Research Square

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# Clinical Impact of Long-term Neoadjuvant Hormone Therapy on Locally Advanced Prostate Cancer Treated with Radical Prostatectomy: A Retrospective Cohort Study

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**Research Article**

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## Abstract

**Background:**

Pathological complete response (pT0) after long-term neoadjuvant hormone therapy (NHT) may reflect a marked treatment response in locally advanced prostate cancer. However, its association with postoperative recurrence remains unclear. This study evaluated the clinical significance of pT0 after long-term NHT followed by robot-assisted radical prostatectomy (RARP).

**Methods:**

In this retrospective single-center cohort study, 51 patients who received NHT were analyzed among 90 patients with cT3-4N0M0 prostate cancer who underwent RARP between 2012 and 2024. Patients were divided into pT0 (n = 18) and non-pT0 (n = 33) groups. Clinicopathological factors and biochemical recurrence-free survival (BCRF) were compared. Cox proportional hazards models were used to identify predictors of biochemical recurrence.

**Results:**

Median NHT duration was significantly longer in the pT0 group than in the non-pT0 group (11 vs. 4 months, $p < 0.00001$). Preoperative prostate-specific antigen was significantly lower in the pT0 group (0.0015 vs. 0.972 ng/mL, $p < 0.00001$). Biochemical recurrence occurred in 1 of 18 patients in the pT0 group and 16 of 33 patients in the non-pT0 group. Kaplan–Meier analysis showed significantly better BCRF in the pT0 group than in the non-pT0 group (log-rank $p = 0.044$). In multivariate analysis, pT0 was independently associated with reduced biochemical recurrence (HR 0.12, 95% CI 0.006–0.699, $p = 0.0488$).

**Conclusions:**

Pathological complete response after long-term NHT followed by RARP was associated with favorable oncological outcomes and may be a potential indicator of treatment response in locally advanced prostate cancer.


## Background

Robot-assisted radical prostatectomy (RARP) has become a treatment option for localized prostate cancer and selected patients with locally advanced prostate cancer [1–3]. However, locally advanced prostate cancer is often accompanied by extracapsular extension and seminal vesicle invasion, and surgery alone is associated with a high risk of positive surgical margins and postoperative recurrence [4,5]. Against this background, neoadjuvant hormone therapy (NHT), sometimes combined with chemotherapy, has been used in clinical practice to improve the efficacy of surgery by reducing prostate tumor volume, achieving pathological downstaging, and lowering the positive surgical margin rate [6–20]. Although NHT has been reported to contribute to these pathological improvements, its impact on biochemical recurrence and survival remains controversial, and it is not currently recommended as a standard treatment in clinical practice guidelines.

We previously reported that a certain proportion of patients who received long-term NHT achieved pathological complete response, defined as the absence of residual cancer cells in the radical prostatectomy specimen (pT0) [21]. We also showed that a longer duration of NHT and the use of combined androgen blockade (CAB) may be associated with the achievement of pT0. These findings suggest that long-term NHT may provide not only tumor shrinkage but also a marked pathological therapeutic effect in prostate cancer.

Currently, it remains unclear whether pathological complete response achieved after long-term NHT is associated with reduced recurrence in patients with locally advanced prostate cancer. Therefore, in the present study, we investigated patients with locally advanced prostate cancer who underwent RARP after long-term NHT and compared the pT0 and non-pT0 groups in terms of patient characteristics, treatment-related factors, pathological findings, and oncological outcomes, including biochemical recurrence. Through this analysis, we aimed to evaluate the clinical significance of pT0 achieved after long-term NHT and assess the utility of surgery combined with neoadjuvant hormonal therapy for locally advanced prostate cancer.

## Methods

1. Study design and patients

This retrospective single-center cohort study was conducted at Saga University Hospital. Of the 464 patients with prostate cancer who underwent RARP at our institution between 2012 and 2024, 90 were preoperatively diagnosed with locally advanced prostate cancer (cT3–4N0M0). Among them, 51 patients who received NHT were included in this study. Patients were divided into two groups: the pT0 group, consisting of 18 patients with no residual cancer in the radical prostatectomy specimen, and the non-pT0 group, consisting of 33 patients with residual cancer.

