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TJS

EDITORIAL

ORIGINAL ARTICLES

CASE REPORTS

ABSTRACTS

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The Thai Journal of Surgery is the official publication of The Royal College of Surgeons of Thailand and is issued quarterly.

The Thai Journal of Surgery invites concise original articles in clinical and experimental surgery, surgical education, surgical history, surgical techniques, and devices, as well as review articles in surgery and related fields. Papers in basic science and translational medicine related to surgery are also welcome.

Aim & Scope

The Thai Journal of Surgery is dedicated to serving the needs of the members of The Royal College of Surgeons of Thailand, specifically the younger researchers and surgical trainees who wish to have an outlet for their research endeavors. The Royal College strives to encourage and help develop Thai Surgeons to become competent researchers in all their chosen fields. With an international outlook, The Thai Journal of Surgery welcomes submissions from outside of Thailand as well.

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2. Corporate Author:

- The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma glutamyltransferase in blood. Scand J Clin Lab Invest 1976; 36:119-25.
- American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

3. Personal Author(s):

- Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice - Hall, 1976.

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- o Chirappapha P, Arunnart M, Lertsithichai P, et al. Evaluation the effect of preserving intercostobrachial nerve in axillary dissection for breast cancer patient. Gland Surg 2019;8:599-608. doi:10.21037/gs.2019.10.06.

Abbreviations

Use only standard abbreviations of commonly used approved abbreviations. Avoid abbreviations in the title. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

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All statistical analyses and the statistical software used must be concisely described. Descriptive statistics for quantitative variables must include an appropriate central tendency measure (e.g., mean or median) as well as a corresponding measure of spread (e.g., standard deviation or range or interquartile range). Categorical variables must be summarized in terms of frequency (counts) and percentage for each category. Ordinal variables can be summarized in terms of frequency and percentage, or as quantitative variables when appropriate. Statistical tests must be named and p-values provided to 3 decimal places. P-values less than 0.001 should be written "< 0.001" and p-values approaching 1 should be written "0.999".

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(see Format https://bit.ly/3IaP4ZB)

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Use the common format. Emphasis is on clinician comprehension. The **Abstract** uses the same common structured format. In the **Main text,** the **Introduction,** in addition to the usual context setting and rationale, should also contain explanations and descriptions of basic science concepts at the level of the educated layman. The **Methods** section should still be concise with sufficient detail for others to replicate the experiment, but one or two paragraphs in between explaining basic processes in plain English would be helpful. In the **Results** section, similar conciseness is still the rule, but a brief simplified summary of the findings should be provided. In the **Discussion,** clinical implications should be clearly stated. The **Conclusion,** again, should answer the research question.

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We encourage publication of case series or case reports if a comprehensive review of the literature is included, with the aim of helping the clinician manage rare and challenging diseases or conditions based on best available evidence in conjunction with practical, local experience. For the Thai Journal of Surgery, this implies that the case report format differs somewhat from that of the common format for research articles.

Abstract: Need not be structured. State objective of the case presentation, present a summary of the case, the outcome and learning points in one concise paragraph.

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Editorial

Doonyapat Sa-Nguanraksa, MD, PhD

Editor of The Thai Journal of Surgery

In this Thai Journal of Surgery issue, we present a series of original articles and case reports highlighting the ongoing progress in the field. These contributions reflect the expertise and dedication of Thai surgeons in improving patient care and outcomes.

Among the original articles, we explore the comparison between early breast cancer patients who underwent sentinel lymph node examination using One-Step Nucleic Acid Amplification (OSNA) versus conventional pathological examination. This study offers compelling evidence that could influence treatment decisions and survival outcomes for early-stage breast cancer patients, marking an important step in precision oncology. We also feature a study on laparoscopic surgery for groin hernia repair, showcasing the advantages of minimally invasive techniques in terms of reduced recovery time and lower complication rates. Additionally, an article on central venous catheterization in general surgery patients provides valuable insights into the success rates and complications associated with this critical procedure, emphasizing the importance of proper technique and training.

We also highlight two unique case reports: the first three simultaneous pancreas-kidney transplants performed at Ramathibodi Hospital, which provide invaluable lessons for multi-organ transplantation, and a rare case of axillary cancer of unknown primary in a male patient with PALB2 pathogenic variants. These case reports underline the complexity of surgical decision-making in rare and challenging scenarios.

The pursuit of knowledge through research is key to the advancement of surgery. This issue of ***TJS*** also features the abstracts from the 49th Annual Scientific Congress of The Royal College of Surgeons of Thailand, including 35 abstracts from the Free Paper sessions in General Surgery and Pediatric Surgery. These abstracts represent the cutting-edge work being done by surgeons across Thailand, covering a wide range of surgical specialties. The contributions of these researchers are vital to the continuous evolution of surgical practices and will undoubtedly inspire further innovation in the field.

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Original Article

Comparison Between Early Breast Cancer Patients Who Underwent Sentinel Lymph Node Examination by One-Step Nucleic Acid Amplification and Conventional Pathological Examination in Terms of Breast Cancer Treatment and Survival Outcome

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Abstract

Background: Sentinel lymph node biopsy (SLNB) is a standard axillary staging for early breast cancer. One-step nucleic acid amplification (OSNA) is a new molecular technique for intraoperative examination to measure the copies of cytokeratin 19 (CK19) mRNA. A higher proportion of micrometastasis detected by OSNA has been reported. However, the impact on treatment planning and survival outcomes is still inconclusive.

Objectives: To compare the adjuvant systemic treatment in the patients who underwent SLNB examination by conventional pathological examination and OSNA assay and survival outcomes between these two groups.

Patients and Methods: A retrospective review of patients with early breast cancer who underwent SLNB from 2014-2018 was performed. Adjuvant systemic treatments were compared between the two groups using Chi-square statistics. The log-rank test analyzed the survival outcome.

Results: There were 109 and 110 patients in the OSNA and conventional groups, respectively. The OSNA group had a higher proportion of positive SLN than the conventional group (40.4% vs. 18.2%; $p = 0.004$). A higher percentage of the patients in the OSNA group received doxorubicin/cyclophosphamide followed by paclitaxel (43.9% vs. 23.0%, $p = 0.041$). A higher proportion of the patients in the OSNA group received HER2-targeted therapy (12.8% vs. 3.6%; $p = 0.013$). There was no difference in axillary recurrence, disease-free survival, or overall survival.

Conclusion: Utilization of the OSNA technique resulted in a higher proportion of positive SLN and led to the escalation of the chemotherapy regimen. However, the impact on survival outcomes could not be demonstrated. The OSNA technique should be applied in selected patients who require immediate ALND after positive SLNs or need a decision to avoid ALND in cases of limited metastasis in SLNs.

Keywords: Breast cancer, One-step nucleic acid amplification, Sentinel lymph node biopsy, Survival outcome

Introduction

Breast cancer is the most common cancer in women worldwide and also in Thailand.[1] Sentinel lymph node biopsy (SLNB) is now a standard axillary staging procedure for patients with clinical node-negative breast cancer.[2] In addition, Bilimoria et al. reported no significant difference in axillary recurrence between the patients who underwent axillary lymph node dissection (ALND) for micrometastasis in SLN and SLNB alone. On the other hand, the patients with macroscopic SLN metastases exhibited a lower risk of axillary recurrence when ALND was performed compared to SLNB alone.[3]

ALND was reported to be associated with paresthesia, lymphedema, seroma, sensory change, and limitation of shoulder motion.[4] These findings indicated that ALND should be omitted in breast cancer patients with one or two micrometastasis. Additionally, there is a sufficient foundation to avoid ALND in cases of SLN macrometastasis or in individuals who have had a mastectomy.

Common intraoperative analysis of sentinel lymph nodes (SLN) is performed by frozen section histopathology (FS) using hematoxylin and eosin (H&E) staining. However, some shortcomings, such as low sensitivity (57% - 74%) and false-negative results in detecting micrometastasis, were found in this examination assay. Consequently, there might be a chance of micrometastasis being understaged.[5] Therefore, a novel intraoperative molecular technique has been developed to solve the problems.[6] One-step nucleic acid amplification (OSNA) is a molecular detection technique for intraoperative examination to measure the copies of cytokeratin 19 (CK19) mRNA, which is approximately 98% expressed in breast cancers. The metastasis is detected by reverse-transcription loop-mediated isothermal amplification of CK19 mRNA.[7] OSNA analysis provides several advantages in objectivity, reproducibility, standardization, and prediction of non-SLN metastasis.[8-12] This technique was developed for the diagnosis of whole nodes during breast cancer surgery. Moreover, it can minimize the need for secondary surgery.[13]

The specificity and sensitivity between OSNA and FS were compared using the postoperative formalin-fixed tissue histological diagnoses as the gold standard.[11,14] The sensitivity of FS histological examination was generally higher than that of the OSNA assay, while the specificity was similar. However, the SLNs detection of the OSNA

assay may fail due to a selection bias in the study's design, and the specimen may be insufficient for the OSNA assay in some cases.[11] Osako et al. reported that a higher proportion of micrometastasis could be detected by OSNA than the conventional pathological method.[15] Wang et al. compared the ability of analysis among OSNA, FS, and imprint cytology. They found that the sensitivity of OSNA was higher than that of FS (77.6% vs. 69.7%) and imprint cytology (83.6% vs. 76.2%).[11] On the other hand, Ruano et al. found that the OSNA assay can improve axillary staging. Still, an improved axillary staging from the OSNA assay failed to alter adjuvant systemic therapy significantly.[16]

The OSNA assay can be performed by a laboratory technician, whereas the technician and pathologist are required for sectioning and diagnosis, respectively, in the frozen section examination.[6] The pathological examination occasionally lacks reproducibility, standardization, and criteria for diagnosing SLNs. OSNA was recommended because it can be used for clinical diagnostic work.[17] The upstaging by the OSNA method increased axillary dissection and may result in different adjuvant treatments, eventually leading to different survival outcomes. This study was conducted to compare the treatment that patients received after being analyzed by OSNA assay, frozen section, and permanent section histological examinations.

Patients and Methods

Patients

Breast cancer patients were retrospectively recruited from the Division of Head Neck and Breast Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, from January 2014 to December 2018. This study was approved by the Siriraj Institutional Review Board (certificate of approval number Si 679/2019). All of the patients were female and more than 18 years old. They were diagnosed with early breast cancer by pathological examination and had no clinical lymphadenopathy on physical examination, which was confirmed by mammography and breast ultrasonography before surgery.

Evaluation of SLNs

SLNB was performed using a standard technique using 1% isosalfan blue dye. The patients with micrometastasis or macrometastasis in the SLNs underwent ALND, and axillary contents were sent for pathological examination. In the conventional group, the tissues were sent for FS after SLNs were dissected from the axilla. The FS was evaluated by step serial section with a 2-millimeter interval. The surgical team was notified intraoperatively to justify further ALND. All SLN tissue was re-evaluated using the standard H&E technique with an interval of 200 microns. In the OSNA group, after SLNs were dissected, perinodal fat was removed from the SLNs and sent for a permanent section. The whole lymph nodes were examined using the OSNA assay as described previously.[12]

Statistical analysis

All statistical data analyses were performed using IBM SPSS version 21.0 (IBM Corp. 2012). Comparisons between categorical parameters were performed using chi-squared statistics. Continuous parameters were compared using an independent *t*-test. A log-rank test was used for survival analysis. The p-value of < 0.05 was considered to be statistically significant.

Results

Patients' characteristics

A total of 219 early breast cancer patients who underwent SLNB were divided into two groups: the OSNA group and the conventional group. The patients in the OSNA group received a mastectomy, had HER2 positivity, and had more advanced nodal staging ($p = 0.041$, 0.038, and 0.004, respectively). Table 1 summarizes the characteristics of the enrolled patients.

Table 1 Characteristics of the patients

	OSNA, n = 109 (%)	Conventional, n = 110 (%)	*p*-values
Age at diagnosis, mean ± SD	56.05 ± 12.11	57.32 ± 11.30	0.422
Menopausal status			
Premenopause	37 (33.9)	30 (27.3)	0.284
Postmenopause	72 (66.1)	80 (72.7)	
Breast Surgery			0.041
Mastectomy	90 (82.6)	78 (70.9)	
Breast-conserving surgery	19 (17.4)	32 (29.1)	
Histologic cell type			
Invasive ductal carcinoma	100 (91.7)	102 (92.7)	0.948
Invasive lobular carcinoma	3 (2.8)	3 (2.7)	
Others	6 (5.5)	5 (4.5)	
Estrogen receptor			
Negative	26 (23.9)	27 (24.5)	0.905
Positive	83 (76.1)	83 (75.5)	
Progesterone receptor			
Negative	38 (34.9)	26 (23.6)	0.068
Positive	71 (65.1)	84 (76.4)	
HER2 status			
Negative	72 (66.1)	88 (80.0)	0.038
Positive	35 (32.1)	19 (17.3)	
Unknown	2 (1.8)	3 (2.7)	
T staging			
T1	55 (50.5)	59 (53.6)	0.666
T2	50 (45.9)	49 (44.5)	
T3	4 (3.7)	2 (1.8)	
N staging			
N0	65 (59.6)	90 (81.8)	< 0.001
N1mi	15 (13.8)	0	
N1	20 (18.3)	17 (15.5)	
N2-3	9 (8.3)	3 (2.7)	

SLNB results

The proportion of micrometastasis was significantly higher in the OSNA group ($p = 0.002$). All patients with positive SLNs in the OSNA group received ALND. Four patients in the OSNA group with negative SLNs underwent ALND due to intraoperative findings of axillary lymphadenopathy (3 patients), and one patient had latissimus dorsi flap reconstruction. Additional axillary node metastasis in the non-SLNs (ALND specimens) was not different between the two groups ($p = 0.350$). In the micrometastasis SLNs subgroup, additional metastasis in non-SLNs was not different between the two groups ($p = 0.286$). Table 2 summarizes the axillary node status in the patients with positive SLNs.

