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Original Article

Effects of neoadjuvant endocrine therapy on surgical prognosis and survival period in patients with high-risk localized prostate cancer

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Abstract: Objective: To investigate the impact of Neoadjuvant Hormonal Therapy (NHT) on surgical prognosis and survival in patients with high-risk localized prostate cancer. Methods: A retrospective analysis was conducted on 371 high-risk prostate cancer patients who were treated at Baoji Central Hospital and Norinco General Hospital from January 2017 to January 2020. The patients were randomly divided into a training set of 286 cases (134 in the non-NHT group and 151 in the NHT group) and a validation set of 86 cases (42 in the non-NHT group and 44 in the NHT group). All patients underwent radical prostatectomy combined with pelvic lymph node dissection (RP+PLND). The baseline characteristics of the training and validation sets were collected. Surgical efficacy indicators (positive surgical margin rate, operative time, blood loss, etc.), 5-year overall survival (OS), metastasis-free survival (MFS), and biochemical recurrence-free survival (BRFS) were compared between the non-NHT and NHT groups in the training set. Independent risk factors for mortality were identified through univariate and multivariate analyses. Results: There were no significant differences in the baseline characteristics between the non-NHT and NHT groups in both the validation and training sets. In the training set, the NHT group demonstrated significantly better outcomes than the non-NHT group in terms of positive surgical margin rate (14.57% vs. 39.55%, $P < 0.001$), intraoperative blood loss (428.64±45.31 ml vs. 494.98±62.36 ml, $P < 0.001$), and operative time (143.00 min vs. 148.00 min, $P < 0.001$). The 5-year OS, MFS, and BRFS rates in the NHT group were 82.12% (124/151), 66.23% (100/151), and 40.02% (71/151), respectively, which were significantly higher than 55.97% (75/134), 44.03% (59/134), and 27.61% (37/134) in the non-NHT group ($P < 0.001$ for all). Multivariate analysis identified non-NHT treatment (OR = 7.528, $P < 0.001$), open surgery (OR = 4.581, $P < 0.001$), high clinical stage, high postoperative Gleason score, and high preoperative Prostate-Specific Antigen (PSA) as independent risk factors for mortality. Robotic-assisted surgery significantly reduced the incidence of long-term complications such as urethral stricture and bladder neck contracture compared with open surgery ($P < 0.05$ for all). Conclusion: Preoperative NHT can improve surgical efficacy and long-term survival in patients with high-risk prostate cancer without increasing perioperative risks. Robotic-assisted surgery reduces long-term complications. NHT and preoperative PSA can serve as strong predictive indicators for the Nomogram model, providing references for individualized treatment. Further exploration of the optimal course of NHT and precision stratification guided by molecular markers is needed in the future.

Keywords: Prostate cancer, neoadjuvant hormonal therapy, radical prostatectomy, survival analysis, robotic surgery

Introduction

Prostate cancer is recognized as one of the most prevalent malignant tumors affecting the male population globally. According to the 2020 statistics released by the International Agency for Research on Cancer (IARC), there were approximately 1.414 million newly diagnosed cases of prostate cancer and 375,000 prostate cancer-related deaths worldwide in 2020 [1]. In China, driven by population aging and widespread adoption of screening techniques, the incidence of prostate cancer has risen rapidly. In 2020, the number of new cases reached 115,000, making it the most common malignant tumor of the male urinary system [2, 3].

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High-risk localized prostate cancer is typically characterized by serum PSA levels ≥ 20 ng/mL, clinical stage T2c-T3, and a Gleason score ≥ 8 [4]. Although these patients have no evidence of distant metastasis, their local tumors are highly invasive, with significantly higher risks of postoperative recurrence and distant metastasis compared to low- and intermediate-risk patients [5, 6]. Radical prostatectomy (RP) remains a key definitive treatment for this population [7]. However, the 5-year biochemical recurrence rate after RP ranges from 30% to 50%, severely compromising patients' quality of life and long-term prognosis [8, 9]. Thus, identifying effective adjuvant strategies to mitigate recurrence and prolong survival represents a critical clinical imperative.

NHT inhibits the proliferation and survival of prostate cancer cells by suppressing androgen activity and blocking the Androgen Receptor (AR) signaling pathway, thus playing a crucial role in the comprehensive treatment of prostate cancer [10]. NHT primarily achieves maximal androgen blockade through Gonadotropin-Releasing Hormone Analogs (GnRHa) or antagonists to inhibit Luteinizing Hormone-Releasing Hormone (LHRH) secretion and reduce testicular androgen synthesis, or in combination with antiandrogen drugs (such as bicalutamide) to competitively bind AR [11, 12].