2. NHT regimen

NHT regimens consisted of androgen deprivation therapy (ADT) alone, CAB, or ADT combined with an androgen receptor signaling inhibitor (ARSI). The duration and type of NHT and preoperative prostate-specific antigen (PSA) levels were collected from the medical records. The presence or absence of NHT-related adverse events was retrospectively reviewed.

3. Variables examined

Patient background factors included age, body mass index (BMI), prostate volume, initial PSA, clinical T stage, biopsy Gleason grade group and NCCN risk classification. The treatment-related factors included the NHT regimen, duration of NHT, and preoperative PSA level. As a surgeon-related factor, the surgeon's RARP experience at the time of the procedure was also evaluated and classified as 50 or more cases or fewer than 50 cases. Perioperative outcomes included console time, blood loss, and the presence of perioperative complications of Clavien–Dindo grade 3 or higher. Pathological and oncological outcomes included the positive surgical margin rate, follow-up duration, and biochemical recurrence-free survival (BCRF).

4. Definitions and study endpoints

pT0 was defined as the absence of pathological residual cancer in the radical prostatectomy specimens. Biochemical recurrence was defined as two consecutive postoperative PSA levels of 0.2 ng/mL or higher. The date of biochemical recurrence was defined as the date of the first PSA elevation to 0.2 ng/mL or higher. The primary endpoint was the comparison of BCRF between the pT0 and non-pT0 groups. The secondary endpoints included comparisons of patient background characteristics, treatment-related factors, perioperative outcomes, and positive surgical margin rates.

5. Statistical analysis

Continuous variables are presented as median values with interquartile ranges (IQRs), and comparisons between the two groups were performed using the Mann–Whitney U-test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. BCRF was analyzed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Factors associated with biochemical recurrence were evaluated using univariate and multivariate Cox proportional hazards models. Statistical analyses were performed using GraphPad Prism (ver. 9.4.0; GraphPad Software, San Diego, CA, USA), and p-values $< 0.05$ were considered statistically significant.

## Results

1. Patient characteristics

The patient characteristics are shown in Table 1. The median age was 69 years in the pT0 group and 70 years in the non-pT0 group, with no significant difference between the groups ($p = 0.7578$). The median initial PSA was 14.4 ng/mL in the pT0 group and 14.9 ng/mL in the non-pT0 group, with no significant difference ($p = 0.8683$). There were no significant differences in the clinical T stage, biopsy Gleason grade group, or NCCN risk classification between the two groups. Likewise, surgeon RARP experience (50 or more cases vs. fewer than 50 cases) did not differ significantly between the groups ($p = 0.6510$).

Table 1. Patient characteristics of the pT0 and non-pT0 groups.

| Clinical characteristics | pT0 group (n=18) | non-pT0 group (n=33) | *p*-value |
|---|---|---|---|
| Age, years, median (IQR) | 70 (65–72) | 69 (64–71) | 0.7578 * |
| BMI, kg/m², median (IQR) | 25 (23–26) | 25 (22–25) | 0.0969 * |
| Prostate volume, mL, median (IQR) | 22 (16–32) | 24 (21–35) | 0.3497 * |
| Initial PSA, ng/mL, median (IQR) | 14.4 (8.4–52.1) | 14.9 (8.7–29.8) | 0.8683 * |
| Clinical T stage, no. (%) | | | 0.6198 † |
| T3a | 12 (67%) | 24 (73%) | |
| T3b | 6 (33%) | 8 (24%) | |
| T4 | 0 (0%) | 1 (3%) | |
| Biopsy Gleason grade group, median (IQR) | 4 (3.75–5) | 4 (3–5) | 0.2764 * |
| NCCN risk, no. (%) | | | 0.0979 † |
| High | 6 (33%) | 19 (58%) | |
| Very high | 12 (67%) | 14 (42%) | |
| Surgeon experience, no. (%) | | | 0.6510 † |
| ≧50 cases | 11 (61%) | 18 (55%) | |
| <50 cases | 7 (39%) | 15 (45%) | |

* Mann–Whitney U test
† Chi-square test

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen; pT0, pathological T0; NCCN, National Comprehensive Cancer Network.