Adjuvant treatments

A higher percentage of the patients in the OSNA group received doxorubicin/cyclophosphamide followed by paclitaxel (ACT) compared to the conventional group. In a subgroup of 15 patients with N1mi (all were in the OSNA group), 3 patients received doxorubicin/cyclophosphamide (AC), 5 patients received ACT, and 1 patient received docetaxel and cyclophosphamide (TC). A higher proportion of the patients in the OSNA group received HER2-targeted therapy ($p = 0.013$) due to more HER2-positive breast cancer in the OSNA group. Subgroup analysis of HER2-positive breast cancer showed that 12

out of 35 patients (34.3%) in the OSNA group received HER2-targeted therapy, while 4 out of 19 patients (21.1%) in the conventional group received the treatment.

More patients in the conventional group received radiotherapy compared to the OSNA group ($p = 0.049$). All the patients with N1mi (all were in the OSNA group) did not receive radiotherapy. Subgroup analysis of the patients who had mastectomy showed that there was no difference in radiotherapy between the OSNA and conventional groups ($p = 0.849$). There was no difference in hormonal therapy between the two groups. Table 3 summarizes the adjuvant treatments of the patients.

Table 2 Axillary node status in the patients with positive SLNs

	OSNA, n (%)	Conventional, n (%)	*p*-values
Sentinel node status			
All micrometastasis	20 (47.6)	1 (5.6)	0.002
Micro+macrometastsis or all macrometastasis	22 (52.4)	17 (94.4)	
Number of SLN with micrometastasis			
1	17 (85.0)	1 (100.0)	1.000
2	3 (15.0)	0	
Axillary lymph node dissection			
No	0 (0.0)	5 (27.8)	< 0.001
Yes	42 (100.0)	13 (72.2)	
Additional axillary node metastasis			
No	25 (59.5)	13 (72.2)	0.350
Yes	17 (40.5)	5 (27.8)	
Additional axillary node metastasis in the patients with micrometastasis			
No	15 (75.0)	0	0.286
Yes	5 (25.0)	1 (100)	

Table 3 Adjuvant treatments of the patients

	OSNA, n (%)	Conventional, n (%)	*p*-values
Chemotherapy			
No	43 (39.4)	49 (44.5)	0.445
Yes	66 (60.6)	61 (55.5)	
Chemotherapy regimen			
AC	29 (43.9)	30 (55.7)	0.041
ACT	29 (43.9)	14 (23.0)	
TC	7 (10.6)	13 (21.3)	
CMF	1 (1.5)	0	
HER2 targeted therapy (in HER2+ subgroup)			
No	23 (65.7)	15 (78.9)	0.309
Yes	12 (34.3)	4 (21.1)	
Hormonal therapy			
No	27 (24.8)	22 (20.0)	0.397
Yes	82 (75.2)	88 (80.0)	
Radiotherapy			
No	80 (73.4)	67 (60.9)	0.049
Yes	29 (26.6)	43 (39.1)	

AC: doxorubicin/cyclophosphamide
ACT: doxorubicin/cyclophosphamide followed by paclitaxel
TC: docetaxel and cyclophosphamide
CMF: cyclophosphamide/methotrexate/fluorouracil

Survival outcome

The median follow-up time was 87 (7-103) months. Axillary recurrence occurred in 2 patients in the OSNA group at 13 and 23 months after surgery (one patient with HER2-positive breast cancer did not receive HER2-targeted treatment and had axillary recurrence at 13 months) and one patient in the conventional group (at 6 months after surgery). There were two in-breast recurrences in the OSNA group. Distant metastasis occurred in 6 and 4 patients in the OSNA and conventional groups. Three deaths occurred in the conventional group. No mortality occurred in the OSNA group. The two groups had no significant difference in disease-free survival and overall survival ($p = 0.385$ and $p = 0.138$, respectively). The survival curves are shown in Figure 1.

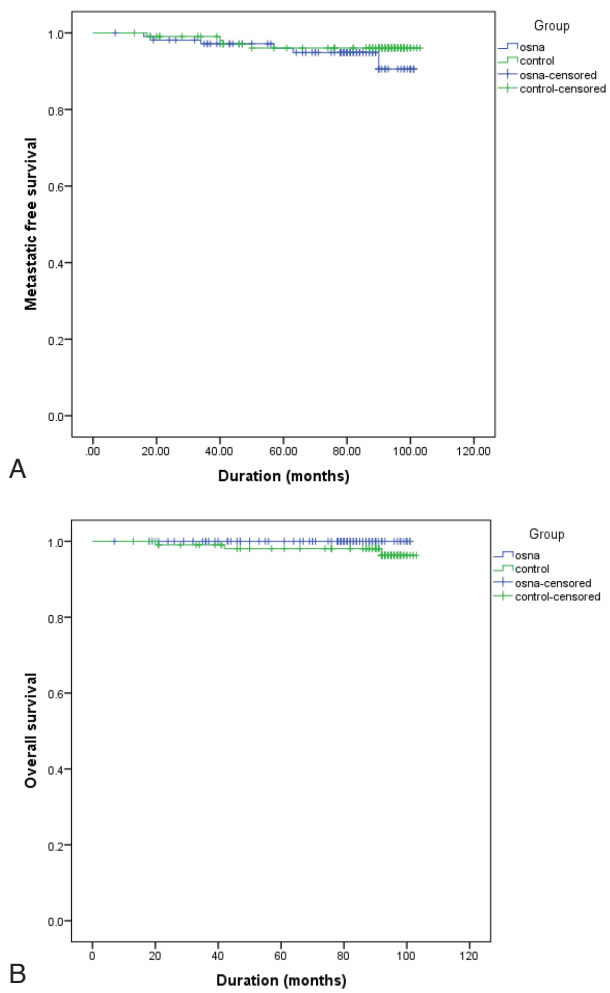

Figure 1 Kaplan-Meier plots comparing (A) metastatic-free survival and (B) overall survival in early breast cancer patients assessed with one-step nucleic acid amplification versus conventional pathological examination for sentinel lymph node evaluation

Discussion

SLNB is an important procedure for axillary staging in breast cancer.[2] After the OSNA technique was introduced for detecting cytokeratin 19 for metastasis lymph nodes, it was found that the OSNA technique could improve axillary staging better than conventional techniques such as FS because of the OSNA assay's ability to detect lower volume nodal metastases.[11,15] This evidence supports the current finding that the OSNA technique can detect more micrometastasis in SLNs. However, a study by Ruano et al. reported that although more micrometastasis was detected, the OSNA technique did not alter adjuvant treatments.[16] The previous study had a questionable pitfall in study design. The patients in the control and OSNA groups were not enrolled simultaneously so that the treatment guidelines might be changed. The current study aimed to improve this pitfall by collecting subjects who received treatment in the same period.

In our recent study, the percentage of SLN micrometastasis detected by OSNA was similar to the study by van Haaren et al. (14.9%) but slightly lower than the previous study by Ruano et al. (18.9%).[16,18] In contrast, SLN micrometastasis detected by conventional technique was similar to the study by van Haaren et al. but much lower when compared to the study by Ruano et al. This might be because no immunohistochemistry staining was performed to detect micrometastasis in our study.

Our study found that 25% of the patients with micrometastasis in SLN had additional axillary node metastasis. This finding was concordant with the study by Viale et al., which reported a percentage of 16% in SLN metastasis of less than 1 mm and 32% in SLN metastasis of 1-2 mm.[19] but higher than the results from the IBCSG 23-01, a randomized control trial study comparing ALND versus omitting ALND in the patients with SLN micrometastasis, that reported 13% additional node involvement.[20] Axillary node status is the significant prognostic factor that guides the plan of treatment. Tumor burden in axillary nodes correlates with prognosis, although there was a very small tumor burden. Several studies showed poorer prognosis in patients with micrometastasis.[21,22] In contrast, IBCSG 23-01 demonstrated similar survival between the two groups. On the other hand, the patients in the ALND group encountered neuropathy and lymphedema.[20]

The patients in the OSNA group had a higher percentage of receiving an ACT chemotherapy regimen than the conventional group due to higher positive SLN rates.

One-third of the patients with N1mi also received the ACT regimen. A higher percentage of the patients in the OSNA group received anti-HER2 therapy. This might be due to the higher number of HER2-positive patients in the OSNA group. However, subgroup analysis in HER2-positive breast cancer showed that the patients in the OSNA group still had a higher percentage of anti-HER2 therapy but not statistically significant. This finding might be due to upstaging by positive SLN in the OSNA group. A larger number of patients might be needed to address this issue.

More patients in the conventional group received radiotherapy compared to the OSNA group. This might be due to the higher proportion of the patients in the conventional group receiving breast-conserving surgery, and all the patients with N1mi (all were in the OSNA group) did not receive radiotherapy.

There were 2 axillary recurrences in the OSNA group, which is higher than the axillary recurrence rate after negative SLNB.[23] This might be due to the SLN misidentification during SLNB, leading to a false negative result. In addition, since CK19 was not expressed in all breast cancer tissue and CK19 expression was not confirmed in the primary cancer, there might be a small chance of metastatic SLN that cannot be detected by OSNA.[24] Another reason might be that one of the patients did not receive HER2-targeted therapy after surgery.

Due to the retrospective nature of the current study, selection bias can occur, leading to a difference in the proportion of HER2-positive breast cancer and more advanced nodal staging in the OSNA group. There was no difference in disease-free survival and overall survival among the patients in the two groups. These findings might be due to the small sample size and the small number of events that occurred during the follow-up period.

Conclusion

The results of the current study indicated that the utilization of the OSNA technique resulted in a higher proportion of positive SLNs, especially micrometastasis. However, this study could not demonstrate the impact on adjuvant therapy and survival outcomes. Intraoperative assessment of SLNs using the OSNA technique should be applied in selected patients who require immediate ALND after positive SLNs or need a decision to avoid ALND in cases of limited metastasis in SLNs. Therefore, OSNA is the alternative method for intraoperative assessment of SLN.

Conflict of Interests

The authors declared no conflict of interest.

Funding

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Original Article

Laparoscopic Surgery for Groin Hernia Repair: Single-Center Experience

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Abstract

Background: Inguinal hernia arises from a condition characterized by a weakened abdominal wall. Laparoscopic inguinal hernia surgery is one treatment option. Due to the increasing use of laparoscopic inguinal hernia repair at Srinagarind Hospital, we are interested in studying these patients' side effects and treatment outcomes.

Materials and Methods: A descriptive study collected data between December 2011 and May 2022 at Srinagarind Hospital, Khon Kaen University. The medical records were reviewed, and data was collected. Descriptive statistics were used to analyze the data and report the side effects and treatment outcomes.

Results: A total of 269 patients underwent laparoscopic inguinal hernia repair. Among these patients, 251 were males (93.31%), and 18 were females (6.69%). The median age of the patients was 64 (IQR, 54-71). The most common comorbidities were hypertension (36.43%) and benign prostatic hyperplasia (BPH) (26.32%). The most common diagnosis was indirect inguinal hernia (40.89%). The overall median operative time was 65 minutes (IQR, 55-90). The median blood loss during the procedure was 5 milliliters (IQR, 5-10). The most common complication observed was hematoma, which occurred in approximately 16 cases (5.95%). Infection occurred in two cases (0.74%), and the recurrence rate was 1.49%.

Conclusions: Laparoscopic surgery for inguinal hernia repair was found to be efficient, safe, and comparable to other international studies regarding complications and recurrent rates, with no reported mortality.

Keywords: Inguinal hernia, Laparoscopic, TAPP, TEP, Complications

Introduction

An inguinal hernia arises from a condition characterized by a weakened abdominal wall, leading to the protrusion of internal abdominal organs such as the intestines and fatty tissue (omentum) into the groin area. It is found in 27-43% of men and 3-6% of women.[1] The condition is often accompanied by symptoms such as pain, swelling, and intestinal obstruction, which require surgical treatment. The traditional classification of inguinal hernias includes indirect inguinal hernia (IIH), direct inguinal hernia (DIH), and femoral hernia.[2]

Laparoscopic inguinal hernia surgery is increasingly popular among patients who have undergone open surgery or experienced recurrence. It is especially ben-

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eficial for patients who require a small surgical incision. Studies have shown that laparoscopic surgery can help reduce groin pain after the procedure when compared to open surgery.[3]

There are two commonly used approaches to laparoscopic repair of inguinal and femoral hernias involve two different anatomical approaches to the preperitoneal space: totally extraperitoneal (TEP) hernia repair and transabdominal preperitoneal (TAPP) hernia repair.

TEP repair was performed in the preperitoneal space and was developed to avoid the risks of entering the peritoneal cavity.[4,5] The surgeon creates a working space between the peritoneum and the anterior abdominal wall. This approach has the advantage of eliminating the risk of intra-abdominal adhesion formation.[5,6]

On the other hand, TAPP repair is performed within the intra-peritoneal cavity by placing the mesh in a preperitoneal position and covering it with the peritoneum to keep it away from the bowel. It provides a larger working space than TEP repair, with easy access to both groins. TAPP repair can also be attempted in patients with prior lower abdominal surgery. Nevertheless, the TAPP repair procedure is not without its potential risks, including the possibility of inflicting injuries upon adjacent intra-abdominal organs, the formation of adhesions leading to intestinal obstruction, or even the occurrence of bowel herniation.[6,7]

Due to the increasing use of laparoscopic inguinal hernia repair at Srinagarind Hospital, researchers are interested in studying the treatment outcomes and potential side effects experienced by these patients.

Materials and Methods

A descriptive study was conducted on patients diagnosed with inguinal hernia and undergoing laparoscopic inguinal hernia treatment, including TAPP and TEP laparoscopic techniques, at Srinagarind Hospital from December 2011 to May 2022. Patients who had lost their medical records were excluded from the study.

