoking		89 (74.8)	23 (25.8)	66 (74.2)	0.578
Family History		38 (31.9)	13 (34.2)	25 (65.8)	0.389
Comorbidity		71 (59.7)	23 (32.4)	48 (67.6)	0.241
ECOG	ECOG-0	91 (76.5)	23 (25.3)	68 (74.7)	0.402
	ECOG-I/II	28 (23.5)	10 (35.7)	18 (64.3)	
Menarche age		13 (12-14)	13 (12-15)	13 (12-14)	0.817
Menopause status	Premenopausal	62 (52.1)	17 (27.4)	45 (72.6)	1.000
	Postmenopausal	57 (47.9)	16 (28.1)	41 (71.9)	
Number of births	No birth	17 (14.3)	2 (11.8)	15 (88.2)	0.221
	1-2 births	48 (40.3)	13 (27.1)	35 (72.9)	
	>2 births	54 (45.4)	18 (33.3)	36 (66.7)	
Age at first labor	No birth	17 (14.3)	2 (11.8)	15 (88.2)	0.062
	>20	74 (62.2)	26 (35.1)	48 (64.9)	
	≤20	28 (23.5)	5 (17.9)	23 (82.1)	
Tumor side	Left	64 (53.8)	21 (32.8)	43 (67.2)	0.258
	Right	55 (46.2)	12 (21.8)	43 (78.2)	
Tumor location†					
Central		30 (25.2)	6 (20)	24 (80)	0.391
Upper		68 (57.1)	20 (29.4)	48 (70.6)	0.790
Lower		28 (23.5)	4 (14.3)	24 (85.7)	0.115
Outer		73 (61.3)	21 (28.8)	52 (71.2)	0.914
Inner		21 (17.6)	5 (23.8)	16 (76.2)	0.862

†The patient's tumor may be located in more than one quadrant.
pCR: Pathological complete response, Non-pCR: No pathological complete response, BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group.

Table 2. Radiological/pathological characteristics of the patients

Variable		All Patients (n= 119)	pCR (n= 33)	Non-pCR (n= 86)	p
Tumor size in cm (USG)		2.6 (1.9-3.5)	2.1 (1.9-2.8)	2.8 (1.9-3.8)	0.022
Extent (USG)	Unifocal	74 (62.2)	20 (27)	54 (73)	0.941
	Multifocal/Multicentric	37 (31.1)	11 (29.7)	26 (70.3)	
	Unknown	8 (6.7)	2 (25)	6 (75)	
Extent (Mammography)	Unifocal	54 (45.4)	10 (18.5)	44 (81.5)	0.067
	Multifocal/Multicentric	13 (10.9)	3 (23.1)	10 (76.9)	
	Unknown	52 (43.7)	20 (38.5)	32 (61.5)	
Extent (MRI)	Unifocal	43 (36.1)	16 (37.2)	27 (62.8)	0.220
	Multifocal/Multicentric	32 (26.9)	7 (21.9)	25 (78.1)	
	Unknown	44 (37)	10 (22.7)	34 (77.3)	
ER status	Negative	31 (26.1)	16 (51.6)	15 (48.4)	0.001
	Positive	88 (73.9)	17 (19.3)	71 (80.7)	
PR status	Negative	28 (23.5)	14 (50)	14 (50)	0.006
	Positive	91 (76.5)	19 (20.9)	72 (79.1)	
HER-2 status	Negative (0)	63 (52.9)	11 (17.5)	52 (82.5)	0.004
	Negative (1+)	12 (10.1)	2 (16.7)	10 (83.3)	
	Positive (3+)	44 (37)	20 (45.5)	24 (54.5)	
Ki-67		20 (15-30)	30 (18-30)	20 (12-30)	0.016
Molecular subtype	Luminal-A	23 (19.3)	2 (8.7)	21 (91.3)	0.001
	Luminal-B	37 (31.1)	4 (10.8)	33 (89.2)	
	Luminal-B (HER2-positive)	33 (27.7)	14 (42.4)	19 (57.6)	
	HER2-positive	11 (9.2)	6 (54.5)	5 (45.5)	
	Triple-negative	15 (12.6)	7 (46.7)	8 (53.3)	
Axillary cytology	Benign	11 (9.2)	5 (45.5)	6 (54.5)	0.148
	Non-diagnostic	8 (6.7)	0 (0)	8 (100)	
	Suspicious	3 (2.5)	0 (0)	3 (100)	
	Malign	59 (49.6)	15 (25.4)	44 (74.6)	
	Not-performed	38 (31.9)	13 (34.2)	25 (65.8)	
cT stage	T1	23 (19.3)	4 (17.4)	19 (82.6)	0.593
	T2	79 (66.4)	25 (31.6)	54 (68.4)	
	T3	4 (3.4)	1 (25)	3 (75)	
	T4	13 (10.9)	3 (23.1)	10 (76.9)	
cN stage	N0	33 (27.7)	11 (33.3)	22 (66.7)	0.561
	N1	74 (62.2)	18 (24.3)	56 (75.7)	
	N2	2 (1.7)	1 (50)	1 (50)	
	N3	10 (8.4)	3 (30)	7 (70)	

pCR: Pathological complete response, Non-pCR: No pathological complete response, USG: Ultrasonography, MRI: Magnetic resonance imaging, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor-2, cT: Clinical tumor size, cN: Clinical lymph node.

Radiological and histopathological characteristics are presented in Table 2. Tumor size was lower in the pCR group [2.1 (1.9-2.8) cm] compared to the non-pCR group [2.8 (1.9-3.8) cm] (p= 0.022). Luminal-B [37 (31.1) patients] and luminal-B (HER2-positive) [33 (27.7) patients] subtypes were the most common molecular subtypes. There was a statistically significant difference for ER status (p= 0.001), PR status (p= 0.006), HER2 status (p= 0.004), and Ki-67 (p= 0.016) between the pCR and non-pCR groups.

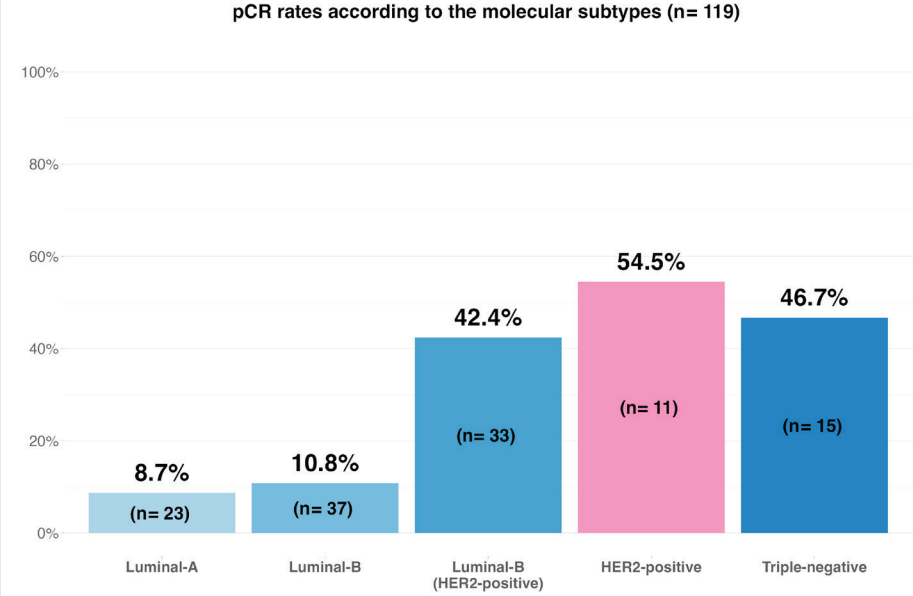

Figure 2. pCR rates according to molecular subtypes.

pCR rates demonstrated a statistically significant difference among the subgroups. Luminal-A and luminal-B showed the highest non-pCR rates. pCR rates according to the molecular subtypes are shown in Figure 2. Treatment- related characteristics are shown in Table 3. The completeness rate of NAC treatment was comparable between the groups (78.8% in pCR and 74.4% in non-pCR groups, p= 0.796). While the surgical management of the breast was similar, management for the axilla showed difference between the groups.

