Clinical and oncological outcomes of robot-assisted radical prostatectomy with nerve sparing vs. non-nerve sparing for high-risk prostate cancer cases

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Abstract. Robot-assisted radical prostatectomy (RARP) is one of the most widely used procedures for localized prostate cancer (PCa). In the present study, the clinical and oncological outcomes of RARP with bilateral or unilateral nerve sparing (NS) for D'Amico high-risk PCa cases were assessed. Among the 767 cases who received RARP at Fujita Health University Hospital between August 2009 and December 2016, 230 high-risk PCa cases who were observed for >6 months comprised the retrospective study cohort. Bilateral NS was performed with the bilateral neurovascular bundle in eight, unilateral in 125 and none in 97 cases. Perioperative parameters [surgery time, console time, estimated blood loss, pathological stage, positive lymph node metastases [pN (+)], and surgical margin positivity] did not exhibit significant differences between the NS and non-NS cohorts. During a median follow-up time of 25 months, the 1- and 3-year biochemical recurrence (BCR)-free survival rates in the NS/non-NS cohorts were 84.4/86.0 and 72.7/75.0%, respectively. There were no significant differences identified between the two groups at each time period. According to multivariate analysis, the resection margin was an important factor for time to BCR, regardless of the NS technique used. The numbers of pads used daily at 3 and 6 months after RARP between the NS/non-NS cohorts were 1.1/1.5 and 0.6/1.0, respectively (P=0.045 and P=0.009), suggesting that the NS technique resulted in significantly improved outcomes regarding urinary continence recovery. In selected high-risk PCa cases, the NS technique resulted in equivalent oncological outcomes and improved urinary continence compared with the non-NS RARP group.

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Introduction

Prostate cancer (PCa) was the most commonly diagnosed and third most fatal cancer among males in 2008 in the developing world (1). Prostate-specific antigen (PSA) is widely used as a tumor marker and aids the diagnosis of PCa at an early stage (2). The most common curative treatment for localized PCa is radical prostatectomy (RP) (3), with robot-assisted radical prostatectomy (RARP) becoming a widely adopted procedure. According to a number of previous studies, RARP improves perioperative and functional outcomes, and at least comparable oncologic outcomes compared with open RP in the localized PCa (4-8). Pound *et al* (9) contributed in the establishment of the natural history of high-risk PCa in surgically-treated cases. After a median of 8 years, Pound *et al* (9) identified biochemical recurrence (BCR) in 15% of cases and reported the development of metastatic disease in 34% of the cohort. In survival analysis, time to biochemical progression, the Gleason score (GS) (10) and PSA doubling time are predictive factors of the probability and time to develop metastatic disease (9). Boorjian *et al* (11) reported that the risks of BCR and cancer-specific mortality are 3.3 and 11.5 times greater, respectively, in cases with high-risk PCa compared with cases of low-risk PCa. Therefore, high-risk localized PCa cases have been formerly characterized as having an increased risk of metastasis and requiring complex treatments, such as surgery (12). However, a number of previous studies support surgery as monotherapy for high-risk localized PCa cases and have revealed optimal outcomes (13,14).

In the RARP procedure, the excision of the neurovascular bundle (NVB) is often performed in patients with intermediate- or high-risk PCa to reduce the probability of a positive surgical margin (PSM) (15). When performing nerve sparing (NS) RARP, there should be a number of cases who obtain successful oncological and functional outcomes, since the 'high-risk' group is notably heterogenous (16).

The present study selected high-risk PCa cases based on original criteria. The patients underwent RARP with NS, to evaluate the feasibility, oncologic safety as compared with non-NS in the intermediate-term and functional outcomes.