The medical records were reviewed, and data was collected across various categories, including gender, age, diagnosis, underlying diseases, previous abdominal surgery, operative time, and complications. Postoperative pain was assessed using a pain score measured on a numeric pain rating scale, ranging from 0 (indicating no pain) to 10 (indicating the possibility of worsening pain). Pain scores were recorded immediately after the operation and on the first postoperative day. Blood loss is evaluated by anesthesiologists. They use several methods, such as visual estimation, surgical suction canisters, or weighing sponges and swabs. Descriptive statistics were employed to report all collected data.

Results

A total of 269 patients underwent laparoscopic inguinal hernia repair. Among these patients, 251 were males (93.31%), and 18 were females (6.69%). The median age of the patients was 64 (IQR, 54-71). The most common comorbidities observed were hypertension (36.43%), benign prostatic hyperplasia (26.32%), and dyslipidemia (17.83%).

Out of the 269 patients, 219 (81.41%) underwent totally extraperitoneal (TEP) repair, while 48 (17.84%) underwent transabdominal pre-peritoneal (TAPP) repair. Two patients required conversion to open hernia repair.

The most common diagnoses were indirect inguinal hernia (40.89%), bilateral direct inguinal hernia (20.07%), recurrent indirect inguinal hernia (12.64%), and direct inguinal hernia (11.15%) (Table 1).

Table 1 Baseline characteristics

Variable	N = 269 (%)
Sex	
Male	251 (93.31)
Age (year)	
Median	64 (IQR, 54-71)
Comorbidity	
Hypertension	98 (36.43)
BPH	70 (26.32)
Dyslipidemia	48 (17.83)
DM	23 (8.55)
Cirrhosis	8 (2.97)
COPD	6 (2.23)
Morbid obesity	3 (1.11)
Procedure	
TEP	219 (81.41)
TAPP	48 (17.84)
Other*	2 (0.74)
Diagnosis	
IIH	110 (40.89)
DIH	30 (11.15)
Pantaloon	4 (1.49)
Bilateral DIH	54 (20.07)
Bilateral IIH	11 (4.09)
Recurrent IIH	34 (12.64)
Recurrent DIH	12 (4.46)
Recurrent bilateral DIH	5 (1.86)
Recurrent bilateral IIH	9 (3.34)

*Convert to open hernioplasty

Among the 110 patients with unilateral indirect inguinal hernia, the distribution was as follows: 4.55% had the bubonocele type, 77.27% had the funicular type, and 18.18% had the scrotal type (Table 2).

Table 2 Indirect inguinal hernia (IIH) type

Unilat IIH	**N = 110 (%)**
Bubonocele	5 (4.55)
Funicular	85 (77.27)
Scrotal	20 (18.18)
Bilat IIH	**N = 11 (%)**
Bubonocele	2 (18.18)
Funicular	8 (72.73)
Scrotal	2 (9.09)
Recurrent IIH	**N = 34 (%)**
Bubonocele	1 (2.94)
Funicular	30 88.24)
Scrotal	3 (8.82)
Recurrent bilat IIH	**N = 9 (%)**
Bubonocele	1 (11.11)
Funicular	8 (88.89)
Scrotal	0

The overall median operative time was 65 minutes (IQR, 55-90). The longest operative time was observed in cases of bilateral indirect inguinal hernia and recurrent indirect inguinal hernia, which averaged around 95 minutes. The overall median blood loss during the procedure was 5 milliliters (IQR, 5-10), with recurrent indirect inguinal hernia showing the highest median blood loss of approximately 10 milliliters. The median hospital stay for all patients was 3 days (IQR, 2-3) (Figure 1).

The overall median immediate postoperative pain score was 4 (IQR, 2-6), while the median pain score on postoperative day 1 was 2 (IQR, 1-4) (Figure 2).

There were two cases (0.74%) of intraoperative complications: corona mortis injury in bilateral indirect inguinal hernia and bradycardia in recurrent indirect inguinal hernia. The most common complication observed was hematoma, which occurred in approximately 16 cases (5.95%). Infection was observed in two cases (0.74%), and the recurrence rate was 1.49% (Table 3).

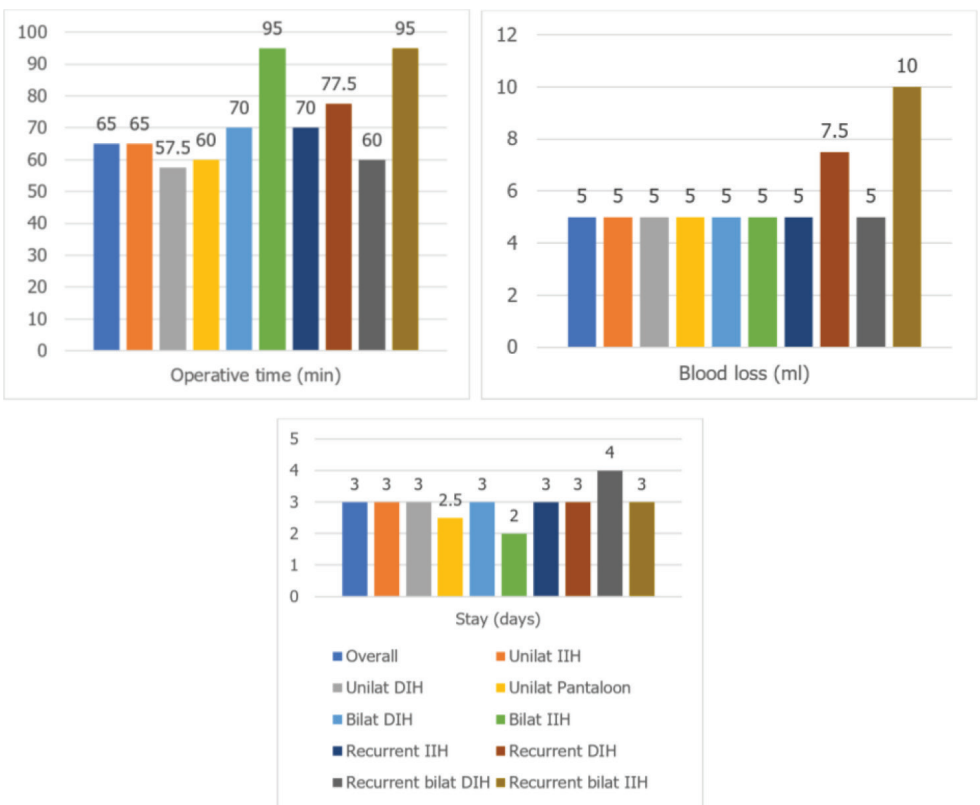

Figure 1 Post-operative pain score by types of inguinal hernia

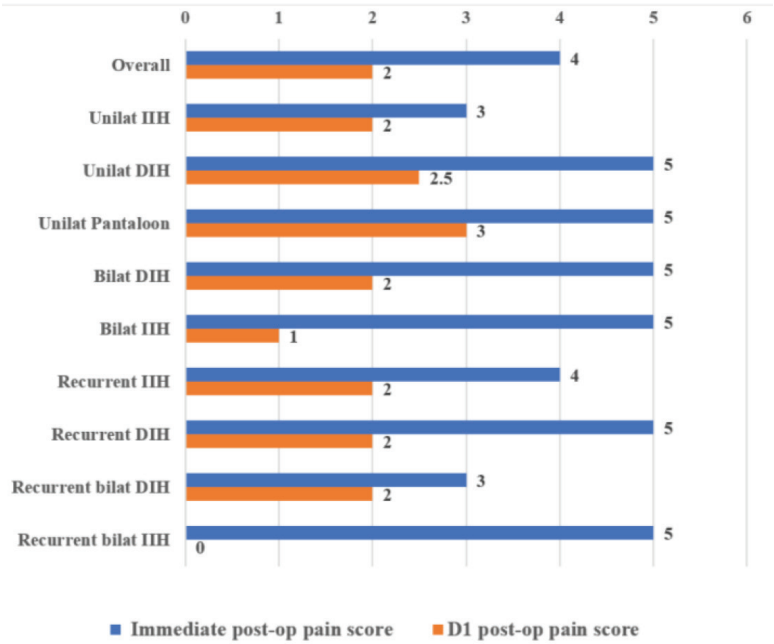

Figure 2 Post-operative pain score by types of inguinal hernia

Table 3 Complication of Laparoscopic surgery for groin hernia repair

Type	Intra-op complication N (%)	Hematoma N (%)	Infection N (%)	Recurrence N (%)
Overall	2 (0.74)	16 (5.95)	2 (0.74)	4 (1.49)
Unilateral IIH	0	6 (5.45)	1 (0.91)	0
Unilateral DIH	0	1 (3.33)	1 (3.33)	0
Unilateral pantaloon	0	1 (25)	0	0
Bilateral DIH	0	4 (7.41)	0	2 (3.7)
Bilateral IIH	1 (9.09)*	0	0	0
Recurrent IIH	1 (2.94)**	4 (11.76)	0	1 (2.94)
Recurrent DIH	0	0	0	1 (8.33)
Recurrent bilateral DIH	0	0	0	0
Recurrent bilateral IIH	0	0	0	0

*Corona mortis injury

**Bradycardia

Discussion

The definitive treatment for most inguinal hernias is surgical repair.[8-11] Laparoscopic inguinal hernia repair is an increasingly helpful procedure because it offers fewer postoperative complications, shorter hospital stays, and quicker recovery times.

Zhu et al. Significant advantages of TEP compared to the open extraperitoneal approach include a lower incidence of total post-operative complications (Odds Ratio, 0.544; 95% confidence interval, 0.369-0.803), a reduction in urinary problems [0.206 (0.064,0.665)], an earlier return to normal activities or work [SMD = -1.798 (-3.322, -0.275)], and a shorter length of hospital stay [-1.995 (-2.358, -1.632)]. No difference was found in operative time, the incidence of hernia recurrence, chronic pain, intraoperative complications, seromas or hematomas, wound infection, and testicular problems between the two techniques.[12]

Haladu et al. Laparoscopic repair was associated with a statistically significant (range: 26-46%) reduction in the odds or risk of chronic pain. Still, there is no evidence of differences in recurrence rates between laparoscopic and open repairs.[3]

For totally extraperitoneal (TEP) repairs, more than 100 cases are required to achieve a learning curve.[1] Transabdominal preperitoneal (TAPP) repairs have significantly improved conversions and admissions after 50 cases.[13]

In this study, the median overall operative time was 65 minutes, with the highest time observed in cases of bilateral indirect inguinal hernia and recurrent bilateral indirect inguinal hernia, which averaged 95 minutes. In comparison, other studies reported an average time of 90 minutes.[14-16]

The overall median blood loss was 5 ml, with recurrent indirect inguinal hernia showing the highest median blood loss of about 10 ml. This can be attributed to the difficulty in identifying anatomy due to postoperative adhesions, whereas other studies reported a blood loss of 3.8 ml.[17]

The overall median hospital stay was 3 days, including the preoperative evaluation, operation, and postoperative observation days. In comparison, other studies reported a median hospital stay of 3.5 days.[17] Zhu et al. Length of hospital stay was, in all cases, significantly shorter ($P < 0.01$) after TEP (1.84 ± 1.45 days) when compared with the open extraperitoneal operation (4.28 ± 2.20 days).[12]

Intraoperative complications occurred in two cases (0.74%): corona mortis injury in bilateral indirect inguinal hernia and bradycardia in recurrent indirect inguinal hernia. The incidence of arterial corona mortis was found to be 28.4%, with a 1.5% risk of injury to the arterial corona mortis.[18]

Hematoma was the most common complication in our study, occurring in approximately 16 cases (5.95%), while other studies reported a lower incidence rate of 3.5%.[14] The infection rate in our study was 0.74%, compared to 0.76% in other studies.[19]

The recurrence rate in our study was 1.49%, compared to 0.9% in other laparoscopic inguinal hernia repair studies.[14] Zhu et al. A meta-analysis of outcomes shows that there were 2.2% recurrences in the TEP group and 1.5% in the open group, respectively ($P = 0.379$).[12]

Wellwood et al. Patients randomized to laparoscopic repair were more satisfied with surgery at 1 month and 3 months postoperatively, as measured by the 36-item short-form survey questionnaire. The mean cost per patient of laparoscopic repair was £335 (95% confidence interval £228 to £441) more than the cost of open repair.[20]

According to our results and those of other studies, patients who underwent laparoscopic repair were more satisfied than those who had open repair. Although laparoscopic inguinal hernia repair is more expensive than open repair, no difference was found in operative time, the incidence of hernia recurrence, chronic pain, intraoperative complications, seromas or hematomas, wound infection, and testicular problems. Therefore, laparoscopic repair is generally preferred for bilateral or recurrent hernias, patients desiring a quicker recovery, and those without contraindications for general anesthesia.

Our study has some limitations. First, its descriptive design constrained it. Second, the surgical technique (TEP or TAPP) selection in our center was based on individual surgeon preferences, with TEP being the more frequently employed approach. Third, due to various factors, we encountered challenges in conducting complete follow-up assessments for all patients, thereby hindering the confirmation of recurrence diagnoses.

On the other hand, the study's notable strength is based on its large sample size, spanning over ten years in a tertiary care setting.

Conclusion

Laparoscopic surgery for inguinal hernia repair has been demonstrated to be efficient, safe, and consistent with international studies, showing fewer postoperative complications, shorter hospital stays, and quicker recovery times, with no reported mortality. However, there is no evidence of differences in recurrence rates between laparoscopic and open repairs.

What is Already Known on this Topic?

Laparoscopic inguinal hernia repair is a widely accepted minimally invasive procedure used to treat inguinal hernias. There are two main approaches to laparoscopic inguinal hernia repair: transabdominal preperitoneal (TAPP) and totally extraperitoneal (TEP). TAPP involves entering the peritoneal cavity to place a mesh over the hernia defect from within the abdomen. At the same time, TEP avoids the peritoneal cavity, working instead within the layers of the abdominal wall to position the mesh.