2. Treatment-related factors

Regarding the NHT regimen, CAB accounted for the majority of cases in the pT0 group (16 patients, 88%), whereas in the non-pT0 group, 16 patients (48%) received ADT alone and 17 patients (52%) received CAB, showing a significant difference in the NHT regimen between the groups ($p = 0.0045$). ADT plus ARSI was administered to one patient (6%) in the pT0 group and to no patients in the non-pT0 group. The median duration of NHT was significantly longer in the pT0 group than in the non-pT0 group (11 vs. 4 months, $p < 0.00001$). In addition, the median preoperative PSA level was significantly lower in the pT0 group than in the non-pT0 group (0.0015 vs. 0.972 ng/mL, $p < 0.00001$) (Table 2). No severe NHT-related adverse events were noted in the medical records.

Table 2. Treatment-related, perioperative, and pathological outcomes of the pT0 and non-pT0 groups.

| Treatment outcomes | pT0 group (n=18) | non-pT0 group (n=33) | *p*-value |
|---|---|---|---|
| NHT regimen, no. (%) | | | 0.0045 † |
| ADT only | 1 (6%) | 16 (48%) | |
| CAB | 16 (88%) | 17 (52%) | |
| ADT + ARSI | 1 (6%) | 0 (0%) | |
| NHT duration, months, median (IQR) | 11.0 (7.75–13.25) | 4.0 (2–7) | <0.00001 * |
| Preoperative PSA, ng/mL, median (IQR) | 0.0015 (0–0.022) | 0.972 (0.041–1.978) | <0.00001 * |
| Console time, min, median (IQR) | 184 (151–230) | 217 (173–266) | 0.1364 * |
| Estimated blood loss, mL, median (IQR) | 113 (50–200) | 102 (48–200) | 0.7715 * |
| Positive surgical margin, no. (%) | 0 (0%) | 8 (24%) | 0.0389 * |
| Major Complications (Clavien–Dindo Grade 3 or higher), no. (%) | 0 (0%) | 2 (6%) | 0.5341 ‡ |

* Mann–Whitney U test
† Chi-square test
‡ Fisher's exact test

Abbreviations: NHT, neoadjuvant hormone therapy; ADT, androgen deprivation therapy; CAB, combined androgen blockade; ARSI, androgen receptor signaling inhibitor; PSA, prostate-specific antigen; pT0, pathological T0.

3. Perioperative and pathological outcomes

Regarding perioperative outcomes, the median console time was 184 min in the pT0 group and 217 min in the non-pT0 group, with no significant difference (p = 0.1364). The median blood loss was also similar between the two groups (113 vs. 102 mL, p = 0.7715). No Clavien–Dindo grade ≥3 perioperative complications occurred in the pT0 group, whereas 2 cases (6%) were observed in the non-pT0 group; however, this difference was not statistically significant (p = 0.5341). Pathologically, no positive surgical margins were observed in the pT0 group, whereas 8 cases (24%) in the non-pT0 group involved positive surgical margins, indicating a significantly lower positive surgical margin rate in the pT0 group (p = 0.0389) (Table 2).

4. Oncological outcomes

The median follow-up duration was 8.5 months in the pT0 group and 12 months in the non-pT0 group, with no significant difference between groups (p = 0.6395). During follow-up, biochemical recurrence occurred in 1 of 18 patients in the pT0 group and in 16 of 33 patients in the non-pT0 group. The Kaplan–Meier analysis demonstrated significantly better BCRF in the pT0 group than in the non-pT0 group (log-rank p = 0.044) (Figure 1).