In multivariable regression analysis, the molecular subtype was identified as the sole statistically significant factor for pCR. When the luminal-A group was taken as the reference, no difference was found in terms of pCR for luminal-B [1.15 (0.19-9.35), 0.881]. However, in the luminal-B (HER2-positive) [11.36 (2.31-88.38), 0.007], HER2-positive [11.87 (1.85- 109.53), 0.014], and triple-negative [12.51 (1.99-115.14), 0.012] subgroups, the odds of pCR were higher compared to the luminal-A subgroup. The results of logistic regression analysis for pCR are presented in Table 4.

Table 3. Treatment-related characteristics

Variable		All Patients (n= 119)	pCR (n= 33)	Non-pCR (n= 86)	p
NAC completeness	Completed	90 (75.6)	26 (78.8)	64 (74.4)	0.796
	Not completed	29 (24.4)	7 (21.2)	22 (25.6)	
Surgery (Breast)	BCS	20 (16.8)	7 (21.2)	13 (15.1)	0.601
	Mastectomy	99 (83.2)	26 (78.8)	73 (84.9)	
Surgery (Axilla)	SLNB only	32 (26.9)	18 (54.5)	14 (16.3)	<0.001
	ALND after SLNB	13 (10.9)	1 (3)	12 (14)	
	ALND only	74 (62.2)	14 (42.4)	60 (69.8)	
SLNB technique	Blue dye	41 (34.5)	16 (48.5)	25 (29.1)	0.007
	Technetium + Blue dye	4 (3.4)	3 (9.1)	1 (1.2)	
	No SLNB	74 (62.2)	14 (42.4)	60 (69.8)	
Total removed LNs		14 (8-18)	11 (6-15)	15 (10-18.8)	0.017
Total removed LNs (SLNB)†		5 (4-7)	6 (4-8.5)	5 (4-6)	0.071
Total removed LNs (ALND)‡		16 (13-20.8)	16 (14-20)	16 (12-20.5)	0.588

†Only for patients having SLNB.
‡Only for patients having ALND.
pCR: Pathological complete response, Non-pCR: No pathological complete response, NAC: Neoadjuvant chemotherapy, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection, LN: Lymph node.

Table 4. Logistic regression analysis for pCR

Variable		ORs (Univariable)†	ORs (Multivariable)†
Age	<55	-	-
	≥55	0.83 (0.37-1.86, p= 0.657)	1.49 (0.54-4.34, p= 0.447)
Age at first labor	No birth	-	-
	>20	4.06 (1.04-27.05, p= 0.076)	5.43 (1.09-42.26, p= 0.060)
	≤20	1.63 (0.31-12.42, p= 0.587)	1.11 (0.16-10.32, p= 0.917)
Extent (Mammography)	Unifocal	-	-
	Multifocal/Multicentric	1.32 (0.26-5.32, p= 0.710)	0.67 (0.11-3.44, p= 0.641)
	Unknown	2.75 (1.16-6.88, p= 0.025)	2.82 (0.99-8.53, p= 0.057)
NAC completeness	Completed	-	-
	Not completed	0.78 (0.28-1.99, p= 0.620)	0.43 (0.13-1.36, p= 0.164)
cT stage	T1/T2	-	-
	T3/T4	0.77 (0.21-2.40, p= 0.677)	0.81 (0.18-3.30, p= 0.774)
cN stage	N0/N1	-	-
	N2/N3	1.34 (0.34-4.62, p= 0.648)	0.99 (0.21-4.21, p= 0.992)
Molecular subtype	Luminal-A	-	-
	Luminal-B	1.27 (0.23-9.76, p= 0.791)	1.15 (0.19-9.35, p= 0.881)
	Luminal-B (HER2-positive)	7.74 (1.85-53.50, p= 0.013)	11.36 (2.31-88.38, p= 0.007)
	HER2-positive	12.60 (2.20-106.63, p= 0.008)	11.87 (1.85-109.53, p= 0.014)
	Triple-negative	9.19 (1.79-71.30, p= 0.014)	12.51 (1.99-115.14, p= 0.012)

†ORs were presented as odds ratio (95% confidence intervals, p value).

pCR: Pathological complete response, OR: Odds ratio, NAC: Neoadjuvant chemotherapy, cT: Clinical tumor size, cN: Clinical lymph node, HER2: Human epidermal growth factor receptor-2.

DISCUSSION

In the study evaluating breast cancer patients undergoing NAC, pCR rate, defined as the absence of residual invasive cancer in both breast and axillary lymph nodes, was found to be 27.7%. Despite cT and cN not exhibiting statistical significance in relation to pCR, factors such as tumor size, ER status, PR status, HER2 status, and Ki-67 index were identified as potential factors with pCR. In multivariable analysis, the molecular subtype emerged as a significant risk factor. Notably, while pCR rates were low in luminal-A and luminal-B subtypes, higher pCR rates were observed in HER2-positive and triple-negative groups.

In breast cancer treatment, achieving pCR is vital as it means that no cancer remains in the breast and lymph nodes after treatment. The general approach to pCR involves treatment strategies for both the primary tumor and lymph nodes. The presented study, in line with the existing literature, reveals that 36.1% of the patients achieved breast pCR, while 48.7% achieved axillary pCR (8,12). Remarkably, 8.4% achieved breast pCR without an axillary response. The significance of achieving axillary pCR after primary systemic treatment cannot be overstated, as it plays a crucial role in reducing the risk of relapse and improving overall survival, particularly in the axillary region. Research at the University of Texas MD Anderson Cancer Center has underscored the significance of axillary pCR, linking it to improved 10-year survival following systemic therapy (13). However, there is an ongoing debate about whether pCR should also indicate the absence of ductal carcinoma in situ (DCIS). Findings from the I-SPY2 trial suggest that the presence or absence of DCIS does not significantly impact the outcomes (7). Standardizing pCR definition and learning more about its clinical effects are important for managing and predicting the prognosis of breast cancer patients who are going through neoadjuvant therapy.

Breast cancer treatments incorporating carboplatin, pembrolizumab, and anti-HER agents have notably increased pCR rates in triple-negative and HER2 subtypes (14,15). According to the data from the presented study, receptors for ER, PR, and HER2 may play pivotal roles in achieving pCR, with the literature corroborating lower pCR rates in luminal-A and luminal-B subtypes (8,9,16). Conversely, luminal-B (HER2-positive), HER2-positive, and triple-negative subtypes have demonstrated appreciably higher pCR rates, underscoring the importance of subtypes in treatment to the success of a complete response. The study also demonstrated that Ki-67 levels, along with the molecular subtype, is a significant

factor of pCR (17). Similarly, the EORTC 10994/BIG 1-00 study emphasized that pCR following chemotherapy is robustly linked with both breast cancer subtype and long-term survival, further illuminating the prognostic implications of pCR (18).

In the presented study, not completing NAC did not significantly affect pCR rates likely due to the small patient sample. However, a meta-analysis has shown that patients who do not complete NAC often have lower pCR rates (19). Adding to the prognostic factors affecting pCR, recent studies have indicated a possible link between higher body mass index (BMI) and decreased pCR rates in breast cancer patients undergoing NAC (20) though the presented study did not find BMI to significantly alter pCR outcomes. The number of patients in the presented study may not be sufficient to determine the true prognostic value of BMI on treatment effectiveness. Analysis from the presented study suggested that neither age nor menopausal status significantly differentiated pCR from non-pCR groups. While some studies point to age as a potential influencer of pCR rates in NAC, other studies, including the one discussed, report no meaningful correlation (3,21,22). Studies also indicate, aligning with the findings from the current study, that menopausal status does not play a crucial role in pCR (21,22).