The benefits include reduced postoperative pain, fewer wound complications, shorter hospital stays, and quicker recovery. Patients typically experience more minor scars and a faster return to normal activities and work. Laparoscopic repair is particularly advantageous for bilateral hernias and recurrent hernias after previous open repairs.

What this study adds?

Single-center experience in studying inguinal hernia patients' side effects and treatment outcomes.

Conflict of Interest

All authors declare no conflict of interest.

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Supplementary appendix

Supplementary Table 1 **Operation time, blood loss, pain score, and hospital stay by types of hernia**

Type	Operative- time (min)	Blood loss (ml)	Pain score immediate post-op	Pain score day 1 post-op	Hospital stays (days)
Overall	65 (55-90)	5 (5-10)	4 (2-6)	2 (1-4)	3 (2-3)
Unilateral IIH	65 (55-90)	5 (5-10)	3 (2-5)	2 (1-4)	3 (2-3)
Unilateral DIH	57.5 (45-60)	5 (3-5)	5 (2-6)	2.5 (0-5)	3 (2-3)
Unilateral Pantaloon	60 (51.5-80)	5 (4-7.5)	5 (1.5-7.5)	3 (1-4.5)	2.5 (2-3)
Bilateral DIH	70 (60-90)	5 (5-10)	5 (4-7)	2 (0-4)	3 (2-4)
Bilateral IIH	95 (55-145)	5 (5-10)	5 (1-5)	1 (0-4)	2 (2-3)
Recurrent IIH	70 (60-90)	5 (5-10)	4 (2-5)	2 (1-4)	3 (2-3)
Recurrent DIH	77.5 (55-120)	7.5 (5-20)	5 (1-7)	2 (0.5-5)	3 (3-3)
Recurrent bilateral DIH	60 (60-70)	5 (3-5)	3 (2-5)	2 (1-5)	4 (4-4)
Recurrent bilateral IIH	95 (65-120)	10 (5-10)	5 (3-7)	0 (0-2)	3 (2-3)

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Original Article

The Success Rate and Complications of Central Venous Catheterization for General Surgery Patients in a Tertiary Hospital

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Abstract

Objective: Central venous catheterization (CVC) is one of the essential surgical procedures. It can lead to life-threatening complications. This prospective study aimed to evaluate the success rate and complications of central venous catheterization.

Methods: This prospective observational cohort study collected data from patients undergoing central venous catheterization at the General Surgery Department, Rajavithi Hospital, from October 2020 to September 2022. Demographic information, the number of insertion attempts, operator details, success rates, the method used (ultrasound (US)-guided or anatomical landmark), and complications were recorded. Data analysis employed descriptive statistics, chi-square tests, student's *t*-tests, and binary logistic regression.

Result: 310 patients were enrolled. The overall success rate for central venous catheter (CVC) insertion was 95.2%. The US-guided method showed a significantly higher success rate compared to the anatomical landmark method (99.3% vs. 91.2%, $P = 0.001$), with 82.1% catheterized successfully on the first attempt using the US-guidance versus 50.9% with the landmark method ($P < 0.001$). The overall mechanical complication rate was 4.2%, including arterial puncture (1.6%), hematoma (0.3%), pneumothorax (0.3%), self-limiting arrhythmias (0.6%), and improper catheter placement (1.3%). The CRBSI rate was 7.7%, higher when occurring more than 15 days post-insertion ($P < 0.001$). Complication rates were significantly lower with the US-guided method compared to the landmark method (0.7% vs. 7.5%, $P = 0.003$). Procedures performed by 3rd to 4th-year residents also had lower complication rates compared to 1st to 2nd-year residents (0.3% vs. 3.9%, $P = 0.023$).

Conclusion: The US-guided catheterization demonstrates a high success rate, fewer attempts, and reduced complication rates. Therefore, its regular use in catheterization procedures is strongly recommended.

Keywords: Success rate, Complications, Central venous catheterization (CVC)

Introduction

Central venous catheterization (CVC) is an essential procedure in the surgical department for hemodynamic monitoring and long-term administration of fluids, antibiotics, total parenteral nutrition (TPN), hemodialysis, and chemotherapy. The common sites for catheterization are the internal jugular, subclavian, and occasionally femoral veins.[1] CVCs have been associated with immediate complications such as pneumothorax, hemothorax, hematoma, catheter misplacement, arterial puncture (10% - 20%)[2] and/or unsuccessful insertion (7%-14%).[3] Late complications include thrombosis and infection. The rate

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of complications varies, depending on operator experience and patient comorbidities such as coagulopathy and hemodynamic instability.

In contemporary practice, ultrasound (US) guidance has substantially reduced mechanical complications associated with central venous catheterization (CVC), minimized cannulation attempts, and increased success rates, thereby prompting its inclusion in several national guidelines.[4-6] The traditional method of catheterization using anatomical landmarks is gradually being replaced by ultrasound (US) guidance. However, Rajavithi Hospital does not routinely employ US-guided catheterization due to various factors such as limited access to ultrasound machines, inexperienced operators, and the need for equipment preparation. Consequently, the Department of Surgery organizes an annual workshop simulation to train general surgery residents in CVC, mainly focusing on those who lack experience with ultrasound-guided techniques before they perform procedures on actual patients. This initiative aims to prevent complications and improve success rates.

Currently, our hospital lacks specific data regarding the success rates and complication rates associated with central venous catheterization. Therefore, this study aimed to evaluate the success rate and complications of central venous catheterization in surgical patients at Rajavithi Hospital.

Methods

This prospective observational cohort study enrolled 310 inpatients treated at the General Surgery Department of Rajavithi Hospital from October 2020 to September 2022. Approval for the study was obtained from the Ethics Committee of Rajavithi Hospital (EC No. 234/2563), and all patients provided written informed consent following a detailed explanation of the study protocol. No exclusion criteria were considered except for patient refusal. All patients undergoing central venous catheterization were monitored and documented until they were no longer indicated for the catheter or until catheter-related bloodstream infection (CRBSI) occurred, at which point the catheter was removed.

Central venous catheterization methods are mainly classified into two methods[7]: the anatomical landmark method, which uses gross anatomical landmarks on the body surface, and the ultrasound (US)-guided method, which uses ultrasound images. All general surgery residents received training through a workshop simulation using both the US-guided and anatomical landmark techniques and successfully completed this training for central venous catheterization (CVC) before performing procedures on actual patients. All catheterizations were performed by general surgery residents and attending physicians. The residents selected either the US-guided or anatomical landmark technique based on their preference.

A triple-lumen catheter set (Certofix®) for catheterization was employed according to indications. The indications for CVC were hemodynamic monitoring, volume resuscitation and assessment, infusion of irritant medication, infusion of TPN, and difficult peripheral venous access.

Patients were positioned supine or in Trendelenburg's position with their heads rotated towards the opposite side. Central venous catheters (CVCs) were typically inserted on the right side; however, if conditions were unfavorable, such as infection at the puncture site or surgical wounds, or if insertion on the right side was not feasible, the CVC was placed on the left side. All procedures adhered to standard aseptic techniques and utilized local anesthesia with a small, 24-gauge needle for venipuncture.

The US-guided method uses a real-time approach, performed with a linear transducer probe 4-12 MHz, with a sterile cover. The central veins were identified along their larger longitudinal axis and their relationship to other anatomical structures. Under the US-guided method, an 18-gauge needle is introduced into the inferior portion of the internal jugular or another vein. This vein is accessed through a transducer placed at the insertion point; the correct introduction of the needle was always confirmed by ultrasound guidance and the easy aspiration of venous blood. The Seldinger technique[8] was used to place the catheter, which was advanced into the superior vena cava until insertion into the right atrium. In the anatomical landmark method, after local anesthesia, the internal jugular vein was located with a 24-gauze needle connected to a 3-ml syringe as the needle advanced through the skin at an angle of 45° toward the ipsilateral nipple. The return of venous blood into the syringe confirmed entry into the vessel; a 24-gauze needle was then used to guide the 18-gauge needle and place the catheter using the Seldinger technique.

A successful catheterization was defined by the following criteria: the catheter tip was visible and parallel to the wall of the superior vena cava on chest radiography, indicating proper placement; the catheter could be used for its intended purpose, and no complications occurred. Conversely, an unsuccessful technique was characterized by the inability to cannulate the central vein after three attempts, failure to locate or puncture the central vein, or the inability to advance the guidewire or catheter. If the initial method failed after three attempts, the operator either sought assistance from an experienced operator or chose an alternative insertion site. The number of attempts was defined as each insertion and withdrawal of the introducer needle from the skin. Following the procedure, all patients underwent chest radiography to assess catheter tip placement and identify any complications.

Demographic data, including age, gender, body mass index (BMI), site of catheterization (jugular, subclavian, or femoral vein), side of catheterization (right or left), indications for CVC insertion, level training of operator, method of insertion, existing of risk factor (such as diabetes mellitus, hypertension, ischemic heart disease, chronic renal disease, malignancy, coagulopathies, and respiratory distress) were evaluated and recorded in checklist. Moreover, the number of attempts, success rate, catheter-related complications (arterial puncture, hematoma, pneumothorax, self-limiting arrhythmias, catheter misplacement, and CRBSI), and follow-up 30 days until catheter removal were also documented in the checklist.

Demographic data and clinical features were analyzed using descriptive statistics. Quantitative variables were summarized using mean and standard deviation. Two methods of study were compared by student's *t*-test. Categorical variables were compared with the chi-square test and summarized as counts and percentages. The *P*-value of less than 0.05 was considered significant. All statistical analysis was performed with a statistical package for social sciences (SPSS) version 17.

Results

In this study, 310 patients were enrolled. Patient demographic and baseline characteristics are shown in Table 1. The mean age was 60.51 ± 14.96 years, with 166 male patients. The mean lifespan of the CVC was 8.9 ± 7.7 days (range 1-39). The US-guided method was used in 151 patients, and the anatomical landmark method was used in 159 patients. The most common location for catheterization was the right internal jugular vein, with 278 patients (89.7%) receiving catheters there.

Table 1 Baseline patient demographic data of the study patient

	Overall populations (n = 310)	US-guide method (n = 151)	Landmark method (n = 159)
Age (year): mean ± SD	60.51 ± 14.96	60.88 ± 15.10	60.16 ± 14.87
Gender: number (%)			
Male	166 (53.5)	81 (53.6)	85 (53.5)
BMI (kg/m^2): mean ± SD	22.23 ± 4.36	23.14 ± 11.78	22.23 ± 4.43
Underlying Disease: number (%)	242 (78.1)	113 (74.8)	32 (20.1)
Diabetes	72	40	32
Hypertension	99	57	42
Chronic kidney disease	35	20	15
Coronary artery disease	21	14	7
Cerebrovascular accident	12	7	5
COPD/Asthma	10	5	5
Malignancy (Breast, Stomach, Colorectal, Esophagus, Thyroid, HPB, Cervix, Brain)	169	71	98
Coagulation profile: number (%)			
INR < 1.5	258 (83.2)	115 (76.2)	143 (89.9)
INR ≥ 1.5	52 (16.8)	36 (23.8)	16 (10.1)

Table 1 (cont.) Baseline patient demographic data of the study patient

	Overall populations (n = 310)	US-guide method (n = 151)	Landmark method (n = 159)
Platelet count (cell/mm^3)			
≥ 100,000	282 (91.0)	128 (84.8)	154 (96.9)
< 100,000	28 (9.0)	23 (15.2)	5 (3.1)
Operator: number (%)			
Resident 1	38 (12.3)	22 (14.6)	16 (10.1)
Resident 2	129 (41.6)	72 (47.7)	57 (35.8)
Resident 3	85 (27.4)	39 (25.8)	46 (28.9)
Resident 4	13 (4.2)	8 (5.3)	5 (3.1)
Staff	45 (14.5)	10 (6.6)	35 (22.1)
Location of catheter: number (%)			
Right internal jugular vein	278 (89.7)	132 (87.4)	146 (91.8)
Left internal jugular vein	12 (3.9)	10 (6.6)	2 (1.3)
Right subclavian vein	10 (3.2)	2 (1.3)	8 (5.0)
Left subclavian vein	2 (0.6)	0 (0.0)	2 (1.3)
Right femoral vein	6 (1.9)	6 (4.0)	0 (0.0)
Left femoral vein	2 (0.6)	1 (0.7)	1 (0.6)

Data are presented as mean ± SD or %

The overall success rate was 95.2%, with the success rate of the US-guided CVC insertion significantly higher than that of the anatomical landmark method [150 (99.3%) vs. 145 (91.2%), $P = 0.001$], as shown in Table 2. In the US-guided method, 82.1% of catheters were successfully placed on the first attempt, compared to 50.9% in the anatomical landmark method ($P < 0.001$), as shown in Table 3. There was no significant difference in success rate between 3rd to 4th-year residents (experienced operators) and 1st to 2nd-year residents ($P = 0.265$).

Table 2 Overall success rate and complications of central venous catheterization

Result (n = 310)	n (%)
Overall successful: number (%)	295 (95.2)
US-guided method	150 (99.3)
Anatomical Landmarks method	145 (91.2)
Mechanical complications: number (%)	13 (4.2)
Arterial puncture	5 (1.6)
Hematoma	1 (0.3)
Pneumothorax	1 (0.3)
Self-limited arrhythmia	2 (0.6)
Improper catheter placement	4 (1.3)
Catheter-related infection (CRBSI): number (%)	24 (7.7)

*Data are presented as No. (%)

Table 3 Comparison of the catheterization outcomes in two methods

Variables	The study Methods		
	US-guided, n (%)	Landmarks, n (%)	*P*-value
Success rate: number (%)			0.001
Successful	150 (99.3)	145 (91.2)	
Unsuccessful	1 (0.7)	14 (8.8)	
Number of attempts: number (%)			
One attempt	124 (82.1)	81 (50.9)	< 0.001
More than one attempts	27 (17.9)	78 (49.1)	
Mechanical complications: number (%)	1 (0.7)	12 (7.5)	0.003
Types of mechanical complications: number (%)			
Arterial puncture	0 (0)	5 (3.1)	
Hematoma	1 (0.7)	0 (0)	
Pneumothorax	0 (0)	1 (0.6)	
Self-limited arrhythmia	0 (0)	2 (1.3)	
Improper catheter placement	0 (0)	4 (2.5)	
Catheter-related bloodstream infection (CRBSI): number (%)	20 (13.2)	4 (2.5)	< 0.001

*Data are presented as No. (%)

The overall mechanical complication rate was 13 (4.2%) [including arterial puncture 5 (1.6%), hematoma 1 (0.3%), pneumothorax 1 (0.3%), self-limiting arrhythmias 2 (0.6%), and improper catheter placement 4 (1.3%)] as shown in Table 2. No major bleeding, life-threatening conditions, or symptomatic venous thrombosis were reported. There was no significant correlation observed between the mean BMI and complications ($P = 0.079$).

