



THE THAI JOURNAL OF SURGERY

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The THAI Journal of SURGERY

Official Publication of The Royal College of Surgeons of Thailand

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ISSN 0125-6068

E-ISSN 2697-5858

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2. Corporate Author:

- o 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.
- o American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

3. Personal Author(s):

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

4. Editor, Compiler, Chairman as Author:

- o Rhoades AJ, Van Rooyen CE, comps. Textbook of virology:

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- o Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr. Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

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- o Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12:(col. 1), 10(col.1).

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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.

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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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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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The THAI Journal of SURGERY

Official Publication of The Royal College of Surgeons of Thailand

Vol. 43

April - June 2022

No. 2

The THAI Journal of SURGERY 2022;43(2):49-56.

Official Publication of The Royal College of Surgeons of Thailand

Original Article

Loco-Regional Recurrence after Nipple-Sparing Mastectomy in Breast Cancer Patients

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Abstract

Objectives: There are relatively few studies of locoregional recurrence (LRR) after nipple-sparing mastectomy (NSM) for breast cancer. The aim of the present study was to determine the oncologic safety of nipple-areolar complex (NAC)-sparing mastectomy in breast cancer patients and to determine risk factors for LRR.

Patients and Methods: We analyzed 65 NSMs that were performed on 63 patients for both therapeutic and prophylactic indications between January 2007 and June 2017. Patient demographics, operative details, oncologic outcomes, and postoperative complications were recorded. Factors associated with LRR were also analyzed.

Results: The mean age of the patients was 43 years (range, 30 to 61 years). Fifty-eight NSMs (89%) were performed for cancer treatment. Skin necrosis was the most common complication (19%), but most cases were successfully managed conservatively. Fifty-one NSMs were included in the oncologic evaluation. Forty of 51 patients (78%) underwent surgery for invasive breast cancer, and the rest had carcinoma in situ. After a mean follow-up period of 70 months (24 to 162 months), four patients (8%) developed LRR, with mostly in the regional lymph nodes. Only one patient developed Paget's disease of the nipple after surgery and required NAC excision. Five-year disease-free survival was 87%. In a subgroup analysis, only tumor size and Ki-67 level showed an association with LRR, but only Ki-67 level was statistically significant (HR 1.07; 95% CI 1.00 to 1.15).

Conclusion: NSM is oncologically safe and is technically feasible in selected patients. A low rate of LRR was also observed. Only Ki-67 level showed an association with LRR. Long-term outcomes should be closely monitored.

Keywords: Breast cancer, Locoregional recurrence, Nipple-areolar complex-sparing mastectomy, Nipple-sparing mastectomy, Oncologic safety

Received for publication 31 August 2021; Revised 5 October 2021; Accepted 6 October 2021

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INTRODUCTION

Breast cancer is the most common cancer affecting women worldwide. There were 1.67 million new cases of breast cancer, with more than 500,000 deaths reported in 2012.¹ The incidence has been increasing over the past decade. Surgery is the mainstay of curative treatment for breast cancer, but more conservative surgical techniques have been developed. Breast conserving surgery (BCS) provides the best aesthetic results with oncologic safety, serving as the gold standard in early breast cancer treatment.² However, mastectomy may play a role in some situations, such as for multicentric breast cancer, large tumors, post-radiated patients, and for prophylaxis.

Success in reconstruction techniques has led to a change from radical to more conservative approaches. In 1991, Toth described the skin-sparing mastectomy (SSM) technique.³ This technique has been widely adopted as a preferred reconstruction technique in terms of oncologic safety and cosmesis. The nipple-areolar complex (NAC) is the signature of the breast and has the greatest impact on patients' satisfaction and feelings of mutilation, but oncologic safety is still a major concern.⁴ Freeman reported on the NAC-sparing technique in 1962 and named it subcutaneous mastectomy, which was used for benign breast lesions.^{5,6} NAC involvement in breast cancer was found to be from 0 to 58% in previous reports.⁷ These results vary widely because of the differences in populations, staging, and sampling techniques among the studies.

Based on Sappey's theory, all lymphatic systems drain towards the subareolar plexus and should be removed in an oncologic resection. Wellings et al. proposed the theory that neoplastic breast lesions are generated from the terminal duct lobular unit (TDLU).^{8,9} Previous publications identified TDLU in nipple specimens in only about 0 to 9% of cases.¹⁰⁻¹⁴ Most were found near the base of the nipple and not at the tip, suggesting that NAC-sparing mastectomy should be safe if there is no tumor involvement at the base of the nipple. However, no randomized study has compared NAC-sparing mastectomy with standard surgical techniques. Previous reported locoregional recurrence (LRR) rate of 2.4% (range, 0 to 19.1%) was comparable to that seen in breast-conserving surgery (BCS).¹⁵ In these studies, almost all the patients experienced recurrence outside the NAC. Factors related to NAC involvement included tumor size, tumor-nipple distance, lymphovascular invasion, and axillary lymph node involvement. There are no standardized patient selection criteria. The objective of the present study was

to determine the oncologic safety and risk factors of LRR in patients who underwent NAC-sparing mastectomy.

PATIENTS AND METHODS

All patients who underwent NSM for therapeutic or prophylactic indications in the Breast and Endocrinology Unit at our institution between January 2007 and June 2017 were included. All patients underwent standard preoperative evaluations, including clinical examination, digital mammography, and breast ultrasonography. Magnetic resonance imaging is not routinely performed at our institution. NSM were performed if the primary tumor located outside of the areola, with the absence of nipple retraction or bloody nipple discharge, and absence of microcalcification in the retroareolar region. Some patients with multicentric/multifocal lesions that were distant from the areola also underwent NSM. Patients with preoperative chemotherapy or radiotherapy were excluded from the study. Patients with inflammatory breast cancer and Paget's disease were not candidates for NSM. The study was approved by the Research Ethics Committee of our institute. A flowchart of patient selection is shown in Figure 1.

The operative technique has been described in a previous study.¹⁶ Different types of skin incisions have also been previously reported.¹⁷ We preferred the superolateral radial incision to provide good exposure and a low rate of ischemic complications. The glandular tissue and all ducts were cored out, and subareolar base tissue was sent for pathological examination in all patients (Figures 2 to 4).

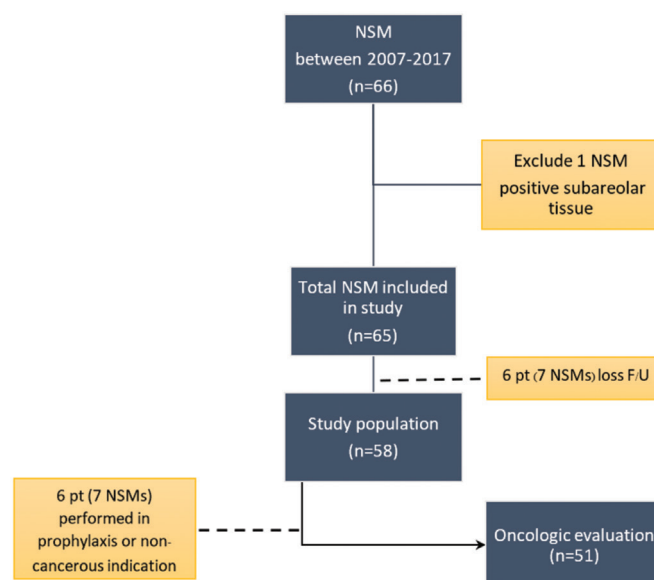


Figure 1 Patient selection flowchart

The NAC was excised if the base tissue was involved by cancer. Immediate reconstruction was performed in all patients with implants, autologous flaps, or both.

The decision for adjuvant treatment was discussed in a multidisciplinary breast cancer care team. All patients were followed up within 1 month after the operation, then every 3 months for the following 2 years, and every 6 months for 5 years thereafter. Only patients with a follow-up duration of > 24 months were included in the oncological analysis.

All demographic data, tumor characteristics, complications, and oncological outcomes were presented using descriptive statistics. Means, standard deviations (SD), medians, and ranges were used for continuous

variables, while frequencies and percentages were used for the categorical variables. The primary outcome was LRR. Unpaired T-test, ranksum test and Fisher's exact test, as appropriate, were used to identify the association between the primary outcome and any risk factor. Cox's proportional hazard regression model was used to identify independent risk factors for LRR. All statistical analyses were performed using STATA version 14.0.



Figure 2 Coring out of glandular tissue from the nipple: subareolar base tissue is identified.



Figure 3 Subareolar base tissue is cored out and sent for frozen section.



Figure 4 All subareolar base tissue has been removed.

RESULTS

Sixty-four women underwent 66 NSMs between January 2007 and June 2017. The subareolar margin was positive for malignant cells in one patient (2%); therefore, this patient was excluded from the study. The mean age of the patients was 43 years (range, 30 to 61 years). Fifty-eight patients (89%) underwent NSM under therapeutic indication (95% were invasive or carcinoma in situ and 5% were phyllodes tumors). Three patients with phyllodes tumors and four NSMs performed for benign diseases were excluded from the oncologic analysis. Patient characteristics are shown in [Table 1](#).

The postoperative complications and types of ischemia are shown in [Table 2](#). Skin ischemia was the most common complication observed in our study. Nipple ischemia occurred in 12 patients (19%). Three developed full-thickness necrosis, but only two required surgical debridement. Only one patient had nipple loss requiring total NAC excision. Partial skin flap ischemia occurred in 13 NSMs (20%) and was successfully managed conservatively. Infection and seroma were also rather common, but most resolved with conservative treatment.

Table 1 Baseline characteristics of 65 nipple-sparing mastectomies (NSM)

Characteristics	Summary
Age (years) : median (range)	43.66 (30 - 61)
BMI (kg/m²): median (range)	23.3 (15.4 - 43.8)
Family history of breast cancer: n (%)	13 (20)
Co-morbidity: n (%)	
None	55 (85)
Diabetes mellitus	4 (6)
Hypertension	3 (5)
Others	3 (5)
Preoperative diagnosis: n (%)	
Cancer	54 (83)
Non-cancer	11 (17)
Indication for surgery: n (%)	
Therapeutic	58 (89)
Prophylaxis	7 (11)

Table 2 Postoperative complications in 65 nipple-sparing mastectomies

Complications	Number (%)
Seroma	18 (28)
Infection	12 (19)
Fat necrosis	5 (8)
Wound dehiscence	1 (2)
Skin flap ischemia	13 (20)
Nipple ischemia	
Partial	9 (14)
Full thickness	3 (5)

We performed an oncologic evaluation of 51 NSMs in patients with breast cancer. Forty (78%) patients had invasive cancer, and the remainder had carcinoma in situ. Ten NSMs (20%) had multifocal cancers. Half of the patients were classified as T2 and T3 according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging. The median tumor size was 2.4 cm (range, 0.1 to 7.7 cm). The median tumor-nipple distance was 3.3 cm (range, 0.9 to 7.8 cm). Seventeen patients (33%) had axillary lymph node metastasis. Eight of 51 patients received postoperative radiotherapy. Half of the patients with invasive cancer had the luminal subtype (hormonal receptor-positive breast cancer).

After a mean follow-up period of 70 months (range, 24 to 162 months), 4 patients (8%) developed LRR. One patient underwent NSM and sentinel lymph node biopsy for ductal carcinoma in situ. She developed Paget's disease of the nipple 31 months after surgery and required NAC excision. Another patient had hormone-positive / HER-2 negative breast cancer staged pT2N1M0. She had cutaneous recurrence at the ipsilateral breast after 47 months and underwent wide excision. The 2 remaining patients had triple-negative invasive breast cancer subtype. One of these was staged pT2N0M0. She had recurrence in the ipsilateral axillary lymph nodes 15 months after surgery without lesions in the NAC. Axillary lymph node dissection and postoperative radiotherapy was performed. The last patient was staged pT2N1M0. She had local recurrence in the ipsilateral breast and internal mammary lymph nodes after 15 months. She was treated with systemic chemotherapy followed by mastectomy, excision of the internal mammary lymph nodes, and postoperative radiotherapy. The patient developed distant metastasis 42 months later. Two patients developed distant metastasis without locoregional disease (one had lung and another liver metastasis), leading to an overall recurrence rate of 12%.

The median time-to-recurrence was 23 months. Five-year disease-free survival was 87%. In our study, LRR in triple-negative breast cancer (TNBC) subtype was 29% compared with 5% in other subtypes. We evaluated factors associated with LRR (Table 3). Only Ki-67 level showed an association with LRR (HR 1.07; 95% CI 1.00 to 1.15) at the 5% level.

DISCUSSION

We evaluated the oncological safety and factors associated with LRR after NSM at our institute. In the past, NSM was only performed in a prophylactic setting because of the lack of strong supporting evidence for the safety of this technique in breast cancer. To date, only large prospective studies have shown recurrence rates comparable to that of BCS.^{15,18}

There is currently no standard NSM, with differences in the surgical techniques used, criteria for patient selection, and adjunctive post-surgery treatment across studies. One large study by Petit et al. reported 934 NSM with 16 Gy of intraoperative radiotherapy (ELIOT). This study showed 3.6% and 4.0% incidences of invasive and non-invasive local recurrences in the breast, respectively.

