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Effect of Diabetes Mellitus on Patients Receiving Robotic-Assisted Laparoscopic Radical Prostatectomy for Prostate Cancer

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Abstract— **Background: The purpose of this study was to evaluate whether diabetes mellitus (DM) affects outcomes in patients receiving robotic-assisted laparoscopic radical prostatectomy (RARP) for prostate cancer.**
Patients and Methods: We compared the early clinical results of diabetic and nondiabetic patients in terms of preoperative (pre-OP) variables and surgical outcomes. Patient records were obtained from a review of the database for prostate cancer patients receiving RARP at Chang-Gung Memorial Hospital, Taiwan, between July 2012 and December 2014. The patients underwent a comprehensive physical examination and medical history review and were classified into two groups: diabetic (DM cohort) and nondiabetic (non-DM cohort). The pre-OP variables and intraoperative and postoperative (post-OP) data of the two cohorts were compared. In addition, biochemical recurrence (BCR)-free survival and urinary continence recovery in the cohorts were compared.
Results: In total, 363 patients (84 DM; 279 non-DM) were enrolled. Compared with the non-DM cohort, patients in the DM cohort were older (68 vs. 65 years, p = 0.002) and had a higher BMI (26.2 vs. 24.8 kg, p = 0.009); the DM cohort also had a higher proportion of clinical T3a (35.7% vs. 26.5%, p < 0.001) and Gleason score 8–10 (26.2% vs. 14.3%, p = 0.019). Intraoperatively, the two cohorts were similar in terms of operative time, blood loss, hospital stay, transfusion rates, and surgical complication rates. However, the final pathology stage of the DM cohort seemed to be more advanced than that of the non-DM cohort. The BCR-free survival was similar in both cohorts, but the speed of recovery from urinary incontinence differed. The continence rates in the DM cohort at post-OP 3 months, 6 months, and 12 months were 30.9%, 45.0%, and 62.8%, respectively, whereas those in the non-DM cohort were 43.0%, 66.5%, and 94.9%, respectively (p < 0.001). Through univariate and multivariate logistic regression analysis, we discovered that DM was an independent factor that affected urinary incontinence at post-OP 6 months.
Conclusion: DM patients could achieve a favorable radical prostatectomy outcome with the utility of da Vinci robotic arms. However, diabetes is an unfavorable factor affecting recovery from post-OP urinary incontinence.

Index Terms— **Prostate, Prostate Neoplasm, Robotic Surgery, Radical Prostatectomy, Diabetes.**

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I. INTRODUCTION

Operating on diabetic patients is a challenge for surgeons. Surgery on diabetic patients is associated with longer hospital stays, higher health care resource utilization, and higher perioperative mortality compared with nondiabetic subjects.1-3 Moreover, perioperative hyperglycemia significantly increases the risk of pneumonia, systemic blood infections, urinary tract infection, skin infections, and acute renal failure during the postoperative (post-OP) period.4 However, whether minimally invasive surgery with the assistance of robotic arms can ameliorate these complications has not been discussed thoroughly. Since approval by the Food and Drug Administration (FDA) in 2000, the da Vinci Surgical System has been the gold standard in minimally invasive surgery.5 The robotic-assisted device enhances surgeons' dexterity and vision and provides several advantages over traditional open methods, such as smaller incisions; lesser pain, bleeding, and risk of infection; faster healing time; and shorter hospital stay.6 Because radical prostatectomy (RP) is a standard surgical treatment for clinically localized prostate cancer (CaP),7 robotic-assisted laparoscopic RP (RARP) is widely used in the United States and Europe, where an estimated >75% of RPs are performed using the da Vinci platform.8 The purpose of this study was to evaluate whether diabetes mellitus (DM) affects outcomes in patients receiving RARP for CaP. We compared the early clinical results of diabetic and nondiabetic patients in terms of preoperative (pre-OP) variables and surgical outcomes. To the best of our knowledge, this is the first study investigating whether DM affects outcomes in patients receiving RARP for CaP. We hypothesize that with the utility of the highly advanced da Vinci platform, DM patients can have similar early-surgical results to that of non-DM patients.