Materials and methods

Study design. A total of 767 male cases received RARP at Fujita Health University Hospital (Toyoake, Japan) between August 2009 and December 2016. Median age was 66 years old and the range was from 45 to 88 years. Among the 767 cases screened for the present study, 230 high-risk PCa cases who were observed for >6 months comprised the study cohort for retrospective analysis. The mean age for the high-risk cohort is provided in Table I. All cases had non-metastatic and clinically high-risk PCa, as defined according to the D'Amico risk stratification system (17), and exhibited at least one of the following: i) A serum PSA level of >20 ng/ml (measured using a American Cancer Society-PSA kit (Ciba Corning Diagnostics Corp.) with chemiluminescent immunoassay, according to the manufacturer's instructions; ii) GS ≥8; or iii) clinical stage ≥T2c. TNM classification was defined using the American Joint Committee on Cancer staging manual (18). The following clinical variables were evaluated: Age, serum PSA level (ng/ml), clinical T stage, GS and neoadjuvant treatment. The criteria for NS RARP were: Bilateral NS, at least two factors (PSA <10 ng/ml, cT1c, <GS 7, <30% of positive-core ratio on the NS side); unilateral NS, <cT2b or <30% positive-core ratio on the NS side; non-NS, other than the aforementioned criteria. All patients received pelvic lymph node dissection. Surgery time, estimated blood loss (EBL), console time, pathological stage (pT stage), positive lymph node metastases [pN (+)], and surgical margin positivity were recorded to assess perioperative parameters. The schedule after RARP surgery consisted of a PSA assay every 3 months for the first 2 years, every 6 months for the following 3 years and annually thereafter. The number of pads used daily, at 3 months and 6 months after RARP, was checked to assess urinary continence recovery. The onset of BCR was defined as the date when the serum PSA level was >0.2 ng/ml. The time to events was calculated from the day of RARP.

The protocol of the present study was approved by the Ethics Committee of Fujita Health University Hospital (approval no. HM 18-115), and the present study was performed in accordance with the ethical standards laid down in the most recent version of the Declaration of Helsinki.

Statistical analysis. All values are presented as the mean ± standard deviation, and statistical comparison of the results was performed using a Student's t-test, a Mann-Whitney test, the χ^2 test or Fisher's exact test. BCR-free survival was estimated using the Kaplan-Meier method, and a log-rank test was used to compare the survival curves. To assess prognostic factors, univariate analysis was performed using the following variables: Age, initial PSA, cT stage, GS, NS, neoadjuvant hormonal therapy (NHT) and resection margin. Significant preoperative variables in the univariate analysis were included in the multivariate analysis using a Cox proportional hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference. All data were analyzed using IBM SPSS Statistics version 23 (IBM Corp.).

Results

Clinical characteristics of cases. Out of the 230 high-risk cases, 133 underwent RARP with NS, while 97 underwent RARP without NS (Table I). The mean age in the NS and non-NS cohorts was 64.6 and 67.1 years, respectively. The serum PSA level in the NS and non-NS cohorts was 10.2 and 14.5 ng/ml, respectively. The clinical stage with the highest number of cases, in each cohort, was T2c. GSs of 8 in the NS cohort and 7 in the non-NS cohort were observed most frequently. For neoadjuvant treatment, 68 cases (51.1%) in the NS cohort and 41 cases (42.3%) in the non-NS cohort did not receive NHT. Among the factors of age, PSA level, T stage, GS and NHT, only NHT exhibited no significant difference between the two cohorts (P=0.102).

Perioperative parameters. The mean operation times in the NS and non-NS cohorts were 171 and 179 min, respectively. The mean console times in the NS and non-NS cohorts were 131 and 137 min, respectively. The mean EBL was 177 ml in the NS cohort and 171 ml in the non-NS cohort. There were no significant differences identified for these three factors between cohorts (operation time, P=0.189; console tine, P=0.259; EBL, P=0.697; Fig. 1).

Urinary continence recovery. In the present study, urinary continence recovery was assessed by evaluating the quantity of pads used daily at 3 and 6 months after RARP. The mean ± standard deviation quantity of pads used daily at 3 months in the NS/non-NS cohorts was 1.12±1.08/1.48±1.11, and that at 6 months was 0.61±0.87/1.03±1.05 (Fig. 2). As expected, the NS procedure resulted in significantly improved outcomes regarding urinary continence.