In the treatment of high-risk localized prostate cancer, NHT is applied to create more favorable surgical conditions by reducing tumor volume, downstaging the disease, and decreasing adhesions between the tumor and surrounding tissues, thereby improving surgical outcomes [10, 13]. Additionally, NHT can modulate the tumor microenvironment, inhibit the activity of invasion-associated factors (e.g., Matrix Metalloproteinases [MMPs]), attenuate tumor cell invasiveness, and lower the risk of positive surgical margins [14, 15], thereby laying a foundation for long-term survival benefits.

Despite the potential of NHT to improve prognosis, its clinical efficacy remains widely debated. Some studies support that NHT can reduce the positive surgical margin rate, decrease intraoperative blood loss, and prolong biochemical recurrence-free survival [14]. However, conflicting conclusions have been drawn in other clinical trials [16, 17]. These controversial findings suggest that the influence of NHT on surgical outcomes and survival in patients with high-risk localized prostate cancer warrants further investigation. Furthermore, long-term administration of NHT is accompanied by a series of non-negligible adverse effects: androgen deprivation can induce adverse reactions including metabolic syndrome, elevated risk of cardiovascular diseases, osteoporosis, cognitive impairment, and sexual dysfunction [18]. These side effects not only affect patients' quality of life but may also offset the potential survival benefits of NHT. Balancing the anti-cancer effects of NHT with its adverse reactions to optimize treatment regimens has become a key challenge in clinical practice.

In summary, there is an urgent need for effective therapies for patients with high-risk localized prostate cancer, and the clinical value of NHT in this setting has yet to reach consensus. Therefore, this study retrospectively analyzed the clinical data of such patients to evaluate the impact of NHT on surgical outcomes and survival, aiming to provide clinical evidence to inform treatment optimization and support the advancement of precision medicine for prostate cancer.

Methods

Study subjects and grouping

A total of 371 patients with high-risk localized prostate cancer who underwent radical prostatectomy combined with pelvic lymph node dissection (RP+PLND) at Baoji Central Hospital and Norinco General Hospital between January 1, 2017, and January 31, 2020, were retrospectively enrolled. Patients were first stratified according to NHT status (NHT group/non-NHT group) and then randomly allocated, within each stratum, to a training set (285 cases) and a validation set (86 cases) at a ratio of 8:2. The comparability of baseline characteristics between the two sets (e.g., age, BMI, and clinical stage) was assessed using the chi-square test and independent samples t-test. No statistically significant differences were found (all $P > 0.05$), confirming the validity of the grouping method. This study was approved by the Ethics Committee of Baoji Central Hospital.

Inclusion criteria: (1) aged 18-80 years; (2) pathologically confirmed adenocarcinoma by preoperative prostate biopsy, fulfilling high-risk

criteria [19]; (3) fulfilling at least one high-risk feature: Gleason score ≥ 8, PSA ≥ 20 ng/mL, or clinical stage cT2c-cT3a; (4) underwent RP+PLND; and (5) complete baseline and postoperative data, with a follow-up duration of ≥ 5 years or until occurrence of an endpoint event. Exclusion criteria: (1) concomitant non-cutaneous malignancies or distant metastasis (cM1); (2) severe comorbidities precluding surgery; or (3) receipt of adjuvant radiotherapy or Androgen Deprivation Therapy (ADT) within 3 months postoperatively.

Patients were divided into two groups based on preoperative treatment. The NHT group received ADT (goserelin 3.6 mg every 4 weeks combined with bicalutamide 50 mg/d) for ≥ 3 months (median 4-6 months), with discontinuation 2-4 weeks before surgery to minimize perioperative risks; the non-NHT group underwent direct RP+PLND within 3 months of diagnosis.

Surgical procedures

Patients were further stratified by surgical approach into two subgroups: robot-assisted laparoscopic RP+PLND and open RP+PLND. In the robot-assisted group, patients were placed in lithotomy position under general anesthesia, and a pneumoperitoneum was established. A laparoscope and trocars were inserted to accommodate robotic arms, enabling precise dissection of peri-prostatic tissues and prostate removal under 3D high-definition visualization. Subsequently, bilateral external and internal iliac lymph node dissection was performed. For open RP+PLND, patients were placed in the supine position, and the prostate was accessed via a lower midline or retropubic incision. Prostate resection was conducted under direct vision, followed by lymph node dissection with the same scope as the robotic approach.