Moreover, the rate of complications was significantly lower in the US-guided method than in the anatomical landmark method (0.7% vs. 7.5%, $P = 0.003$). Additionally, the rate of complications in procedures performed by 3rd to 4th-year residents also had lower complication rates compared to 1st to 2nd-year residents (0.3% vs. 3.9%, $P = 0.023$).

The catheter-related bloodstream infection (CRBSI) rate was found to be 24 (7.7%), and the associated incidence on the day of insertion was more than 15 days ($P < 0.001$). In addition, we found that US-guided catheterization was associated with an increased risk of CRBSI compared to anatomical landmarks [20 (13.34%) VS 4 (2.76%), $P < 0.001$].

Discussion

In this study, the overall success rate was 95.2%. The success rate of the US-guided method for CVC insertion was 99.3%, whereas the anatomical landmark method had a success rate of 91.2% ($P = 0.001$). Consistent with previous research, these findings highlight the notably high success rate associated with the use of the US-guided method.[1,9-11] Verghese et al.'s study demonstrated a 100% success rate for catheterization using the US-guided method, compared to a 77% success rate for patients using the anatomical landmark method.[12] Despite the significantly higher success rate of the US-guided method, the efficacy of both approaches relies heavily on the skills and experience of the operator.[13,14] Therefore, the implementation of a CVC simulation workshop training program is warranted to promote the routine adoption of US-guided methods for CVC insertion.

The number of attempts for catheter insertion, especially on the first attempt ($P < 0.001$) in the central vein, was significantly lower with the US-guided method compared to the anatomical landmark method. This is a critical concern for critically ill patients, where saving time is of paramount importance.[15] Mansfield et al. noted that the complication rate after three or more attempts was six times higher compared to the first attempt when comparing anatomical landmarks with the US-guided method.[16] Another critical finding is the markedly lower complication rate associated with the US-guided method. These results are consistent with prior studies investigating the

frequency of catheter insertion attempts. The central issue here underscores the direct correlation between shorter access times and fewer attempts, thereby mitigating the risk of complications.[1,17,18]

The incidence of overall complications was significantly higher ($P = 0.003$) in catheterizations utilizing anatomical landmarks, especially among 1st- to 2nd-year general surgery residents. Karakitsos et al. found no cases of hematoma or pneumothorax with the US-guided method, whereas eight patients experienced these complications when anatomical landmarks were used.[19] Similar results were reported by Rando et al.[20] Randolph et al.'s meta-analysis demonstrated the advantages of US-guided techniques across operators of varying experience levels in central venous catheterization[21] Miller et al. observed that skilled operators using ultrasound achieved a notable reduction in time to blood flash and fewer attempts compared to inexperienced operators who struggled with both methods. Additionally, lower complication rates associated with US guidance enhance its cost-effectiveness, as highlighted by Calvert et al.'s systematic review and economic evaluation of US-guided CVC.[22] Therefore, proficiency in US-guided catheterization is crucial for physicians. Recognizing this need, Feller et al. emphasized the importance of training surgeons and nurses in US-guided techniques due to their simplicity, applicability, and economic benefits.[23] This necessity led to the introduction of CVC simulation workshops at Rajavithi Hospital's Department of Surgery, aimed at improving trainees' procedural skills in real-world scenarios.[24]

As outlined above, US-guided central venous catheterization has been endorsed and adopted by junior resident operators. However, there remains debate regarding the continued teaching of anatomical landmark methods. Operators exclusively trained in US-guided techniques may lack proficiency in anatomical landmark cannulation when ultrasound is unavailable.[25]

A meta-analysis by Jun Takeshita et al. suggests that US-guided central venous catheterization potentially reduces the incidence of catheter-related bloodstream infections (CRBSI).[26] In contrast, our study revealed a different outcome: US-guided catheterization showed a higher risk of CRBSI compared to anatomical landmarks [20 cases (6.4%) vs. 4 cases (1.3%), $P < 0.001$]. This finding aligns with research by Buetti et al., who conducted a post hoc analysis of three randomized controlled trials and found an increased risk of CRBSI associated with the US-guided insertion (HR, 2.21; 95% CI, 1.17 - 4.16; $P = 0.014$)[27] A limitation noted in Buetti's study was uncertainty surrounding ultrasound techniques, including adherence to hygiene protocols. Furthermore, since patient randomization in these trials considered factors such as catheter insertion site, skin asepsis, and dressings rather than insertion technique, various confounders may have influenced the results, particularly given that ultrasound guidance is typically employed in challenging or severe cases.

Limitation

The primary limitations of the study include the absence of a control group and its single-institution design. Despite these constraints, this prospective observational cohort study was conducted within a representative population, which is particularly relevant for physicians undergoing residency training and helps mitigate potential selection bias. It is important to note that recording bias may have influenced the reported complications due to the lack of standardized monitoring datasets and specific charting tools for these outcomes. Additionally, the lack of statistical significance in our cohort could be attributed to an insufficient sample size for certain complications with very low incidences, such as pneumothorax and thrombosis. Furthermore, it is crucial to acknowledge that this study was conducted during the COVID-19 pandemic, which may impact the generalizability of its findings.

Conclusion

Ultrasound-guided catheterization presents several advantages, such as high success rates, fewer attempts needed, and decreased complication rates. Therefore, its regular use in catheterization procedures is strongly recommended. Training in procedural ultrasound techniques and the integration of ultrasound guidance for central venous catheterization should be considered the standard of care.

Conflict of interest

No authors have any potential conflict of interest to disclosure.

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Case Report

A Comprehensive Case Series: Outcomes and Insights from the First Three Simultaneous Pancreas Kidney Transplants at Ramathibodi Hospital

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Abstract

Background: Pancreas transplantation, particularly in the context of Type 1 diabetes mellitus (T1DM) with end-stage renal disease (ESRD), has emerged as a pivotal therapeutic intervention, substantially ameliorating both the clinical and quality-of-life outcomes for affected individuals. While previous research has underscored its efficacy in enhancing longevity, mitigating cardiovascular risks, and improving overall well-being, its widespread adoption, particularly the simultaneous pancreas-kidney transplantation (SPK) approach, remains constrained by various factors, notably donor availability and the requisite multidisciplinary care infrastructure.

Methods: This study presents the treatment outcomes of the initial three cases of SPK performed at Ramathibodi Hospital in Thailand. The operative techniques employed adhered to established protocols, including intraoperative porto-enteric drainage for endocrine function and enteric drainage for exocrine function. Noteworthy intraoperative considerations encompassed meticulous vascular reconstruction, heparinization protocols, and vigilant monitoring of hematological parameters to forestall potential complications.

Results: Each case presented unique clinical profiles and postoperative trajectories. Complications, such as postoperative hematoma and declining hematocrit levels, were managed judiciously, with successful resolution and favorable graft outcomes observed during subsequent follow-up periods. Importantly, all patients demonstrated prompt postoperative glycemic control and satisfactory renal function, obviating the need for further dialysis or medical intervention.

Conclusion: SPK emerges as a highly efficacious therapeutic avenue for individuals afflicted with T1DM and ESRD, offering tangible improvements in health outcomes and the prospect of restored quality of life. As evidenced by the outcomes of the initial cases presented herein, SPK holds promise as a viable treatment modality warranting further exploration and dissemination within the clinical landscape.

Keywords: Simultaneous pancreas-kidney transplantation, Type 1 diabetes mellitus, End-stage renal disease, Kidney transplantation

Introduction

In type I diabetes mellitus(T1DM), pancreas transplantation is the most effective treatment option for improving quality of life,[1,2] prolonging life,[3] and decreasing the risk of atherosclerotic disease and cardiovascular events,[4,5] cerebrovascular events, cardiovascular disease, and kidney disease. In the case of type I diabetes mellitus that turns into end-stage renal disease (ESRD), simultaneous pancreas-kidney transplantation (SPK) is still a treatment of choice to correct both T1DM and ESRD at the same time.[3,6] For the patient who underwent a simultaneous pancreas-kidney transplant in 2018-2019 in the USA, the one-year mortality rate remained low at 2.6%; the 5-year survival rate was 92.7%,[7] and the glycemic control and diabetes-related complications were significantly better after the transplantation.[8-11]

Anyway, in Thailand, the SPK is not a widespread operation that can performed in many hospitals due to the lack of quality donors, the complexity of the operation, and post-operative care that requires multidisciplinary team care after the surgery.

In Ramathibodi Hospital, the first 3-case of SPK was performed from 2022-2023. This report objects to presenting the treatment outcome of the first 3 cases in our hospital.

Operative Details

Bench Surgery

After the kidney graft's dissection and vascular reconstruction were done, the kidney graft was then perfused with HTK solution until clear. For the pancreas, the dorsal end of SMA and splenic artery were side-to-end anastomosed using Prolene 8-0 and the ventral end of SMA was sutured with Prolene 6-0 continuously. The duodenal C-loop was flushed with 100 ml of Nystatin solution.

Operation

The operation was done by intraperitoneal approach with a midline incision. The kidney was first placed at the right iliac fossa after the ascending colon was mobilized along the white line of Toldt. The arterial inflow came from the external iliac artery, and venous outflow came via an external iliac vein. A urologist performed the ureteroneocystostomy using the Lich-Gregoir technique.

The pancreas was then placed intraabdominal at the root of the mesentery, the arterial inflow came from the donor's iliac vein graft that extended from an external iliac artery, and the pancreas's portal vein to the recipient's SMV was anastomosed with Prolene 6-0. The side-to-side jejunojejunostomy was performed with Maxon 3-0.

After the bleeding was carefully controlled and stopped, the Jackson-Pratt drain was placed just below the pancreas.

Post-operative care

After surgery, the patient was admitted to the ICU. The patient's vital signs and fasting blood sugar were monitored hourly for the first 8-24 hours. Systemic heparinization and insulin were administered intravenously to keep PTT level 40-50 seconds and fasting blood sugar 100-150 mg/dl. The goal of urine output was 1.5-2 ml/kg/hour. The patient's hematocrit test was done every 6 hours to monitor the bleeding complication.

After 24 hours post-operation, if the patient was extubated, vital signs and laboratory tests showed no active problem, the patient was moved to the inpatient unit. At the ward, blood tests were done daily, including CBC, serum creatinine, fasting blood sugar, serum amylase, and FK506 level. After five days of operation, intravenous heparin was off, and 75 mg of clopidogrel was started instead. The parameters are shown in Figures 1-4.