Oncological findings. Oncological findings, including pT stage, PSM, pN (+) and BCR, are shown in Table II. pT stage T2c was most frequent in the NS and non-NS cohorts. The overall PSM rate was 22.6% (Fig. 1D), with rates of 18.0% in the NS group and 28.9% in the non-NS group. No significant difference in the PSM rates between cohorts was observed (P=0.053). The PSM rates in the NHT/non-NHT cohorts were 24.8 and 20.2%, respectively, with no significant differences identified between them (P=0.406). For pN (+), only one case was observed in each cohort. The BCR rates in the NS and non-NS cohorts were 23.3 and 19.6%, respectively, with no significant difference identified between them (P=0.501).

BCR-free survival rates. BCR-free survival rates in the NS and NHT categories are indicated in Figs. S1 and S2. A total of 16 cases (7.0%) were observed with PSA ≥0.2 ng/ml at the first postoperative measurement. The BCR-free survival rates at 3 years after RARP in the NS and non-NS cohorts were 72.7 and 75.0%, respectively (Fig. S1). When BCR-free survival rates within the NS and NHT categories were compared, no significant differences were observed (NS, P=0.6572; NHT, P=0.0812; Figs. S1 and S2). These results suggest that the NS and NHT treatments did not affect cancer control in D'Amico high-risk PCa cases.

Cox regression analysis for time to BCR. When risk parameters in high-risk PCa cases were compared, the factors of age, initial PSA, GS 7, and resection margin exhibited significant differences. In multivariate analysis, the factors of age, initial PSA, GS 8-10, and resection margin were associated with time to BCR, whereas the factors of cT stage, NS and NHT were not

Table I. Clinical characteristics of NS and non-NS robot-assisted radical prostatectomy cases.

Baseline patient characteristics	NS cohort (n=133), n (range or %)	non-NS cohort (n=97), n (range or %)	P-value
Mean age, years	64.6 (45-76)	67.1 (49-77)	<0.01[a]
Mean serum PSA level, ng/ml	10.2 (1.6-57.1)	14.5 (3.9-158.3)	0.01[a]
T stage			
cT1c	12 (9.0)	1 (1.0)	<0.01[a]
cT2a	31 (23.3)	7 (7.2)	
cT2b	37 (27.8)	9 (9.3)	
cT2c	46 (34.6)	65 (67.0)	
cT3a	7 (5.3)	14 (14.4)	
cT3b	0 (0.0)	1 (1.0)	
Gleason score			
6	12 (9.0)	15 (15.5)	<0.01[a]
7	43 (32.3)	51 (52.6)	
8	55 (41.4)	17 (17.5)	
9	23 (17.3)	12 (12.4)	
10	0 (0)	2 (2.1)	
Neoadjuvant treatment			
Anti-androgen monotherapy	46 (34.6)	29 (29.9)	0.10
LHRH agonist alone	5 (3.8)	4 (4.1)	
Combined androgen blockade	11 (8.3)	16 (16.5)	
Others	3 (2.3)	7 (7.2)	
None	68 (51.1)	41 (42.3)	

[a]P<0.05. LHRH, luteinizing hormone-releasing hormone; NS, nerve sparing; PSA, prostate-specific antigen.