Table 3 Locoregional recurrence (LRR) in 51 NSMs performed for cancerous lesions

Variable	LRR (N=4)	No LRR (N=47)	p-value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	p-value
Age (years): mean ± SD	41.3 ± 2.2	44.0 ± 8.0	0.498			
BMI (kg/m²): mean ± SD	22.3 ± 1.4	23.7 ± 5.6	0.614			
Family history of breast cancer: n (%)			0.564			
Yes	0	10 (23)				
No	4 (100)	33 (77)				
Breast density: n (%)			0.403			
Scatter dense	0	5 (12)				
Heterogeneous dense	4 (100)	22 (52)				
Extremely dense	0	15 (36)				
Tumor size (cm): median (IQR)	2.9 (2.5, 4.3)	2.1 (1.5, 2.8)	0.079	2.23 (1.03, 4.78)	1.50 (0.63, 3.58)	0.353
Tumor-Nipple distance (cm): median (IQR)	2.87 (2.30, 5.16)	2.75 (2.32, 4.60)	0.826			
Multifocal lesion: n (%)			0.999			
Yes	1 (25)	9 (19)				
No	3 (75)	36 (77)				
Unknown	0	2 (4)				
T-stage: n (%)			0.577			
In situ	1 (25)	10 (21)				
1	0	14 (30)				
2	3 (75)	22 (47)				
3	0	1 (2)				
Number of lymph node involvement: median (IQR)	0.5 (0, 1)	0 (0, 1)	0.705			
N-stage: n (%)			0.259			
0	2 (50)	32 (68)				
1	2 (50)	9 (19)				
2	0	6 (13)				
Stage: n (%)			0.249			
In situ	1 (25)	10 (22)				
1A	0	9 (20)				
1B	1 (25)	1 (2)				
2A	1 (25)	14 (30)				
2B	1 (25)	5 (11)				
3A	0	7 (15)				
Tumor grading: n (%)			0.699			
1	0	3 (6)				
2	3 (75)	21 (47)				
3	1 (25)	21 (47)				
Hormone receptors: n (%)			0.310			
Positive	2 (50)	34 (26)				
Negative	2 (50)	12 (74)				
HER-2: n (%)			0.999			
Negative	3 (75)	25 (56)				
Equivocal	0	5 (11)				
Positive	1 (25)	15 (33)				
Subtypes: n (%)			0.176			
Luminal	2 (50)	34 (74)				
HER-2	0	7 (15)				
Triple negative	2 (50)	5 (11)				
Ki-67: median (IQR)	65 (45, 80)	30 (15, 50)	0.034	1.07 (1.01, 1.15)	1.07 (1.00, 1.15)	0.050
Lymphovascular invasion: n (%)			0.530			
Yes	1 (25)	7 (16)				
No	3 (75)	37 (84)				
Radiotherapy: n (%)			0.999			
Yes	0	8 (17)				
No	4 (100)	39 (83)				

SD: standard deviation; IQR: interquartile range; BMI: body-mass index; LRR (locoregional recurrence)

Only 11 patients (1.2%) had recurrence at the NAC after a 50-month median follow-up time. A 5-year cumulative incidence of breast-related events in invasive cancer patients was 14.7% and overall survival was 95.5%.¹⁸

In the present study, after a mean follow-up time of 70 months, 2 of 40 patients with invasive cancer (5%) had in-breast recurrence. Only one patient (2%) with non-invasive (in situ) cancer who underwent NSM developed Paget's disease of the nipple after 31 months. Our 5-year local recurrence rate for both invasive and non-invasive cancer was 10% and the overall 5-year survival was 97.5%. This result was not substantially different from those of previous studies, even though intraoperative radiotherapy was not used in the present study. Eight patients (22%) received postoperative radiotherapy, but the local recurrence rates were not different between patients who had and those who did not have radiotherapy.

The previous study by Petit et al. reported that LRR after NSM was related to the tumor size, number of positive lymph nodes, histological subtype, and the biological features of the disease (e.g., HER-2/neu, Ki-67, nuclear grading, and vascular invasion). Our study also seemed to show an association between LRR and the Ki-67 level (HR 1.07; 95% CI 1.00 to 1.15). A positive HER-2 status is associated with increased LRR, and is used as a contraindication for NSM in some institutions. The present study, however, could not demonstrate an association between HER-2 status and LRR, nor any association between LRR and other biological factors. Although LRR was more common in the triple-negative subtype (see Table 3), this was not statistically significant. Tumor size has also been used to select patients for NSM in the literature. Although LRR was more common in larger tumors, but again, the difference was not statistically significant in the present study.

Major complications after NSM include NAC and skin flap ischemia. The nipple necrosis rate from previous reports was 5.9% (range, 0 to 37.5%).^{15,17} Our study showed 3 patients (5%) with full-thickness necrosis of the NAC and a 1.5% rate of NAC removal, which is consistent with the results of previous studies. Although the rates of partial NAC and skin flap ischemia were quite high (14% and 20%, respectively), in most cases the involved area was tiny, and all were successfully managed conservatively.

CONCLUSION

In summary, the present study demonstrated the feasibility and oncological safety of performing NSM in selected patients, with a low risk of NAC removal and low LRR rate after a mean follow-up of 70 months. Only Ki-67 level seemed to show an association with LRR. Further study is needed to confirm the oncologic safety and to standardize techniques of NSM, as well as to highlight NSM as a standard option for breast reconstruction in breast cancer patients.

ACKNOWLEDGEMENT

Special thanks to Songphol Phosuwan, Jirat Teerapradith, Tanet Chatmongkonwat, Serm Sri Pongratanakul, Sivaporn Pondeenana, Manunya Phattaravittakon, and Jirawadee Ruamjaroenchai for assistance during surgery and in gathering data. We would like to thank Editage (www.editage.com) for English language editing. We also thank Dr. Napaphat Proprom and Ms. Pattawia Choikrua for their assistance with statistical analysis.

CONFLICT OF INTEREST

No authors have any potential conflict of interest to disclose or none of the authors disclose any potential conflict of interest. We did not receive any specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

DATA SHARING STATEMENT

The protocol is registered in the Thai Clinical Trials Registry (TCTR) which is in a primary registry of the World Health Organization (WHO) registry network (UIN TCTR20200106004).

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บทคัดย่อ การกลับเป็นซ้ำเฉพาะที่ในผู้ป่วยมะเร็งเต้านมภายหลังการผ่าตัดเต้านมออกทั้งหมดแบบสงวนหัวนม และลานหัวนม

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ความเป็นมา: แม้ว่าในปัจจุบันการผ่าตัดแบบสงวนเต้านมจะได้รับการยอมรับอย่างแพร่หลายและเป็นการรักษาหลักในการรักษาผู้ป่วยมะเร็งเต้านมระยะเริ่มต้น แต่อย่างไรก็ตามการผ่าตัดเต้านมออกทั้งหมดยังคงมีบทบาทสำคัญในผู้ป่วยที่มีเนื้อมะเร็งหลายตำแหน่งภายในเต้านม และในการผ่าตัดเพื่อป้องกันการเกิดมะเร็งเต้านม จากผลการศึกษาที่ผ่านมาพบว่าการกลับเป็นซ้ำเฉพาะที่ภายหลังการผ่าตัดเต้านมออกทั้งหมดแบบสงวนหัวนมไม่แตกต่างจากการผ่าตัดแบบสงวนเต้านม แต่จนถึงปัจจุบันยังคงไม่มีเกณฑ์มาตรฐานในการคัดเลือกผู้ป่วยที่เหมาะสมเพื่อเข้ารับการผ่าตัดดังกล่าว

วัตถุประสงค์: เพื่อศึกษาถึงความปลอดภัย และอัตราการกลับเป็นซ้ำเฉพาะที่ภายหลังการผ่าตัดเต้านมออกทั้งหมดแบบสงวนหัวนม

วิธีการศึกษา: ผู้วิจัยได้ทำการวิเคราะห์ข้อมูลจากจำนวนครั้งของการผ่าตัดเต้านมออกทั้งหมดแบบสงวนหัวนมทั้งหมด 65 ครั้ง ในผู้ป่วยมะเร็งเต้านม 63 ราย ที่เข้ารับการผ่าตัดเพื่อรักษามะเร็งเต้านม และผู้ที่เข้ารับการผ่าตัดเพื่อป้องกันการเกิดมะเร็งเต้านมตั้งแต่เดือนมกราคม พ.ศ. 2550 ถึงเดือนมิถุนายน พ.ศ. 2560 โดยทำการเก็บรวบรวมข้อมูลพื้นฐานของผู้ป่วย ข้อมูลการผ่าตัด ผลการรักษา และภาวะแทรกซ้อนจากการผ่าตัด เพื่อวิเคราะห์หาความสัมพันธ์กับการกลับเป็นซ้ำเฉพาะที่

ผลการศึกษา: ในกลุ่มผู้ป่วยที่ศึกษาพบมีค่าเฉลี่ยของอายุที่ 43 ปี (30-61 ปี) แบ่งเป็นการผ่าตัดเพื่อรักษามะเร็งเต้านม 58 ครั้ง คิดเป็นร้อยละ 89 ของการผ่าตัดทั้งหมด ภาวะแทรกซ้อนที่พบได้บ่อยที่สุด ได้แก่ การเกิดเนื้อตายบริเวณแผลผ่าตัดพบได้ร้อยละ 19 แต่ทุกรายมีอาการที่ดีขึ้นภายหลังการรักษาแบบประคับประคองโดยไม่ต้องผ่าตัด จากการผ่าตัดทั้งสิ้น 65 ครั้ง มีการผ่าตัด 51 ครั้ง ที่เข้าเกณฑ์การคัดเลือกเพื่อนำมาวิเคราะห์ผลการรักษา โดยแบ่งเป็นผู้ป่วย 40 ราย (ร้อยละ 78) ที่เข้ารับการผ่าตัดเพื่อรักษามะเร็งเต้านมชนิดดุกลาม และอีก 11 ราย ที่ทำการผ่าตัดในมะเร็งเต้านมชนิดยังไม่ลุกลาม ภายหลังการตรวจติดตามการรักษาเป็นระยะเวลาเฉลี่ย 70 เดือน (24-162 เดือน) พบมีการกลับเป็นซ้ำเฉพาะที่ในผู้ป่วย 4 ราย คิดเป็นร้อยละ 7.8 โดยพบมีการกลับเป็นซ้ำมากที่สุดบริเวณต่อมน้ำเหลืองใกล้เคียง พบผู้ป่วยเพียง 1 ราย ที่มีโรคมะเร็งชนิดไม่ลุกลามบริเวณหัวนม และได้รับการผ่าตัดเพื่อนำหัวนม และลานหัวนมออกในเวลาต่อมา จากการศึกษาพบมีอัตราการรอดชีวิตแบบปลอดโรคที่ 5 ปีร้อยละ 87 เมื่อทำการวิเคราะห์กลุ่มย่อยเพิ่มเติมพบว่ามีเพียงค่าความสามารถในการแบ่งตัวของเซลล์มะเร็ง (Ki-67) เท่านั้นที่มีความสัมพันธ์กับการกลับเป็นซ้ำเฉพาะที่ (HR 1.07; 95% CI 1.00 to 1.15)

สรุปผลการศึกษา: การผ่าตัดเต้านมออกทั้งหมดแบบสงวนหัวนมมีความปลอดภัยเมื่อทำการคัดเลือกผู้ป่วยอย่างเหมาะสม โดยพบมีการกลับเป็นซ้ำเฉพาะที่ต่ำ จากการศึกษาพบเพียงค่าความสามารถในการแบ่งตัวของเซลล์มะเร็งเท่านั้นที่สัมพันธ์กับการกลับเป็นซ้ำเฉพาะที่ อย่างไรก็ตามยังคงต้องการข้อมูลการศึกษาในระยะยาวเพิ่มเติม

Outcomes of Wound Drainage versus No Wound Drainage in the Patients Undergoing Mastectomy

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Abstract

Background and objective: Seroma formation is the most common complication after total mastectomy or axillary lymph node dissection (ALND). The role of drainage is still controversial since some evidence suggests that it does not prevent the formation of seroma. This study aimed to evaluate seroma formation and postoperative complications in patients undergoing mastectomy with or without drainage.

Patients and Methods: A cohort of female patients with breast cancer or other breast conditions were retrospectively studied at the Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital from November 2018 to August 2019. The patients were divided into drain and no drain groups. Demographic data, seroma formation, and postoperative complications were recorded and compared.

Results: A total of 129 patients were included in this study, 67 patients with drainage and 62 patients without drainage. The incidence of seroma formation was similar between the two groups. The total volume of aspirated seroma was significantly higher in the no drain group ($p = 0.010$). When combining the volume of seroma (drained + aspirated), the volume in the drain group was significantly higher than that in the no drain group ($p = 0.020$). The number of aspirations was higher in the drain group: 2 (0-9) vs 3 (0-14), $p = 0.031$. The patients in the no drain group had a significantly shorter length of hospital stay, 2.0 (1.0-3.0) vs 4.0 (2.0-10.0) days, $p < 0.001$.

Conclusions: No drainage is a feasible option in patients undergoing mastectomy in terms of reducing hospital stay but not increasing the incidence of symptomatic seroma and wound complications compared to routine drain placement.

Keywords: Mastectomy, Seroma, Suction drainage

INTRODUCTION

Breast cancer is the most common female malignancy in Thailand.¹ The treatment for breast cancer is planned based on staging and its subtype. Surgery is the mainstay of the treatment, removing gross tumor and

providing accurate pathological staging. Radical surgery for breast cancer has been replaced with breast conserving surgery in suitable patients.² However, mastectomy is still the major surgical procedure for treatment of breast cancer in our institute.³

Received for publication 9 September 2021; Revised 14 October 2021; Accepted 15 October 2021

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Seroma formation is the most common complication after total mastectomy or axillary lymph node dissection (ALND).⁴ The incidence of seroma formation was reported, ranging from 15 to 81%.⁵ This may cause discomfort, flap necrosis, wound dehiscence, or infection. Furthermore, it may prolong recovery and delay adjuvant therapy.⁶

There are various techniques to reduce seroma formation, such as the use of drains, pressure dressing, flap fixation, fibrin sealants, and harmonic scalpel.^{5,7-10} Application of drains was expected to obtain negative pressure and get rid of the dead space after breast tissue removal and ALND.^{5,7} The timing of drain removal is still a controversy, ranging from within 24 hours to 8 days after surgery or discharge early with the drain *in situ*.^{5,11,12}

On the other hand, the role of drainage is still controversial since some evidence has demonstrated that it does not prevent the formation of seroma.⁵ Use of suction drainage for short periods can prevent seroma or reduce its incidence compared to patients without drainage.¹³ Several recent studies have indicated that there is no difference in seroma formation among no drainage, short, and long interval drainage, while drainage might increase morbidity in patients and length of hospital stay.¹⁴⁻¹⁸ Nevertheless, there were increases in volume, duration, and number of visits for seroma aspiration in the patients without drainage.¹⁶

Closed suction drainage was frequently used in our institute after mastectomy with or without ALND. However, there was no consensus regarding drainage placement and duration of drainage placement. To our knowledge, there was no report that compared seroma formation between mastectomy with and without drainage in Thailand. This study aimed to compare seroma formation and postoperative complications in patients who underwent mastectomy with or without drainage.

