Original Article

Outcome of Adjuvant versus Salvage Androgen Deprivation Therapy (ADT) with/without Radiotherapy Following Radical Prostatectomy for Prostate Cancer Patients with Adverse Pathologic Feature(s) or with Positive Regional Lymph Node Metastasis

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Objective: To evaluate and compare the overall survival of patients after radical prostatectomy, who had high-risk feature(s) or regional lymph node metastasis compared to those who received adjuvant androgen deprivation therapy (ADT) and those who received salvage ADT.

Materials and Methods: All patients with prostate cancer who had high-risk feature(s) or regional lymph node metastasis and who underwent radical prostatectomy at the Division of Urological Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during February 2000 to November 2016 were retrospectively reviewed.

Results: Five hundred and four patients were included. At 15 years, overall survival was 87.3% and 90.2% in the adjuvant ADT and salvage ADT groups, respectively (p = 0.955). Recurrence-free survival was 83.2% in the adjuvant group, and 26.8% in the salvage group (p<0.001). Metastasis-free survival at 15 years in the adjuvant group and the salvage group was 68.3% and 74.1%, respectively (p = 0.261). CVS-morbidity-free survival was 91.9% in adjuvant patients, and 82.8% in salvage patients (p = 0.333).

Conclusion: No difference in overall survival between the adjuvant and salvage ADT groups was demonstrated at 15 years after therapy. The adjuvant ADT group had significantly better recurrence-free survival at 15 years. There was no statistically significant difference for metastasis-free survival or CVS-morbidity-free survival between groups.

Keywords: Adjuvant androgen deprivation therapy, ADT, Salvage ADT, Prostate cancer, Post radical prostatectomy, Adverse feature

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Prostate cancer is currently the 4th most common cancer among men in Thailand[1]. The standard treatment for localized disease is radical prostatectomy. Despite aggressive surgical management, the risk of biochemical recurrence at 2 years after surgery is approximately 45%[2]. Androgen deprivation therapy (ADT) in combination with radiotherapy after radical prostatectomy has been recommended for patients with regional lymph node metastasis or that have high-risk feature(s)[3-5]. However, the duration and timing of ADT has not been well studied. Some studies suggest early ADT due to better survival benefit. However, an increased risk of developing cardiovascular events in the early ADT group has also been reported[6,7]. Moreover, after initiation of ADT, the patient will eventually develop castration-resistant prostate cancer and the disease will progress further until death[8].

At Siriraj Hospital, prostate cancer accounts for 6.3% of all newly diagnosed cancer, and it is the second most common cancer found in men treated at our center[9]. The aim of the present study was to investigate the survival outcome of prostate cancer patients, after radical prostatectomy, who had adverse feature(s) or regional lymph node metastasis on pathology report at Siriraj Hospital, which is a large prostate cancer surgery center in Thailand.

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Materials and Methods

All patients with prostate cancer who had high-risk feature(s) or regional lymph node metastasis and who underwent radical prostatectomy at the Division of Urological Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand from February 2000 to November 2016 were retrospectively reviewed. Patients were classified into the following 2 groups:

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the adjuvant ADT group comprised patients who received ADT within 3 months after surgery; and, the salvage ADT group included patients who had delayed ADT for more than 3 months after surgery, or who started ADT after PSA recurrence.

The PSA failure is defined as a PSA level greater than 0.2 ng/mL at 3 months after surgery or after the initiation of ADT (with 2 consecutive rising on measurements). When a PSA failure occurred, the authors took this as a biochemical recurrence.

Time to recurrence, time to metastasis, time to CVS-event, and time to death were measured upon completion of each chart review. Time to recurrence was calculated by measuring the time from the start of ADT to the time the patient was documented with 1st PSA recurrence in the adjuvant ADT group. Time to recurrence in the salvage ADT group was defined as the time from 1st PSA recurrence to the time of 2nd PSA recurrence. Time to metastasis, time to CVS-event, and time to death were measured from the time of operation to the documented time of the event. Patients with a follow-up time of less than 2 years or having incomplete data were excluded. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA No. 831/2561 (EC2)).