5. Analysis of factors associated with recurrence

Univariate and multivariate Cox proportional hazards analyses of factors associated with biochemical recurrence are shown in Table 3. In the univariate Cox proportional hazards analysis, pT0 (vs. non-pT0) showed a trend toward an association with a reduced risk of recurrence, although this did not reach statistical significance (HR 0.16, 95% CI 0.009–0.810, p = 0.0780). In the multivariate analysis, pT0 was identified as an independent predictor of reduced biochemical recurrence (HR 0.12, 95% CI 0.006–0.699, p = 0.0488). Biopsy Gleason grade groups 1–3 (vs. 4–5) independently predicted reduced biochemical recurrence (HR 0.24, 95% CI 0.051–0.889, p = 0.0441). In contrast, NCCN very high risk and CAB regimens were not identified as independent factors.

Table 3. Univariate and multivariate Cox proportional hazards analyses of factors associated with biochemical recurrence.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Variable | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| pT0 (vs. non–pT0) | 0.16 | 0.009–0.810 | 0.0780 | 0.12 | 0.006–0.699 | 0.0488 |
| Gleason grade group 1–3 (vs. 4–5) | 0.35 | 0.080–1.093 | 0.1030 | 0.24 | 0.051–0.889 | 0.0441 |
| NCCN very high risk (vs. high risk) | 0.84 | 0.308–2.303 | 0.7336 | 1.17 | 0.380–3.487 | 0.7734 |
| CAB (vs. ADT alone) | 0.65 | 0.225–1.808 | 0.4074 | 1.08 | 0.353–3.077 | 0.8940 |

Abbreviations: HR, hazard ratio; CI, confidence interval; NCCN, National Comprehensive Cancer Network; CAB, combined androgen blockade; ADT, androgen deprivation therapy; pT0, pathological T0.

## Discussion

In the present study, we compared treatment outcomes between the pT0 and non-pT0 groups in 51 patients with locally advanced prostate cancer who underwent RARP after NHT. The pT0 group had a significantly longer NHT duration and significantly lower preoperative PSA levels than the non-pT0 group. In addition, biochemical recurrence was observed in only 1 of 18 patients in the pT0 group, and the Kaplan–Meier analysis demonstrated significantly better BCRF in the pT0 group than in the non-pT0 group. Furthermore, multivariate analysis identified pT0 as an independent predictor of reduced recurrence rates. These findings suggest that, in locally advanced prostate cancer, pT0 achieved after long-term NHT may represent not only a pathological finding but also a marker of favorable oncological outcomes.

The role of NHT in locally advanced prostate cancer has been discussed in previous studies, which have shown benefits in local control, including reductions in prostate volume, pathological downstaging, and lower rates of positive surgical margins. However, its impact on biochemical recurrence and overall survival remains inconclusive [6–20]. Accordingly, current clinical guidelines do not recommend NHT as a standard treatment before radical prostatectomy [1–3]. In this context, the clinical value of NHT should be evaluated not only in terms of pathological improvement but also in terms of whether such effects translate into actual oncological benefits, particularly recurrence prevention. The present study is meaningful in that it specifically focused on locally advanced prostate cancer and demonstrated an association between pT0 achieved after long-term NHT and recurrence outcomes.

We previously reported that a certain proportion of patients who received long-term NHT achieved pT0 and that a longer duration of NHT and CAB use might be associated with this outcome [21]. Whereas our previous report was a pathological study demonstrating an association between long-term NHT and pT0 achievement, the present study extends these findings by examining whether pT0 is actually associated with recurrence suppression in locally advanced prostate cancer. In other words, our results suggest that pT0 achieved after long-term NHT may serve not only as a pathological observation but also as a clinically meaningful indicator of favorable postoperative outcomes.