II. MATERIAL AND METHODS

Patient records were obtained from a review of the database for localized CaP patients who received da Vinci Surgical System(Intuitive Surgical, Inc., Sunnyvale, CA, USA)-assisted RARP from July 2012 to December 2014. This study was approved by the Institutional Review Board of Chang-Gung Memorial Hospital, Taiwan. The patients underwent a detailed medical history review and physical examination. The patients' age, body mass index (BMI), initial prostatic specific antigen (iPSA) level, prostate volumes measured through transrectal ultrasonography, and biopsy Gleason scores were recorded. CaP staging was based on the American Joint Committee on Cancer (AJCC) staging guidelines, seventh edition.[9] D'Amico's risk classification was used to predict the patients' biochemical recurrence (BCR) risk. [10] The patients were sub-grouped into two categories: DM cohort and non-DM cohort. We defined patients as having DM if they had at least one inpatient admission record or two outpatient visits with a diagnosis of DM and were prescribed antidiabetic medication within 12 months before their RARP. Blood sugar levels had been carefully controlled by the patients' primary care physicians before the surgery. Patients who had poor blood sugar control, missing PSA data, a history of the endoscopic bladder neck or prostate treatment, a history of diagnosed overactive bladder, received prior hormone or radiation therapy, or had adjuvant treatments before documented BCR were excluded. In total, 363 patients were enrolled in the present analysis. RARP was performed by three surgeons, all of whom were approved robotic urologic surgeons in our hospital; on average, they had conducted more than 50 RARP procedures per year in the past 5 years. The patients' intraoperative and post-OP data variables, including operative time, blood loss, hospital stay, blood transfusion rate, surgical complication rate, surgical margin positive rate, and pathology reports, were recorded. After they were discharged from the hospital, their blood was drawn to test the serum PSA level at the first post-OP month and every 3 months thereafter for at least 2 years. BCR was defined as a serum PSA > 0.2 ng/ml with a confirmatory value.[11] In addition, the amount of diaper and pad usage was recorded at post-OP 3, 6, and 12 months. Continence status in our study was defined as diaper- or pad-free without the aid of an antimuscarinic agent. Patients who received radiation therapy because of BCR during the observation period were excluded from the subsequent continence evaluation.

Table 1. Patient Characteristics and Pre-Op Variables

Characteristics	**DM**	**Non-DM**	***P* value**
Patient number	84	279	
Age (y) (median)	68 (83-53)	65 (79-49)	0.002*
BMI (median)	26.2 (19.1-34.6)	24.8 (19.0-38.1)	0.009*
ASA score (median)	3 (2-3)	3 (2-3)	0.900
Prostate volume (gm) (median)	41.1 (20.0-85.3)	42.4 (15.6-96.1)	0.611
iPSA (ng/ml)	10.6 (0.8-40.2)	10.9 (0.7-67.6)	0.492
Clinical stage (%)			
T1	5 (5.9%)	9 (3.2%)	0.328
T2a	14 (16.7%)	43 (15.4%)	0.864
T2b-c	35 (41.7%)	153 (54.8%)	0.046*
T3a	30 (35.7%)	74 (26.5%)	<0.001*
Biopsy GS (%)			
≤ 6	31 (36.9%)	109 (39.1%)	0.799
7	31 (36.9%)	130 (46.6%)	0.133
8 -10	22 (26.2%)	40 (14.3%)	0.019*
D'Amico classification (%)			
Low risk group	3 (3.6%)	11 (3.9%)	1.000
Intermediate risk group	16 (19.0%)	38 (13.6%)	0.224

Abbreviations: DM: Diabetes mellitus; BMI: body mass index; ASA: American Society of Anesthesiologists; iPSA: initial prostate specific antigen; GS: Gleason score

Table 2. Intraoperative and Postoperative Data

Characteristics	**DM**	**Non-DM**	**P value**
Operative time (hr)	3.5 (2.0-7.2)	3.5 (1.7-6.8)	0.720
Blood loss (ml)	100 (30-1200)	100 (30-1400)	0.556
Hospital stay (days)	6 (3-21)	6 (3-18)	0.269
Blood transfusion (%)	6 (7.1%)	7 (2.5%)	0.085
Complications (%)	6 (7.1%)	26 (9.3%)	0.663
Class I	3	21	
Class II	3	3	
Class III	0	2	
Pathologic stage (%)			
T2a	10 (11.9%)	38 (13.6%)	0.854
T2b-c	33 (39.3%)	158 (56.6%)	0.006*
T3a-T4	41 (48.8%)	83 (29.8%)	0.002*
Lymph node positive (%)	4 (4.8%)	4 (1.4%)	0.087
Pathology GS (%)			
≤ 6	11 (13.1%)	62 (22.2%)	0.087
7	56 (66.7%)	181 (64.9%)	0.795
8 -10	17 (20.2%)	36 (12.9%)	0.048*
SM positive (%)	26 (30.9%)	69 (24.7%)	0.260

Abbreviations: DM: Diabetes mellitus; GS: Gleason score; SM: surgical margin. Complications were classified according to the Clavien–Dindo classification.