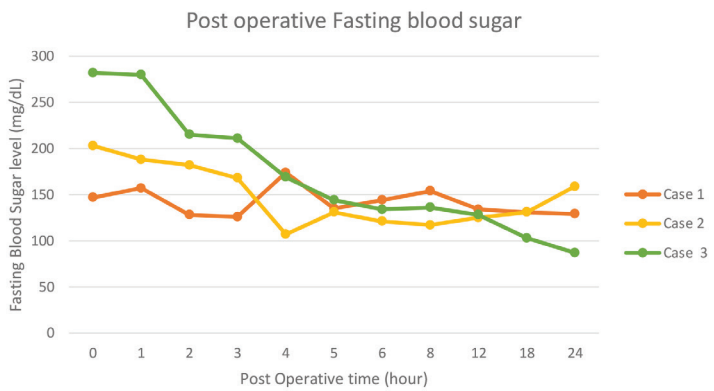

Figure 1

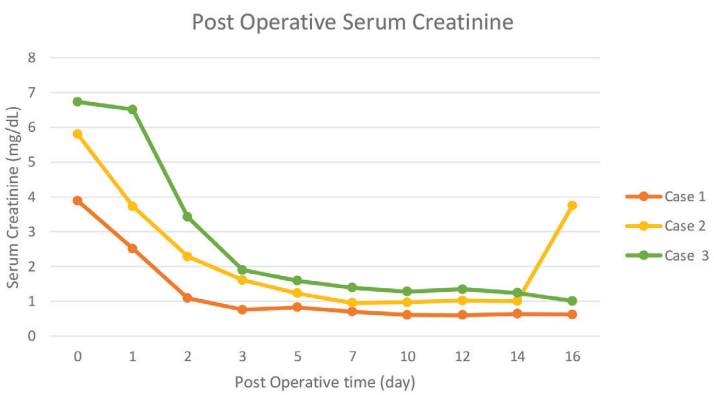

Figure 2

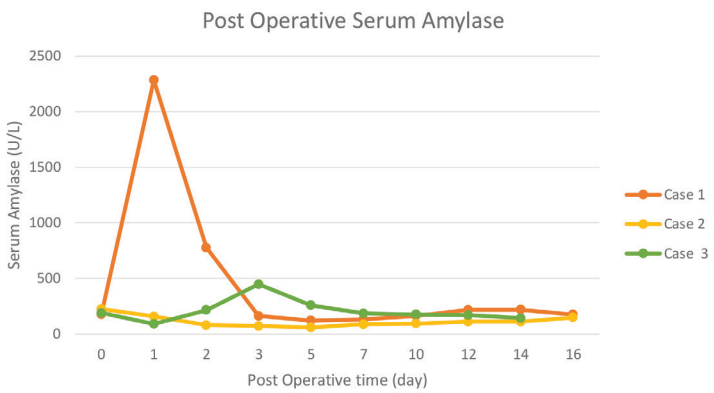

Figure 3

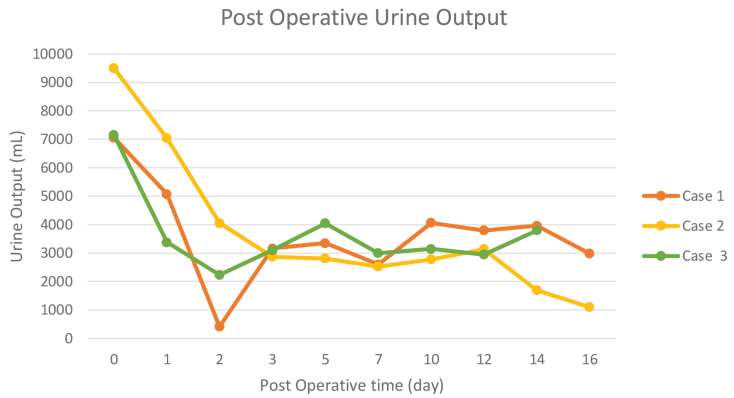

Figure 4

Case 1

Recipient profile

A 36-year-old Thai female was diagnosed with T1DM at ten years of age and turned to ESRD at nine years before transplantation. She needed to be hemodialyzed three times/week via the left arteriovenous fistula at the left forearm and control her blood sugar by using 12 units of long-acting insulin (Lantus) once daily and four units of short active insulin (Novorapid) premeal subcutaneously. Her baseline HbA1C was 6.9. She also had diabetic retinopathy in both eyes, a history of right 5th toe amputation from an infected diabetic foot ulcer many years ago, which was healed at the time of the surgery, pulmonary tuberculosis, which was completely treated in 2015 with 1TRZE + 1IRZ + 7IR regimen. she was given 75mg of clopidogrel daily from her central vein stenosis. Her physical examination was unremarkable, with no old abdominal surgical scar. Her body weight was 45.9 kg, and her height was 156 cm.

Donor profile

A 20-year-old Myanmar male with subarachnoid hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 55 kg, his height was 170 cm, and his BMI was 25.9 kg/m2. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.66 mg/dl, peak creatinine was 0.91 mg/dL, and terminal creatinine was 0.89 mg/dl; his urine output was 1,260 ml in the last 8 hours.

Both are blood group B and Rh positive. Their HLA mismatch was 4/6 (HLA-A 0/2, HLA-B 2/2, HLR-DR 2/2), and their panel reactive antibodies were 0%. The serum crossmatch showed negative T and B cells. The induction regimen was anti-thymocyte globulin (ATG), followed by a maintenance regimen of tacrolimus (Prograf), MMF (Cellcept), and prednisolone.

The kidney's cold ischemic time was 7 hours 35 minutes, and the kidney's relative warm ischemic time was 35 minutes. The pancreas's cold ischemic time was 9 hours 34 minutes, and the pancreas's relative warm ischemic time was 12 minutes. Intraoperative blood loss was 2,000 ml.

Post-operative monitoring

In the first 24 hours, the patient had hypovolemic hypotension and required large-volume resuscitation and vasopressor. The urine output was 250-300 ml/hour in the first 24 hours.

Because of the raising of the serum amylase, to rule out vascular complication or collection, a CT scan of the whole abdomen was performed on postoperative day 9. The findings were: patent all vascular anastomosis, focal enlargement of pancreatic parenchyma, no collection, no active contrast extravasation.

After adjusting the immunosuppressive level, the patient was discharged on postoperative day 17 with a serum creatinine of 0.62 mg/dl, and none of the glycemic control medication was needed. At 1-year follow-up, serum creatinine was 0.82 mg/dl, and fasting blood glucose was 90 mg/dl.

Case 2

Recipient profile

A 32-year-old Thai female was diagnosed with T1DM at 19 years of age and turned to ESRD three years prior to transplantation; she needed to be hemodialyzed two times/week and control her blood sugar by using eight units of insulatard non-hemodialysis day. Her baseline HbA1C was 6.46. Her physical examination was unremarkable, with no old abdominal surgical scar. Her body weight was 50.15 kg, and her height was 156 cm.

Donor profile

A 33-year-old Thai male with subarachnoid hemorrhage and intraventricular hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 62 kg, his height was 155 cm, and his BMI was 25.8 kg/m^2. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.66 mg/dl, peak creatinine was 0.91 mg/dL, and terminal creatinine was 0.89 mg/dl; his urine output was 940 ml in the last 8 hours, and no proteinuria.

Both are blood group O, Rh positive, their HLA mismatch was 4/6 (HLA-A 1/2, HLA-B 2/2, HLR-DR 1/2), panel reactive antibodies 0%, the serum cross matches showed negative both T and B cells, the induction regimen was anti-thymocyte globulin (ATG) and followed by maintenance regimen of tacrolimus (prograf), MMF (cellcept) and prednisolone.

The kidney's cold ischemic time was 6 hours 17 minutes, and the kidney's relative warm ischemic time was 23 minutes. The pancreas's cold ischemic time was 8 hours 21 minutes, and the pancreas's relative warm ischemic time was 21 minutes. Intraoperative blood loss was 1,500 ml.

Post-operative monitoring

In the first 24 hours, the urine output was 250-300 ml/hour in the first 24 hours. Plasma glucose and PTT levels were closely monitored by adjusting the insulin and heparin levels, with the goal of FBS being 100-150 mg/dl and PTT 40-50 seconds.

After following up on the hemoglobin level at post-operative days 0-3, the hemoglobin level declined from 14.6 to 4.5 g/dL, without any hemodynamic instability nor shortage of urine noted. To rule out intraabdominal hemorrhage/hematoma, the CT whole abdomen study was performed, with the finding of a 6-cm acute hematoma at the posterior aspect of the transplanted pancreas (Figure 5).

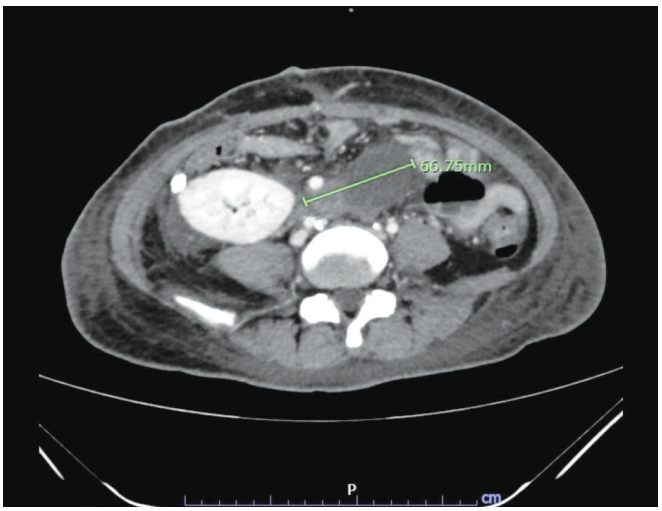

Figure 5 Hematoma at pancreas

The patient underwent re-operation due to intraabdominal hematoma with suspected active intraabdominal bleeding. However, the intraoperative finding was only an old blood clot at the Cul de sac, with no active bleeding from vascular anastomosis or pancreas graft. After the reoperation, the hemoglobin has become stable.

On postoperative day 9, the serum creatinine rose from 2.9 to 4.7 and up to 5.6 on postoperative day 13. A kidney biopsy was performed to rule out graft rejection (Figure 6).

The pathological report was shown transplant glomerulitis with peritubular capillaritis. (Figure 6) Negative for C4d staining, no evidence of BKVAN (SV40 negative), Banff schema: i0, t0, g2, v1, ptc2, ci0, ct1, cv0, mm0, ah0, c4d0, ti0, i-IFTA0, t-IFTA0 and DSA was negative. Laboratory screening: HLA Ab screening negative, Lipase 429 U/L (23-300), Amylase 148 U/L (30-110), urine protein 3+, UPCR 2.48

This finding made the active antibody-mediated rejection suspicious. Methylprednisolone 500 mg daily, ATG 1.5 mg/kg/day for three days, IVIG 2 g/kg, and plasmapheresis once a couple of days were done for three sessions, and the serum creatinine and amylase were declined.

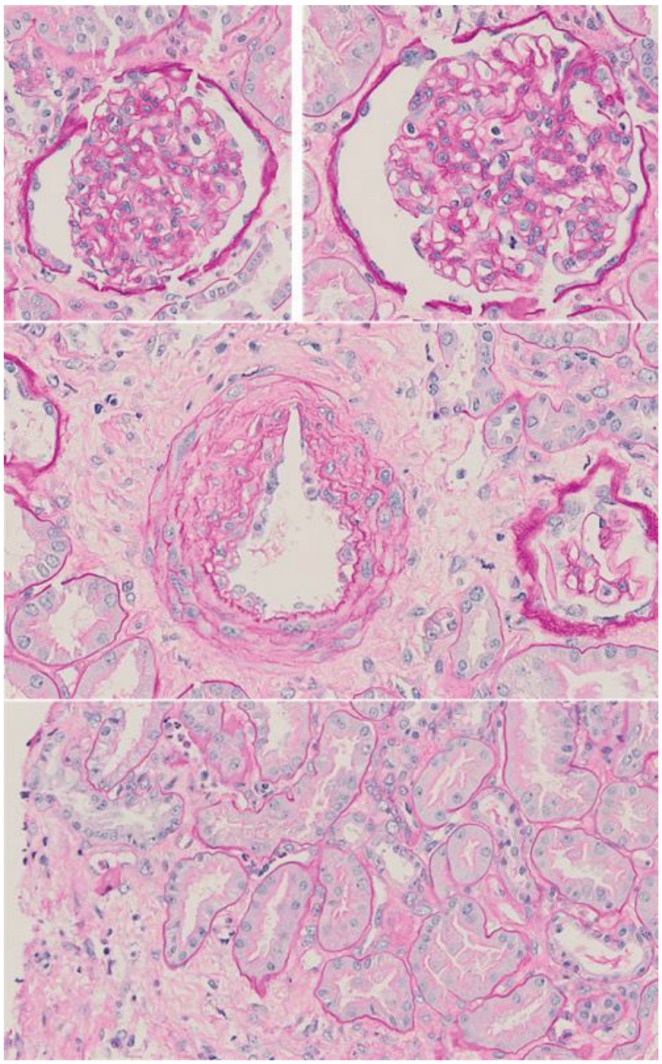

Figure 6 Kidney biopsy

She was discharged at postoperative day 39 with a serum creatinine of 1.29 mg/dl, and non-glycemic control was needed.

After following up at eight months post-operative, the patient did well with a serum creatinine of 0.81 mg/dl, fasting plasma glucose of 78 mg/dl, HbA1C of 5.45%, and C-peptide of 2.32 ng/ml.

Case 3

Recipient profile

A 31-year-old Thai male was diagnosed with T1DM at 15 years of age and turned to ESRD at 2.5 years before transplantation; he needed to be hemodialyzed three times/week and control his blood sugar by using eight units of Lantus subcutaneously, and 8 unit of Novorapid premeal. His baseline of HbA1C was 9.26. His physical examination was unremarkable, with no old abdominal surgical scar. His body weight was 69 kg, her height was 172 cm.

Donor profile

A 23-year-old Thai male with subdural hemorrhage from head trauma. He didn't have a known underlying disease. His body weight was 60 kg, his height was 180 cm, and his BMI was 18.51 kg/m^2. No history of cardiac arrest nor CPR was noted, and his blood pressure was controlled by inotropic drugs. His initial creatinine was 0.5 mg/dl, peak creatinine was 0.8 mg/dL, and terminal creatinine was 0.8 mg/dl; his urine output was 1040 ml in the last 8 hours and no proteinuria.

Both are blood group O, Rh positive. Their HLA mismatch was 4/6 (HLA-A 1/2, HLA-B 2/2, HLR-DR 1/2), and their panel reactive antibodies were 0%. The serum cross-matches showed negative T and B cells. The induction regimen was anti-thymocyte globulin (ATG), followed by a maintenance regimen of tacrolimus (Prograf), MMF (Cellcept), and prednisolone.

The kidney's cold ischemic time was 4 hours 2 minutes, and the kidney's relative warm ischemic time was 28 minutes. The pancreas's cold ischemic time was 5 hours 28 minutes, and the pancreas's relative warm ischemic time was 20 minutes. Intraoperative blood loss was 700 ml.

Post-operative monitoring

In the first 24 hours, the urine output was 250-300ml/hour in the first 24 hours. Plasma glucose and PTT levels were closely monitored by adjusting the insulin and heparin levels, with the goal of FBS being 100-150mg/dl and PTT 40-50 seconds.

The patient's hematocrit dropped from 29.9% to 19.9% without hemodynamic change, no inotropic drug requirement, and no decrease in the urine output. Ultrasound bedside was performed, and it found that the vascular anastomosis of the transplant kidney and pancreas were intact with a good flow. So, conservative management with close monitoring was done. After a serial blood transfusion, the patient's hematocrit was stable at 24%. On postoperative day 5, after the drainage fluid test for pancreatic leakage was negative, the Jackson drain was pulled off.

On postoperative day 11, the patient developed a fever with a body temperature of 38-38.5 ˚C. the empirical antibiotic was prescribed. After the septic workup was done and negative for all tests. The patient's fever was resolved on 3rd day of antibiotics, and the course of antibiotics was seven days.

After the immunosuppressive drugs were carefully adjusted, the patient was discharged from the hospital with a length of stay of 22 days with serum creatinine of 1.17 mg/dl and fasting plasma glucose of 95-140 mg/dl without glycemic control.

At four months follow-up after the surgery, the patient was doing well with a serum creatinine of 1.15 mg/dl and fasting plasma glucose of 113 mg/dl.