NAC aims to reduce surgical extent in breast cancer treatment, as established by previous research. Contrarily, the presented study observed a preference for more extensive surgeries, including ALND, even when NAC was administered. The ACOSOG Z1071 (Alliance) trial has demonstrated an association of tumor biology with higher rates of BCS (8). Additionally, axillary pCR rates post-NAC are significantly affected by breast cancer subtypes, particularly in hormone receptor (HR) negative/HER2-positive and triple-negative cases (23). Patients undergoing ALND report more frequent adverse effects like motor neuropathy, sensory neuropathy, and lymphedema (24). Due to these complications, there is a shifting preference towards less invasive treatments over ALND (25). The presented study showed high rates of ALND and mastectomy based on physician and patient preferences.

The presented study had limited radiological access opportunities and did not include survival and recurrence analyses with a retrospective nature. Sample sizes for certain breast cancer subtypes and biomarker groups were small, which might limit the generalizability of our results. The research was confined to a single center, which could influence the applicability of the findings to a wider population. Future studies should aim to incorporate the relation between pCR and survival outcomes.

CONCLUSION

The presented study demonstrates variations in pCR rates among molecular subtypes, highlighting more favorable responses in HER2-positive and triple-negative patients compared to other subtypes. Luminal-type breast tumors exhibited significantly lower pCR rates. Future investigations should focus on these findings, emphasizing personalized treatment strategies targeting molecular subtypes for enhanced responses to NAC.

Ethics Committee Approval: This study was approved by Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (Decision date: 01.02.2022, No: 24237859-51).

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2024; 40 (1): 73-81

Neoadjuvan kemoterapi sonrası meme kanserinde patolojik tam yanıt ve ilişkili faktörler: Retrospektif çalışma

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı, neoadjuvan kemoterapi (NAC) uygulanan meme kanseri hastalarında patolojik tam yanıtı (pCR) belirleyen klinik ve patolojik faktörleri tespit etmektir.

Gereç ve Yöntem: İnvaziv meme kanseri teşhisi patoloji ile konulmuş, Temmuz 2016 ile Ekim 2021 tarihleri arasında NAC almış, 18 yaş üstü kadınları değerlendiren retrospektif, tek merkezli bir çalışma yürütüldü. Hasta demografik verileri, klinik, radyolojik, tedaviye ait ve patolojik veriler elektronik hastane kayıtları gözden geçirilerek elde edildi. Birincil amaç pCR olarak tanımlandı ve bu, hem meme hem de aksiller lenf düğümlerinde rezidüel invaziv meme kanserinin yokluğu olarak belirlendi. pCR ile ilişkili faktörleri belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı.

Bulgular: Analize toplam 119 hasta dahil edildi. Yaş dağılımı 54,5 ± 11,5 yıl idi. pCR 33 (%27,7) hastada gözlendi. Meme dokusu için pCR 43 (%36,1) hastada mevcuttu. Klinik evre ile pCR arasında istatistiksel olarak anlamlı bir ilişki saptanmadı. Multivariabl modelde yaş, ilk doğum yaşı, memedeki hastalığın yayılımı, NAC'nin tamamlanma durumu, klinik tümör boyutu (cT) evresi, klinik lenf nodu (cN) evresi ve moleküler alt tip analiz edildi. Analiz, moleküler alt tipin pCR ile ilişkili tek bağımsız faktör olduğunu gösterdi. Moleküler alt tiplere göre pCR oranları: luminal-A'da %8,7, luminal-B'de %10,8, insan epidermal büyüme faktörü reseptörü 2 (HER2)-pozitifte %54,5, luminal B (HER2-pozitif)'te %42,4 ve üçlü negatiflerde %46,7 idi. Luminal-A ve luminal-B alt grupları arasında istatistiksel olarak anlamlı bir fark bulunmadı (odds oranı 1,15, %95 güven aralığı 0,19-9,35, p= 0,881). HER2-pozitif ve üçlü negatif gruplardaki hasta sayısı sınırlı olmasına rağmen, her ikisi de referans grubuna göre istatistiksel olarak anlamlı derecede daha yüksek oddsa sahipti.

Sonuç: Sunulan çalışma, meme kanseri hastalarında neoadjuvan kemoterapiye yanıtın belirlenmesinde moleküler alt tiplerin önemini vurgulamaktadır. Özellikle HER2-pozitif ve üçlü negatif alt tipler, daha olumlu yanıt oranları sergileyebilir.

Anahtar Kelimeler: Meme kanseri, neoadjuvan kemoterapi, patolojik tam yanıt, moleküler alt tipler

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CASE REPORT
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Musinous cystic neoplasia mimicking hydatid cyst in the liver: Two rare cases

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ABSTRACT

Mucinous cystic neoplasm of the liver (MCN-L) is a rare tumor which accounts for less than 5% of all liver cysts. Although they are considered to be "benign cysts" radiologically and clinically because of their slow growth, they are considered as premalignant. We present two radiologically misdiagnosed cases that operated in a short time range, in order to increase awareness for these rare tumors. A 47-year-old female patient who had no active complaints 58 x 40 mm cystic lesion was detected in the liver, which was diagnosed hydatid cyst radiologically. The pathological examination showed multiloculated cysts which was covered by low-grade mucinous epithelium and ovarian-type stroma on the cyst wall. A 50-year-old female patient presented with abdominal distention. The radiographical screening revealed a 204 x 140 mm cystic lesion that completely fills left lobe of liver which interpreted in favor of hydatid cyst. Histopathologically, the inner surface of the cyst was covered with low grade mucinous epithelium. Ovarian-type stroma was detectable only by immunohistochemistry due to significant bleeding and edema on the wall. The diagnosis of both of our cases was low grade MCN-L. Since cysts were not intact at the time of gross examination, we could not make any comment about surgical margins or total excision. MCN-L is a tumor that creates difficulty in presurgical differential diagnosis because of its rarity and lack of specific radiologic features. Although the prognosis is excellent as a result of total excision in the benign group, relapses have also been reported.

Keywords: Liver, musinous cystic neoplasia, hydatid cyst

INTRODUCTION

MCN-L, formerly known as hepatobiliary cystadenoma/cystadenocarcinoma, is a very rare tumor and clinically important. MCN-L is also interesting regarding its ovarian-type stroma and unknown pathogenesis. It constitutes less than 5% of all liver cysts. These tumors may considered to be completely harmless cysts, due to their good long-term clinical behavior, or they may cause diagnostic difficulties, because they might appear suspicious radiologically (1). While 90% of noninvasive forms are seen in women, invasive ones are equally distributed between both sexes. The mean age at diagnosis is 45 in noninvasive tumors, but they are typically seen a decade later in patients with invasive disease. Most tumors originate from the intrahepatic biliary system and typically grow slowly (2). It has been reported in the literature that cysts can reach 1.2 cm to 40 cm in size (3).

The most important cause of diagnostic and surgical errors is thought to be low awareness due to rarity of these tumors (4). We aimed to raise awareness to these rare but prognostically important tumors by presenting two cases of MCN-L, which had the same incorrect radiological pre-diagnosis before surgery, with their clinical, radiological and pathological features, and also with review of the literature and current developments.