Statistical analysis

The authors used IBM SPSS Statistics version 24 for Windows for analysis. Demographic data is reported using mean $\pm$ standard deviation (SD), median (minimum, maximum), or number and percentage. Overall survival, CVS event-free survival, and recurrence-free survival were calculated and reported using Kaplan-Meier estimation and curve, log-rank test for comparison, and Cox regression to identify potential risk factors.

Results

Five hundred and four patients were included. There were 320 patients in the adjuvant ADT group, and 184 patients in the salvage ADT group. There was no significant difference between groups for age, ASA classification, BMI, type of operation, or initial PSA. In contrast, significant difference between groups was observed for Gleason grading, pathological staging, positive surgical margin, and detectable PSA after surgery (Table 1). A greater proportion of Gleason grade group 5 was found in the adjuvant group compared to the salvage group (35.8% vs. 22.7%). Higher pathological staging was found in the adjuvant group (pT3: 83.1% vs. 69.2%, pN1: 11.9% vs. 5.7%). There was more positive surgical margin in the adjuvant group (87.5% vs. 78.3%). A larger proportion of patients with postoperative detectable PSA was demonstrated in the adjuvant group compared to the salvage group (88.4% vs. 81.9%).

The most common ADT was GnRH agonist/antagonist or bilateral orchiectomy (59.4% in adjuvant ADT, and 67.4% in salvage ADT) (Table 2). The median ADT duration was 55.75 months (range: 30 to 93) in the adjuvant ADT group, and 34.89 months (range: 19 to 59) in the salvage ADT group.

Survival analysis

The median time to follow-up was 7.2 years (range: 6.5 to 7.8). Overall survival at 15 years for adjuvant ADT and salvage ADT was 87.3% and 90.2%, respectively (p = 0.955) (Figure 1). Recurrence-free survival at 15 years was 83.2% and 26.8% (p<0.001) (Figure 2). Metastasis-free survival was 68.3% in adjuvant patients, and 74.1% in salvage patients (p = 0.261) (Figure 3). CRPC-free survival was 67.0% and 75.7% (p = 0.907) (Figure 4). Cardiovascular (CVS) morbidity-free survival was 91.9% and 82.8% (p = 0.333) (Figure 5).

Multivariate analysis

Multivariate analysis using multiple Cox regression revealed the presence of lymphovascular invasion (hazard ratio [HR]: 2.26, 95% confidence interval [CI]: 1.30 to 3.94; p = 0.004) and detectable PSA after surgery (HR: 3.335, 95% CI: 2.04 to 5.46; p<0.001) which were independent risk factors for biochemical recurrence (Table 3).

Discussion

Our data revealed significant differences between the adjuvant and salvage ADT groups for initial PSA, Gleason grade, type of operation, TNM staging, margin status, presence of extracapsular extension, seminal vesicle invasion, and lymphovascular invasion. Despite the aggressive tumor characteristics in the adjuvant group, we found recurrence-free survival to be better in the adjuvant ADT group than in the salvage ADT group (83.2% vs. 26.8%, p<0.001), but we found no significant difference between groups for CRPC-free survival or CVS-morbidity-free survival.

Messing, et al found that immediate ADT benefits patients with regional node-positive prostate cancer after radical prostatectomy in terms of increasing overall survival. The overall survival rate was 80% and 65% for the immediate ADT and deferred ADT groups, and the progression-free survival rate was 80% and 20%, respectively[10]. The present study had different inclusion criteria relative to pathological staging compared to that of Messing, et al compared to the present study, their group focused only on regional node-positive patients. Most of the patients in our study had locally-advanced cancer (pT2-3) with adverse features, and a smaller subset of patients (47 patients) had node-positive disease. Due to the low mortality rate in our study, a longer follow-up in these groups of patients may be needed to determine the difference in overall survival. Teoh and his colleague reported the risk of acute myocardial infarction (MI) in patients following androgen deprivation therapy, especially in patients with hyperlipidemia or poor ECOG performance (n = 452). The hazard ratio was 6.78 in patients who were receiving ADT. Acute MI-free survival at 10 years for the ADT and non-ADT groups was 96% and 86%, respectively[6]. Comparison between the adjuvant and salvage ADT groups in the present study revealed rates of CVS morbidity-free survival of 91.9% and 82.8%,