Table 3: Logistic regression analysis of parameters associated with urinary incontinence at post-OP 6 months

	Univariable			**Multivariable**		
	SHR	95% CI	*P* value	SHR	95% CI	P value
BMI	1.09	1.02-1.67	0.008*	1.09	1.07-1.15	0.031*
Diabetes						
Non-DM group	1.0[REF]			1.0[REF]		
DM group	2.03	1.24-3.33	0.005*	1.89	1.09-3.27	0.021*
PV (gm)	0.99	0.97-1.01	0.115			
iPSA(ng/ml)	0.97	0.95-1.20	0.601			
Pathology GS						
≤ 6	1.0[REF]					
7-10	1.09	0.85-1.38	0.483			
Surgical margin						
negative	1.0[REF]					

positive	1.07	0.68-1.67	0.759			
NVB						
preserved	1.0REF					
not preserved	0.93	0.91-1.37	0.493			
Pathology stage						
T2	1.0REF					
T3-T4	1.10	0.98-1.29	0.627			

Abbreviations: SHR: subdistribution hazard ratio; CI: confidence interval; BMI: body mass index; DM: diabetes mellitus; PM: prostate volume; iPSA: initial prostate specific antigen; GS: Gleason score; SM: surgical margin; NVB: neurovascular bundle

Normality of the parameters was tested using Kolmogorov–Smirnov test. Fisher's exact test was applied to test qualitative data and Mann–Whitney U-test was used to test numerical variables. The probabilities of BCR-free survival in the two cohorts were estimated using Kaplan–Meier survival curves and log-rank tests. Univariate and multivariate logistic regression analyses were performed to identify factors that were predictive of outcomes. MedCalc version 16.2.1 for Windows (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis, and P < 0.05 was considered statistically significant.

III. RESULTS

Among the enrolled 363 patients, 84 and 279 patients were classified into the DM and non-DM cohorts, respectively (Table 1). Pre-OP American Society of Anesthesiologists scores, prostate volumes, iPSA levels, and D'Amico's risk classification did not differ significantly between the two cohorts. However, patients in the DM cohort were older (68 vs. 65 years, p = 0.002) and had higher BMIs (26.2 vs. 24.8, p = 0.009). Patients in the DM cohort also had a more advanced clinical stage. Furthermore, 35.7% of the DM patients were classified as clinical T3a, meaning that the tumor extended beyond the prostate capsule during pre-OP evaluation, whereas only 26.5% of the non-DM patients were classified as clinical T3a (p < 0.001). Similarly, tumor grading was higher in the DM cohort; 26.2% of the DM patients had biopsy Gleason scores ≥ 8–10, whereas the corresponding proportion in the non-DM cohort was only 14.3% (p = 0.019).

In terms of intraoperative and post-OP data (Table 2), the two cohorts did not differ significantly in operative time, blood loss, days of hospital stay, blood transfusion rate, surgical complication rate, lymph node positive rate, and surgical margin positive rate. However, the final pathology stage differed between the cohorts. The proportion of T3a-4 patients in the DM and non-DM cohorts were 48.8% and 29.8%, respectively (p = 0.002). In other words, in the final pathology report, the tumor extended beyond the prostate capsule in almost half the DM patients, whereas the corresponding proportion was only less than one-third in the non-DM patients. Similarly, the distributions of the final pathology Gleason scores differed between the cohorts: 20.2% of DM patients had Gleason scores ≥ 8–10, but the corresponding proportion in the non-DM cohort was 12.9% (p = 0.048).