CASE REPORT

Case 1

A 47-year-old female patient was diagnosed with thyroid papillary carcinoma six months ago, and during the follow up examinations, liver and spleen mass was detected. On ultrasonography, cystic, lobulated mass lesion was observed in the third segment of the liver. The lesion was 58 x 40 mm in size and contained smaller multiple cysts in the lumen which appear to be daughter vesicles. The findings were interpreted as consistent with hydatid cyst radiologically. The patient was sched-

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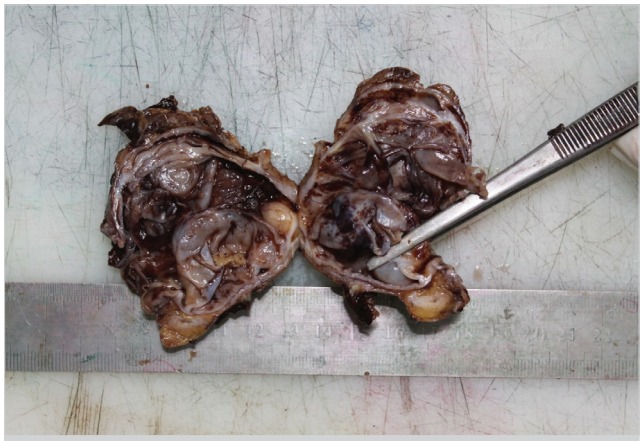

Figure 1. Cystic and multiloculated appearance, case 1, macroscopic feature.

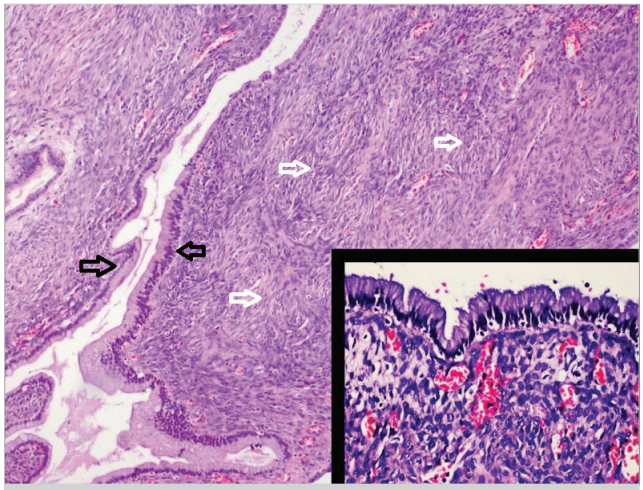

Figure 2. Low grade mucinous epithelium in inner surface of cyst (black arrows), prominent ovarian-type stroma in cyst wall (white arrows), case 1, H&E.

uled to undergo splenectomy because of the solid mass in the spleen. During that operation, the lesion in the liver was also excised in the same session. The specimen was disrupted, 6.9 x 6 x 3 cm in size and was of gray-purple color in most areas. It contained normal liver tissue measuring 3 x 2 x 0.8 cm. The rest of it was of cystic nature, appearing multiloculated with septations (Figure 1). Histopathological examination showed that the inner surface of multiloculated cyst was covered with low grade mucinous epithelium. A prominent ovarian-type stroma was noted in the cyst wall (Figure 2). Immunohistochemistry panel showed cytokeratin 19, MUC 1, MUC 5AC and MUC 6 expression in epithelial cells lining the cyst wall (Figure 3). Ovarian-type stroma was revealed by Estrogen receptor immunohistochemistry. Surgical margins could not be interpreted due to the disruption of tumor integrity. In addition, the pathological evaluation of the patient's spleen mass was diagnosed as diffuse large B cell lymphoma.

Case 2

A 50-year-old female patient whom was admitted to hospital with abdominal distention complaint was found to have a liver mass. Computed tomography revealed a nodular lesion, which involved the entire left lobe of the liver, starting from segment 4A. The lesion was 204 x 140 mm in size, and of purely cystic density with a contrast-free septa. This lesion was reported radiologically in favor of the hydatid cyst. (Figure 4). With the preliminary diagnosis of hydatid cyst, surgical excision of the cystic lesion from the liver was performed. The specimen was disrupted, irregularly shaped and 20 x 12 x 7 cm in size. It appeared hemorrhagic and the thickest area of the cyst wall was 0.6 cm. On histopathological sections of the specimens, the lesion was multiloculated and the cyst epithelium was not observed in most areas depending on the pressure of the cyst content or due to the intervention during the surgical procedure. The internal surface of the cyst was covered with low-grade mucinous

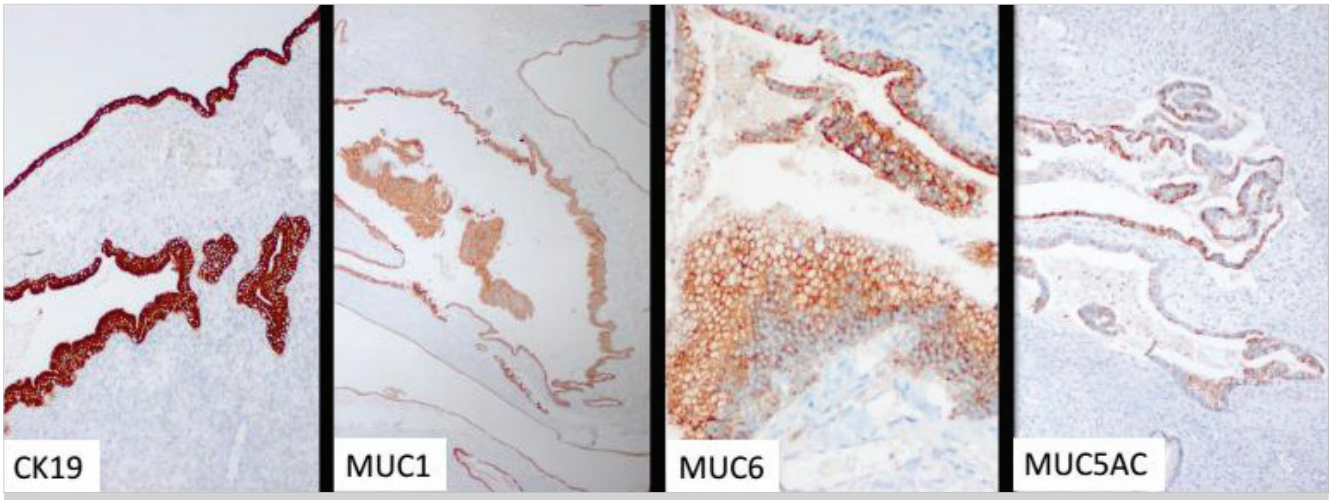

Figure 3. Cytokeratin 19, MUC 1, MUC 5AC and MUC 6 expression in epithelial cells lining the cyst, case 1.

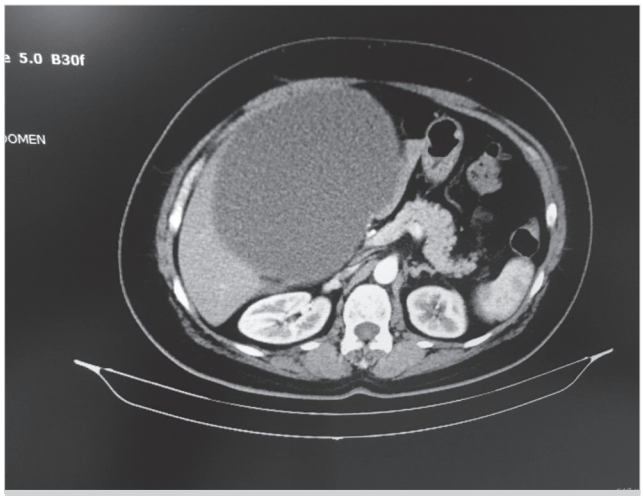

Figure 4. A nodular lesion, 204x140 mm in size, purely cystic density with a contrast-free septa and completely filled the left lobe starting from segment 4A, Computed tomography.

epithelium in the evaluable areas. The ovarian stroma could not be clearly observed though, due to the presence of significant hemorrhage and edema of the stroma. Immunohistochemically, cytokeratin 7, cytokeratin 19, CDX2 and MUC 1 expression was observed in cyst epithelial cells. Ovarian-type stroma was revealed by Progesterone receptor immunohistochemistry. Surgical margins could not be interpreted due to the disruption of tumor integrity.