Table 1. Demographic and clinical data

	Adjuvant ADT (n = 320)	Salvage ADT (n = 184)	*p*-value
Age (years), mean ± SD	68.0±8.0	67.0±7.0	0.737
ASA classification, n (%)			0.716
1	39 (12.3)	17 (9.2)	
2	239 (75.4)	145 (78.8)	
3	39 (12.3)	22 (12.0)	
BMI (kg/m^2), median (min, max)	24.3 (11.3, 37.2)	24.2 (17.5, 36.7)	0.709
PSA (ng/mL), median (min, max)	19.0 (1, 250)	15.9 (0, 258)	0.226
Gleason grade group, n (%)			0.017
1	15 (4.8)	8 (4.7)	
2	68 (21.7)	55 (32.0)	
3	50 (16.0)	35 (20.3)	
4	68 (21.7)	35 (20.3)	
5	112 (35.8)	39 (22.7)	
Type of operation, n (%)			0.178
RRP	77 (24.1)	45 (24.5)	
EERPE	41 (12.8)	26 (14.1)	
LRP	39 (12.2)	34 (18.5)	
RALRP	163 (50.9)	79 (42.9)	
Pathological staging, n (%)			
T staging			<0.001
pT2	45 (14.1)	55 (30.2)	
pT3	266 (83.1)	126 (69.2)	
pT4	1 (0.3)	1 (0.5)	
Lymph node			
pN0	273 (88.1)	165 (94.3)	0.026
pN1	37 (11.9)	10 (5.7)	
Margin			
Positive	280 (87.5)	144 (78.3)	0.006
Negative	40 (12.5)	40 (21.7)	
Seminal vesicle invasion			
Yes	150 (46.9)	39 (21.2)	<0.001
No	170 (53.1)	145 (78.8)	
Extraprostatic extension			
Yes	248 (77.5)	121 (66.1)	0.005
No	72 (22.5)	62 (33.9)	
Detectable PSA after RP			
Yes	37 (11.6)	33 (18.1)	0.044
No	281 (88.4)	149 (81.9)	
Combination with RT			0.962
Yes	93 (29.1)	135 (29.2)	
No	227 (70.9)	327 (70.8)	

A *p*-value <0.05 indicates statistical significance
ADT = androgen deprivation therapy; SD = standard deviation; ASA = American Society of Anesthesiologists; BMI = body mass index; PSA = prostate-specific antigen; RRP = open retropubic radical prostatectomy; EERPE = endoscopic extraperitoneal radical prostatectomy; LRP = laparoscopic radical prostatectomy; RALRP = robotic assisted laparoscopic radical prostatectomy; RP = radical prostatectomy; RT = radiotherapy

Table 2. Types of androgen deprivation therapy used

	Adjuvant ADT (n = 320)	Salvage ADT (n = 184)
Antiandrogen monotherapy, n (%)	18 (5.6%)	18 (9.8%)
GnRH agonist/antagonist (including orchiectomy), n (%)	190 (59.4%)	124 (67.4%)
Combined androgen blockade, n (%)	112 (35.0%)	42 (22.8%)

ADT = androgen deprivation therapy; GnRH = gonadotropin-releasing hormone

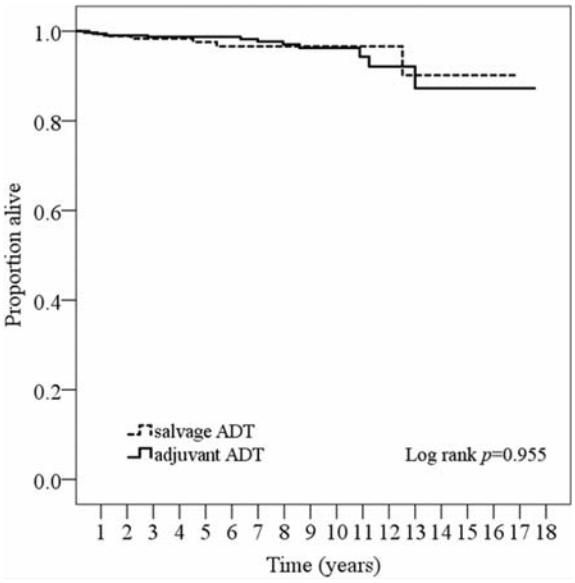

Figure 1. Kaplan-Meier curve for overall survival. Salvage ADT; Adjuvant ADT.

