

Surgical and Oncological Outcomes of Robot-Assisted Radical Prostatectomy as Part of Multimodal Therapy for NCCN Very High-Risk Prostate Cancer: A Single-Institution Retrospective Analysis

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Abstract

Purpose

Very high-risk prostate cancer (VHR-PCa) carries a poor prognosis, and the optimal integration of radical prostatectomy with neoadjuvant therapy (NAT) and adjuvant therapy (AT) remains undefined [1, 2]. We report perioperative and oncological outcomes of robot-assisted radical prostatectomy (RARP) as part of multimodal therapy for NCCN VHR-PCa and examine the association of NAT and AT with survival.

Methods

Of 209 patients with VHR-PCa who underwent RARP at a single Japanese institution (2019–2025), 88 with sufficient follow-up for survival analysis were retrospectively reviewed; the remainder were excluded chiefly for insufficient follow-up time. Perioperative outcomes, urinary continence, overall survival (OS), and progression-free survival (PFS) were assessed, and outcomes were compared by NAT and AT status using Kaplan-Meier analysis with log-rank testing (IRB Approval No. 1439).

Results

Median age was 71.0 years and median initial PSA was 18.7 ng/mL. Median operative time was 247.5 min and median blood loss was 60 mL. The positive surgical margin rate was 39.7%, and lymph node metastasis was present in 17.0%. At last follow-up (median 44.6 months), 73.8% of patients used fewer than one pad per day. Five-year OS was 97.6% and cancer-specific survival was 100%; 5-year PFS was 37.1%. NAT was associated with a numerically higher 5-year PFS (41.0% vs. 26.7%) that did not reach statistical significance ($p = 0.345$); AT was not associated with improved PFS ($p = 0.239$), likely reflecting preferential use of AT in patients with more adverse pathology.

Conclusions

RARP achieved favorable perioperative safety, continence, and oncological control as part of multimodal therapy for VHR-PCa. The numerical PFS advantage associated with NAT warrants confirmation in larger, prospective, multi-institutional studies with standardized treatment protocols.

1 | Introduction

Prostate cancer is one of the most diagnosed malignancies in men worldwide, and clinically advanced disease continues to pose significant management challenges. The National Comprehensive Cancer Network (NCCN) classifies prostate cancer into distinct risk groups to guide treatment selection. Very high-risk prostate cancer (VHR-PCa) represents the most aggressive locally advanced category and is defined by at least one of the following features: clinical stage cT3b–cT4, primary Gleason pattern 5, two

or three high-risk features (cT3a, Grade Group 4–5, or PSA > 20 ng/mL), or more than four biopsy cores with Grade Group 4 or 5.[1]

VHR-PCa is associated with a substantially elevated risk of biochemical recurrence, distant metastasis, and cancer-specific mortality compared to lower-risk categories.[1, 2] Because of the aggressive nature of this disease, multimodal therapy combining local treatment with systemic androgen deprivation therapy (ADT) or novel androgen receptor signaling inhibitors (ARSIs) is generally advocated.[2, 3] While radiotherapy combined with ADT has historically been the standard of care for locally advanced prostate cancer, robot-assisted radical prostatectomy (RARP) has emerged as a viable and increasingly used surgical alternative, with several studies demonstrating favorable oncological and functional outcomes.[6, 7]

Comparative evidence suggests that radical prostatectomy may provide comparable or superior oncological outcomes relative to radiotherapy for high-risk disease, particularly in terms of cancer-specific survival.[8, 9] Nevertheless, the proper integration of local surgery with systemic neoadjuvant and adjuvant treatment remains under investigation. Multiple trials have evaluated neoadjuvant hormonal therapy and novel ARSI-based regimens, but results have been heterogeneous and no standard multimodal protocol has been established.[10, 11]

We herein report our single-institution experience with RARP-based multimodal therapy for NCCN VHR-PCa at Saiseikai Kumamoto Hospital. The primary objectives of this study were: (1) to evaluate surgical and oncological outcomes of RARP in patients with VHR-PCa; and (2) to assess the impact of NAT and AT on OS and PFS.

2 | Methods

2.1 | Study Design and Patient Selection

This study employed a retrospective single-institution design. Consecutive patients with VHR-PCa who underwent RARP at Saiseikai Kumamoto Hospital between January 2019 and March 2025 were identified from a prospectively maintained surgical database. VHR-PCa was defined in accordance with the NCCN Clinical Practice Guidelines in Oncology (Prostate Cancer, Version 2024–2025) as the presence of at least one of the following: clinical stage cT3b–cT4, primary Gleason pattern 5, two or three high-risk features, or more than four biopsy cores with Grade Group 4 or 5.[1] The study was conducted with institutional review board approval (Approval No. 1439).