Discussion

Following the first pancreas transplantation at the University of Minnesota in 1966,[12] the outcomes of this procedure underscored the efficacy of Simultaneous Pancreas Kidney Transplantation (SPK) as a preeminent therapeutic intervention capable of enhancing patients' quality of life while concurrently mitigating morbidity and mortality.[1] The evolution of the operative technique for SPK has transpired progressively, encompassing diverse approaches such as intra-/retro-peritoneal methodology, along with porto-enteric/systemic-enteric drainage for endocrine function and bladder/enteric drainage for exocrine function. Numerous studies have documented surgical complications, prominently featuring vascular graft thrombosis or bleeding as the most prevalent, in addition to intraabdominal infection, pancreatitis, and enteric anastomosis/duodenal stump leakage, along with small bowel obstruction.[13,14]

In all instances, our operative approach adhered to intraoperative Porto-enteric drainage for endocrine function and enteric drainage for exocrine function. Given the proclivity for vascular complications, encompassing both thrombosis and bleeding, a systematic heparinization protocol was implemented, accompanied by vigilant monitoring of Partial Thromboplastin Time (PTT) levels, drain output, and hematocrit levels.

In a singular case, a patient necessitated re-laparotomy due to a declining hematocrit level associated with a hematoma observed on a computed tomography (CT) scan despite elevated serum amylase and lipase levels. However, no pathological findings were discerned. Another case exhibited a postoperative hematoma and diminished hematocrit levels, successfully managed through conservative measures.

All cases demonstrated the ability to transition off intravenous insulin within 24 hours postoperatively, with a concurrent urine output ranging between 250-300 ml/hour during the initial 24 hours. In the 6 to 12-month postoperative follow-up, all patients exhibited commendable graft function, obviating the need for hemodialysis or medical glycemic control.

Finally, pancreas transplantation is an effective treatment for patients with type 1 Diabetes Mellitus, particularly simultaneous pancreas-kidney transplantation, which improves patients' quality of life and reduces morbidity and mortality rates. However, in Thailand, the scarcity of suitable donors and the limited dissemination of surgical techniques pose challenges, restricting data collection for research and hindering the development of systems and surgical techniques to maximize patient benefits in the future.

Conclusion

Simultaneous pancreas-kidney transplantation represents a highly effective treatment modality for individuals with Type 1 diabetes mellitus (DM) and end-stage renal disease (ESRD). This approach offers significant advantages in reducing cardiovascular risks and enhancing long-term quality of life, enabling patients to regain a semblance of normalcy.

Authorship Contribution Statement

N.K. participated in research design, the writing of the paper, data collection, critical revision, and approval of the final version of the article. R.K. participated in data collection and the writing of the paper. N.A. participated in writing the paper, as well as in interpretation and critical revision. G.G., B.S., S.K., C.N., S.W., J.B., and S.L. participated in the data collection and critical revision and approved the article

Ethical Approval

The Ramathibodi Hospital Institutional Review Board reviewed and approved this study (Approval No. MURA2024/247).

Conflict of Interest

The authors declare no conflicts of interest.

Abbreviations

T1DM – Type 1 diabetes Mellitus

ESRD – End-stage renal disease

SPK – Simultaneous Pancreas Kidney Transplantation

HTK solution – Histidine-Tryptophan-Ketoglutarate solution

SMA – Superior Mesenteric artery

SMV – Superior Mesenteric vein

HLA – Human Leukocyte Antigen

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Case Report

Rare Axillary Cancer of Unknown Primary Originating from the Breast in Male Patient with PALB2 Pathogenic Variants: A Case Report

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Abstract

Background: Cancer of unknown primary (CUP) accounts for less than 5% of all cancers. Male breast cancer is a rare disease. The occurrence of bilateral breast involvement is even rarer, at approximately 0.5-2.5%. Genetic factors contribute to about 5-10%, with partner and localizer of BRCA2 (PALB2) gene mutations accounting for 1-2%.

Case Report: We found a male with breast cancer who initially presented with metastatic adenocarcinoma at the axillary lymph node of unknown primary origin. After axillary lymph node dissection (ALND) with radiation therapy (RT), adjuvant chemotherapy, and regular surveillance, recurrence was observed on the same other side as the axillary lymph node. The PALB2 gene abnormality was also identified. Finally, he underwent prophylactic bilateral mastectomy, and the pathology report included bilateral benign breast tissue.

Conclusion: Patients without Breast cancer gene (BRCA)mutations should be offered next-generation sequencing (NGS) multi-gene panel testing to detect other abnormalities when personal is suggestive of a hereditary syndrome. The roles of bilateral prophylactic mastectomy, ALND, and RT will be discussed with the patient.

Keywords: Cancer of unknown primary, (PALB2) pathogenic variants, Male breast cancer

Introduction

Cancer of unknown primary (CUP) refers to cancer that has spread without a detectable primary tumor, and even after standard diagnostic tests, its origin remains unidentified. It accounts for less than 5% of all cancers,[1] with approximately 70% diagnosed as adenocarcinoma.[2] Histopathologically, these are typically adenocarcinomas, with about 50% of CUP cases being well-to-moderately differentiated adenocarcinomas.[1] The most common primary sites for cancers of unknown primary (CUP) that metastasize include the pancreas (20-26%), lung (17-23%), and colon and rectum (4-10%).[3] In cases with axillary lymph node involvement, the primary tumor is often a hidden breast cancer, particularly in women. Ductal adenocarcinoma is the most common histopathology.[1]

Imaging, either a computed tomography (CT) scan with contrast or a magnetic resonance imaging (MRI) of

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the neck, thorax, abdomen, and pelvis, is used to locate potential primary tumors. For female patients, mammography is important to rule out breast cancer.[1]

Immunohistochemistry (IHC) is crucial in determining the primary tumor. Carcinomas can be identified using cytokeratin AE1/AE3 and are categorized with markers like cytokeratin 7 (CK7) and cytokeratin 20 (CK20) for adenocarcinomas and cytokeratin 5/6 (CK5/6) and p63 for squamous cell carcinomas. Lymphomas, melanomas, and sarcomas can be identified using clusters of differentiation 45 (CD45), S100, and Vimentin, respectively.[1]

In male breast cancer (MBC) cases, Breast cancer gene 2 (BRCA2) mutations are more common than Breast cancer gene 1 (BRCA1) mutations.[4] These mutations are associated with an approximately 8.9% lifetime risk of developing MBC.[5] In previously published studies, the frequency of BRCA2 mutations in MBC varied from 4 to 40%.[6]

The detection rate of germline pathogenic/likely pathogenic (P/LP) variants in breast cancer in Thailand was 11.8%. BRCA gene mutations accounted for 36.3%, whereas non-BRCA gene mutations accounted for 35% of patients with germline P/LP variants, with the Ataxia Telangiectasia Mutated (ATM) gene being the most common non-BRCA gene mutation.[7]

Male breast cancer accounts for less than 1% of all breast cancers.[8] The occurrence of bilateral breast involvement is even rarer, at approximately 0.5-2.5%.[9] Genetic factors contribute to about 5-10%,[10] with PALB2 gene mutations accounting for 1-2%.[10] This gene mutation is associated with a sevenfold increased risk of breast cancer[2] and is typically identified in individuals aged 42-77.[2] Most male breast cancers are hormone receptor-positive,[2] which increases the risk of metastasis by 9.63 to 17.30 times.[11] Indeed, 10-year survival was 48% in PALB2 mutation carriers with breast cancer.[11]

Case Report

In January 2014, a 70-year-old man presented with palpable right axillary lymph nodes. Ultrasonography with a mammogram revealed multiple right axillary lymphadenopathies. Excisional biopsy of the lesion revealed a metastatic adenocarcinoma with positive for CK7 and gross cystic disease fluid protein 15 (GCDFP-15) and negative for CK20, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), prostate-specific antigen (PSA) and thyroid transcription factor 1 (TTF1). Consequently, a total-body CT scan revealed no primary source or distant metastasis. MRI breast was not performed on this patient. The multidisciplinary team considered that the patient was diagnosed with metastatic adenocarcinoma at the right axilla of unknown primary origin. Therefore, he underwent right axillary lymph node dissection (ALND). The pathology report revealed metastatic carcinoma in 5 out of 27 lymph nodes. Based on the pathology results and immunohistochemical characteristics, a chemotherapy schedule was initiated with paclitaxel for a total of six cycles. Radiation therapy in the right axilla and covering the right breast totaled 50 grays (Gy) in 25 fractions (Fr) was performed. He was followed up with regular surveillance imaging until 2016. He again showed right axillary lymph node enlargement. Fine needle aspiration of the lesion revealed metastatic adenocarcinoma. A total body CT scan revealed no primary source or distant metastasis. The patient was referred for genetic counseling and germline testing. BRCA 1 and 2 testing was performed showing no pathogenic variants. The patient underwent a wide excision of the right axillary content. The pathology report was metastatic carcinoma in 1 lymph node, free of all resection margins, and negative for ER, PR, HER2, and Antigen Kiel 67 (Ki 67) 40%. He was followed up with regular surveillance imaging until 2019. He again showed right axillary lymph node enlargement. Fine needle aspiration of the lesion revealed metastatic adenocarcinoma. A total-body CT scan revealed no primary source or distant metastasis. The patient underwent a wide excision of the right axillary content. The patho-logy report was metastatic carcinoma in 1 lymph node, free of all resection margins, and negative for ER, PR, HER2, and Ki 67 40%. The patient was treated with four cycles of endoxan plus docetaxel. He was followed up with regular surveillance imaging until 2021. He again noted axillary lymph node enlargement but on the left side. Fine needle aspiration of the lesion revealed metastatic adenocarcinoma. A total-body CT scan revealed no primary source or distant metastasis. Subsequent positron emission tomography (PET) scans revealed no primary sources. The patient underwent a left axillary lymph node dissection. The pathology report revealed metastatic carcinoma in 2 out of 7 lymph nodes that were positive for CK7, GCDFP-15, GATA3, and androgen receptors and negative for ER, PR, HER2, CK20, and TTF1. The patient was again referred for genetic counseling and germline testing, which confirmed the presence of a constitutional PALB2 mutation in the blood. The extended family history was significant

for a sister and grandmother with cancer in the axilla at the age of 80 (Figure 5). He was treated with bicalutamide as an antiandrogenic drug. He underwent a prophylactic bilateral mastectomy after triple-vessel coronary artery disease (TVD) was managed. The pathology report included bilateral benign breast tissue.