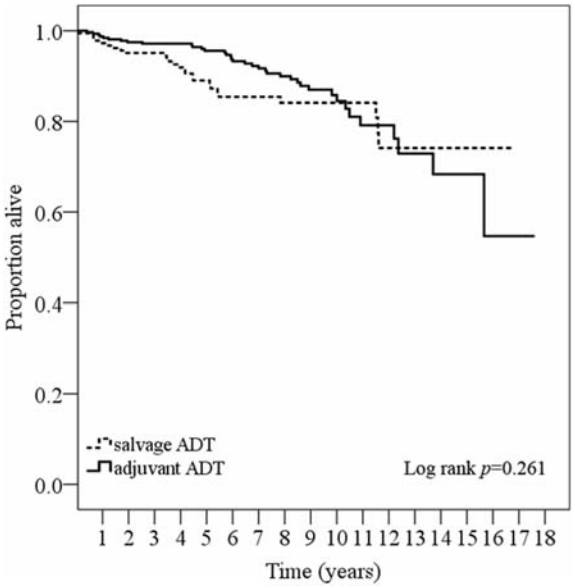

Figure 3. Kaplan-Meier curve for metastasis-free survival. Salvage ADT; Adjuvant ADT.

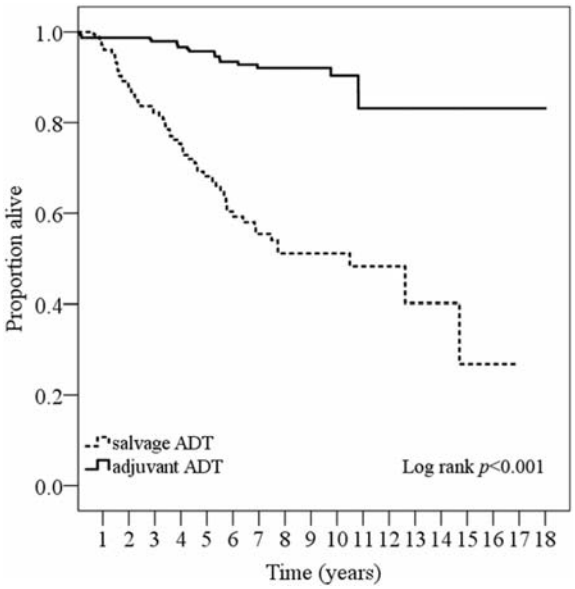

Figure 2. Kaplan-Meier curve for biochemical-recurrence-free survival. Salvage ADT; Adjuvant ADT.

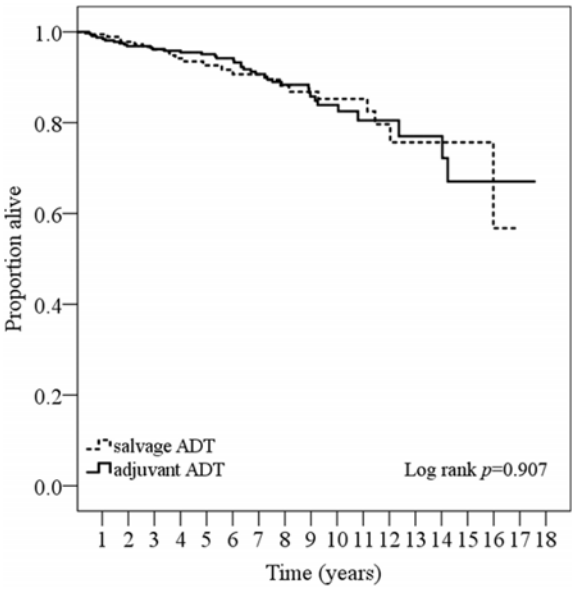

Figure 4. Kaplan-Meier curve for castration-resistance-free survival. Salvage ADT; Adjuvant ADT.

respectively (p = 0.333).