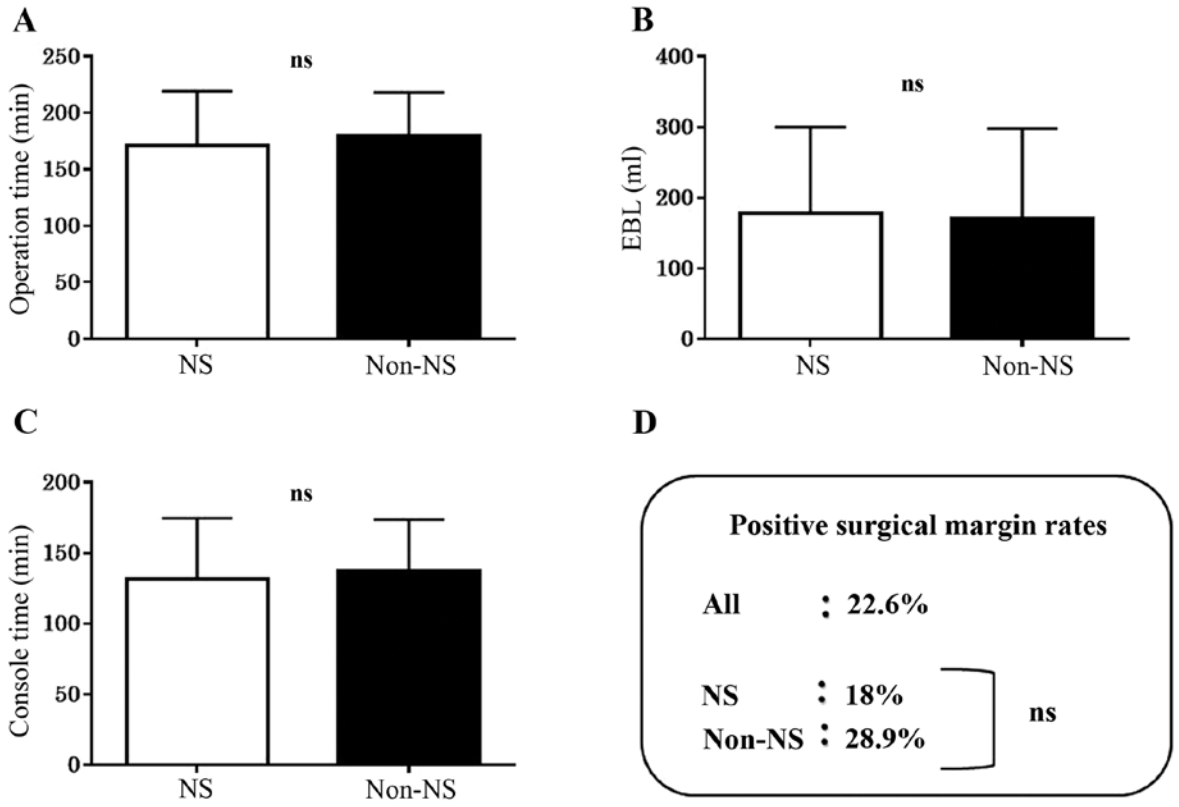

Figure 1. Perioperative parameters. (A) Operation time. (B) EBL. (C) Console time. (D) Surgical margin positivity. EBL, estimated blood loss; NS, nerve sparing; ns, not significant.