PATIENTS AND METHODS

A cohort of female patients with breast cancer or other breast conditions were retrospectively studied at the Division of Head Neck and Breast Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital from November 2018 to August 2019. The inclusion criteria were female patients, age 18 years or older, and received total mastectomy with sentinel lymph node biopsy (SLNB) or ALND. The exclusion criteria were: undergoing immediate breast reconstruction, receiving

neoadjuvant treatment, immunocompromised patients, and being discharged with the drain *in situ*. Data including age, body mass index (BMI), antiplatelet or anticoagulant use, preoperative antibiotics, preoperative serum creatinine, preoperative serum albumin, type of surgery, operative time, estimated blood loss, dressing procedure, length of postoperative hospital stay, the weight of the breast specimen, T stage, N stage, incidence of symptomatic seroma, volume of seroma, and duration of seroma were collected. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of Faculty of Medicine Siriraj Hospital, Mahidol University (certificate of approval number Si 206/2019).

The management of wound drainage in the institution depended on surgeons' preference, ranging from no drain placement, removal of the drains on the third postoperative day, removal of the drains when the volume of drain content is less than 50 milliliters, or discharge the patients with drain *in situ*. The follow-up interval of the patients in both groups depended on symptoms and the volume of aspirated seroma. Symptomatic seroma was diagnosed if the patient had clinically palpated seroma at the time of the outpatient department visit and required aspiration. The duration of seroma was defined as the duration from surgery to the last aspiration.

Two independent proportions formulas were used to calculate sample size. The estimated incidences of seroma formation in the drain group and no drain group were 50% and 75%, respectively. These incidences were estimated according to the incidences of seroma formation and the incidences of seroma requiring drainage reported in the previous retrospective study in patients undergoing total mastectomy with or without axillary surgery.¹⁹ With test significance level 0.05 and 80% power, the number of patients in each group was 58. Categorical data was presented as percentage and analyzed by Chi-square or Fisher's exact test. Quantitative data was presented as mean $\pm$ standard deviation or median (range) and analyzed by a 2-sample t-test or Mann-Whitney U test. All statistical analyses were carried out using SPSS version 21.0 (IBM Corp., NY, USA). A *p*-value of < 0.05 was considered as statistically significant.

RESULTS

A total of 129 patients were included in this study. Closed suction drainage was applied after surgery in 67 patients and classified as the drain group. While 62 pa-

tients did not have drainage and were classified as part of the no drain group. Baseline characteristics of the patients in both groups were not different in terms of age, BMI, antiplatelet or anticoagulant use, preoperative antibiotics, serum creatinine level, type of surgery, operative time, weight of breast specimen, and pathological staging.

Most of the patients had serum creatinine levels within the normal limit (0.51 to 0.95 mg/dL). A few patients had creatinine levels higher than the upper limit. However, the highest creatinine level was 1.3 mg/dL. Three patients in the no drain group had no invasive carcinoma. Two of them had phyllodes tumors and another had atypical ductal hyperplasia. The latter patient had previous contralateral breast cancer, post total mastectomy, and underwent total mastectomy due to the presence of atypical ductal hyperplasia by core needle

biopsy. The majority of patients had T1-T2 stage, 75% in the drain group and 68% in the no drain group. More than half of the patients in both groups had negative pathological nodes.

All of the patients had serum albumin levels within the normal limit (3.5 to 5.2 g/dL). The patients in the no drain group had significantly higher serum albumin levels when compared to those in the drain group ($p = 0.035$). However, the mean difference was 0.11, with a 95% confidence interval of 0.01 to 0.21. All of the patients in the no drain group had external pressure dressings while only 42 patients (63%) in the drain group had pressure dressings after surgery ($p < 0.001$). The median weight of the breast specimen tended to be higher in the no drain group. Estimated blood loss was significantly higher in the no drain group (Table 1).

Table 1 Baseline characteristics of patients

	Drain n = 67	No drain n = 62	p-values
Age (years): mean $\pm$ SD	57.2 $\pm$ 11.8	54.5 $\pm$ 12.1	0.203
BMI (kg/m²): mean $\pm$ SD	23.8 $\pm$ 4.5	24.0 $\pm$ 4.2	0.790
Antiplatelet/anticoagulant: n (%)			
No	61 (91)	60 (97)	0.178
Yes	6 (9)	2 (3)	
Preoperative antibiotics: n (%)			
No	48 (72)	44 (71)	0.933
Yes	19 (28)	18 (29)	
Creatinine level (mg/dL): mean $\pm$ SD	0.72 $\pm$ 0.16	0.71 $\pm$ 0.17	0.552
Albumin levels (g/dL): mean $\pm$ SD	4.42 $\pm$ 0.28	4.53 $\pm$ 0.28	0.035
Pressure dressing: n (%)			
No	25 (37)	0	< 0.001
Yes	42 (63)	62 (100)	
T stage: n (%)			
Tis	13 (20)	8 (13)	0.157
T1	25 (37)	21 (34)	
T2	25 (37)	21 (34)	
T3	4 (6)	9 (15)	
Others	0	3 (4)	
N stage: n (%)			
N0	43 (64)	36 (63)	0.801
N1	17 (26)	13 (23)	
N2	3 (5)	5 (9)	
N3	3 (5)	3 (5)	
Breast weight (g): median (range)	570 (75 - 1,215)	605 (175 - 3,500)	0.138
Estimated blood loss (mL): median (range)	20 (5 - 300)	35 (10 - 850)	0.004
Type of surgery: n (%)			
Total mastectomy $\pm$ SLNB	44 (66)	39 (63)	0.743
Total mastectomy + ALND	23 (34)	23 (37)	
Operative time (min): median (range)	90 (40 - 175)	86.5 (40 - 150)	0.232

The incidence of seroma formation was similar between the two groups. The majority of the patients in both groups had symptomatic seroma requiring aspiration during outpatient department visits. The total volume of aspirated seroma was significantly higher in the no drain group ($p = 0.006$). When combining the volume of seroma that was drained by suction drainage in the drain group with the volume of seroma that was aspirated at the outpatient department, the volume of seroma in the drain group was significantly higher than that in the no drain group ($p = 0.040$).

The duration of seroma resolution was approximately 1 month in both groups. The number of aspirations was higher in the drain group: 2 (0 to 9) vs 3 (0 to 14), $p = 0.031$. The patients in the no drain group had significantly shorter hospital stay, 2 days (1 to 3) vs 4 days (2 to 10), $p < 0.001$, respectively (Table 2). There were no immediate postoperative complications that required reoperation in both groups. Hematoma occurred in one patient without drainage which could be managed conservatively. No patients in either group visited the emergency department due to wound complications.

Table 2 Comparison of outcomes between drain and no drain group

	Drain n = 67	No drain n = 62	p-values
Symptomatic seroma: n (%)			
No	7 (10)	6 (10)	0.885
Yes	60 (90)	56 (90)	
Volume of aspirated seroma, (mL): median (range)	120 (0 - 3,350)	300 (0 - 3,475)	0.006
Drain volume (mL): median (range)	270 (35 - 1,960)	N/A	N/A
Total volume of seroma (drain + aspirated, mL): median (range)	445 (90 - 5,310)	300 (0 - 3,475)	0.040
Time to no seroma (days): median (range)	24 (0 - 163)	25 (0 - 165)	0.346
Number of aspirations: median (range)	2 (0 - 9)	3 (0 - 14)	0.031
Length of postoperative hospital stay (days): median (range)	4 (2 - 10)	2 (1 - 3)	< 0.001

DISCUSSION

Different methods for reducing postoperative seroma formation in breast cancer surgery are currently performed at the authors' institution depending on the surgeon's preference. In this retrospective study, the authors found that closed suction drainage neither reduced the volume of seroma nor the time to no seroma. On the other hand, it resulted in a longer length of hospital stay. The volume of aspirated seroma was significantly higher in the no drain group. In contrast, the total volume of seroma was significantly higher in the drain group.

There were some patients' characteristics that were different between the two groups. The statistically significant higher serum albumin levels in the no drain group had no clinically significant effect on seroma formation since all of the patients had normal serum albumin levels and the mean difference was 0.11 g/dL. The estimated blood loss was higher in no drain group. This might be due to the higher breast weight of the patients in this

group.

The current findings were in concordance with a previous study by Taylor *et al.* The authors found that in the patients with drain placement, the volume of aspirated seroma was lower than in the patients without drainage. However, there was no difference in the incidence of symptomatic seroma, or wound complications.¹⁷ In contrast, the number of aspirations in our study was higher in the no drain group. After the patient with the most aspirations was excluded, the median number of aspirations in the no drain group was 3 (0 to 8). Although the difference was still statistically significant ($p = 0.044$), it might not have clinical significance.

In a systematic review of seven studies that compared wound drainage with no wound drainage in individuals after ALND for breast carcinoma, there was no difference in the wound infection rate between the two groups. The length of the hospital stay was longer in the drain group. Subgroup analysis of the patients who

received mastectomy in 2 studies showed that drainage did not significantly reduce the incidence of seroma formation.¹³ Seroma was formed in response to surgical trauma and the acute phase of wound healing.⁶ Thus, the formation of seroma should be highest in the first 24 hours after surgery and then gradually decrease.

Some studies compared short-term drainage with long-term drainage, but the results were still controversial. Baas-Vrancken Peeters *et al.* reported that short-term drainage (24 hours) after modified radical mastectomy or lumpectomy with ALND did not significantly increase the volume of aspirated seroma. Moreover, it facilitated early hospital discharge compared to long-term drainage, and wound-related complications were quite higher in the patients with long-term drainage.¹² Andeweg *et al.* performed a cohort study to compare the outcome between short-term and long-term axillary drainage after ALND. They found that the patients with short-term drainage had a higher incidence of seroma and a larger volume of aspirated seroma, but this did not lead to wound complications.¹¹

Other techniques were used to reduce postoperative seroma. Application of pressure dressing in patients who underwent modified radical mastectomy resulted in a lower incidence of symptomatic seroma that needed aspiration.²⁰ A randomized controlled trial comparing axillary padding without drainage with closed suction drainage for the axillary wound after ALND in breast conserving surgery showed that axillary padding without drainage was feasible and safe. Postoperative complications and quality of life were similar.²¹ In the present study, while all of the patients in the no drain group received pressure dressings, more than one-third of the patients in the drain group did not receive pressure dressings. When we excluded the patients without pressure dressing, the incidence of seroma in both groups was still similar. This finding might be due to the very low number of patients that did not have seroma.

Jain *et al.* reported that the incidences of seroma formation among the patients with drainage, no drainage, and no drainage with fibrin sealant were not different.¹⁵ However, fibrin sealant in patients without drainage can reduce the volume of aspirated seroma. Purushotham *et al.* compared the patients who underwent conventional mastectomy with drainage and underwent mastectomy with suturing flap without drainage. There was no difference in seroma rates, volume of seroma, fluid aspirated or wound sepsis.¹⁴ This technique was not performed in

our institute. Suturing of the flap might complicate the aspiration of seroma due to multi-loculation created by suturing.

This study had some limitations. The decision to place drains was according to surgeons' preference that might lead to selection bias. This study was a retrospective medical record review with consequent incomplete data retrieval. A randomized controlled trial with an adequate number of patients might be needed to further address this question.

CONCLUSIONS

No drainage is a feasible option in patients undergoing mastectomy in terms of reducing hospital stay, without increasing the incidence of symptomatic seroma and wound complications compared to routine drain placement.