According to these findings, we have found that the adjuvant ADT group demonstrated better recurrence-free survival without difference in CVS-morbidity rate. Some might argue that the better findings in RFS from this group might be possibly due to concurrent administration of radiotherapy with ADT, although the authors had found that only 29.1% and 29.2% of patients in adjuvant ADT group and salvage ADT group, respectively, had received radiotherapy. Thus it can be implied that the majority of patients had not received any radiotherapy at the end of the study and the confounding effect of radiotherapy on the RFS

would not be significantly found in the present study.

The limitation of the present study is retrospective design, which can lead to selection bias. The authors suggest further prospective study with a match-controlled design.

Conclusion

Adjuvant androgen deprivation therapy post radical prostatectomy benefits patients with adverse feature(s) or regional lymph node metastasis relative to improved recurrence-free survival; however, no difference in metastasis-free survival or overall survival was found.

What is already known on this topic?

Androgen deprivation therapy (ADT) after radical prostatectomy is recommended in prostate cancer patients with adverse features or regional lymph nodes metastasis, but some argument exists on timing to initiate ADT due to the risk of increasing cardiovascular events or non-prostate cancer death.

What this study adds?

Adjuvant ADT after radical prostatectomy (given within 3 months) in prostate cancer patients with adverse features or regional lymph nodes metastasis is an effective approach to improve biochemical recurrence-free survival without increasing risk of cardiovascular morbidity.

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Funding disclosure

This was an unfunded study.

Potential conflicts of interest

The authors declare no conflict of interest.

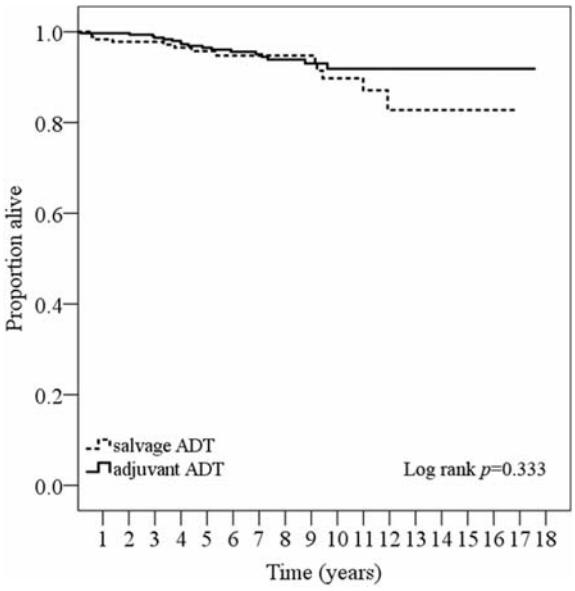

Figure 5. Kaplan-Meier curve for CVS-morbidity-free survival. Salvage ADT; Adjuvant ADT.

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Table 3. Multivariate analysis for association between biochemical recurrence and possible risk factors

Parameters	Adjusted HR	95% CI	*p*-value
Lymphovascular invasion	2.26	1.30 to 3.94	0.004
Detectable PSA after surgery	3.335	2.04 to 5.46	<0.001
Adjuvant ADT	0.12	0.07 to 0.21	<0.001
Gleason grade group (equal to or greater than 4)	1.17	0.72 to 1.91	0.521
Extraprostatic extension	1.02	0.61 to 1.71	0.933
Seminal vesicle invasion	1.06	0.61 to 1.84	0.824
Perineural invasion	1.30	0.49 to 3.45	0.592
Regional lymph node metastasis	1.50	0.68 to 3.27	0.313
Positive margin	1.39	0.80 to 2.41	0.248

A *p*-value <0.05 indicates statistical significance
HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; ADT = androgen deprivation therapy

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ผลการรักษาด้วยวิธีระงับฮอร์โมนแอนโดรเจนทันทีหลังการผ่าตัดมะเร็งต่อมลูกหมากที่มีผลชิ้นเนื้อไม่น่าพึงพอใจ หรือมีการแพร่กระจายไปยังต่อมน้ำเหลืองข้างเคียง เทียบกับการรักษาโดยการชะลอการระงับฮอร์โมนภายหลังการผ่าตัด