A total of 209 patients with VHR-PCa underwent RARP during the study period. Of these, 121 were excluded from the oncological outcome analysis, primarily because they underwent surgery within approximately the final 1–2 years of the study period and had therefore not yet accrued sufficient follow-up time for meaningful survival assessment, with a smaller number excluded because of incomplete follow-up records at referring clinics. The remaining 88 patients with adequate follow-up data were included in the final analysis. All surgical procedures were performed by experienced robotic urological

surgeons using a standardized transperitoneal approach. Extended pelvic lymph node dissection was performed in the majority of cases. [15]

2.2 | Neoadjuvant and Adjuvant Treatment Protocols

NAT was administered prior to surgery based on physician discretion and multidisciplinary discussion. NAT regimens included: bicalutamide monotherapy (n = 30, 34.1%), combined androgen blockade (CAB; n = 32, 36.4%), and ARSIs or other agents including chemohormonal therapy (n = 3, 3.4%). Twenty-three patients (26.1%) did not receive NAT.

AT was initiated postoperatively based on pathological findings and physician judgment. AT regimens included: CAB (n = 18, 20.5%), ARSIs or other agents (n = 11, 12.5%), and bicalutamide monotherapy (n = 1, 1.1%). Five patients (5.7%) received adjuvant radiation therapy (ART). Fifty-two patients (59.1%) did not receive any AT. For subgroup analysis, patients were classified into four groups: Group A (NAT-/AT-, n = 14), Group B (NAT-/AT+, n = 9), Group C (NAT+/AT-, n = 38), and Group D (NAT+/AT+, n = 27).

2.3 | Outcome Assessment

Perioperative outcomes included operative time, estimated blood loss, PSM rate, and lymph node metastasis rate. Urinary continence was assessed at the final follow-up visit and classified as: pad-free (no pad), safety pad (prophylactic, not wet), one pad per day, or two or more pads per day.[12] Functional continence was defined as use of fewer than one pad per day.

Oncological outcomes included OS, PFS, and cancer-specific survival (CSS). Biochemical recurrence (BCR) was defined as a serum PSA level of 0.2 ng/mL or greater after reaching a nadir, confirmed on a subsequent measurement. The date of BCR was used as the event date for PFS analysis.

2.4 | Statistical Analysis

For comparisons of preoperative patient characteristics between NAT groups (Section 3.2) and postoperative pathological features between AT groups (Section 3.3), the Mann-Whitney U test was applied for continuous variables (age, initial PSA, and number of GG4/5-positive biopsy cores), and Fisher's exact test or Pearson's chi-square test was used for categorical variables (biopsy grade group, clinical T stage, clinical nodal status, pathological T stage, lymph node status, extraprostatic extension, surgical margin status, pathological treatment response, pathological downstaging, and adjuvant radiation therapy). All tests were two-sided, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using Python (version 3.10) with the SciPy library (scipy.stats).

OS and PFS were estimated using the Kaplan-Meier method. Differences in survival between groups were evaluated using the log-rank test. Survival analyses were performed for the overall cohort and then stratified by NAT status (NAT + vs. NAT-), AT status (AT + vs. AT-), and the combined four-group classification (Group A: NAT-/AT-, Group B: NAT-/AT+, Group C: NAT+/AT-, Group D: NAT+/AT+).

3 | Results

3.1 | Patient Characteristics

Eighty-eight patients with NCCN VHR-PCa met the inclusion criteria and were analyzed. Patient demographics and clinical characteristics are presented in Table 1. The median patient age was 71.0 years (range, 52–83), and the median iPSA was 18.7 ng/mL (range, 4.4–234.67). The median follow-up duration was 44.6 months (range, 6–85 months).

With respect to preoperative Grade Group, 5 patients (5.7%) had GG3 or lower, 23 (26.1%) had GG4, and 60 (68.2%) had GG5. Clinical T staging showed that the majority of patients had cT3a disease (n = 56, 63.6%), followed by cT2 (n = 15, 17.0%), cT3b (n = 14, 15.9%), T4 (n = 2, 2.3%), and T1c (n = 1, 1.1%).

3.2 | Preoperative Patient Characteristics by NAT Status

To evaluate baseline patient profiles associated with NAT allocation, preoperative characteristics were compared between the NAT-positive (n = 65) and NAT-negative (n = 23) groups (Table 2). The NAT group had a significantly higher median iPSA (24.2 vs. 12.4 ng/mL, p = 0.001), a greater median number of GG4/5-positive biopsy cores (5 vs. 3, p < 0.001), and a higher proportion of cT3b–T4 disease (24.6% vs. 0%, p = 0.009). Age and GG distribution were comparable between groups. These findings indicate that NAT was preferentially administered to patients with more aggressive preoperative disease features.