ACKNOWLEDGEMENT

The authors would like to acknowledge the contribution of the patients who participated in this study through being interviewed or observed as part of our work and the nursing team who kindly take care of the patients.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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บทคัดย่อ การศึกษาเปรียบเทียบระหว่างการใส่สายระบายและการไม่ใส่สายระบายที่แผลผ่าตัดในผู้ป่วยที่ได้รับการผ่าตัดเต้านมออกทั้งเต้า

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ความเป็นมาและวัตถุประสงค์: การเกิดน้ำเหลืองที่แผลผ่าตัดเป็นภาวะแทรกซ้อนที่พบบ่อยที่สุดหลังการผ่าตัดเต้านมออกทั้งเต้าหรือการผ่าตัดเต้านมและต่อมน้ำเหลืองรักแร้ ความสำคัญของการใส่ระบายที่แผลผ่าตัดยังคงเป็นที่ถกเถียงกันอยู่ มีการศึกษาที่รายงานว่า การใส่สายระบายไม่สามารถป้องกันการเกิดน้ำเหลืองในแผลผ่าตัดได้ การศึกษานี้มีวัตถุประสงค์เพื่อประเมินการเกิดน้ำเหลืองและภาวะแทรกซ้อนหลังการผ่าตัดในผู้ป่วยที่ตัดเต้านมออกทั้งเต้าโดยมีการใส่หรือไม่ใส่สายระบายที่แผลผ่าตัด

วิธีการศึกษา: ผู้ป่วยมะเร็งเต้านมหรือโรคเต้านมอื่นๆ ถูกคัดเลือกจากสาขาศัลยศาสตร์ศีรษะ คอ และเต้านม ภาควิชาศัลยศาสตร์ โรงพยาบาลศิริราช ตั้งแต่เดือนพฤศจิกายน 2561 ถึง สิงหาคม 2562 โดยผู้ป่วยแบ่งออกเป็นกลุ่มใส่สายระบายและไม่ใส่สายระบาย ทำการเปรียบเทียบข้อมูลทางพยาธิวิทยาคลินิก การเกิดน้ำเหลืองในแผลผ่าตัดและภาวะแทรกซ้อนหลังการผ่าตัด

ผลการศึกษา: ในการศึกษานี้มีผู้ป่วยทั้งหมด 129 ราย ผู้ป่วยที่มีการใส่สายระบาย 67 ราย และผู้ป่วยที่ไม่ใส่สายระบาย 62 ราย อุบัติการณ์การเกิดน้ำเหลืองใกล้เคียงกันทั้งสองกลุ่ม ปริมาตรของน้ำเหลืองที่ดูดได้ในกลุ่มไม่ใส่สายระบายสูงกว่ากลุ่มใส่สายระบายอย่างมีนัยสำคัญ ($p = 0.010$) เมื่อรวมปริมาตรของน้ำเหลืองจากสายระบายและน้ำเหลืองที่ดูดได้เข้าด้วยกันพบว่ากลุ่มที่ใส่สายระบายมีปริมาตรสูงกว่าในกลุ่มไม่ใส่สายระบายอย่างมีนัยสำคัญ ($p = 0.020$) ผู้ป่วยในกลุ่มไม่ใส่สายระบายมีระยะเวลาพักรักษาตัวในโรงพยาบาลสั้นกว่าอย่างมีนัยสำคัญ คือ 2.0 (1.0-3.0) เทียบกับ 4.0 (2.0-10.0) วัน ($p < 0.001$)

สรุปผลการศึกษา: การผ่าตัดเต้านมออกทั้งเต้าโดยไม่ใส่สายระบายสามารถทำได้ สามารถลดระยะเวลาการพักรักษาตัวในโรงพยาบาลโดยไม่เพิ่มอุบัติการณ์การเกิดน้ำเหลืองในแผลผ่าตัดและไม่เพิ่มภาวะแทรกซ้อนหลังการผ่าตัด

Outcomes of Off-Pump Coronary Artery Bypass Grafting in Ischemic Cardiomyopathy

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Abstract

Objective: Surgical coronary revascularization for coronary artery disease (CAD) with reduced left ventricular ejection fraction (LVEF) entails a high risk of postoperative complications and mortality. This study aimed to evaluate the surgical outcomes of off-pump coronary artery bypass grafting (OPCAB) in ischemic cardiomyopathy patients in our hospital.

Patients and Methods: From January 2012 to December 2018, eighty CAD patients with low LVEF $\leq 35\%$ who underwent isolated OPCAB were included in the present study. In-hospital mortality, major adverse cardiovascular and cerebrovascular events were evaluated, and factors associated with mortality were analyzed.

Results: The mean preoperative LVEF was 26%, while their mean EuroSCORE II was 11.9, and their in-hospital mortality rate was 16% (13 patients). Low cardiac output syndrome was found in 3 patients, congestive heart failure in 2 patients, and cardiogenic shock in 3 patients. There were no postoperative strokes or myocardial infarction, and postoperative LVEF was significantly improved, with an average of 38% ($P = 0.040$). Insulin-dependent type II diabetes mellitus was significantly associated with increased in-hospital mortality ($P < 0.001$).

Conclusions: Patients with coronary artery disease and ischemic cardiomyopathy showed significantly improved left ventricular ejection fraction after off-pump coronary artery bypass grafting surgery. There were no postoperative myocardial infarction or stroke in the present study. Insulin-dependent type II diabetes mellitus was significantly associated with increased in-hospital mortality.

Keywords: Off-pump coronary artery bypass, Cardiomyopathy, Left ventricle dysfunction, Coronary artery disease

INTRODUCTION

Ischemic cardiomyopathy is currently defined as significantly impaired left ventricular dysfunction (LVEF $\leq 35\%$) which results from coronary artery disease. Lack of adequate blood supply, which results in the inability to meet myocardial metabolic demands, can lead to cell death, fibrosis, left ventricular enlargement, and dilation.¹⁻³ Initially, there is a reversible loss of cardiac contractile function due to decreased oxygen supply to

the myocardium; however, when myocardial ischemia persists for a prolonged period of time, irreversible myocardial damage ensues, resulting in cardiac remodeling, primarily brought about by myocardial fibrosis, which results in decreased cardiac function, arrhythmia, and possible cardiac conduction system impairment and abnormality.^{4,5} In such patients, the decision about whether or not to perform coronary revascularization is difficult.

Received for publication 12 November 2021; Revised 31 January 2022; Accepted 16 February 2022

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The Surgical Treatment for Ischemic Heart Failure (STICH) study was designed to test the hypothesis that coronary artery bypass grafting (CABG) plus guideline-directed medical therapy for coronary artery disease, heart failure, and left ventricular dysfunction would achieve better survival than that of optimum medical therapy alone. The STICH study randomized 1,212 patients with ischemic cardiomyopathy with an ejection fraction of less than 35%, with a median follow-up of 56 months. The rate of death from any cause was not significantly different in the CABG group and the medical-therapy group;⁶ however, the results from the STICH Extension Study (STICHES) demonstrated improved long-term outcomes over a median period of 9.8 years, revealing that the risk of all-cause death, death resulting from cardiovascular causes, and all-cause death or hospitalization for cardiovascular causes, was significantly lower among patients randomized to receive CABG and guideline-directed medical therapy compared with those who received medical therapy alone.⁷

Coronary artery bypass grafting has been shown to be superior to medical therapy alone in patients with low LVEF, demonstrating significant clinical improvement and increased long-term survival. Nevertheless, CABG in patients with reduced left ventricular (LV) function remains a surgical challenge. Off-pump coronary artery bypass (OPCAB) has been increasingly utilized to prevent deleterious effects of cardiopulmonary bypass, including associated inflammatory response, global myocardial ischemia, and reperfusion injury, and also to preserve heart function. Low LVEF patients have weakened heart function and may not be able to tolerate ischemia and reperfusion in conventional CABG; therefore, these patients could be the best candidates for OPCAB.⁸

Currently, 2018 ESC/EACTS Guidelines on myocardial revascularization recommend the use of the off-pump coronary artery bypass (OPCAB) technique in CAD patients with the atherosclerotic aortic disease (Recommendation I, LOE B) and that experienced off-pump teams should consider it for subgroups of high-risk patients (Recommendation IIa, LOE B).⁹ We aimed to study the surgical outcomes of OPCAB for ischemic cardiomyopathy patients in our center.

PATIENTS AND METHODS

The present retrospective observational study included all patients ≥ 18 years of age with CAD and

left ventricular ejection fraction $\leq 35\%$ who underwent isolated off-pump coronary artery bypass from January 2012 to December 2018 in a single center. Demographic, angiographic, and operative data were collected from hospital charts and computer databases in our hospital. Pre- and postoperative left ventricular ejection fraction (LVEF) was measured using a transthoracic echocardiogram by certified cardiologists before surgery and after surgery (before discharge from the hospital, or not more than 1 month after surgery). The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was used to calculate the predicted risk of mortality for each patient. EuroSCORE II > 8 was considered as high risk of mortality.

The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCE) defined as in-hospital mortality (death from cardiovascular or any other causes), acute myocardial infarction (AMI), or ischemic stroke. The secondary outcome was factors associated with mortality. All continuous data were expressed as mean $\pm$ standard deviation, while categorical data were given as frequency and percentages. Comparisons of continuous variables between two groups were performed using student T-test or Mann-Whitney U-test and categorical variables were compared using Chi-square test. P -values < 0.05 was considered statistically significant, and all statistical calculations were performed using SPSS version 22.

RESULTS

During the 7-year study period, 379 patients underwent isolated OPCAB, and 299 of these were excluded from the study due to having preoperative LVEF $> 35\%$. The study sample, therefore, included 80 patients (Table 1) whose mean age was 63.4 ± 10.6 years and mean EuroSCORE II was 11.91, which are considered as high-risk patients. The average preoperative LVEF was $26 \pm 5\%$.

The average number of revascularizations per patient was 2.2 ± 0.9 , with complete revascularization in 45 patients. Thirty-two out of the 80 patients had aortic non-touch surgery. Most (69%) had elective surgery and bilateral internal mammary arteries were used in 29 patients (36%). LV aneurysm plication, performed using the off-pump technique, and surgical endarterectomy were performed in 2 and 8 cases respectively. No patient required conversion from off-pump to on-pump CABG (Table 2).

Table 1 Preoperative patient characteristics.

Patient characteristics	Summary (n = 80)
Age (years) : mean $\pm$ SD	63.4 $\pm$ 10.6
Male sex: n (%)	62 (78)
EuroSCORE II : median (range)	6.0 (2.0 - 59.0)
Cardiac characteristics	
Preoperative LVEF (%): median (range)	25.7 (15 - 35)
Left main disease: n (%)	34 (43)
Single Vessel disease: n (%)	4 (5)
Double Vessels disease: n (%)	19 (24)
Triple Vessels disease: n (%)	57 (71)
LV aneurysm: n (%)	2 (3)
Coronary risk factors: n (%)	
Hypertension	67 (84)
Diabetes mellitus	28 (35)
Insulin-dependent type2 Diabetes mellitus	10 (13)
Dyslipidemia	61 (76)
CKD	35 (44)
ESRD	14 (18)

EuroSCORE II: European System for Cardiac Operative Risk Evaluation, LVEF: left ventricular ejection fraction, LV: left ventricular, CKD: chronic kidney disease, ESRD: End-Stage Renal Disease.

Table 2 Operative characteristics

Operative characteristics	Summary (n =80)
No. of revascularizations : mean $\pm$ SD	2.2 $\pm$ 0.9
Complete revascularization: n (%)	45 (56)
Total arterial revascularization: n (%)	33 (37)
Aortic non-touch surgery: n (%)	32 (36)
Elective surgery: n (%)	55 (69)
Urgent surgery: n (%)	9 (11)
Emergency surgery: n (%)	16 (20)
Endarterectomy: n (%)	8 (10)
LV aneurysm plication: n (%)	2 (3)
Conversion to CABG: n (%)	0
Conduits: n (%)	
Single IMA	50 (63)
Bilateral IMA	29 (36)
Radial artery	1 (1)
Right gastroepiploic artery	3 (4)
Saphenous vein	44 (55)

LV: left ventricular, CABG: coronary artery bypass grafting, IMA: internal mammary artery

Of 80 patients, 13 (16%) died during admission: 4 succumbed to sepsis, 3 died from ventricular arrhythmia, and 2, 3, and 1 from multiple organ failure, severe left ventricular dysfunction, and cardiogenic shock respectively. Mean postoperative ICU and hospital stays were 5.6 days and 12.3 days respectively. The mean postoperative left ventricular ejection fraction was 38% which was significantly improved from preoperative LVEF (26%) ($p = 0.04$). No case of perioperative or postoperative myocardial infarction was reported during the study period and no patient developed ischemic stroke (Table 3).

Table 3 Postoperative outcomes

Postoperative outcomes	Summary (n =80)
In-hospital mortality: n (%)	13 (16)
Mean ICU stay (days) : median (range)	4 (2 - 53)
Mean postoperative hospital stay (days): median (range)	10 (2 - 90)
Postoperative LVEF (%):	
Median (range)	25.7 (15 - 35)
Mean $\pm$ SD	25.6 $\pm$ 5.0
Postoperative myocardial infarction: n (%)	0
Reoperation for bleeding: n (%)	0
Hospital-acquired pneumonia: n (%)	6 (8)
Sternal wound infection: n (%)	0
Low cardiac output syndrome: n (%)	3.0 (3.8)
Stroke/transient ischemic attack: n (%)	0.0 (0.0)
Congestive heart failure: n (%)	2.0 (2.5)
Cardiogenic shock: n (%)	3.0 (3.75)
Cardiac arrest: n (%)	2.0 (2.5)
Hemodialysis: n (%)	3.0 (3.75)
Multiple organ failure: n (%)	2.0 (2.5)
Ventricular arrhythmia: n (%)	3.0 (3.8)

ICU: intensive care unit, LVEF: left ventricular ejection fraction

Our study showed that insulin-dependent type2 diabetes mellitus was associated with an increased early mortality rate (p -value < 0.001). However, no association was found between other underlying diseases and mortality. Type of operation, endarterectomy, and LV aneurysm plication procedure were not associated with in-hospital mortality (Tables 4 and 5).