DISCUSSION

In the 2000 World Health Organization (WHO) classification of digestive system tumors, liver cystic tumors with mucinous epithelium or less frequently serous epithelium were identified as hepatobiliary cystadenoma/cystadenocarcinoma. Stroma was not considered as a diagnostic feature in these tumors. Since the WHO 2010 classification, there are categories of low-intermediate-high grade and invasive carcinoma-related MCN-L. The requirement of ovarian-type stroma is emphasized in WHO 2010 classification. In cases which ovarian-type stroma could not be demonstrated, these tumors should be diagnosed as intraductal papillary neoplasia with marked cystic changes (1). Studies have shown that hepatobiliary cystadenomas without ovarian stroma have significantly poor prognosis which led up to changes in classification (5).

In the majority of MCN-L, neoplastic epithelium has a cubic or columnar appearance similar to bile duct epithelium and mucin secretion is not significant (6). For example, in a series consisting of 20 cases with MCN-L, intestinal differentiation including goblet cells in the epithelium was seen only in two cases (7). Gastric, intestinal and squamous differentiation might also be observed in the epithelium (1). However, the degree of mucinous differentiation has been shown to be parallel with the incidence of K-RAS mutation and invasive carcinoma (6).

High-grade intraepithelial neoplasia is characterized by glandular crowding, marked nuclear pleomorphism and increased mitotic activity. Papillary projections or stromal crypt-like invaginations indicate structural deterioration in this entity. Invasion is the hallmark of malignancy and should be reported as 'MCN associated with invasive carcinoma' (1). Invasion in MCN-L has been reported in very variable rates (2- 15.4%) (6,8). Although it is quite rare, sarcomatous transformation can also be seen in MCN of liver and pancreas (5,9). Our cases which we examined carefully with multiple samples and serial sections in order to exclude invasion were reported as low grade MCN-L, because of absence of nuclear pleomorphism and low mitotic activity, in single-layer mucinous epithelium that covers the inner surface of the cysts.

Histopathological differential diagnosis includes serous cystadenoma, endometriosis, intraductal papillary neoplasia along with other simple and parasitic cysts. The presence of estrogen and progesterone expression in epithelial cells in addition to stroma and CD10 immunoreactivity in stroma are helpful parameters in differential diagnosis for endometriosis (10). The fact that intraductal papillary neoplasia and serous cystadenoma do not contain ovarian-type stroma is important in the differential diagnosis (11). In our cases, we excluded endometriosis since the cysts were covered with mucinous epithelium. The presence of ovarian-type stroma demonstrated by immunohistochemistry allowed us to exclude intraductal papillary neoplasia. However, the presence of multiloculated septation in both lesions caused presurgical radiological evaluation to be in favor of hydatid cyst.

In studies of small case series, MUC1, MUC2, MUC5A and MUC6 immunohistochemical stains usually have been reported to be positive for MCN-L's with high-grade dysplasia / carcinoma in situ (11,12). Although both of our cases were positive with MUC1 and one with MUC5A and MUC6, high grade dysplasia area was not observed in our multiple samples. MUC immunohistochemical staining may also be positive in intraductal papillary neoplasia, so it is not useful in differential diagnosis. Larger case series are necessary to clarify the prognostic significance of MUC staining pattern.

Liver function tests are usually normal in the absence of biliary compression. Serum CA 19-9 levels may be elevated, but CEA and AFP levels are usually within normal limits, so they are not helpful in differential diagnosis. Although liver function tests were normal in our cases, no data were obtained regarding serum CA19-9, CEA and AFP levels.

The primary treatment is radical excision in MCN-L. Recurrence rate is high after partial excision (80%); even after total excision, in 10-20% of cases recurrence has been reported. (13). Prognosis varies depending on the presence of invasion. The prognosis of benign tumors is excellent when it's totally excised with 90% overall survival rate at 18-year follow-up (14). Invasive MCN-L has a significantly better prognosis than conventional intrahepatic

cholangiocarcinoma. 5-year survival rate was reported to be 65-70% in invasive carcinoma related MCN-L, 40% in hepatocellular carcinoma, and 22% in cholangiocarcinoma (14,15).

In conclusion, as these rare tumors have unknown etiopathogenesis, non-specific clinical presentations, wide-variety of radiological differential diagnosis, high recurrence rate and premalignant nature, it is of critical importance to give a precise pathological diagnosis for accurate treatment and follow-up. There are still controversial aspects regarding this entity, even though new diagnostic criteria have been introduced by WHO in the final classification. Increased radiological and clinical awareness of these tumors will increase the correct diagnosis rates.

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OLGU SUNUMU-ÖZET
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Karaciğerde hidatik kisti taklit eden müsinöz kistik neoplazi: İki nadir olgu

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ÖZET

Karaciğerin müsinöz kistik neoplazisi (KMKN) bütün karaciğer kistlerinin %5'inden azını oluşturan nadir bir tümördür. Yavaş büyümeleri nedeniyle radyolojik ve klinik olarak benin kist lehine değerlendirilse de aslında premalin lezyonlardır. Biz bu nadir tümörlere olan farkındalığı arttırmak amacıyla, radyolojik olarak yanlış tanı ile opere olmuş iki olgu sunduk. Aktif şikayeti olmayan 47 yaşında kadın hastanın karaciğerinde radyolojik olarak hidatik kist düşünülen 58 x 40 mm boyutunda kistik lezyon saptandı. Patolojik incelemede multiloküle kistin duvarında düşük dereceli müsinöz epitel altında ovaryan tip stroma izlendi. Abdominal distansiyon şikayeti bulunan 50 yaşında kadın hastada yapılan radyolojik görüntülemede hidatik kist lehine değerlendirilen karaciğerin sol lobunu dolduran 204 x 140 mm boyutunda kistik lezyon saptandı. Histopatolojik olarak kist iç yüzeyi düşük dereceli müsinöz epitelle döşeli olup kist duvarındaki yaygın ödem ve kanama nedeniyle ovaryan tip stroma ancak immünhistokimya ile gösterilebildi. Her iki olgunun da tanısı düşük dereceli KMKN idi. Makroskopik inceleme sırasında kist duvarı intakt olmadığı için, total eksizyon ya da cerrahi sınırlar hakkında yorum yapılamadı. KMKN nadir görülmesi ve spesifik radyolojik özelliklerinin olmaması nedeniyle cerrahi öncesi ayırıcı tanıda zorluk yaratan tümörlerdir. Benin olanlarda total eksizyon sonrası prognoz mükemmel olması ile birlikte nüksler de bildirilmiştir.

Anahtar Kelimeler: Karaciğer, müsinöz kistik neoplazi, hidatik kist

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CASE REPORT
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A rare cause of upper gastrointestinal system obstruction: Superior mesenteric artery syndrome (Wilkie's syndrome); two different case reports

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ABSTRACT

Superior mesenteric artery syndrome is defined as a collection of clinical symptoms and findings that result from compression of the third part of the duodenum between the aorta and the superior mesenteric artery. Here, we describe two patients who were diagnosed with superior mesenteric artery syndrome. Two patients, 18 and 38 years old, respectively, presented to our clinic with complaints of nausea, vomiting, and weight loss. Computed tomography scans of both patients supported diagnoses of superior mesenteric artery syndrome. The 18-year-old patient recovered with conservative treatment. However, our 38-year-old patient did not recover with conservative treatment and required two surgeries. In the first operation, duodenal release with Treitz's ligament dissection and pyloroplasty were performed because of concomitant hypertrophic pyloric stenosis. Because the patient exhibited gastroparesis and gastric ptosis after the first operation, subtotal gastrectomy and Roux-n-Y gastrojejunostomy were performed in the second operation. No complications were observed during follow-up after the second operation. Superior mesenteric artery syndrome should be considered in the differential diagnosis of patients with nausea, vomiting, and weight loss of unknown cause. During treatment, weight-gaining conservative approaches should be attempted initially, but surgical treatment should not be excessively delayed in patients who do not respond to medical treatment.