In total, 36 patients (10 DM and 26 non-DM patients) were identified as having a BCR during the mean follow-up time of 30.1 months. The mean time to BCR was 9.5 months. Fig 1 depicts the BCR-free survival curves; no significant differences were observed between the two cohorts. Data on recovery of urinary continence after RARP is presented in Fig 2. Non-DM patients recovered faster than did DM patients. Although no significant differences were noted at post-OP 3 months (p = 0.056), a larger percentage of non-DM cohort recovered from urinary incontinence at post-OP 6 months (66.5% vs. 45.0%, p < 0.001) and post-OP 12 months (94.9% vs. 62.8%, p < 0.001). Using univariate and multivariate logistic regression analyses, we discovered that DM and BMI were the only two independent factors that affected urinary incontinence at post-OP 6 months (Table 3).

IV. DISCUSSIONS

Over the past 30 years, the population of DM patients has more than doubled globally, making it one of the most crucial public health challenges worldwide.12 Approximately 382 million people worldwide were estimated to have DM in 2013, equivalent to 8.3% of the entire adult population.12 CaP is the leading cancer for men in the United States and the second most common malignancy affecting men worldwide.13 DM and CaP are two major growing health problems affecting millions of men worldwide. Consequently, the evaluation and management of patients with concomitant DM and CaP is a crucial and no that cannot be ignored. The purpose of this study was to evaluate whether DM affects the outcome of patients receiving RARP for CaP. After most traditional open surgeries, diabetic patients are highly associated with longer hospital stays, higher health care resource utilization, higher rate of surgical complications, and higher perioperative mortality.1-4 However, these findings were not observed in our study; our data revealed no significant differences in operative time; blood loss; days of hospital stay; and blood transfusion, surgical complication, and surgical margin positive rates between the two cohorts. In other words, RARP exerts less surgery-related physical stress and tissue damage on patients and therefore DM patients could achieve a relatively more favorable surgical result.

The relationship between DM and CaP is interesting. Unlike several diseases that are related to DM, for unknown reasons, hyperglycemia protects men from CaP. A meta-analysis of 19 population-based studies published between 1971 and 2005 showed that men with DM had a 16% lower risk of CaP.14 Another meta-analysis provided strong evidence for type 2 diabetes being significantly inversely associated with CaP development.15 Gong et al. showed that, for yet unknown reasons, type 2 DM reduced the risk of high-grade and low-grade cancers by 28% and 47%, respectively.16 Some studies have found that lower circulating testosterone is associated with diabetes and that changes in insulin-like growth factor-1 probably affects the development of cancer cells in the prostate.17 However, somewhat paradoxically, observational evidence indicates that DM is linked to increased CaP aggressiveness and worse outcomes.18 In a prospective study of men with CaP, even well-treated diabetes was associated with a higher risk of cancer fatality and all-cause mortality.19 Although our study focused on localized CaP, we found that DM patients were at an advanced cancer stage at diagnosis; moreover, compared with the non-DM cohort, a larger proportion of patients in the DM cohort had cancers extending beyond the prostatic capsule as well as patients with high Gleason scores 8–10. This finding is consistent with the literature, implying that CaP in DM patients is more aggressive in nature and has worse outcomes. However, BCR-free survival curves in the two cohorts were similar during the 30-month follow-up period. We suspect that the curves would diverge over a longer observation period.

Compared with the control cohort, DM patients had poorer recovery from incontinence following RARP. In a systematic meta-analysis that employed the using a no-pad definition, 12-month urinary incontinence ranged from 4%–31%, with a mean of 16%.20 The post-OP urinary continence rate in our study is similar to most of the recent studies. However, the continence rate is rather poor in the DM cohort; patients with DM took longer to regain continence after RARP than did non-DM patients, and only 62.8% of DM patients had achieved urinary continence at post-OP 12 months. Several predictors such as age, BMI, comorbidity index, lower urinary tract symptoms, and prostate volume were the most relevant pre-OP predictors of urinary incontinence after RARP have been studied and addressed in the literature but the conclusions are inconsistent.20 Our study revealed that DM patients were older in age and had a higher BMI, which contributed to poor post-OP urinary continence rate. In addition, DM was an independent factor for urinary incontinency at post-OP 6 months. Regaining urinary continence after RARP requires recovery from destruction of the sphincter system, supporting system, and nerve system and from disorders of the bladder detrusor muscles.21 However, DM is not conducive to all these conditions. According to Yamaguchi et al., the bladder of a DM patient is characterized by impaired bladder sensation, increased bladder capacity, and decreased detrusor contractility.22 Long-standing hyperglycemia might also lead to bladder storage symptoms through sympathetic nervous system activation and neuronal apoptosis.23 DM was the most common cause of peripheral neuropathy.24 The altered metabolism of glucose, tissue ischemia, superoxide-induced free-radical formation, and impaired axonal transport are all mechanisms that have been proposed to contribute to the peripheral nerve dysfunction seen in patients with DM.24 Cianfarani et al. reported that diabetes impairs adipose tissue-derived stem cells, resulting in the release of lower amounts of hepatocyte growth factor, vascular endothelial growth factor-A, and insulin-like growth factor-1, all of which are critical for wound healing and tissue reconstruction.25 Consequently, compared with the control cohort, DM patients have poor recovery from incontinence after RARP. 26