3.3 | Postoperative Pathological Characteristics by AT Status

To characterize the selection bias associated with AT allocation, postoperative pathological features were compared between AT-positive (n = 36) and AT-negative (n = 52) groups (Table 3). The AT group showed significantly higher rates of pT3b–T4 disease (61.1% vs. 17.3%, p < 0.001), pN1 (27.8% vs. 9.6%, p = 0.042), extraprostatic extension (EPE; 41.7% vs. 13.5%, p = 0.005), and positive surgical margins (PSM; 63.9% vs. 23.1%, p < 0.001). Conversely, pathological downstaging was significantly less frequent in the AT group (25.0% vs. 67.3%, p < 0.001). NAT administration rate, pathological treatment response (rim), and BCR rates did not differ significantly between groups. These data confirm that AT was disproportionately administered to patients with more adverse pathological features, providing statistical support for the selection bias that confounds outcome interpretation in the AT group. (Table 3)

3.4 | Perioperative Outcomes

Perioperative outcomes are summarized in Table 4. The median operative time was 247.5 minutes (range, 151–396 minutes), and the median estimated blood loss was 60 mL (range, 5–600 mL). The PSM rate was 39.7% (35/88), and pelvic lymph node metastasis was identified in 17.0% of patients (15/88). These outcomes are comparable to those reported by high-volume robotic surgery centers in Japan[4, 5] and are consistent with contemporary published data for high-risk cohorts.[6, 7]

3.5 | Oncological Outcomes — Overall Cohort

Oncological outcomes are summarized in Table 5. The 3-year and 5-year OS rates were both 97.6%. The 5-year CSS rate was 100%, indicating no prostate cancer-specific deaths during the follow-up period. The 3-year and 5-year PFS rates were 62.4% and 37.1%, respectively, reflecting the high rate of biochemical recurrence expected in VHR-PCa.

3.6 | OS and PFS Stratified by Neoadjuvant Therapy

In the NAT-positive group (n = 65), the 3-year and 5-year OS rates were 98.3% and 98.3%, respectively. In the NAT-negative group (n = 23), the corresponding rates were 95.7% and 95.7% (log-rank p = 0.436). Regarding PFS, the NAT-positive group demonstrated 3-year and 5-year rates of 65.5% and 41.0%, compared to 53.4% and 26.7% in the NAT-negative group (log-rank p = 0.345). Although the difference was not statistically significant, a consistent numerical trend favoring NAT was observed across all time points. (Table 5)

3.7 | OS and PFS Stratified by Adjuvant Therapy

In the AT-positive group (n = 36), the 3-year and 5-year OS rates were 97.1% and 97.1%, versus 98.1% and 98.1% in the AT-negative group (n = 52; p = 0.824). In terms of PFS, the AT-positive group showed 3-year and 5-year rates of 53.9% and 36.6%, compared to 68.2% and 34.9% in the AT-negative group (p = 0.239). The AT-positive group showed numerically inferior early PFS, likely reflecting selection of more advanced cases for adjuvant treatment. (Table 5)

4 | Discussion

This retrospective single-institution study evaluated RARP as part of multimodal therapy for NCCN VHR-PCa in 88 patients (median follow-up 44.6 months). Perioperative outcomes were comparable to those of leading robotic surgery centers in Japan [4, 5] and internationally [6, 7]. The 5-year CSS was 100% and OS was 97.6%. NAT was associated with a numerically higher 5-year PFS (41.0% vs. 26.7%) that did not reach statistical significance (p = 0.345), while AT was not associated with a survival advantage, likely reflecting selection bias toward more advanced disease.

The perioperative metrics observed in this cohort reflect the technical proficiency of a high-volume robotic surgery program. The PSM rate of 39.7% must be interpreted in the context of a predominantly cT3 or higher cohort and is consistent with published data for high-risk and very high-risk disease.[6, 7] The 17.0% rate of lymph node metastasis underscores the aggressive nature of VHR-PCa and highlights the importance of extended pelvic lymph node dissection in this setting, as lymph node involvement has been associated with worse oncological outcomes and may guide decisions regarding adjuvant systemic therapy.[15]

From a technical standpoint, RARP for VHR-PCa poses distinct challenges relative to lower-risk disease: bulky, locally extended tumors often require wider periprostatic dissection, more extensive seminal vesicle and posterior plane mobilization, and a lower threshold for extended pelvic lymphadenectomy, all of which increase the technical demand on the console surgeon. In this cohort, the combination of a

short operative time (median 247.5 min), minimal blood loss (median 60 mL), and preserved continence despite wide resection suggests that the three-dimensional visualization and articulated instrumentation of the robotic platform can offset some of this added complexity, consistent with prior reports describing RARP as a technically feasible alternative to open or laparoscopic approaches even in locally advanced disease.