Keywords: Superior mesenteric artery syndrome, Wilkie's syndrome, upper gastrointestinal system obstruction

INTRODUCTION

Superior mesenteric artery (SMA) syndrome is defined as a collection of clinical symptoms and findings that result from compression of the third part of the duodenum between the aorta and SMA. This syndrome is also known as chronic duodenal ileus, cast syndrome, mesenteric root syndrome, intermittent arterio-mesenteric obstruction, and Wilkie syndrome (1). In patients with nonspecific symptoms of proximal intestinal obstruction (e.g., nausea, vomiting, and abdominal pain), SMA syndrome is often not considered during differential diagnosis. In these instances, diagnosis is often delayed; late diagnosis may lead to complications such as electrolyte anomalies, gastric perforation, gastric pneumatosis and portal venous gas, and obstructive gastric bezoar (2). With the widespread use of cross-sectional imaging methods, SMA syndrome has been diagnosed with increasing frequency (3). Herein, we describe two patients who presented to our hospital with signs of gastrointestinal obstruction and were diagnosed with SMA syndrome based on computed tomography (CT) findings.

CASE REPORT

Case 1

An 18-year-old man was admitted to our hospital with long-standing intermittent abdominal pain, nausea, and vomiting. Physical examination revealed that the patient had a cachectic appearance, with sensitivity in the epigastric region. The patient reported no significant disease in his medical history or family history. Haemogram and biochemical parameters were normal. Abdominal CT revealed that the third segment of the duodenum was compressed between the aorta and SMA. The angle between the abdominal aorta and SMA was 12 degrees; the aortomesenteric distance was 5 mm (Figure 1). Dilatation was present in proximal segments

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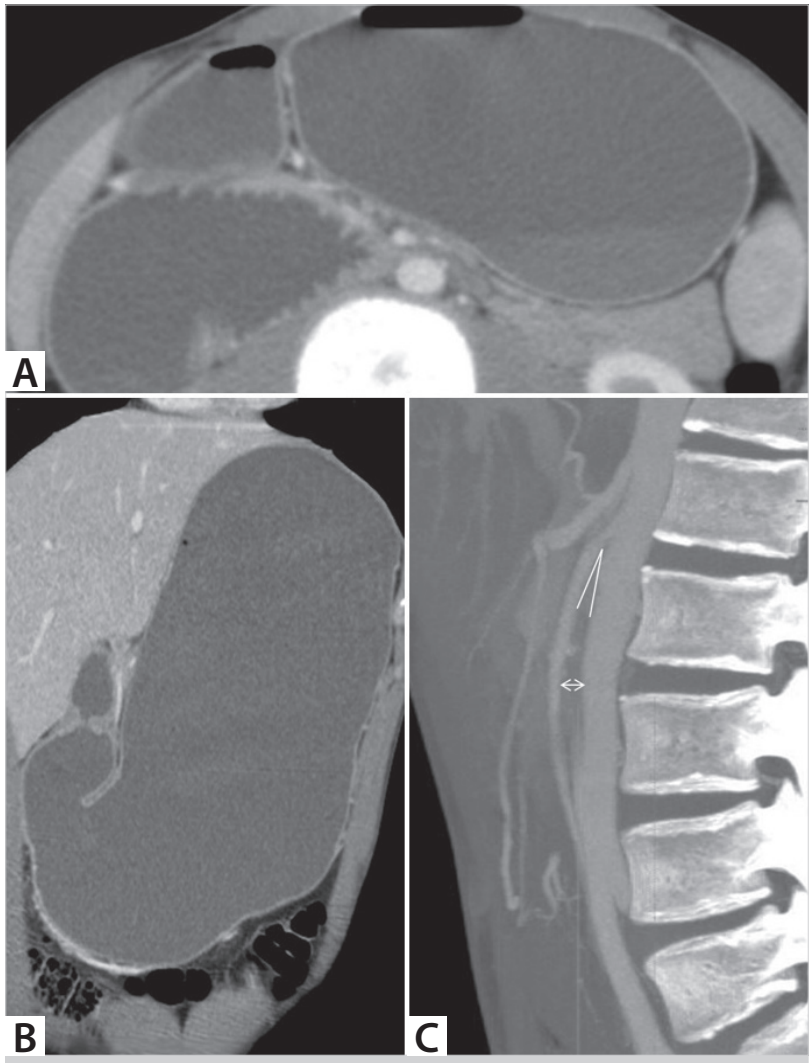

Figure 1. A. Axial and **B.** coronal CT scans show excessive stomach dilation. **C.** Sagittal CT scan shows narrowed SMA-Aort angle (Patient 1).

of the duodenum and in the stomach (Figure 1). The patient was diagnosed with SMA syndrome based on radiological and clinical findings. The patient's height was 172 cm, weight was 44 kg, and body mass index was 14.9 kg/m^2. Total parenteral nutrition and enteral nutrition solutions and a fluid regimen were initiated. The patient gained two kg in two weeks. After medical treatment, the patient's complaints and radiological findings improved. He was discharged with proper feeding and intermittent clinical follow-up recommendations. Four months after discharge, the patient was contacted by telephone; he reported no complications and a weight of 48 kg.

Case 2

A 38-year-old man was admitted to our outpatient clinic with complaints of nausea, vomiting, and abdominal pain. The patient exhibited cachexia and pale colour. No clinically significant findings were present in the patient's laboratory values; moreover, there was no significant disease in his medical history or family history. The patient was subsequently hospitalised. Abdominal CT revealed that the aortomesenteric angle was reduced, the third part of the duodenum was compressed, and the stomach and proximal duodenum were dilated (Figure 2a, b). Thus, the patient was diagnosed with SMA syndrome. Nasogastric decompression was applied; the patient then began to receive intravenous hydration and total parenteral nutrition. The nasogastric tube was withdrawn when it was no longer needed, and a fluid regimen was initiated. Enteral nutrition solutions were added to the diet. The patient's height was 190 cm, weight was 52 kg, and body mass index was 14.4 kg/m^2; the patient was weighed daily during hospitalisation. After two weeks, his weight had increased by three kg and he was able to tolerate a semi-solid regimen; he was discharged with a prescription for enteral nutrition solutions. One week after discharge, he was