Table 4 Factors associated with mortality: univariable analysis

Factors	Total (n = 80) n	Alive (n = 67) n (%)	Dead (n = 13) n (%)	p-value
Sex				0.999
Male	62	52 (78)	10 (77)	
Female	18	15 (22)	3 (23)	
Diabetes mellitus	28	25 (37)	3 (23)	0.526
Insulin-dependent type 2 diabetes mellitus	10	4 (6)	6 (46)	0.001*
Hypertension	67	56 (84)	11 (85)	0.999
Dyslipidemia	61	51 (76)	10 (77)	0.999
Chronic kidney disease	35	31 (46)	4 (31)	0.303
End-Stage Renal Disease	14	10 (15)	4 (31)	0.227
Left main disease	34	29 (43)	5 (39)	0.748
Vessel disease				0.053
Single vessel disease	4	3 (5)	1 (8)	
Double vessels disease	19	19 (28)	0	
Triple vessels disease	57	45 (67)	12 (92)	
Left ventricular aneurysm	2	2 (3)	0	0.999
Post cardiac arrest	4	3 (5)	1 (8)	0.515
Type of operation				0.124
Elective	55	49 (73)	6 (46)	
Urgency	9	7 (10)	2 (15)	
Emergency	16	11 (16)	5 (39)	
Left ventricular aneurysm plication	2	2 (3)	0	0.999
Endarterectomy	8	8 (12)	0	0.999
Off-pump coronary artery bypass				0.608
1 vessel	23	18 (27)	5 (39)	
2 vessels	25	20 (30)	5 (39)	
3 vessels	27	24 (36)	3 (23)	
4 vessels	5	5 (8)	0	

Table 5 Risk factors associated with mortality: multivariable analysis

Factor	Crude OR (95% CI)	p-value	Adj. OR (95% CI)	p-value
Diabetes mellitus	0.5 (0.1 - 2.0)	0.331	1.2 (0.2 - 5.5)	0.871
Insulin-dependent type2 Diabetes mellitus	13.5 (3.1 - 59.7)	0.001*	14.3 (2.8 - 72.8)	0.001*

OR (95% CI) = Odds Ratio (95% confidence interval) from logistic regression analysis, *Significant at $p < 0.05$

DISCUSSION

Off-pump coronary artery bypass (OPCAB) has recently gained widespread acceptance and entered mainstream clinical practice, propelled by a greater awareness of potential morbidity from cardiopulmonary bypass and aortic manipulation.¹⁰ Several previous retrospective

studies have reported that OPCAB is associated with lower incidences of death and stroke compared with conventional on-pump coronary artery bypass grafting,¹¹⁻¹³ while multiple studies have highlighted the potential benefits of OPCAB in high-risk patients. A recent meta-analysis in 2016 by Kowalewski M. et al. demonstrated

a significant correlation between patient risk profile and the benefits of OPCAB, with a reduction in perioperative morbidity.¹⁴ With regards to patients with low left ventricular ejection fraction, a report from the Society of Thoracic Surgeons National Database from 2008 to 2011 of 25,667 patients with low LVEF (< 30%) found that the risks of death, stroke, and major adverse cardiac events (MACE) were significantly lower among OPCAB groups than in those undergoing conventional CABG.¹⁵ These findings were supported by an analysis of the Japan Adult Cardiovascular Surgery Database in which OPCAB was associated with reduced early morbidity and mortality in patients with EF < 30%.¹⁶

A meta-analysis in 2011 by Jarra OA, et al. summarized that OPCAB may be associated with a lower incidence of early mortality in patients with impaired LVEF; however, the method of handling the conversion-related mortality was unclear and may have affected the results. Furthermore, incomplete revascularization (IR) in the OPCAB group occurred more often, and this may explain why the early superiority in mortality was not maintained in the long term.¹⁷ In our study, 44% of patients received incomplete coronary revascularization, resulting from the presence of large infarcted myocardium on preoperative myocardium perfusion scan or unsuitable target vessels for anastomosis. Later in 2017, a network meta-analysis was performed by Zhao DF et al. to compare postoperative outcomes of all CABG techniques, and this report showed that avoidance of aortic manipulation in OPCAB may decrease the risk of postoperative stroke. In addition, the elimination of cardiopulmonary bypass may reduce short-term mortality, renal failure, atrial fibrillation, bleeding, and length of stay in intensive care units.¹⁸

A study published in 2017 compared the effects of low and normal EF on clinical outcomes after off-pump coronary artery bypass grafting. The results revealed a significantly higher in-hospital mortality rate of 19.51% in patients with EF ≤ 35% than in those with EF > 35% (8.02%).¹⁹ With regard to the results of the present study, CAD patients with poor left ventricular ejection fraction in our center had a mortality rate of 16% which is comparable with the low LVEF group in the mentioned study.

Insulin-dependent diabetes patients in our study showed a 14.3 times higher mortality rate than diabetes patients. This finding was similar to an observational cohort multicenter study over a period of 11 years evalu-

ated the impact of type 2 diabetes mellitus on short- and long-term mortality after CABG and concluded that diabetes was an independent predictor of long-term mortality; furthermore, mortality was even higher when the diabetes treatment included insulin.²⁰ According to Kragelund C, et al. Insulin treatment is a marker for more advanced disease, its underlying mechanism has not been fully understood. It may be associated with the impact of a procoagulant imbalance, chronic exposure to high glucose levels, or direct effects of hyperinsulinemia.²¹

The main limitations of the present study included a small sample size and being based on a single center, so our findings might not be representative of the results of other institutions. An extended study with larger populations is required.

CONCLUSIONS

CAD patients with ischemic cardiomyopathy displayed significantly improved left ventricular ejection fraction after off-pump coronary artery bypass surgery, and there were no incidences of postoperative myocardial infarction or stroke. Insulin-dependent type II diabetes mellitus was significantly associated with increased in-hospital mortality.

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Five-Year Survival and Prognostic Factors of Patients with Periapillary Carcinoma Who Underwent Pancreaticoduodenectomy

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Abstract

Objective: Periapillary carcinomas are defined as tumors that arise within 2 cm of the major papilla. The pancreaticoduodenectomy is the standard curative treatment for these tumors. However, the long-term survival may vary due to many factors. This study aimed to identify prognostic factors and 5-year survival of periapillary carcinoma; and to evaluate the surgical outcomes of a pancreaticoduodenectomy.

Patients and Methods: We conducted a retrospective review of the medical records of patients with periapillary carcinoma who underwent pancreaticoduodenectomy from January 2010 to December 2014 in a tertiary hospital. Patient characteristics, perioperative data and pathological data were analyzed. Univariate and multivariate analysis of prognostic factors for survival was analyzed by the Cox proportional hazard model. The Kaplan-Meier survival curve was used to describe survival rate. The *P*-value less than 0.05 was considered as statistically significant.

Results: Of 61 patients (with a median age of 58 years), cancer of the ampulla of Vater was the most common tumor. The 3-year and 5-year overall survival rates were 52.5% and 34.4%, respectively. The 30-day postoperative mortality rate was 4.9%. Median overall survival time is 37.4 months. The independent prognostic factors were lymphovascular invasion (hazard ratio (HR): 9.10, 95% confidence interval (95% CI): 2.51 to 32.96, *p* = < 0.001) and moderate or poor tumor differentiation (HR: 2.28, 95% CI: 1.08 to 4.84, *p* = 0.03).

Conclusion: In this study, the 5-year overall survival rate was 34.4%. Poor prognostic factors of periapillary carcinoma after pancreaticoduodenectomy included the presence of lymphovascular invasion and poor to moderate tumor differentiation.

Keywords: Periapillary carcinoma, Pancreaticoduodenectomy, Survival rate

INTRODUCTION

Periapillary carcinoma is defined as a tumor arising within 2 cm of the major papilla. It comprises cancer of the ampulla of Vater, distal common bile duct cancer, cancer presented in the second portion of the duodenum, and tumor of the pancreatic head.¹ The standard curative treatment for this condition is pancreaticoduodenectomy or its variation. Although these tumors have similar clinical

presentations, anatomical location, and therapeutic approaches,^{2,3} their long-term outcomes may vary.^{2,4} Few studies in Thailand have reported the long-term survival and prognostic factors of these tumors.⁵⁻⁷ This study aimed to investigate the 5-year survival and determine the factors affecting survival in patients who underwent pancreaticoduodenectomy for periapillary carcinoma at a tertiary hospital.

Received for publication 18 November 2021; Revised 13 May 2022; Accepted 17 May 2022

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PATIENTS AND METHODS

Approval was obtained from the institutional review board. We proceeded to review the medical and surgical records of patients with periampullary carcinoma who underwent either pancreaticoduodenectomy or pyloric preserving pancreaticoduodenectomy from January 1, 2010 to December 31, 2014 in Maharat Nakhon Ratchasima Hospital.

We targeted the following data: patient characteristics (age, sex, comorbid diseases, history of cholangitis, preoperative biliary drainage, clinical signs and symptoms); laboratory data (total bilirubin, serum CA19-9, serum albumin); waiting time to surgery, postoperative chemotherapy, tumor characteristics (size, regional lymph node status, paraaortic lymph node status, margin status, superior mesenteric vein resection, histologic grade, lymphovascular invasion); type of surgery, estimated blood loss, operative time, recurrence rate, in-hospital and 30-day mortality rate, 3- and 5-year survival rates. The in-hospital mortality was defined death at any time during admission after surgery and 30-day mortality was defined as death within 30 days after surgery.

All the data were analyzed using the RStudio program version 1.2.5033 with R version 3.6.3. Continuous variables were presented as mean and standard deviation (SD), or as medians and ranges where appropriate. Categorical variables were presented as frequency and percentages. Survival time was defined as time between the day of surgery and the day of death from any cause, or last day of contact entered in the medical records. Univariate and multivariate analyses of survival prognostic factors were conducted via the Cox proportional hazard model. Kaplan-Meier survival estimation was used to describe survival rates. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents patient characteristics. This study included a total of 61 patients, all of whom underwent a pancreaticoduodenectomy. There were 32 men and 29 women, and the median age at the time of surgery was 58 years (range 34 to 78 years). Twenty-three patients (38%) were diagnosed with cholangitis prior to definitive treatment. These patients (with cholangitis) received preoperative drainage, mostly via endoscopic trans papillary stents. The most common comorbid diseases encountered were hypertension and diabetes mellitus in 15 patients (25%) and 12 patients (20%), respectively. A history of smoking was found in 14 patients (23%).

Table 1 Patient characteristics

Patient characteristics	Summary (n = 61)
Age (years): median (range)	58 (34 – 78)
Sex: n (%)	
Male	32 (53)
Female	29 (47)
Cholangitis before surgery: n (%)	23 (38)
Preoperative biliary drainage: n (%)	
Trans papillary stent	21 (34)
PTBD	3 (5)
T-tube	1 (2)
No drainage	36 (59)
Comorbid disease: n (%)	
DM	12 (20)
HT	15 (25)
DLP	6 (10)
Gout	3 (5)
Cardiac disease	4 (7)
Pulmonary disease	4 (7)
CKD	2 (3)
Other	6 (10)
Smoking: n (%)	
Yes	14 (23)
No	47 (77)
Presenting symptom: n (%)	
Obstructive jaundice	55 (90)
Abdominal pain	3 (5)
GI bleeding	1 (2)
Gastric outlet obstruction	2 (3)
Serum CA 19-9 (U/mL): median (range)	108.6 (0.8 – 63,542.6)
Elevated CA 19-9 (> 37 U/mL): n (%)	42 (70)
Total bilirubin (mg/dL): median (range)	12.4 (0.5 – 39.6)
Total bilirubin ≥ 2: n (%)	54 (89)
Serum albumin (mg/dL): n (%)	
< 3.5	37 (61)
≥ 3.5	24 (39)
Waiting time (days): median (range)	30 (4 – 95)
Adjuvant Chemotherapy: n (%)	27 (44)

Abbreviations: PTBD = Percutaneous Transhepatic Biliary Drainage, DM = Diabetes Mellitus, HT = Hypertension, DLP = dyslipidemia, CKD = Chronic kidney disease, GI bleeding = Gastrointestinal bleeding, CA = Cancer

The most common symptom was obstructive jaundice, which was found in 55 (90%) patients. The median total bilirubin was 12.9 mg/dL, which ranged between 0.5 to 39.6 mg/dL. Median serum CA19-9 level was 108.6 U/mL (range 0.8 to 63,542.6 U/mL) and there was 42 patients (69%) with elevated CA 19-9 (> 37 U/mL). Hypoalbuminemia (albumin < 3.5 mg/dL) was found in 37 (61%) patients. The median waiting time (time from the diagnosis to the surgery) was 30 days (range 4 to 95 days). Only 27 patients (44%) received adjuvant chemotherapy.

The primary tumor location in descending order of occurrence were ampulla of Vater in 39 patients (64%), pancreatic head in 17 patients (28%), distal common bile duct in 4 patients (7%), and duodenum in 1 patient (2%). The median tumor size was 2 cm for those located at the ampulla of Vater, 3.5 cm for the pancreatic head, 2.8 cm for the duodenum, and 5 cm for the distal common bile duct. Regional lymph node metastasis was found in 26 patients (43%). The median number of lymph nodes retrieved was 6 (range 0 to 43 lymph nodes). Concomitant superior mesenteric vein or portal vein resection was performed in 3 patients (5%). Regarding the histological grading of the tumors, the following was observed: 31 (51%) were well-differentiated, 27 (44%) were moderately differentiated, and 3 (5%) were poorly differentiated. Lymphovascular invasion was reported in 34 patients (56%). Negative resected margins were identified in 59 patients (97%). The pathological data of the tumors are displayed in Table 2.

The perioperative outcomes and survival data are summarized in Table 3. Forty-five patients (74%) underwent classical pancreaticoduodenectomy and 16 patients (26%) underwent pylorus-preserving pancreaticoduodenectomy. The median intra-operative blood loss was 1,000 mL (range 200 to 8,000 mL) and the median operative time was 335 minutes (range 180 to 645 minutes). Overall, postoperative complications occurred in 25 patients (41%). The occurrence of pancreatic fistulas was encountered in 5 patients (8%). Three patients (5%) underwent re-exploratory laparotomy for the treatment of intra-abdominal collection or postoperative bleeding. The median hospital stay was 19 days (range 10 to 102 days). Four patients died on the 2nd, 24th, 28th and 56th postoperative day respectively. The in-hospital mortality was 6.6% and the 30-day mortality rate was 4.9%.

The 3- and 5-year overall survival rates for pa-

Table 2 Pathological characteristics

Pathological characteristics	Summary (n = 61)
Tumor location: n (%)	
Ampulla of Vater	39 (65)
Pancreatic head	17 (28)
Duodenum	4 (5)
Distal CBD	1 (2)
Tumor size (cm) : median (range)	
Ampulla of Vater	2 (1 – 5)
Pancreatic head	3.5 (2 – 6)
Duodenum	2.75 (2 – 3)
Distal CBD	5 (5 – 5)
Total lymph node retrieved : median (range)	6 (0 – 43)
Positive regional lymph node: n (%)	26 (43)
Positive paraaortic lymph node: n (%)	1 (2)
SMV resection: n (%)	3 (5)
Histological grade: n (%)	
Well-differentiated	31 (51)
Moderately differentiated	27 (44)
Poorly differentiated	3 (5)
Lymphovascular invasion: n (%)	
No	27 (44)
Yes	34 (56)
Resection margin: n (%)	
Negative	59 (97)
Positive	2 (3)
Pathologic T staging: n (%)	
pT1	9 (15)
pT2	18 (30)
pT3	2 (3)
pT4	31 (51)
Pathologic N staging: n (%)	
pN0	34 (56)
pN1	17 (28)
pN2	10 (16)

Abbreviations: CA = Cancer, CBD = common bile duct, SMV resection = Superior Mesenteric Vein resection

tients were 52.5% and 34.4%, respectively. The median overall survival time for the cohort was 37.4 months, as presented in Figure 1. Patients diagnosed with ampullary carcinoma exhibited better survival rates compared to those with other types of cancer, with 3-year survival rates of 64.1% and 5-year survival rates of 46.1%.