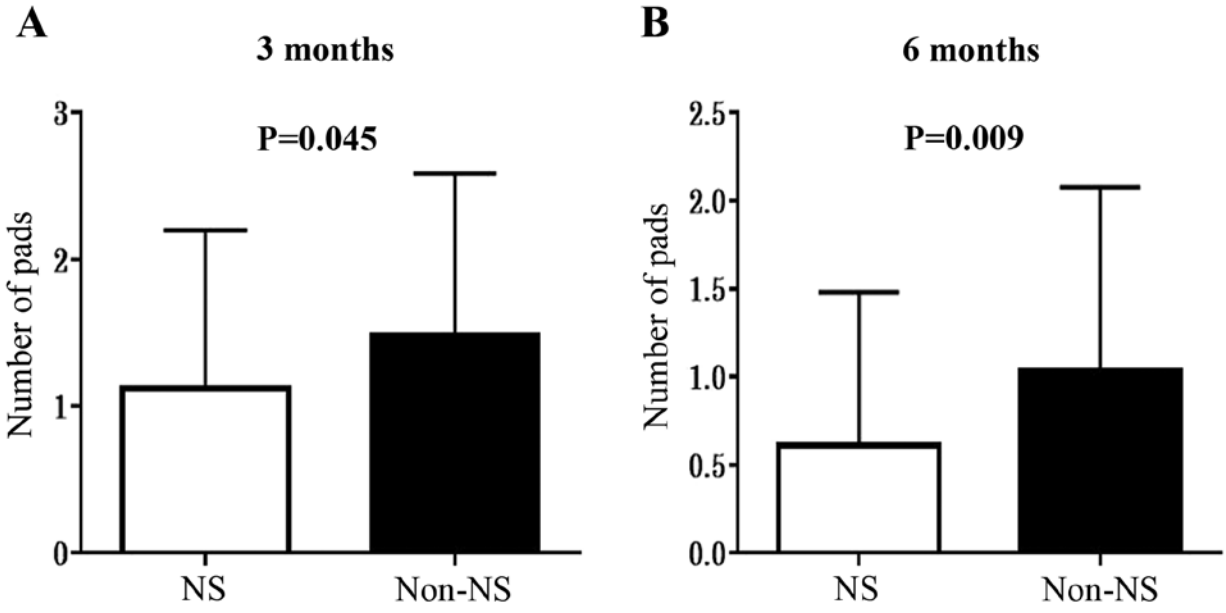

Figure 2. Urinary continence recovery after robot-assisted radical prostatectomy. (A) At 3 months. (B) At 6 months. NS, nerve sparing.

associated with time to BCR (Table III). These results suggest that NS and NHT did not affect BCR-free survival following RARP in high-risk PCa cases.

Discussion

Walsh (19) was the first to demonstrate that NVBs run posterolateral to the prostate between two layers of lateral pelvic fascia, the prostatic fascia medially and levator fascia laterally, in an intraoperative study. The effect of the preservation of the NVBs during RP on erectile function is evident (20); however, its influence on urinary continence remains unclear. According to a recent cohort study, the NS technique is not associated with worse cancer outcomes but is associated with improved urinary and erectile function (21). Additionally, Michl *et al* (22) indicated that the meticulous apical dissection associated with the NS technique rather than the preservation of the NVBs, can impart a positive impact on long-term urinary continence rates.

RP with NS is challenging for D'Amico-classified high-risk PCa cases, as such cases are more likely to have 'non-organ-confined disease', which possibly leads to BCR (23). However, Shikanov *et al* (24) reported that even PCa cases whose preoperative biopsy GS is 8 had organ-confined (pT2N0) disease in 47% of this population. These findings indicate that the 'high-risk' group is heterogeneous, and it is important to select cases in the high-risk group when performing RP with NS. The criteria of RP with NS for high-risk PCa cases are unclear. In the present study, the criteria for NS RARP were: Bilateral NS, at least two factors (PSA <10 ng/ml, cT1c, <GS 7, <30% of positive-core ratio on the NS side); unilateral NS, <cT2b or <30% positive-core ratio on the NS side and non-NS, other than the aforementioned criteria. However, a recent study has reported their criteria as follows: Complete, non-palpable disease with <3 cores involved on the prostate biopsy; partial, non-palpable disease with <4 cores involved on the prostate biopsy; and none, clinically palpable disease with ≥4 cores involved on the prostate biopsy and intraoperative visual cues of locally advanced disease (25).

In the present study, there were no significant differences between the perioperative parameters of operation time, EBL, console time and PSM rates in the NS and non-NS cohorts of high-risk cases. Yossepowitch *et al* (15) reported that the long-term impact on survival of patients with PCa after radical prostatectomy is variable and largely affected by risk modifiers other than surgical margin positivity; however, it is still considered as an adverse oncological outcome. The overall PSM rate in the present study was 22.6%, whereas PSM rates have been reported as 35% (12-53%) following RARP in high-risk PCa cases in previous studies (24,26,27). The present study demonstrated that the factor of PSM was important for time to BCR regardless of the NS technique in RARP in high-risk cases. A number of studies have reported significant positive associations between NS and surgical margin positivity; however, other studies have not identified them (6,7,15). As a result, the association between NS and surgical margin positivity remains controversial.

In the context of NHT treatment, a number of previous studies have reported favorable BCR-free survival in high-risk PCa cases treated with a neoadjuvant gonadotropin-releasing hormone agonist or antagonist, and estramustine phosphate followed by RP surgery (28,29). However, in the present study, NHT treatment did not affect BCR-free survival rates in D'Amico high-risk PCa cases.