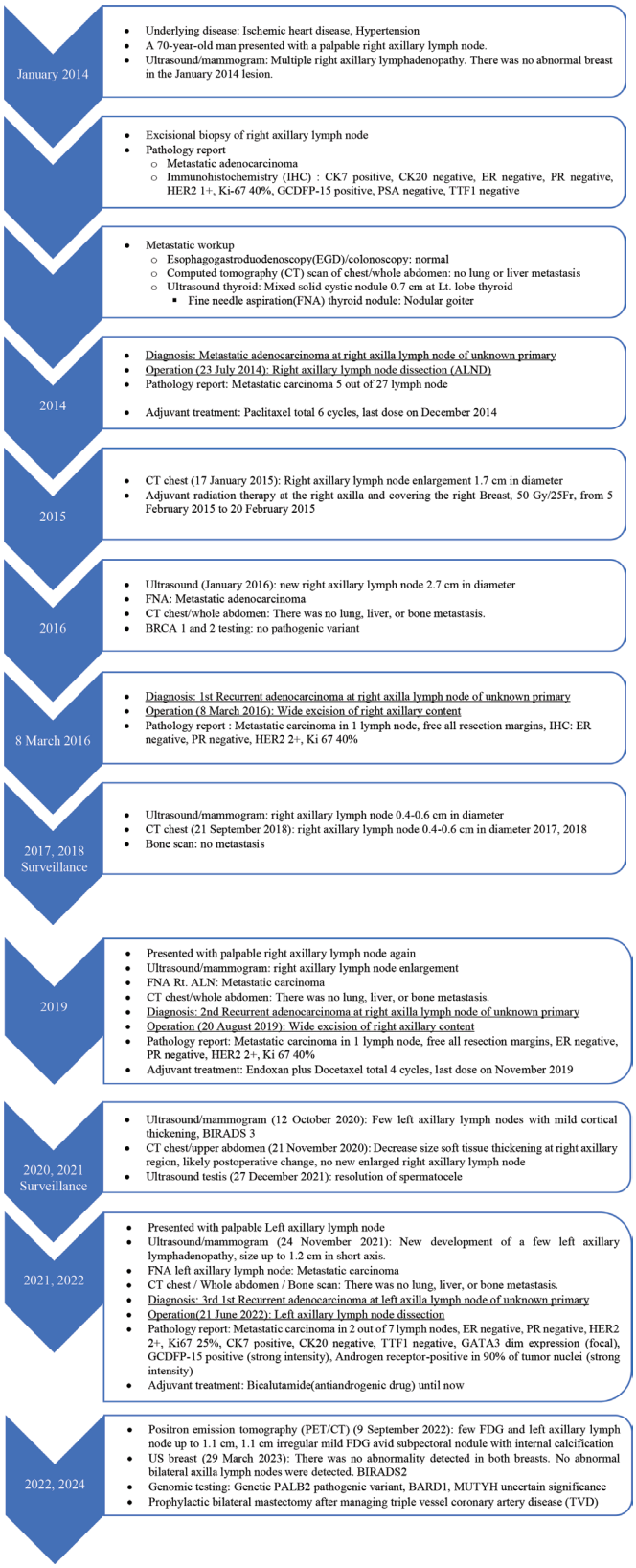

Figure 1 Case report timeline

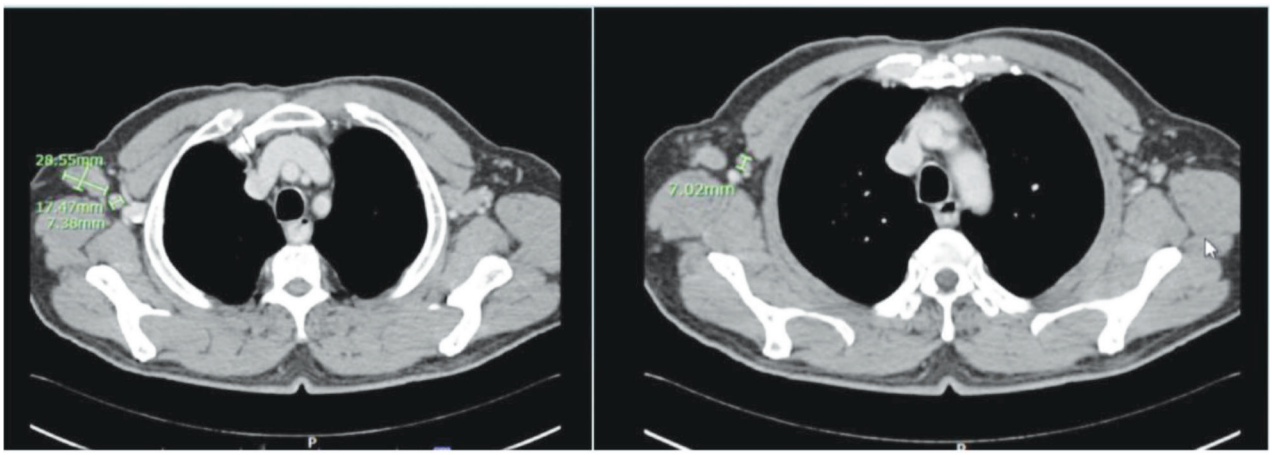

Figure 2 CT chest (January 2014) Multiple right axillary lymphadenopathy

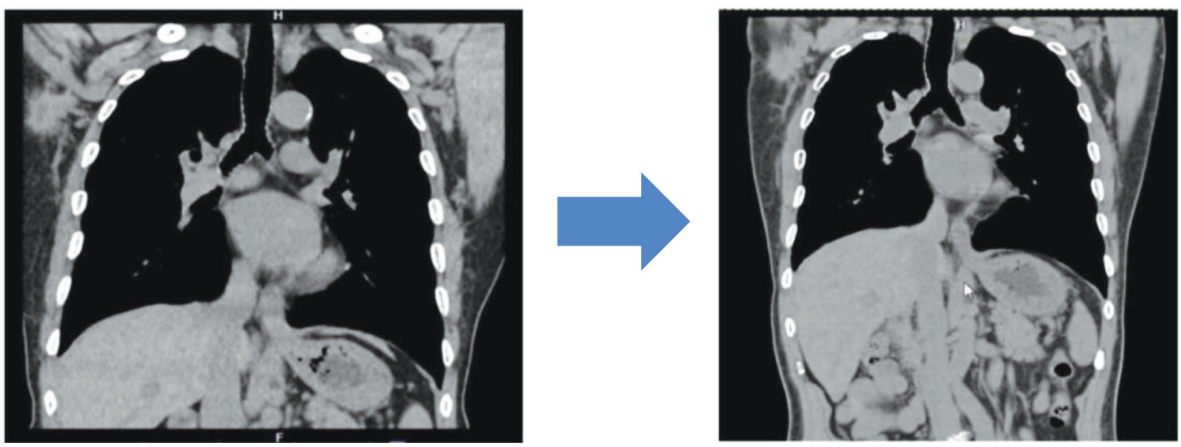

Figure 3 CT chest comparing 2015 and 2016
A: CT chest (17 January 2015). Right axillary lymph node enlargement 1.7 cm in diameter
B: CT chest (January 2016). Right axillary lymph node 2.7 cm in diameter

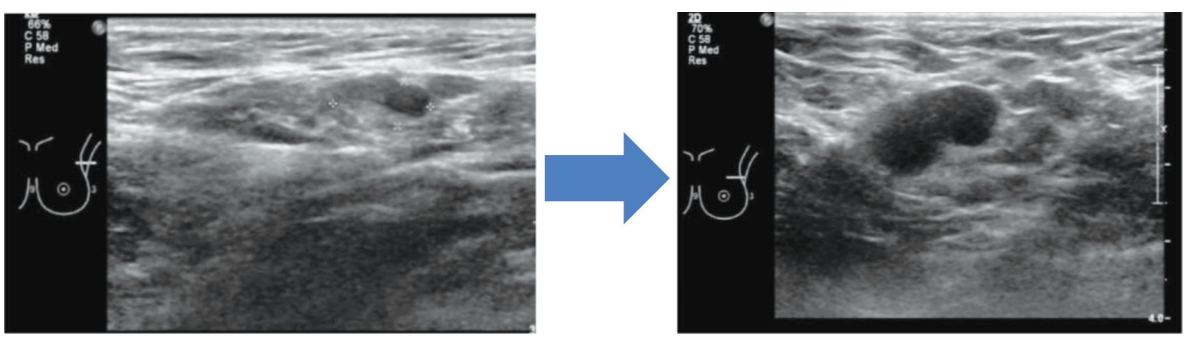

Figure 4 Ultrasound comparing 2020 and 2021
A: Ultrasound (12 October 2020). Few left axillary lymph nodes with mild cortical thickening, BIRADS 3
B: Ultrasound (24 November 2021). New development of few left axillary lymphadenopathy, size up to 1.2 cm in short axis

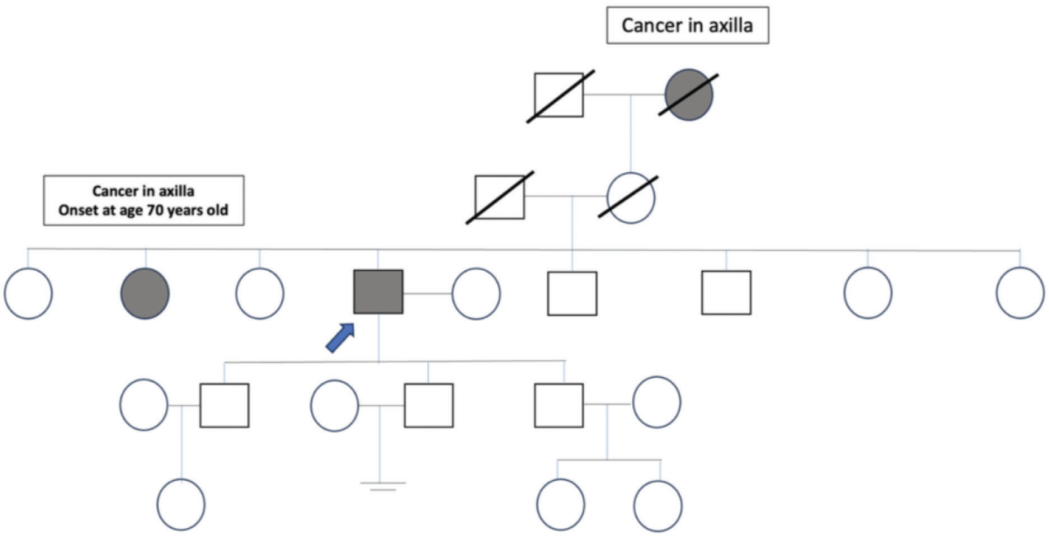

Figure 5 Family pedigree
The proband is indicated by the black arrow. Circle, female; square, male; filled symbols, individuals with cancer diagnosis; cross-hatched symbols, affected individuals already deceased

Discussion

PALB2 is a partner and localizer of BRCA2 that plays a key role in the homologous recombination (HR) pathway.[12] The loss of both PALB2 alleles causes the activation of the nonhomologous end joining (NHEJ), resulting in genomic instability.[13]

Germline pathogenic variants of the PALB2 tumor suppressor gene are associated with an increased risk of breast, pancreatic, and ovarian cancer.[8]

PALB2-associated breast cancer showed aggressive clinicopathological phenotypes, particularly triple-negative subtypes.[14]

A previous study by Lyer P[2] reported a case of a male patient with an abnormally enlarged right axillary lymph node. A tissue biopsy revealed a metastatic adenocarcinoma. Immunohistochemistry was performed to identify the primary origin, but the results were initially inconclusive. Chemotherapy was administered, but the metastasis increased and spread to the bladder, muscles, and lungs, and abnormalities were detected in the breast. Subsequent immunohistochemistry of the lung fluid confirmed the origin of the breast tissue. Further genetic testing revealed abnormalities in the PALB2 gene.

For male breast cancer presenting with axillary lymph node metastasis and an unidentified primary breast lesion, the management should follow protocols used for breast cancer with an undetected primary lesion,[1] as in cases of breast-like CUP. The management options based on the information provided:[15]

1. Axillary Lymph Node Dissection (ALND)[15]

Axillary lymph node dissection is widely accepted as a key part of the treatment for such cases. Removing the affected lymph nodes can help manage the local disease and reduce the risk of further spread.

2. Ipsilateral Mastectomy with Axillary LN Dissection[15]

Performing a mastectomy along with axillary lymph node dissection can help manage both the presumed primary breast cancer and the metastasis. This option is typically recommended when there's suspicion of occult breast cancer, as it lowers the risk of recurrence and may improve survival. This approach treats the breast and lymph nodes simultaneously, making it a more comprehensive option for local disease control.

3. Axillary Lymph Node Dissection with Radiation Therapy (RT)[15]

An alternative to mastectomy is combining axillary dissection with radiation therapy targeting the ipsilateral breast. Studies suggest that RT after axillary dissection is as effective as mastectomy in preventing locoregional recurrence. Therefore, patients may avoid surgery on the breast if radiation therapy is chosen. This option is considered when preserving the breast is a priority or surgery is not feasible.

4. Radiation Therapy Alone[15]

In some cases, radiation therapy alone might be considered, particularly if surgery is contraindicated. While this can help control the local disease, it is less commonly recommended as the sole treatment since surgery generally offers better locoregional control in combination with radiation or systemic therapy. When RT is selected, there is also no agreement on whether the supraclavicular or internal mammary lymph nodes should be included in the radiation field.[16]

5. Systemic Therapy[15]

Systemic therapy (chemotherapy, hormonal therapy, or targeted therapy) should follow the same guidelines as for node-positive breast cancer. It is essential to align systemic treatment with the latest breast cancer protocols, given the rapid advancements in this field. This would address the possibility of micrometastases and improve overall outcomes.

In this patient, the decision to administer a taxane-based regimen instead of the standard anthracycline-based regimen for locally advanced breast cancer was due to the presence of ischemic heart disease and reduced ejection fraction (EF). Anthracyclines, such as doxorubicin, are known for their cardiotoxic effects, which can further compromise heart function, particularly in patients with pre-existing cardiac conditions like ischemic heart disease. A taxane-based chemotherapy agent is less cardiotoxic and is commonly used in breast cancer treatment when anthracyclines are contraindicated.

In summary, axillary lymph node dissection is essential for these patients, with the addition of either mastectomy or radiation therapy for local control. The choice between mastectomy and radiation therapy depends on individual circumstances, but both approaches are effective in reducing recurrence and improving survival. Systemic therapy remains an important component of the overall treatment plan.

This gene increases the risk of female breast cancer risk by 32-53%, male breast cancer risk by 0.9% at age 70 y,[17] in epithelial ovarian cancer risk by 3-5%, and pancreatic cancer risk by 2-5%.[18]

For male patients with a PALB2 mutation, the risk of breast cancer is also increased, although it is generally lower than in women. The lifetime risk of male breast cancer in PALB2 carriers is significantly higher compared to the general male population. Prophylactic mastectomy is a consideration, but it is less commonly performed in men due to the lower incidence of breast cancer. Instead, enhanced surveillance, including regular clinical breast exams and patient education on self-examination, is often the first line of defense. Genetic counseling is crucial for male PALB2 carriers to discuss the potential benefits and risks of prophylactic surgery versus surveillance.[18]

The recommendations[18] for breast cancer risk management for men and people assigned male at birth include beginning at age 35. Individuals should learn how to perform a breast self-exam and be aware of any changes in their breasts. From age 35 onward, a breast exam by a doctor is recommended every 6 to 12 months. At Age 50 (or earlier if there is a family history of male breast cancer), patients should discuss with their doctor the benefits, risks, and costs of annual mammograms.

In addition to breast cancer, male PALB2 mutation carriers are also at an increased risk for other cancers, such as pancreatic cancer. Surveillance18 for pancreatic cancer should start at age 50 or earlier based on family history, with annual imaging like magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), or a combination of both. Male carriers should also discuss the potential risks, benefits, and limitations of regular screenings with their healthcare provider. The goal of such surveillance is early detection, which is critical in improving outcomes for high-risk cancers.

This management strategy aligns with NCCN guidelines[18] and underscores the importance of personalized care for male carriers of the PALB2 mutation, particularly in the context of genetic counseling and a tailored surveillance plan.

From our case report, it appears to be an extremely rare case of male breast cancer that initially presented with metastatic adenocarcinoma of unknown primary origin at the axillary lymph node of unknown primary. After treatment, there was a recurrence on the same and other side of the axillary lymph node, and an association with the PALB2 gene abnormality was identified. This case is noteworthy because it seems to be the first of its kind globally, given the absence of similar reported cases in the literature review.

Conclusion

In conclusion, to the best of our knowledge, this study aimed to understand the nature of PALB2 mutations in male breast cancer. Patients without BRCA mutations should be offered next-generation sequencing (NGS) multi-gene panel testing to detect other abnormalities when personal is suggestive of a hereditary syndrome.

The roles of bilateral prophylactic mastectomy, ALND, and RT will be discussed with the patient.

Statement of Ethics

This study protocol was reviewed and approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA. MURA2023/452).

Written informed consent was obtained from the patient for publication of the details of their medical care and any accompanying images.

Conflicts of Interest

The authors have no conflict of interest to declare.

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Data Availability Statement

All data generated from this study are included in this article. Further inquiries can be directed to the corresponding author.

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