We recognize several disadvantages and limitations in our study. First, this study had a relatively small patient cohort and a short observation period. Within the average 30.1 months of observation, we could not obtain objective data on BCR-free survival, cancer-specific survival, and overall survival. This observation is ongoing, and any differences between the cohorts will be reported in the future. Second, we used dichotomously classified the patients into the DM and non-DM cohorts. However, our database lacks data on patients' diabetes duration, treatment methods, and how well their blood sugar was controlled, all of which are variables potentially affecting the surgical outcomes. Finally, pre- and post-OP urodynamic studies were not conducted in our routine practice. Pre-OP urodynamic studies would have helped screen the underlying urinary dysfunction, and post-OP urodynamic studies would have clarified how RARP affects urinary continence. Additional studies are warranted to obtain a more objective result. Despite these limitations, our study is valid because it clearly demonstrates that DM is an independent predictor of incontinence after RARP.

V. CONCLUSIONS

Our study confirms our hypothesis that DM patients can achieve a favorable surgical outcome after RP with the utility of da Vinci robotic arms. No comparative differences were noted in days of hospital stay, surgical complication rate, and surgical margin positive rate between the study and control cohorts. In addition, their BCR-free survivals were similar. However, diabetes is an unfavorable factor affecting recovery from post-OP urinary incontinence. DM patients should be carefully counseled regarding the negative effect of DM on post-OP continence after RARP.

VI. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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FIG LEGENDS

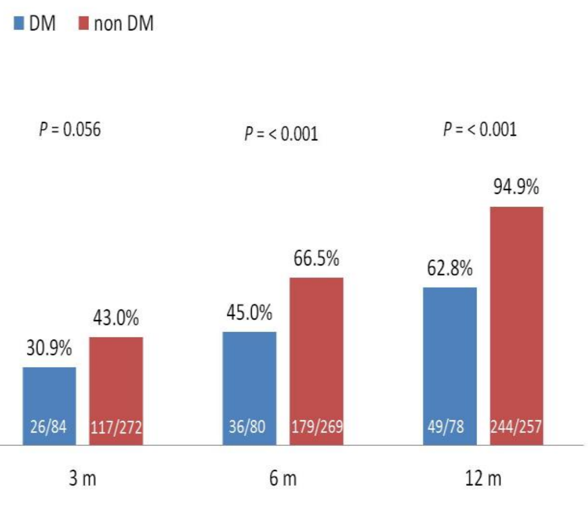

Fig 1: Post-OP Urinary Continence At Different Time Points.

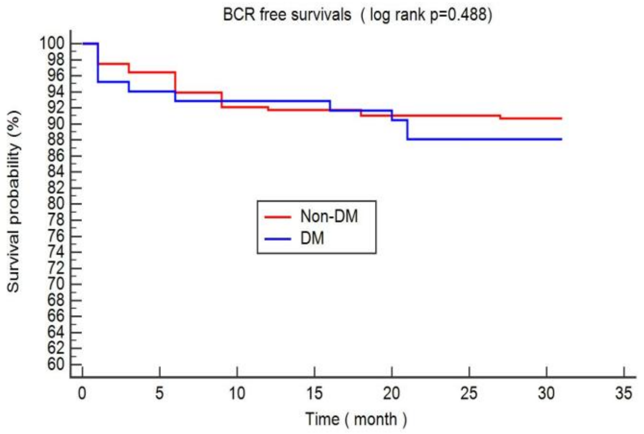

Fig 2: BCR-Free Survival In The Two Cohorts.

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