The role of NS during RARP in high-risk PCa cases has been reported in only a few previous studies (30,31). Kumar *et al* (25) reported that the overall BCR rate, at a mean follow-up of 24.3 months, was 19.2% and the mean time to BCR was 7.9 months in high-risk PCa cases, which is comparable to other previous studies (24,26,27,32,33). Kumar *et al* (25) performed RARP with NS in 89.4% of cases of high-risk PCa without compromising the PSM/BCR rate, while also providing improved postoperative continence and potency outcomes, using preoperative clinical variables along with intraoperative

Table II. Oncological findings of NS and non-NS robot-assisted radical prostatectomy cases.

Oncological findings	NS cohort (n=133), n (%)	Non-NS cohort (n=97), n (%)	P-value
Pathological stage			
pT0	2 (1.5)	2 (2.1)	0.358
pT2a	23 (17.3)	9 (9.3)	
pT2b	12 (9.0)	5 (5.2)	
pT2c	69 (51.9)	61 (62.9)	
pT3a	15 (11.3)	11 (11.3)	
pT3b	12 (9.0)	8 (8.2)	
pT4	0 (0.0)	1 (1.0)	
Positive surgical margin	24 (18.0)	28 (28.9)	0.053
pN(+)	1 (0.8)	1 (1.0)	0.823
Biochemical recurrence	31 (23.3)	19 (19.6)	0.501

NS, nerve sparing.

Table III. Cox regression analysis for time to biochemical recurrence.

	Univariate analysis		Multivariate analysis	
Characteristic	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	0.95 (0.91-0.99)	0.019[a]	0.95 (0.91-0.99)	0.024[a]
Initial PSA	1.02 (1.01-1.03)	0.002[a]	1.01 (1.00-1.03)	0.042[a]
cT stage				
T1c, T2a, T2b				
T2c	0.71 (0.29-1.75)	0.462		
T3a, T3b	0.48 (0.19-1.21)	0.120		
Gleason score				
6				
7	0.23 (0.05-0.94)	0.041[a]	0.25 (0.06-1.03)	0.055
8-10	0.58 (0.32-1.06)	0.077	0.50 (0.27-0.92)	0.025[a]
Nerve sparing				
No				
Yes	0.93 (0.52-1.64)	0.789		
Neoadjuvant hormonal therapy				
No				
Yes	0.59 (0.33-1.04)	0.068		
Resection margin				
None				
Positive	0.43 (0.25-0.77)	0.004[a]	0.43 (0.24-0.78)	0.006[a]

[a]P<0.05. HR, hazard ratio; PSA, prostate-specific antigen.

visual cues as a guide for NS. Consistent with these results, the present study reported that NS RARP in high-risk PCa resulted in equivalent oncological outcomes compared with non-NS RARP according to the estimation of BCR-free survival rates. Additionally, we demonstrated that NS and NHT did not affect BCR-free survival following RARP of high-risk PCa cases.

Limitations of the present study included the retrospective collection, its small sample size of a single center, a lack of well-designed analyses and short follow-up duration. Therefore, further studies are required to demonstrate the clinical utility of RARP with NS in high-risk PCa cases in the future.

In conclusion, NS RARP could provide intermediate-term oncological safety and successful functional outcomes in selected high-risk PCa cases based on the original criteria used in the present study. However, rigorous selection is required when performing NS RARP in high-risk PCa cases.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KT, MS, HS, MK and RS conceived and designed the study. KT, KF, TJ, MN, MH, KZ, TN, MI and NF acquired the data. KT, MS, KZ and TN drafted the manuscript. KT, MS, KZ and MK performed the statistical analysis. RS supervised the study.

Ethics approval and consent to participate

The protocol of the present study was approved by the Ethics Committee of Fujita Health University Hospital (approval no. HM 18-115), and the present study was performed in accordance with the ethical standards laid down in the most recent version of the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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