In the present study, the pT0 group had a significantly longer duration of NHT and a higher proportion of CAB than the non-pT0 group. This finding suggests that sufficiently prolonged and intensive endocrine treatment may reduce tumor burden to an extremely low level in patients with locally advanced prostate cancer. In many previous reports, the duration of NHT before radical prostatectomy was relatively short, generally around 3 to 6 months. Xu et al. [6] reported a mean duration of 5.6 months using a combination of goserelin and flutamide, and in the meta-analysis by Liu et al. [11], the median duration reported in the available studies was 4.3 months. Matsumoto et al. also reported that 90% of patients receiving NHT were treated for 3 to 6 months [12]. Although these short-term NHT regimens contributed to pathological downstaging and improved local control, they were not clearly associated with better biochemical control or survival outcomes. In contrast, the median duration of NHT in the pT0 group in our study was 11 months, which was longer than in previous reports. Moreover, both our previous report [21] and the study by Fujimoto et al. [7] suggest that pT0 may be achieved through long-term NHT and sufficiently intensive androgen blockade. Because recurrence was rare and BCRF was favorable in the pT0 group in the present study, pT0 may be considered a pathological marker of the treatment response associated with a reduced recurrence risk.

In recent years, attempts have been made to intensify neoadjuvant treatment for locally advanced or very high-risk prostate cancer by adding chemotherapy or novel androgen receptor signaling inhibitors to hormonal therapy to achieve greater tumor shrinkage and improved recurrence control [18–20]. Docetaxel-based neoadjuvant chemo-hormonal therapy has been reported to improve biochemical recurrence-free survival compared with NHT alone, although additional benefits in pathological downstaging and minimal residual disease have not been consistently demonstrated [18]. Furthermore, docetaxel-based treatment requires careful attention to treatment discontinuation and severe adverse events; therefore, careful patient selection is necessary before applying it widely in the neoadjuvant setting [20]. In contrast, CAB is a familiar treatment strategy in daily clinical practice in Japan and has the advantage of being relatively easy to introduce in real-world settings. No severe NHT-related adverse events were observed in our cohort. These findings suggest that long-term endocrine therapy, including CAB, may represent a practical and potentially effective neoadjuvant treatment option in routine clinical practice.

Locally advanced prostate cancer is frequently associated with extracapsular extension and seminal vesicle invasion, and a high positive surgical margin rate is one of the factors contributing to the postoperative recurrence. By reducing tumor volume and local extension, NHT may improve the completeness of surgical resection, which, in turn, may contribute to a lower recurrence rate. Regarding perioperative outcomes, no significant differences were observed between the two groups in terms of console time, blood loss, or severe complications. Therefore, in this cohort, long-term NHT followed by pT0 achievement was not associated with impaired surgical safety.

This study had several limitations. First, this was a retrospective, single-center study with a small sample size of 51 patients, including only 18 patients in the pT0 group, which may have affected the reliability of the findings. Second, although pathological complete response (pT0) was associated with favorable biochemical recurrence-free survival in this cohort, this result may have been influenced by the longer duration of neoadjuvant hormone therapy and the higher use of combined androgen blockade in the pT0 group. Third, the follow-up period was relatively short, and longer follow-up is needed to clarify the long-term oncological significance of these findings.

## Conclusions

In patients with locally advanced prostate cancer treated with long-term NHT followed by RARP, pathological complete response was associated with favorable oncological outcomes. pT0 achieved after long-term NHT may serve as a clinically meaningful indicator of treatment response and prognosis in locally advanced prostate cancer. Further multicenter studies with larger cohorts and longer follow-ups are needed to clarify the reproducibility and clinical significance of these findings.

## Abbreviations

ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor; BCRF, biochemical recurrence-free survival; BMI, body mass index; CAB, combined androgen blockade; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; NHT, neoadjuvant hormone therapy; PSA, prostate-specific antigen; pT0, pathological T0; RARP, robot-assisted radical prostatectomy.

## Declarations

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Saga University Hospital (approval number: 2020-03-R-04). The requirement for informed consent was waived because of the retrospective nature of this study, and patients were given the opportunity to opt out in accordance with institutional policy. This study was conducted in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Availability of data and materials**

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

**Competing interests**

The authors declare that they have no competing interests.

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The authors received no specific funding for this work.

**Authors' contributions**

Akihiro Maeda: First author, study design, data collection, data analysis, and manuscript writing.