Urinary continence outcomes, with 73.8% of patients achieving functional continence (fewer than one pad per day), are clinically meaningful. These rates compare favorably with previous reports and international meta-analyses in robotic prostatectomy cohorts.[12] The somewhat lower pad-free rate of 31.8% is expected given the need for wide resection in locally advanced disease and the avoidance of aggressive nerve-sparing techniques.

The 5-year CSS of 100% and OS of 97.6% in our VHR-PCa cohort are noteworthy. These results compare favorably with outcomes reported for RARP in high-risk prostate cancer series[6, 7] and with data from comparative studies of radical prostatectomy versus radiotherapy in high-risk disease.[8, 9] The dissociation between PSA recurrence (5-year PFS 37.1%) and cancer-specific mortality (CSS 100%) underscores that BCR does not inevitably translate into cancer death, particularly with diligent surveillance and timely salvage therapy.

The numerically higher 5-year PFS in the NAT+ group (41.0% vs. 26.7%, $p = 0.345$), although not statistically significant in this modestly sized cohort, is consistent with the hypothesis that preoperative tumor volume reduction may improve surgical and oncological outcomes. Multiple randomized phase II trials have demonstrated that neoadjuvant hormonal therapy improves pathological outcomes including downstaging and reduction in positive surgical margins [10, 11]. The landmark CALGB 90203 trial demonstrated that neoadjuvant chemohormonal therapy significantly improved favorable pathological response rates, supporting the rationale for systemic treatment prior to surgery [11].

Notably, the NAT regimens in this cohort predominantly consisted of conventional hormonal agents (bicalutamide and CAB). Contemporary phase II data suggest that more intensive ARSI-based regimens may achieve greater pathological downstaging.[10] Future studies at our institution will incorporate novel agents such as enzalutamide, apalutamide, or darolutamide into neoadjuvant protocols.[3]

The absence of a PFS benefit in the AT+ group likely reflects the well-recognized confounding that affects retrospective analyses of adjuvant treatment: patients receiving AT were disproportionately those with the most adverse pathological findings, inherently placing them at higher recurrence risk. This selection effect has been observed in other non-randomized datasets and mirrors the challenge of interpreting adjuvant therapy outcomes in the post-prostatectomy setting.[13]

In node-positive patients after radical prostatectomy, Messing et al. demonstrated a significant OS benefit with immediate adjuvant ADT versus observation [14]. However, extrapolating these findings to a heterogeneous VHR-PCa cohort requires caution. Adjuvant radiation therapy has also been shown to reduce biochemical recurrence risk in patients with adverse pathological features (EORTC 22911 trial)

[13]. These data underscore that adjuvant therapy decisions should be individualized based on specific pathological findings.

This study has several limitations. The retrospective design introduces selection bias and confounding by indication. The sample size of 88 limits statistical power to detect subgroup differences. Heterogeneity of NAT and AT regimens precludes agent-specific analyses, and the median follow-up of 44.6 months may be insufficient to capture late events. The absence of a concurrent non-surgical control group also limits direct treatment comparisons. In addition, exclusion of 121 patients with insufficient follow-up, although largely attributable to recent surgery date, cannot fully rule out unmeasured selection effects, and generalizability of these findings to the full 209-patient VHR-PCa cohort should be interpreted with caution.

Despite these limitations, the present analysis demonstrates that RARP-based multimodal therapy for NCCN VHR-PCa yields excellent disease-specific and overall survival (5-year CSS 100%, OS 97.6%) with acceptable urinary continence, achieved with a wide-resection technical approach appropriate to locally advanced disease. NAT was associated with a numerically higher 5-year PFS (41.0% vs. 26.7%) without reaching statistical significance, whereas AT did not demonstrate a survival benefit, most likely reflecting confounding by disease severity. Taken together, these findings support integrating RARP into multimodal treatment strategies for VHR-PCa at experienced robotic surgery centers. Prospective studies with larger cohorts, standardized treatment protocols, and longer follow-up are needed to define the optimal multimodal approach for this challenging patient population.

Declarations

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. Approval was granted by the Institutional Review Board of Saiseikai Kumamoto Hospital (Approval No. 1439).

Consent to participate

This is a retrospective study using routinely collected clinical data. The Institutional Review Board of Saiseikai Kumamoto Hospital waived the requirement for individual informed consent in view of the retrospective, observational nature of the study.

Consent to publish

Not applicable. This manuscript does not contain any individual person's identifiable data, images, or videos.

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Author Contribution

Y.O.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. T.M.: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. K.M., K.A., T.Mi., H.M.: Data curation, Investigation, Resources, Writing – review & editing. S.W.: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Supplementary Files

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