The recurrence rate was 50.8% and the median time-to-recurrence was 14.4 months (range 3.6 to 42.4 months),

as shown in Table 3. Figure 1 shows the overall 5-year survival curve of the 61 patients.

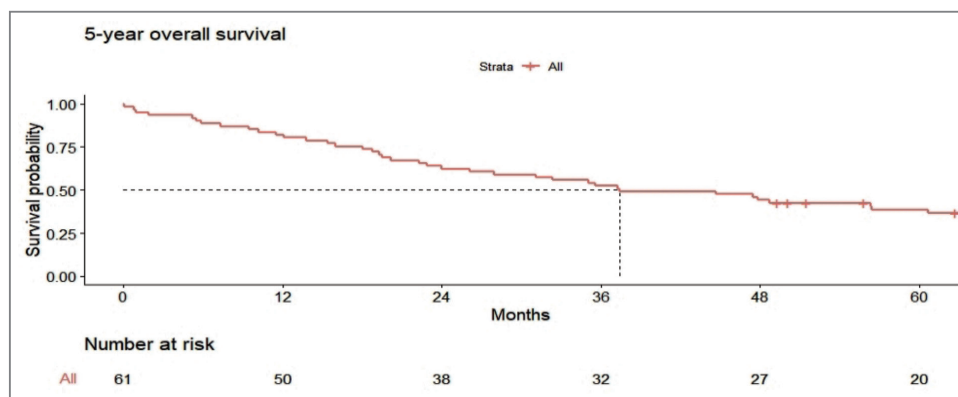


Figure 1 Overall survival rates at 5 years

Table 3 Perioperative outcomes and survival rates

Perioperative outcomes	Summary (n = 61)
Type of surgery: n (%)	
Classical pancreaticoduodenectomy	45 (74)
Pylorus-preserving pancreaticoduodenectomy	16 (26)
Estimated blood loss (ml) : median (range)	1,000 (200 – 8,000)
Operative time (min) : median (range)	335 (180 – 645)
Postoperative complication: n (%)	
Pancreatic fistula	5 (8)
Wound complications	4 (7)
Intra-abdominal collection	4 (7)
Enterocutaneous fistula	2 (3)
Post-pancreatectomy hemorrhage	1 (2)
Delayed gastric emptying	1 (2)
Respiratory complications	5 (8)
Renal complications	3 (5)
Hospital stays (days): median (range)	19 (10 – 102)
In-hospital mortality: n (%)	4 (7)
30-day mortality: n (%)	3 (5)
Median overall survival (months): median (range)	37.4 (0 – 60)
3-year survival: n (%)	
Overall	32 (53)
Ampullary cancer	25 (78)
Non ampullary cancer	7 (22)
5-year survival: n (%)	
Overall	21 (34)
Ampullary cancer	18 (86)
Non ampullary cancer	3 (14)
Recurrence: n (%)	
No	30 (49)
Yes	31 (51)
Time to recurrence (months) : median (range)	14.36 (3.58 – 42.35)

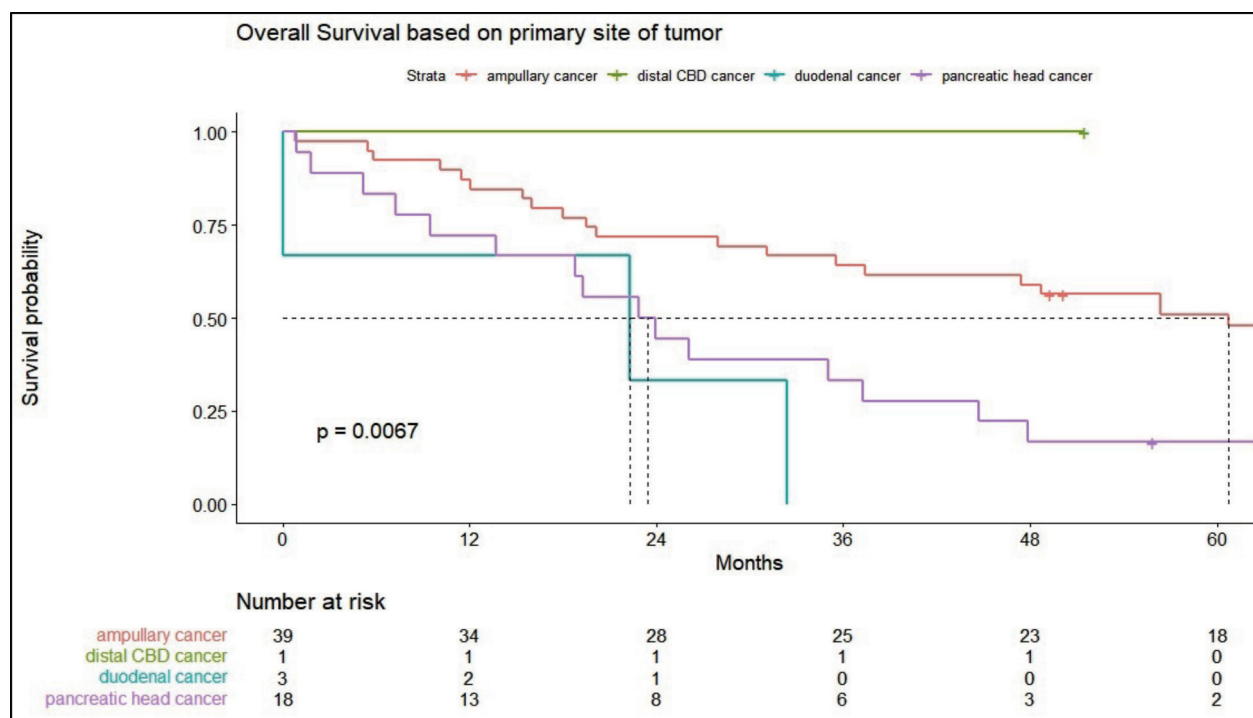


Figure 2 Overall survival based on primary site of tumor

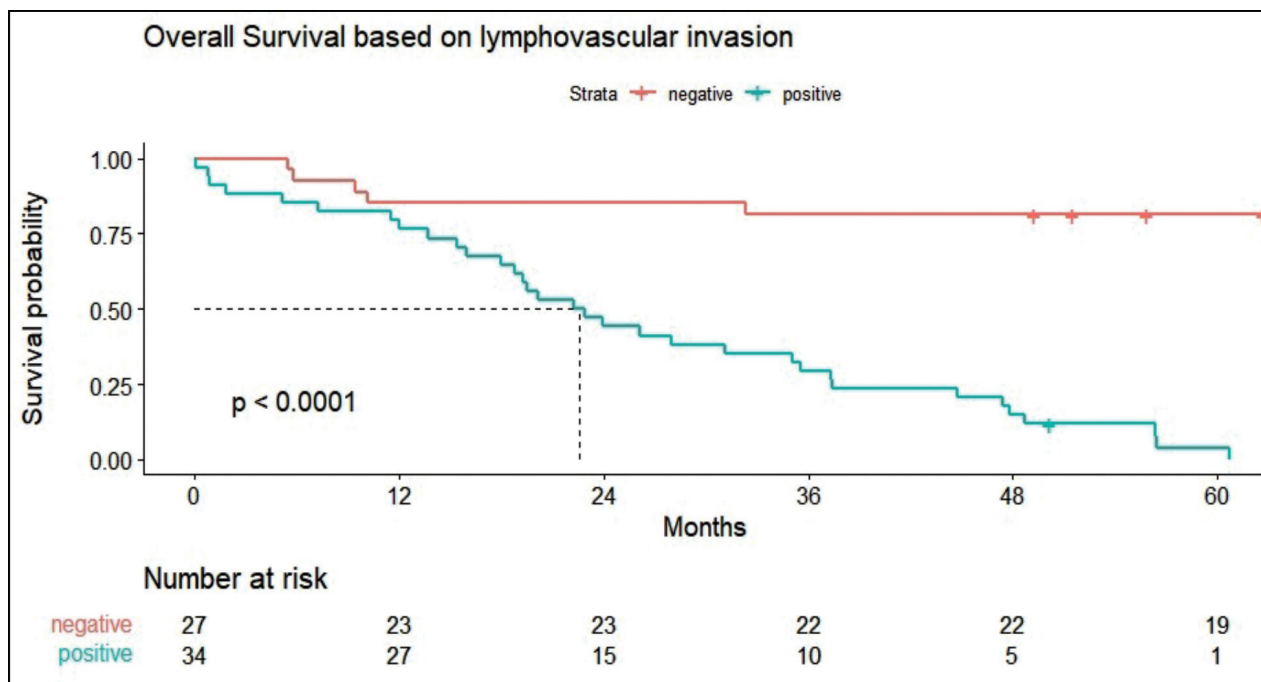


Figure 3 Overall survival based on lymphovascular invasion

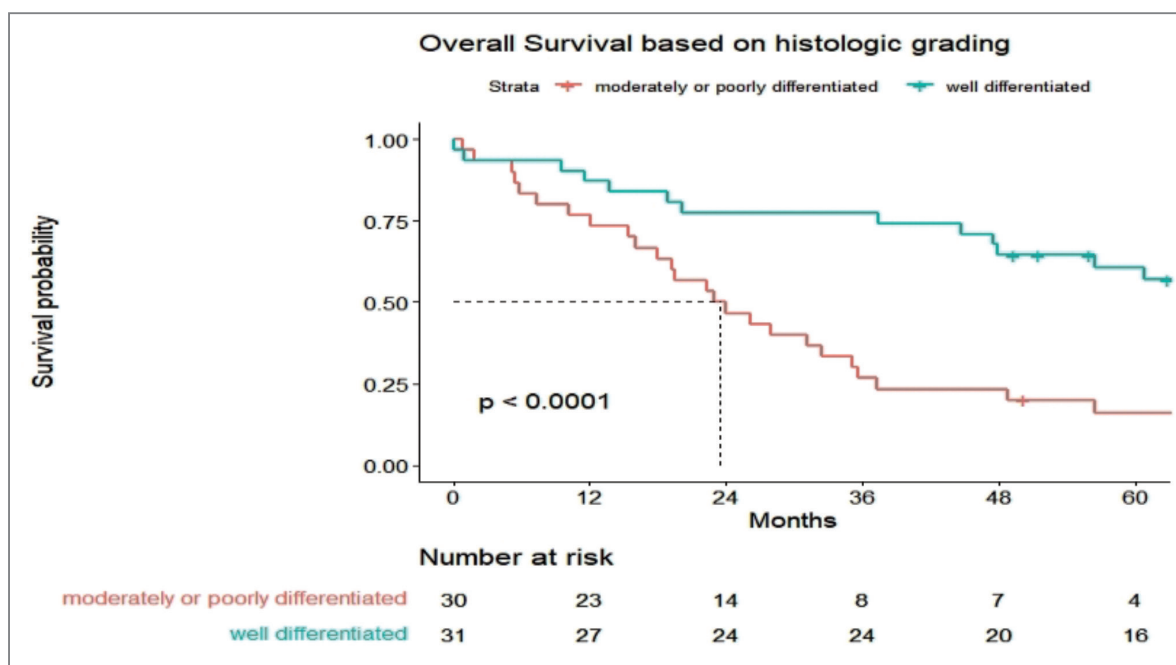


Figure 4 Overall survival based on histological grading

Table 4 Univariate analysis of prognostic factors

Factors	Crude HR (95% CI)	P-value
Age ≥ 65 years	1.12 (0.55, 2.30)	0.749
Male	1.36 (0.73, 2.55)	0.327
Smoking	1.22 (0.59, 2.50)	0.598
Cholangitis before surgery	1.23 (0.66, 2.30)	0.513
Preoperative biliary drainage	0.78 (0.41, 1.47)	0.4
Primary tumor location		
Ampulla of Vater	0.40 (0.21, 0.77)	0.006
Other locations	1	
Tumor size ≥ 2 cm	1.12 (0.55, 2.30)	0.749
Regional LN metastasis, Positive	7.38 (3.55, 15.34)	< 0.001
SMV resection (Yes)	2.92 (0.88, 9.72)	0.127
Positive resection margin	6.56 (1.47 – 29.25)	< 0.001
Lymphovascular invasion positive	12.43 (4.59 – 33.68)	< 0.001
Histological grade		
Well-differentiated	1	
Moderate or poorly differentiation	3.54 (1.83 – 6.87)	< 0.0001
Serum CA 19-9 (> 37 U/mL)	1.49 (0.73, 3.05)	0.258
Total bilirubin ≥ 2 mg/dL	0.72 (0.28, 1.83)	0.501
Serum albumin < 3.5 mg/dL	1.29 (0.67, 2.45)	0.441
Adjuvant chemotherapy (Yes)	1.54 (0.82, 2.89)	0.174

Abbreviations: LN = Lymph Node, SMV resection = Superior Mesenteric Vein resection

Table 5 Multivariate analysis of prognostic factors

Factors	Adjusted HR (95%CI)	P-value
Ampullary cancer	0.56 (0.28 – 1.13)	0.09
Regional lymph node positive	1.65 (0.68 – 4.02)	0.27
Margin positive	31.2 (0.67 – 15.11)	0.14
Lymphovascular invasion positive	9.10 (2.51 – 32.96)	< 0.001
Moderately or poorly differentiation	2.28 (1.08 – 4.84)	0.03
Adjuvant chemotherapy (Yes)	0.52 (0.25 – 1.07)	0.08

Several clinicopathological factors influenced the survival rates as revealed by the univariate and multivariate analyses shown in Tables 4 and 5. Based on univariate analyses; primary tumor location, nodal status, positive resection margin, lymphovascular invasion, and histological grading were identified as significant prognostic factors for survival. The independent prognostic factors identified from the multivariate analyses were the presence of lymphovascular invasion (HR: 8.11, 95% CI: 2.18 to 30.19, $p < 0.001$) and moderate or poorly differentiated tumors (HR: 2.18, 95% CI: 1.99 to 4.82, $p < 0.001$).