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Maki Kawasaki: Data collection and review of the manuscript.

Hiroaki Kakinoki: Data collection and review of the manuscript.

Mitsuru Noguchi: Final author, study supervision.

All authors read and approved the final manuscript.

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**Authors' information**

Not applicable.

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## Figures

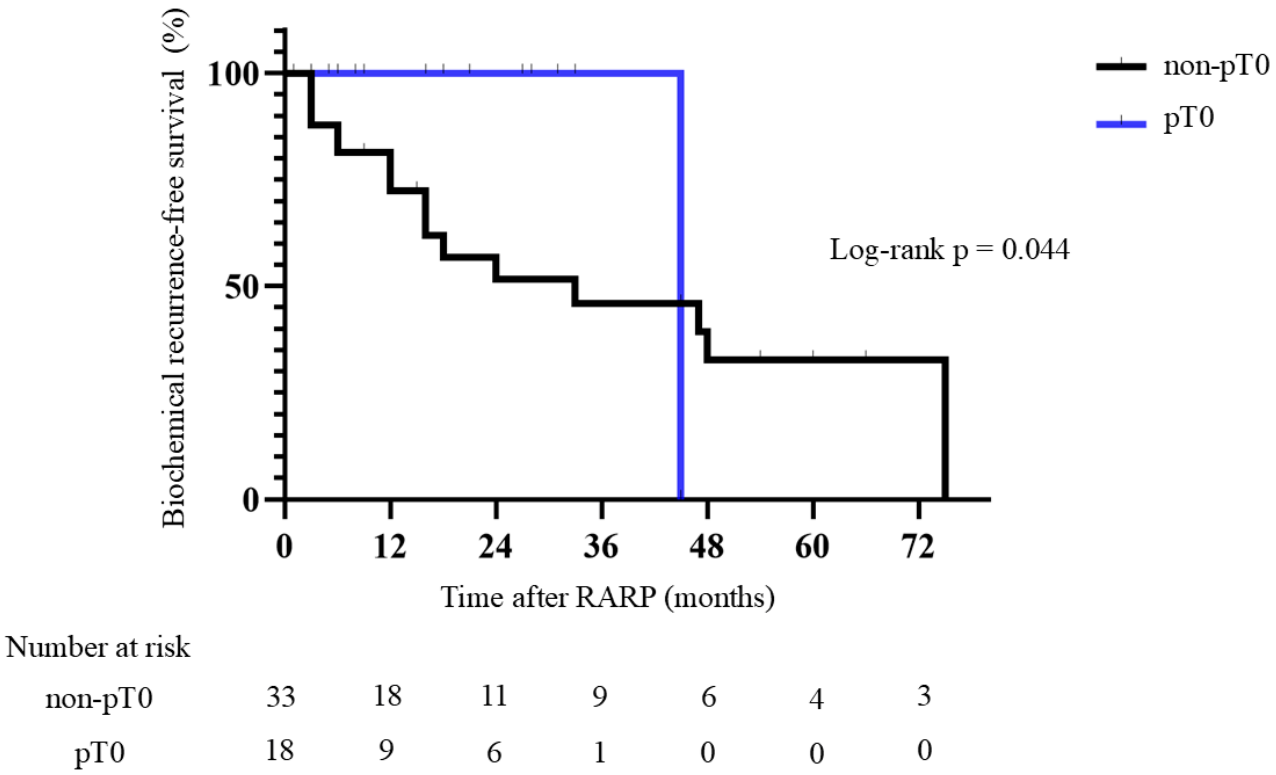


**Figure 1**

Kaplan–Meier curves for biochemical recurrence-free survival in the pT0 and non-pT0 groups.

The pT0 group showed significantly better biochemical recurrence-free survival than the non-pT0 group (log-rank p = 0.044). The abrupt decline in the pT0 curve reflects a single recurrence event occurring when only one patient remained at risk.

Abbreviations: pT0, pathological T0; RARP, robot-assisted radical prostatectomy.