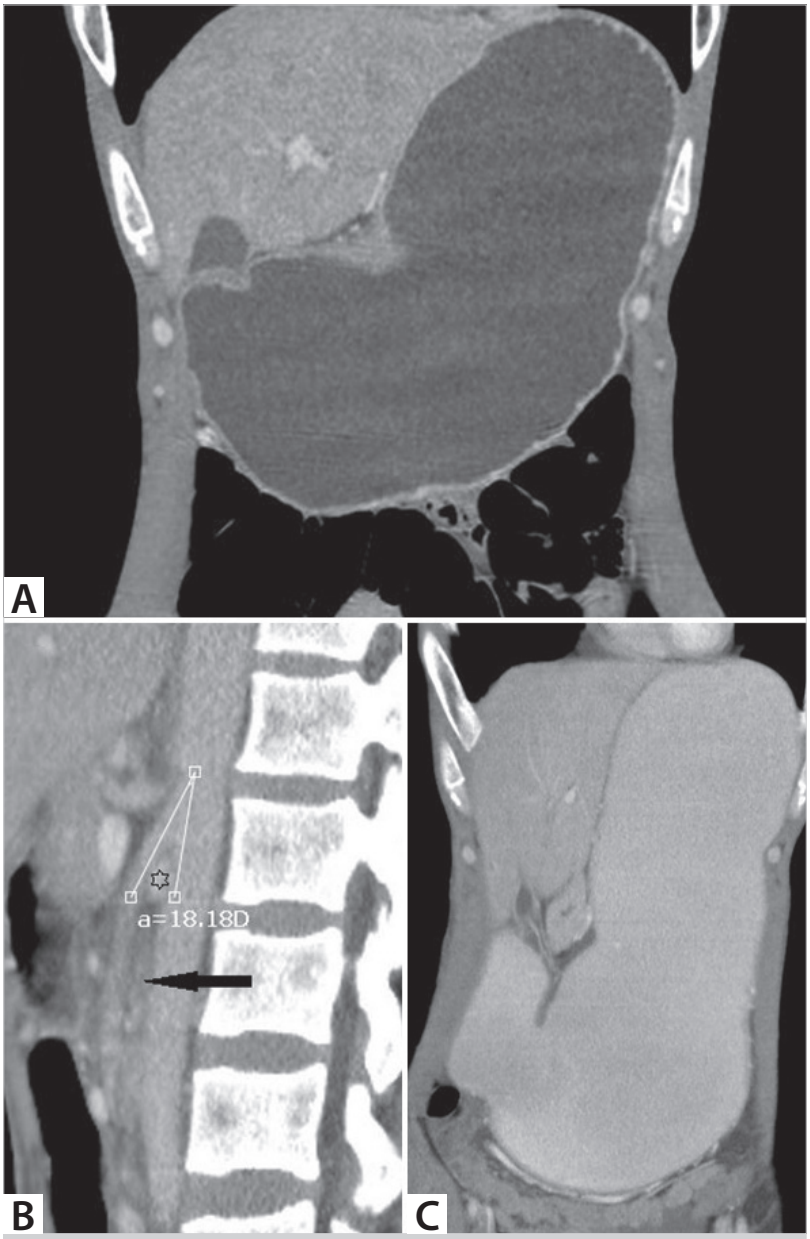

Figure 2. A. Preoperative coronal CT image shows gastric dilatation. **B.** Sagittal CT scan shows narrowing of the aortomesenteric angle and reduction of the aorta-SMA distance. **C.** CT image shows gastric ptosis and gastroparesis after initial surgery (Patient 2).

hospitalised again with the complaint of nausea and vomiting. A nasogastric tube was inserted and total parenteral nutrition was started. Because the patient could not tolerate oral intake, surgery was planned. During laparotomy, the third part of the duodenum was subjected to compression; however, hypertrophic pyloric stenosis was observed. The Treitz ligament was dissected to partially free the duodenum, and pyloroplasty was performed. The postoperative day 4 regimen was started; three days later, a nasogastric tube was inserted again due to excessive vomiting. During subsequent endoscopy, the pylorus was easily passed, the duodenum was easily accessed until the third part, and reflux gastritis and gastric dilatation were observed. Administration of a proton pump inhibitor was initiated, along with domperidone, metoclopramide, and ursodeoxycholic acid. The patient was discharged after treatment and his symptoms returned. Three days after discharge, the patient was again admitted to the ward with excessive abdominal distention and vomiting. CT showed gastric ptosis, gastroparesis, and excessive stomach dilatation (Figure 2c). After routine procedures, reoperation was planned. In the second operation, subtotal gastrec-

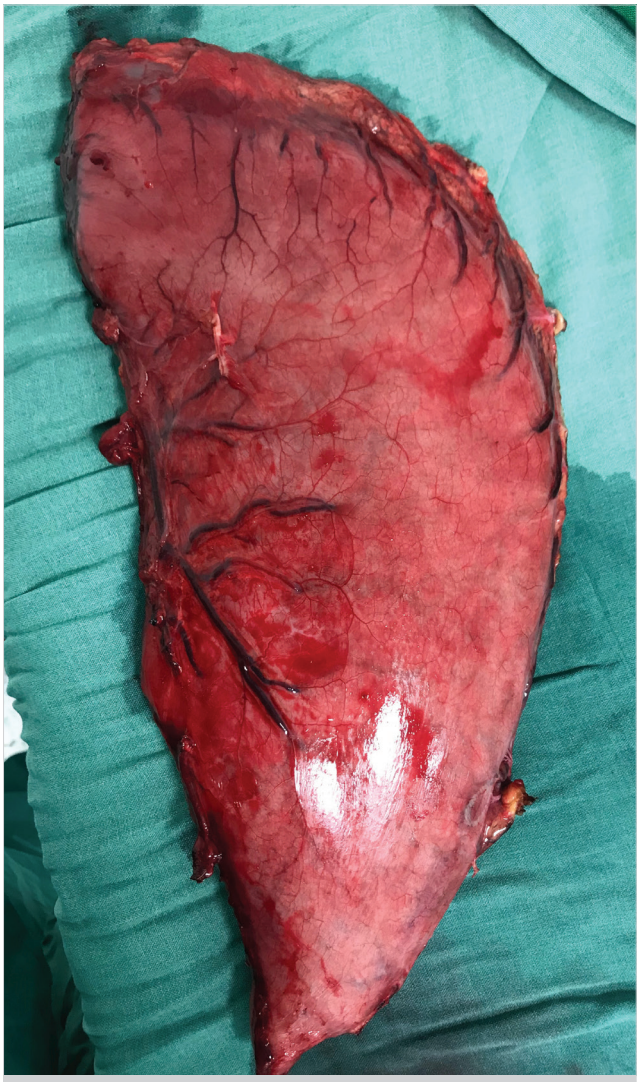

Figure 3. Subtotal gastrectomy and Roux-n-Y gastrojejunostomy specimen obtained during the second operation (Patient 2).

tomy and Roux-n-Y gastrojejunostomy were performed (Figure 3). Intraoperative arterial pressure was monitored by placement of an intraarterial cannula from the radial artery before each induction. Because the patient's body mass index was low, he was given low doses of drugs. After surgery, the patient was safely awakened without any anaesthesia complications. Oral intake was started on the fourth postoperative day, and the patient was discharged on the seventh postoperative day. There were no complications in the second postoperative month, and the patient's weight was 57 kg.

DISCUSSION

SMA syndrome was first mentioned in an anatomy book published by Austrian professor Card von Rokitansky in 1842 (4). A number of patients have been described in the literature. In 1927, Wilkie published a series of 75 cases. Therefore, SMA syndrome is also known as Wilkie's syndrome (1). According to radiological studies, the incidence of SMA syndrome is between 0.2% and 0.78% (5). SMA syndrome is reportedly twofold more common in women than in men; two-thirds of affected patients are between 10 and 39 years of age (1). Our patients were 18 and 38 years old, and both were men.

According to the literature, the factors leading to SMA syndrome may be congenital or acquired. The congenital presence of a short mesentery, presence of an abnormally located SMA or its branches, excessive mobility of the right colon, intestinal malrotation, and abnormal fixation of the duodenum by the Treitz ligament are congenital causes that may lead to the development of SMA syndrome (6). Normally, retroperitoneal adipose and lymphoid tissues serve as a cushion under the SMA, separating it from the vertebral column; this prevents the duodenum from being pinched between the aorta and the SMA. Excess weight loss creates a risk of SMA syndrome by reducing retroperitoneal fat and lymph tissues. Conditions such as anorexia nervosa, burns, obesity surgery, pulmonary tuberculosis, and cardiac cachexia reduce the retroperitoneal fat tissue and cause SMA syndrome. Symptoms may be acute (often after surgical procedures) or progressive. The most common symptoms include anorexia, postprandial epigastric pain, weight loss, nausea, and biliary vomiting (1). Similar symptoms were present in our patients.