Figures 2 to 4 demonstrate the overall 5-year survival rate based on the primary tumor site, lymphovascular invasion, and histologic grading, respectively.

DISCUSSION

In our study, the median age was 58 years with the male gender slightly predominating, with a male-to-female ratio of 1.1 : 1. Ampullary cancer (64%) occurred most commonly, followed by pancreatic head cancer (28%); our results differed from a study conducted in Western countries that reported pancreatic cancer as the most commonly occurring periampullary cancer.^{8–11} The overall 5-year survival rate for periampullary cancer in this study was 34.4%. Ampullary cancer had a more favorable 5-year survival rate than that of other periampullary cancers (46.1% vs 13.6%). The lower survival rate in the second group might have been due to the fact that 77% of cancer in the second group was pancreatic head cancer, which is known to be more aggressive. The higher proportion of resectable ampullary cancer might be due to ampullary cancer usually causing symptom, e.g., obstructive jaundice, at the earlier stage of disease compared to pancreatic cancer. In patients with pancreatic cancer, the early stage of tumor may be asymptomatic¹². However,

there is no screening program for pancreatic cancer in Thailand. Therefore, symptomatic pancreatic cancer patient is usually at a more advanced stage with lower resectability than asymptomatic patients.

The 34.5% 5-year overall survival observed in the present study was higher than the 24% 5-year survival from a similar but larger American study based on the Surveillance, End Results and Epidemiology (SEER) database,¹³ and higher than the 16% in a study from single tertiary hospital in Thailand.⁶ The better 5-year overall survival than those reported in previous studies was found possibly because of the higher proportion of ampullary carcinoma in the present study.^{6,7,13}

Pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy are curative surgical treatments for these tumors. In the present study, the hospital mortality rate was 6.6% and 30-day mortality rate was 4.9%. We also found that the lymphovascular invasion and histological grading of moderately or poorly differentiated tumors were significant prognostic factors. Chen et al. proposed that the total number of harvested lymph nodes and lymph node metastasis are significant prognostic factors.^{14,15} However the present study did not demonstrate significant difference in survival by lymph node status. This might be explained by the relatively low number of lymph nodes harvested in the present study, as 21 out of 35 negative lymph nodes patients (60%) had the total number of harvested lymph nodes less than 10 lymph nodes. The recommended minimal number of harvested lymph nodes for optimal staging in periampullary carcinoma and pancreatic cancer is at least 10 lymph nodes.^{16,17}

There were several limitations in the present study. Due to the small number of patients, we were unable to demonstrate significant differences in outcomes in terms of lymph node metastasis, margin status, tumor

size, primary tumor site, and adjuvant chemotherapy, as reported in other studies.^{8–10,18,19} There were no data regarding perineural invasion, which could have been investigated as a prognostic factor for survival.²⁰ Only 44% of patients in the present study received adjuvant chemotherapy, the outcome after which could have significantly changed their survival rates.

CONCLUSION

The present study showed that the 3- and 5-year average overall survival rates were 52.5% and 34.4%, respectively, and lymphovascular invasion and higher histologic grading of tumors were independent poor prognostic factors, for periampullary cancer after pancreaticoduodenectomy.

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Comparison between Laparoscopic Subtotal Cholecystectomy and Open Conversion in Difficult Laparoscopic Cholecystectomy

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Abstract

Objective: Laparoscopic subtotal cholecystectomy (LSC), without approaching Calot's triangle, is an acceptable option when standard laparoscopic cholecystectomy (LC) is not feasible. The aim of the present study was to verify the safety and efficacy of LSC as an alternative to open conversion (OC) in difficult LC, and to compare the clinical outcomes between LSC and OC in this setting.

Patients and Methods: From June 2011 to May 2021, there were 525 consecutive patients who underwent LC by the same surgeon. Three patients with suspected of gallbladder cancer were excluded. Open conversion was used in difficult cholecystectomy during the early period of LC, which will be called the "OC period". Since June 2017, LSC was used as an alternative to OC, and the latter period was named the "LSC period". The medical records of these 522 patients were analyzed retrospectively.

Results: There were 260 patients who underwent LC with 31 open conversion during the OC period and 262 patients underwent LC with 2 open conversion during LSC period. There were no differences in preoperative characteristics of patients between the two periods. The open conversion rate in the LSC period was significantly lower than that in OC period (0.8% versus 11.9%, respectively). Overall complication rates in LSC and OC periods were 1.6% and 5.4%, respectively. There was a significant difference in operative times (40.1 ± 16.0 versus 50.8 ± 22.7 minutes) and post-operative length of hospital stay (1.7 ± 1.2 versus 2.9 ± 2.5 days) between the LSC and OC periods, respectively. There was no significant difference in the 30-day readmission rates, and there was no 30-day mortality in the present study. All LSCs ($n = 22$) were completed without conversion to open surgery. Only one bile leakage (4.5%) and one case of retained common bile duct with retained remnant cystic duct stones was observed in these patients.

Conclusions: LSC as an alternative to OC in difficult LC has excellent clinical outcomes. LSC is a safe and effective alternative in the hands of experienced laparoscopic surgeons.

Keywords: Laparoscopic subtotal cholecystectomy, Laparoscopic cholecystectomy

INTRODUCTION

The standard management of gallbladder disease is laparoscopic cholecystectomy (LC).¹ However, the risk of damage to bile ducts and structures in the hepatic hilum during LC is increased when Calot's triangle cannot be safely dissected, particularly in the presence of severe inflammation or fibrosis,^{2,3} Mirizzi syndrome, or anomalous biliary anatomy.^{4,5}

Conventionally, open conversion (OC) has been recommended in such difficult situations,⁶ but it does not guarantee adequate identification of anatomical structures, and therefore does not eliminate the risk of injury to the bile ducts.^{7,8} Furthermore, with open conversion, the advantages of laparoscopic surgery are lost.⁹

Received for publication 28 November 2021; Revised 27 May 2022; Accepted 2 June 2022

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Subtotal cholecystectomy is a less than complete cholecystectomy that leaves behind a portion of the gallbladder in continuity with the cystic duct.¹⁰ It was first described by Bornman and Terblanche in 1985,¹¹ and since 1993, the procedure has also been performed laparoscopically.¹² Laparoscopic subtotal cholecystectomy (LSC) that avoids hazardous dissection at the triangle of Calot has been advocated to be an alternative to open conversion in cases of complicated cholelithiasis.¹³⁻¹⁶ Acceptable outcomes of LSC have been shown with lower rates of both open conversion and major inadvertent injuries, reported to be a safe and feasible alternative during difficult LC.^{17,18} However, LSC has a 18% bile leak rate and 3.1% incidence of recurrent symptomatic gallbladder.¹⁹

Theoretically, LSC should remove nearly the entire gallbladder and should close the gallbladder mucosa or gallbladder remnant adjacent to cystic duct junction without vasculo-biliary injury. It was found, as might be expected, to reduce the incidence of postoperative bile fistula and retained stones.¹⁹⁻²¹ There are still limited number of studies that compare outcomes in laparoscopic cholecystectomy between using LSC as an alternative versus open conversion (OC). The present study aimed to assess the effectiveness and safety of LSC, and to compare clinical outcomes between OC and LSC for difficult LC.

PATIENTS AND METHODS

At Phetchabun Hospital, LC was performed only in the elective setting, in patients with gallstones, gallbladder polyps and those undergoing interval cholecystectomy after acute cholecystitis has subsided. Complicated cholecystitis not responsive to conservative treatment was managed by open surgery. Diagnostic procedures such as blood test, abdominal ultrasound and abdominal CT were performed in all patients at the initial consultation. Magnetic resonance cholangiopancreatography (MRCP) was performed when choledocholithiasis was suspected, such as when abnormal liver function test or bile duct dilatation from imaging studies were observed. If choledocholithiasis was confirmed, endoscopic retrograde cholangiopancreatography (ERCP) to remove the stones would be done prior to LC, which would be performed in a different setting.

From June 2011 to May 2021 patients who underwent LC by the author at the Department of General Surgery, Phetchabun Hospital were included in the

study. Patients with suspected gallbladder cancer were excluded. Open conversion (OC) was used for difficult LC during an early period (from June 2011 to January 2017), named the “OC period”. After the author had completed a 4-month Weary Dunlop-Boonpong Fellowship Program in minimally invasive surgery, obtaining the necessary skills in advanced laparoscopic techniques, LSC was considered as an alternative to OC. Since June 2017, LSC was mainly used for difficult LC, which was named the “LSC period”. Data in the LSC period were prospectively collected. The electronic medical record for each of these patients was reviewed up to September 2021, to evaluate long term outcomes.

The medical records of all patients were retrospectively reviewed. Information obtained included demographic characteristics, preoperative history, and indication for surgery, time from diagnosis of acute cholecystitis to surgery, surgical technique, and reasons of conversion, operative time, complication, and post-operative length of stay, 30-day mortality, 30-day readmission and long term outcomes.

Quantitative variables were summarized as mean and standard deviation (SD) or median and range, while categorical variables were summarized as frequencies and percentages. The unpaired t-test was used to compare quantitative variables between two groups, while for comparison between three groups, the analysis of variance (ANOVA) was used. The Chi-square test and Fisher exact test were used to compare categorical variables. A p -value < 0.05 was considered statistically significant. All the analysis was carried out using SPSS 16.0 version. The study was approved by the institutional research ethics committee.

All procedures began with the standard 3-port LC with the initial purpose of total gallbladder removal, following the concept of critical view of safety (CVS). Open conversion or LSC technique was used when dense inflammation or fibrosis would result in hazardous entry into Calot's triangle. For LSC, another, 5-mm, 4th port was added for exposure. Two types of LSC were carried out when dealing with difficult LC's.

LSC Type 1: When the difficulty was associated with inadequate exposure of cystohepatic triangle, Hartmann's pouch or wall of gallbladder against the impacted stone was incised, followed by aspiration of bile, and removal of all stones into a collecting bag. Using this technique, it is possible to verify and identify the opening of the cystic duct. Then the incision was continued into

the posterior wall under direct vision in circumferential fashion by vessel sealing device nearby the junction of gallbladder and cystic duct. The mucosa of remnant gallbladder was ablated by electrocautery. Interrupted simple or figure of eight polygalactin 3-0 sutures were used to close the flap.

LSC Type 2: When the risks were associated with both inadequate exposure of the cystohepatic triangle and the gallbladder bed, the gallbladder was transected to leave the smallest possible strip of the fused portion between the posterior gallbladder wall and the thickened cystic plate, avoiding hazardous dissection, which might injure the right hepatic duct and vessels. The gallbladder contents were evacuated, and the absence of stones in the gallbladder remnant was confirmed under direct vision. Residual gallbladder mucosa was ablated by cautery. Full thickness bite of anterior gallbladder wall was sutured

interruptedly to the partial thickness of remnant posterior wall by intracorporeal technique, so as to diminish the inner cavity of the remnant gall bladder rather than to close the stump neatly.

After LSC, the operative field was washed copiously and subhepatic drain was often placed. Endoscopic stapler and the fundus-first technique were not used in the present study.

RESULTS

There were 525 consecutive patients who underwent LC during the study period. Three patients with gall bladder cancer were excluded, leaving 522 patients in the analysis. Of these, 260 patients underwent LC with 31 open conversion during the OC period and 262 patients underwent LC with 2 open conversion during the LSC period (Figure 1).

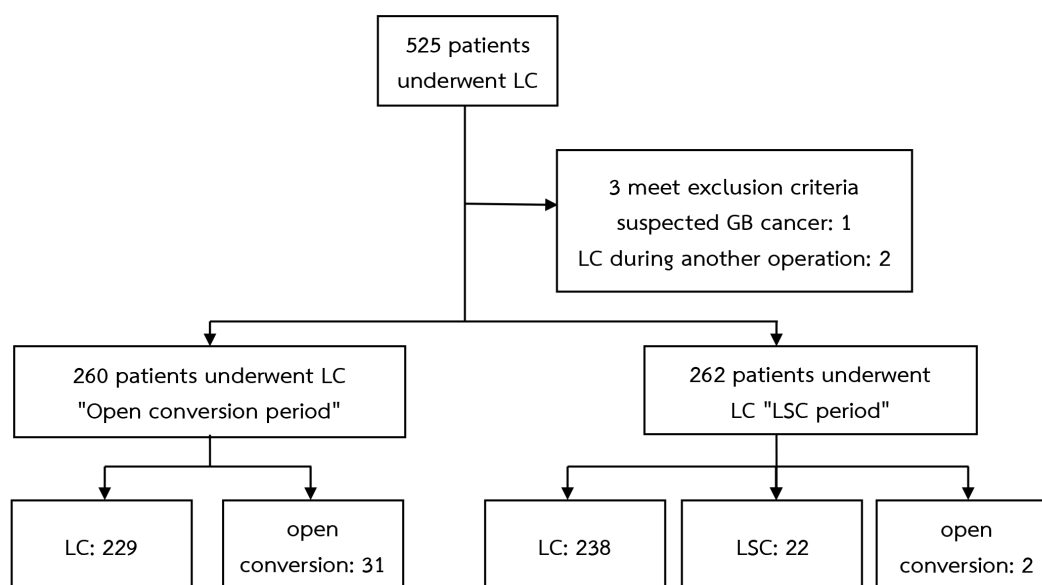


Figure 1 Flow diagram of patients in the study

There were no significant differences in age, sex, BMI, indication for LC and preoperative ERCP rates between the two periods. Interval LC constituted 49% of all LC's in OC period and 47% in the LSC period. The average time to surgery after acute cholecystitis was 8.7 weeks in the OC period and 12.8 weeks in the LSC period, a significant difference partly due to the hospital's policy to suspend elective surgery during the Covid-19 pandemic beginning in March 2020 (Table 1). Overall, patients were followed for of 57.6 months on average (range, 4 to 122 months). In OC period the mean follow-up time was 87.8 months, and in the LSC

period, 27.3 months.