ภาวิชญ์ บุญญะพานิชสกุล, สุนัย ลีวันแสงทอง, ไชยยงค์ นวลยง, สิทธิพร ศรีนวลนัด, ธวัชชัย ทวีมั่นคงทรัพย์, วรัชญ์ วรนิสรากุล

วัตถุประสงค์: ประเมินและเปรียบเทียบอัตราการรอดชีวิตของผู้ป่วยมะเร็งต่อมลูกหมากภายหลังการผ่าตัดต่อมลูกหมากที่มีผลทางพยาธิวิทยาไม่น่าพึงพอใจหรือมีการกระจายไปยังต่อมน้ำเหลืองข้างเคียง ระหว่างผู้ป่วยที่ได้รับการรักษาโดยการให้การระงับฮอร์โมนแอนโดรเจนทันที และผู้ป่วยที่ได้รับการชะลอการระงับฮอร์โมนหลังผ่าตัด

วัสดุและวิธีการ: ทำการศึกษาย้อนหลังจากการค้นเวชระเบียนผู้ป่วยมะเร็งต่อมลูกหมาก ที่ได้รับการผ่าตัดต่อมลูกหมาก และมีผลทางพยาธิวิทยาไม่น่าพึงพอใจหรือมีการกระจายไปยังต่อมน้ำเหลืองบริเวณข้างเคียงโดยศึกษาจากผู้ป่วยที่ได้รับการผ่าตัดในโรงพยาบาลศิริราช ตั้งแต่เดือนกุมภาพันธ์ พ.ศ. 2542 ถึง เดือนพฤศจิกายน พ.ศ. 2559

ผลการศึกษา: มีผู้ป่วยที่ได้รับการศึกษาทั้งหมด 504 คน ซึ่งมีอัตราการรอดชีวิตที่เวลา 15 ปีภายหลังการผ่าตัดคิดเป็นร้อยละ 87.3 ในกลุ่มที่ได้รับการระงับฮอร์โมนทันทีหลังผ่าตัด และ ร้อยละ 90.2 ในกลุ่มที่ได้รับชะลอการระงับฮอร์โมนภายหลังการผ่าตัด ($p = 0.955$) อัตราการรอดจากการกลับเป็นซ้ำคิดเป็นร้อยละ 83.2 ในกลุ่มที่ได้รับการระงับฮอร์โมนทันทีเทียบกับร้อยละ 26.8 ในกลุ่มที่ได้รับการชะลอการระงับฮอร์โมน ($p<0.001$) อัตราการรอดจากการแพร่กระจายไปยังอวัยวะห่างไกลคิดเป็นร้อยละ 68.3 ในกลุ่มที่ได้รับการระงับฮอร์โมนทันที เทียบกับร้อยละ 74.1 ในกลุ่มที่ได้รับการชะลอการระงับฮอร์โมน ($p<0.261$) โดยในกลุ่มที่ได้รับการระงับฮอร์โมนทันที มีอัตราการรอดจากการเกิดโรคทางระบบไหลเวียนโลหิตคิดเป็นร้อยละ 91.9 และกลุ่มที่ได้รับการชะลอการระงับฮอร์โมนคิดเป็นร้อยละ 82.8 ($p = 0.333$)

สรุป: ไม่พบความแตกต่างอย่างมีนัยสำคัญระหว่างอัตราการรอดชีวิตของผู้ป่วยที่ได้รับการรักษาด้วยวิธีการระงับฮอร์โมนทันที เทียบกับการชะลอการระงับฮอร์โมน ในผู้ป่วยมะเร็งต่อมลูกหมากภายหลังการผ่าตัดต่อมลูกหมากที่มีผลทางพยาธิวิทยาไม่น่าพึงพอใจภายหลังติดตามผู้ป่วยไป 15 ปี ทั้งนี้ผู้ป่วยที่ได้รับการรักษาด้วยการระงับฮอร์โมนทันทีหลังผ่าตัดมีอัตราการกลับเป็นซ้ำของโรคน้อยกว่าอย่างมีนัยสำคัญทางสถิติ โดยไม่พบความแตกต่างของการเกิดโรคทางระบบไหลเวียนโลหิตระหว่างผู้ป่วยทั้งสองกลุ่ม