The diagnosis should be confirmed by performance of specific radiological examinations in patients with clinical symptoms suggestive of SMA syndrome. Upper abdominal X-ray, upper gastrointestinal system barium radiography, CT, CT angiography, magnetic resonance angiography, ultrasonography, and endoscopy are useful in the diagnosis of SMA syndrome (1). Our patients were diagnosed by CT examination. On plain abdominal X-ray, the presence of gas in the duodenum and stomach is an important finding that supports a diagnosis of SMA syndrome (6). Barium radiography plays an important role in diagnosis. With the expansion of the proximal duodenum, abrupt interruption of barium in the third part is a classical, but non-specific, finding in patients with SMA syndrome. The following findings in barium radiography are important criteria for the diagnosis of SMA syndrome: enlargement in the first and second parts of the duodenum with or without expansion in the stomach; sudden external pressure obstruction in the third part of the duodenum in oblique or vertical style; antiperistaltic current proximal to the obstruction; 4-6 hours' delayed barium passage in the stomach and duodenum; and reduction of obstruction by lying on the left side, in the prone position, and in the knee-elbow position (7).

CT contrast angiography is considered the most important diagnostic method in the diagnosis of SMA syndrome because it shows the aortomesenteric angle, the distance between

the aorta and the SMA, the amount of adipose tissue, the location of the obstruction in the duodenum, and the enlargement proximal to the obstruction. CT can also show tumours and aneurysms, which may cause congestion, and provides a substantial advantage over other diagnostic methods. CT angiography and magnetic resonance angiography are considered equivalent in terms of measuring the aortomesenteric angle and the distance between the aorta and SMA (8). Important diagnostic criteria for SMA syndrome include reduction of the aortomesenteric angle to <20° (normal, 28-65°; in our patients, the aortomesenteric angles were 12 and 18 degrees, respectively), aortomesenteric distance reduction to <8 mm (normal, 10-28 mm; in our patients, the aortomesenteric distances were 5 and 7 mm, respectively) (Figures 1c and 2b), and gastric and proximal duodenal dilatation (5,8).

Upper gastrointestinal endoscopy should be performed in patients with SMA syndrome to exclude obstruction due to intraluminal pathological conditions in the duodenum. In endoscopy, dilation of the first and second parts of the duodenum and stomach, duodenal and gastric ulcers, and alkaline reflux gastritis may be findings that support the diagnosis of SMA syndrome (1).

The purpose of conservative treatment is to provide nutritional support to the patient, to help the patient gain weight, and to recover the loss of the fatty tissue paddle that is presumed to cause narrowing of the aortomesenteric angle. Surgical treatment should be performed in patients with long-lasting complaints who do not respond to conservative treatment (9). Here, we initially treated both patients conservatively and discharged them when they exhibited recovery. However, the development of concomitant hypertrophic pyloric stenosis in our second patient negatively influenced the clinical course and caused the patient to return for further assessment. Surgical treatment options include duodenojejunostomy, gastrojejunostomy, and Strong's procedure (mobilisation of the duodenum by division of Treitz's ligament); currently, duodenojejunostomy is most commonly performed. As a less invasive method, laparoscopic duodenojejunostomy is becoming increasingly common (10). In our second patient, hypertrophic pyloric stenosis had been more prominent in the first operation; thus, we presumed that we could provide palliation by allowing the release of the duodenum via Strong's procedure accompanied by pyloroplasty. However, during postoperative follow-up, gastroparesis and gastric dilatation (Figure 2c) led to persistent vomiting that did not respond to medical treatment; we were compelled to perform subtotal gastrectomy and Roux-n-Y gastrojejunostomy in a second operation (Figure 3).

SMA syndrome should be considered in the differential diagnosis of patients with nausea, vomiting, and weight loss of unknown cause, as well as those who are presumed to exhibit an obstruction at an upper level of the gastrointestinal tract. In the treatment of patients with SMA syndrome, weight-gaining conservative approaches should be tried initially, but surgical treatment should not be excessively delayed in patients who do not respond to medical treatment.

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OLGU SUNUMU-ÖZET
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Üst gastrointestinal sistem tıkanıklığının nadir bir nedeni: Superior mezenterik arter sendromu (Wilkie sendromu); iki farklı olgu sunumu

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ÖZET

Superior mezenterik arter sendromu, duodenumun üçüncü bölümünün aort ve superior mezenterik arter arasında sıkışmasından kaynaklanan klinik semptom ve bulguların bir derlemesi olarak tanımlanmaktadır. Burada superior mezenterik arter sendromu tanısı konan iki farklı olgu sunmak istedik. 18 ve 38 yaşlarında iki hasta kliniğimize bulantı, kusma ve kilo kaybı şikayetleri ile başvurdu. Her iki hastaya bilgisayarlı tomografi yapıldı ve superior mezenterik arter sendromu tanısı kondu. 18 yaşındaki hasta konservatif tedavi ile düzeldi. Ancak 38 yaşındaki hastamız konservatif tedavi ile düzelmedi ve iki kez ameliyat olmak zorunda kaldı. İlk ameliyatta, eşlik eden hipertrofik pilor stenozu nedeniyle Treitz ligamenti diseksiyonu ve piloroplasti ile duodenal geçişi sağladık. İlk ameliyattan sonra gelişen gastroparezi ve gastropitoz nedeniyle ikinci operasyonda subtotal gastrektomi ve Roux-en-Y gastrojejunostomi yapıldı. İkinci ameliyattan sonra hastanın takibinde herhangi bir problem gözlenmedi. Sebebi bilinmeyen bulantı, kusma ve kilo kaybı olan hastalarda ayırıcı tanıda superior mezenterik arter sendromu düşünülmelidir. Tedavide ilk önce kilo aldırıcı konservatif yaklaşımlar denenmeli, ancak tıbbi tedaviye yanıt vermeyen hastalarda cerrahi tedavi çok fazla gecikmemelidir.

Anahtar Kelimeler: Superior mezenterik arter sendromu, Wilkie sendromu, üst gastrointestinal sistem tıkanıklığı

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LETTER TO THE EDITOR
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Comments on 'Percutaneous gas decompression can ease endoscopic derotation in sigmoid volvulus'

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Dear Editor,

I read the article written by Uylas et al. (1) on urgent non-operative treatment of sigmoid volvulus (SV). The authors presented a practice on percutaneous needle decompression in a patient with unsuccessful endoscopic decompression before the second endoscopic trial. My comments relate to the details of urgent SV management based on our 1071-case experience treated over a 57-year period from June 1966 to July 2023, which contains the largest single-centre SV data over the world (2).

In SV, flexible endoscopic decompression is the first-line treatment option in patients without bowel ischemia and perforation (3). This procedure may be performed with 55%-94% of success, 0%-2% of mortality, and 2%-20% of morbidity rates (4). In our 777-patient endoscopy experience including 351 rigid and 426 flexible practices, the success rate is 83.4%, while mortality and morbidity rates are 0.5% and 1.8%, respectively. Patients with unsuccessful endoscopic decompression are potential candidates for urgent surgery with 1%-30% of mortality and 5%-60% of morbidity rates. In our series, these rates are 17.3% and 34.2%, respectively, in the 486-case urgent surgery group. Due to the poor prognosis of urgent surgery, percutaneous needle decompression may be an alternative option in selected patients in the management of SV, as was demonstrated by the authors.

Although percutaneous needle decompression has some advantages when admitted before surgery or endoscopy, unfortunately, patient selection criteria and technical details are still unclear (5). This procedure is not free of complications including perforation and peritonitis, which is possible due to the excessive dilatation of the sigmoid colon in addition to bleeding (1). For this reason, in my theoretical opinion and clinical experience, percutaneous needle decompression requires some practical rules mentioned below:

1. Primary SV cases are not proper candidates, while patients with unsuccessful endoscopic decompression constitute the main indication field.
2. Before the procedure, the practitioners must be sure about the absence of bowel gangrene, which requires urgent surgery without any delay.
3. Application during the first unsuccessful endoscopy instead of second procedure may prevent a repetitive preparation and practice.
4. The procedure is relatively painful, which may require deep sedation and/or local anesthesia.
5. Following the procedure, medical observation is required to see the complications on time.
6. When a perforation is suspected or determined, urgent surgery must be performed following an early and effective resuscitation.

I congratulate the authors and I look forward to their reply.

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