The open conversion rates in the LSC and OC periods were 0.8% and 11.9%, respectively. Not surprisingly, open conversion in LSC period was significantly lower than that in the OC period ($p < 0.001$). The overall complication rate was significantly lower in the LSC period, with rates 1.6% in LSC and 5.4% in OC periods ($p = 0.030$). There were also significant differences in the operative times and post-operative lengths of stay between the two periods. There was no significant difference in the 30-day readmission rate, and no 30-day mortality in the present study.

There were significant differences in long term outcomes between patients in the OC period and LSC period. In the OC period, 11 patients returned to the hospital with pancreatitis in 2, cholangitis in 5, and CBD stones in 4 patients. Of these 9 patients had findings of CBD stones and were treated by ERCP and stone retrieval. In LSC period, 3 patients returned to hospital with cholangitis in 2 and pancreatitis in 1 patient. One of these had findings of CBD stones with concomitant with remnant cystic duct stone, and ERCP was performed to remove CBD stones (Table 2).

Standard LC was completed in 88% and 91% of

patients in the OC and LSC periods, respectively. Four ports were used 5% and 11% of patients in the OC and LSC periods, to enhanced exposure and control large cystic ducts by complex techniques such as extracorporeal or intracorporeal suture ligation. Five-port technique was used in one patient with a BMI of 30.1 kg/m² and a gallbladder embedded within the liver.

There were 31 patients who underwent open conversion in the OC period, including 24 open cholecystectomies, 4 open subtotal cholecystectomies, 1 open cholecystectomy with bile duct repair and 2 Roux-en-Y hepaticojejunostomies.

Table 1 Preoperative characteristics of patients.

	OC period (n = 260)	LSC period (n = 262)	p-value
Age (years): mean (range)	53.1 (10 - 85)	53.8 (19 - 81)	0.521
Women: n (%)	203 (78)	196 (75)	0.436
BMI (kg/m²): mean (SD)	25.2 (4.2)	25.4 (4.3)	0.633
Setups for LC			
Elective LC: n (%)	132 (51)	139 (53)	0.664
Interval LC: n (%)	128 (49)	123 (47)	
Time to surgery (days): mean (SD)	61.4 (40.2)	90.2 (61.5)	< 0.001
Preoperative ERCP: n (%)	21 (8)	29 (11)	0.311

OC: open cholecystectomy; LSC laparoscopic subtotal cholecystectomy; LC: laparoscopic cholecystectomy; SD: standard deviation; ERCP: endoscopic retrograde cholangiopancreatography

Table 2 Operative outcomes

Outcomes	OC period (n = 260)	LSC period (n = 262)	p-value
Operative time (min): mean (SD)	50.8 (22.7)	40.1 (16.0)	< 0.001
Open conversion: n (%)	31 (11.9)	2 (0.8)	< 0.001
Length of hospital stay (days): mean (SD)	2.9 (2.5)	1.7 (1.2)	< 0.001
Complication: n (%)	14 (5.4)	4 (1.6)	0.030
Bile leak	3 (1.2)	2 (0.8)	
Iatrogenic bile duct injury	4 (1.5)	1 (0.4)	
Bowel injury	2 (0.8)	0	
Bleeding	4 (1.5)	1 (0.4)	
Surgical site infection	1 (0.4)	0	
30-day readmission rates (%)	1 (0.4)	0	0.498
Biliary tract symptoms: long term: n (%)			
No intervention	2 (0.8)	2 (0.8)	0.027
Require intervention	9 (3.5)	1 (0.4)	

OC: open cholecystectomy; LSC laparoscopic subtotal cholecystectomy; SD: standard deviation

There were 22 LSC in the LSC period (8.4%), and 2 open conversions, the latter including 1 open cholecystectomy and 1 bile duct repair (Table 3). Intraoperative cholangiography was rarely performed in these cases.

Reasons for conversion to open surgery in the OC period include unclear anatomy, unable to control cystic duct, uncontrolled bleeding, iatrogenic bile duct injury, and severe adhesions. In the LSC period reasons included uncontrolled bleeding and iatrogenic bile duct injury, and these were reactive conversions. There was no preemptive conversion (conversion due to unclear anatomy, adhesion or problems with management of the cystic duct) in the LSC period (Table 4).

To verify safety and efficacy of LSC as an alternative to open conversion, patients who underwent open

conversion both in the OC and LSC periods ($n = 33$) and those who underwent LSC in the LSC period ($n = 22$) were compared. Patients were classified as being in the LSC group, the OC with preemptive conversion group, and OC with reactive conversion group, as shown in Table 5.²² Almost all patients underwent interval LC, except one patient who had LC for symptomatic gallstone. There were no significant differences in patient characteristics among groups. While there were no significant differences in hospital stay, operative time, and complications between the LSC and preemptive OC groups, there were significant differences in these outcomes between the former groups and the reactive OC group (Table 5).

Table 3 Operative procedures

Procedures	OC period (n = 260)	LSC period (n = 262)	P-value
Standard LC: n (%)	229 (88.1)	238 (90.8)	< 0.001
LC 3 ports	215 (82.7)	210 (80.1)	
LC 4 ports	13 (5)	28 (10.7)	
LC 5 ports	1 (0.4)	0	
Laparoscopic subtotal cholecystectomy: n (%)	0	22 (8.4)	NA
LSC type 1		19	
LSC type 2		3	
Open cholecystectomy (OC): n (%)	24 (9.2)	1 (0.4)	
Open subtotal cholecystectomy: n (%)	4 (1.5)	0	
OC + Repair CBD/CHD: n (%)	1 (0.4)	1 (0.4)	
OC + Roux-en-Y hepaticojejunostomy: n (%)	2 (0.8)	0	

OC: open cholecystectomy; LSC laparoscopic subtotal cholecystectomy; LC: laparoscopic cholecystectomy; CBD: common bile duct CHD: common hepatic duct

Table 4 Reasons for conversion from laparoscopic to open cholecystectomy

Reasons	OC period (n = 260)	LSC period (n = 260)	p-value
Uncontrolled bleeding: n (%)	4 (1.5)	1 (0.4)	0.215
Iatrogenic bile duct injury: n (%)	4 (1.5)	1 (0.4)	0.215
Adhesion: n (%)	2 (0.8)	0	0.248
Unclear anatomy: n (%)	14 (5.4)	0	< 0.001
Uncontrolled cystic duct stump: n (%)	7 (2.7)	0	0.007

OC: open cholecystectomy; LSC laparoscopic subtotal cholecystectomy

Table 5 Patient characteristics and operative outcomes in each group of alternatives in difficult laparoscopic cholecystectomy

Characteristics	LSC (n = 22)	Preemptive OC (n = 23)	Reactive OC (n = 10)	p-value
Age (years): mean (SD)	53.3 (10.7)	52.6 (10.7)	47.3 (13.2)	0.355
Women: n (%)	15 (70)	17 (74)	7 (70)	0.926
BMI (kg/m²): mean (SD)	24.9 (4.4)	25.4 (4.1)	26.5 (4.1)	0.634
Setups for LC				0.999
Elective LC (%)	0	1 (4)	0	
Interval LC (%)	22 (100)	22 (96)	10 (100)	
Time to surgery (days): mean (SD)	99 (76)	64 (40)	70 (52)	0.142
Preoperative ERCP: n (%)	2 (9)	1 (4)	2 (20)	0.317
Operative time (min): mean (SD)	70 (15)	68 (16)	103 (51)	0.002
Drain placed: n (%)	21 (96)	8 (39)	7 (70)	< 0.001
Days in place: mean (SD)	4.2 (2.6)	6.3 (1.9)	5.9 (1.2)	< 0.001
Length of stay (days): mean (SD)	4.0 (1.9)	4.9 (1.8)	8.0 (7.8)	0.019
Overall complications: n (%)	1 (4)	1 (4)	10 (100)	< 0.001
Uncontrolled bleeding	0	0	5 (50)	
Iatrogenic bile duct injury	0	0	5 (50)	
Bile leakage	1 (4)	0	0	
Surgical site infection	0	1 (4)	0	
30-day readmission: n (%)	0	1 (4)	0	0.999
Biliary tract symptoms: n (%)				0.923
No intervention	1 (4)	1 (4)	1 (10)	
Require intervention	1 (4)	1 (4)	0	

OC: open cholecystectomy; LSC laparoscopic subtotal cholecystectomy; LC: laparoscopic cholecystectomy; SD: standard deviation; ERCP: endoscopic retrograde cholangiopancreatography

DISCUSSION

While it is well-established that early cholecystectomy for acute cholecystitis is advantageous,²³⁻²⁵ delayed surgery after an episode of acute cholecystitis is still widely prevalent.²⁶ In the present study all patients who presented with acute cholecystitis and responded to conservative treatment would later undergo interval LC. This was due to certain institutional limitations, making emergency LC infeasible. In contrast to the technical difficulty attributed to edema and acute inflammation when surgery was performed early, chronic inflammation and fibrosis were the main reasons in this series for the need for OC or LSC to avoid major injury. In the present study, interval LC, as compared with elective LC, was associated with higher conversion rates, at 12.7% and 0.4%, respectively ($p < 0.001$).

Overall complication rates between the two periods were statistically different. Iatrogenic bile duct injury

(IBDI) is a serious complication in LC. IBDI occurred in 4 patients in OC period, 3 of which were detected and immediately repaired intraoperatively, 1 was detected in the early postoperative period and underwent Roux-en-Y hepaticojejunostomy. In the LSC period, only 1 patient had IBDI which was detected intraoperatively, and the procedure was converted to open cholecystectomy with common hepatic duct repair. This low incidence of IBDI in the LSC period is comparable to that of the literature.²⁷ There were 5 uncontrolled bleeding in the present study, requiring OC, but without needing blood transfusions. Four patients had uncontrolled bleeding in OC period and 1 patient in LSC period. Bleeding from liver bed is theoretically avoided in LSC by not removing the posterior gallbladder wall. In LSC group no uncontrolled bleeding was observed.

In the literature, bile leakage was the most common complication of LSC, with incidences between 10.6 and

18%.¹⁶⁻¹⁸ Although bile leakage may resolve spontaneously or after ERCP and biliary stenting, it is better to prevent its occurrence. According to a systematic review by Henneman et al., bile leakage occurred in 5.6% of patients with closed gallbladder remnant compared with 16% of patients who had opened remnant gallbladder. In the 22 cases of LSC, only one (4.5%) bile leakage was observed in a patient with LSC type 2, where part of the posterior gall bladder wall was left in situ. The patient was discharged with drainage on post-operative day 4, and the drain was removed after 14 days without complications. In the present study a subhepatic drain was placed in almost all cases of LSC to detect leakage and remained in situ for a median of 3 days (range, 2 to 14 days).

The open conversion rates were 11.9% and 0.8% in the OC and LSC periods. Although increasing laparoscopic experience may have affected the difference in the open conversion rates, previous studies have reported that conversion due to unclear or obscure anatomy (preemptive conversion) does not diminish regardless of increased surgical experience and skill.²⁸ There was no preemptive conversion in the LSC period, and this could explain part of the difference, that LSC was effective in preventing preemptive OC. Also, there were only 2 reactive conversions in LSC period, performed to control bleeding and bile duct injury. If LSC were used at the right time, before proceeding to total cholecystectomy with subsequent injury, reactive open conversion could be avoided. This would explain the remaining difference in the OC rates. A recent meta-analysis of LC in the setting of severe gall bladder inflammation showed that a lower threshold of conversion seems to reduce local postoperative complications.²⁹ After the author became familiar with LSC, there was no OC in last 187 consecutive LCs. The 8.4% rate of LSC in the LSC period is comparable to that of the literature,¹² and was similar to the 8.8% preemptive OC in the present study, which showed that LSC was not overused in the present study.

A concern of LSC is that gallbladder cancer may unexpectedly coexist in 0.2-0.8% of patients undergoing LC.³⁰ The incidence of gallbladder cancer in this series was 0.4%. In gall bladder cancer, if the gallbladder wall is cut open, cancer dissemination may occur. LSC requires cutting through the gall bladder mucosa, with consequent intraabdominal leakage of gallbladder contents. Therefore, preoperative and intraoperative awareness of gallbladder cancer is very important.

In the present study, retained stones occurred in 1 (4.5%) of the 22 LSC, after a mean follow-up of 27.3 months. This is similar to the result of a systematic review, where 3.1% of patients had retained stones.¹⁶ In our patient, CBD stones were detected concomitant with a remnant cystic duct stone. ERCP was performed to remove CBD stones while the remnant cystic duct stone was managed conservatively. Although the incidence of retained stones in LSC period was significantly lower than that in the OC period (0.4% vs 3.5%, p -value 0.027), the mean follow-up time in LSC period was shorter than that in OC period (27.7 vs 87.8 months, p -value < 0.001). Longer term of follow-up is needed.

CONCLUSIONS

LSC is a safe and effective alternative to open conversion. It seems that preemptive OC can be partly obviated by LSC, when dissection of Calot's triangle would be hazardous. Although reactive OC is also reduced, appropriate timing of or decision to perform preemptive OC may reduce reactive OC even further. More study is needed to clarify when this timing might be. However, the surgeons should never hesitate to do OC when he or she is in doubt of the risks of injuries. Experience of and mastery in LSC technique should enable surgeons to make better OC decisions during difficult LC.

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