Outcome measures and follow-up

Patient grouping and indicator collection: Patients were divided into the NHT group and the non-NHT group based on whether they received preoperative NHT. Baseline data of patients were collected through retrospective analysis of electronic medical records, including age, Body Mass Index (BMI), surgical approach, Gleason score, clinical stage, and International Prostate Symptom Score (IPSS). Meanwhile, perioperative indicators and postoperative outcome indicators were recorded to evaluate surgical efficacy. The perioperative indicators included positive surgical margin status (defined as the presence of cancer cell infiltration at the edge of the prostate specimen in postoperative pathological sections, regardless of the depth of infiltration [20]), intraoperative blood loss, operation time, and complications. The postoperative outcome indicators included 5-year long-term complications, postoperative hospital stay, 1-month postoperative Gleason score (a pathological grading system for assessing the differentiation degree and malignancy of prostate cancer tissue, which is determined by evaluating the primary and secondary structural patterns of the cancer tissue (each scored 1-5 points), with the total score ranging from 2 to 10 points by summing the two scores [21]), gastrointestinal function recovery, and hemoglobin difference (defined as the difference between the peripheral blood hemoglobin level measured on the day before surgery and the fasting peripheral blood hemoglobin level measured on the morning of the first day after surgery [22]).

Correlation analysis, follow-up, and model construction: A linear correlation scatter plot was used to analyze the correlation between the PSA biochemical recurrence time and the PSA level at first recurrence. All patients were followed for 5 years (every 3 months during years 1-3 and every 6 months during years 3-5). For both groups, 5-year overall survival (OS; defined as the time from the day of RP+PLND to death from any cause within 5 years), MFS metastasis-free survival (MFS; defined as the time from the day of RP+PLND to the first occurrence of metastasis or death from any cause), and biochemical recurrence-free survival (BRFS; defined as the time from completion of RP+PLND to the first detection of serum PSA ≥ 0.2 ng/mL [23]) were calculated, and Kaplan-Meier (K-M) curves were plotted. Univariate and multivariate analyses were conducted to identify independent risk factors for 5-year mortality risk, after which a nomogram model was constructed. Receiver operating characteristic (ROC) curves and calibration plots for both the validation set and training set were used to evaluate the model performance.

Statistical analysis

Data were analyzed using SPSS 20.0 (IBM, USA). Continuous variables were expressed as

Table 1. General baseline characteristics of non-NHT and NHT groups in the training set

Item	Non-NHT Group (n = 134)	NHT Group (n = 151)	χ^2/t/Z	P
Age (years)	65.55±12.96	64.50±12.23	0.707	0.480
BMI	24.58 [21.85, 27.52]	26.08 [21.98, 28.40]	1.789	0.074
Surgical Approach			0.552	0.458
Robot-assisted RP+PLND	83 (61.94%)	87 (57.62%)		
Open RP+PLND	51 (38.06%)	64 (42.38%)		
Gleason Score			0.508	0.776
8	69 (51.49%)	79 (52.32%)		
9	52 (38.81%)	54 (35.76%)		
10	13 (9.70%)	18 (11.92%)		
ASA Classification			1.257	0.533
Grade I	89 (66.42%)	91 (60.26%)		
Grade II	38 (28.36%)	52 (34.44%)		
Grade III	7 (5.22%)	8 (5.30%)		
Clinical CT Stage			0.504	0.478
cT2c	81 (60.45%)	85 (56.29%)		
cT3a	53 (39.55%)	66 (43.71%)		
Clinical CN Stage			0.198	0.656
N0	99 (73.88%)	108 (71.52%)		
N1	35 (26.12%)	43 (28.48%)		
Diabetes Mellitus			0.103	0.748
No	99 (73.88%)	109 (72.19%)		
Yes	35 (26.12%)	42 (27.81%)		
Hypertension			0.892	0.345
No	105 (78.36%)	125 (82.78%)		
Yes	29 (21.64%)	26 (17.22%)		
Preoperative PSAD (ng/mL^2)	0.99 [0.65, 1.24]	1.07 [0.76, 1.31]	1.273	0.203
Preoperative PSA (ng/mL)	27.27 [23.51, 31.43]	26.49 [22.09, 31.58]	0.860	0.390
Urinary Flow Rate (mL/s)			3.051	0.218
≥ 15	74 (55.22%)	86 (56.95%)		
10-15	36 (26.87%)	29 (19.21%)		
< 10	24 (17.91%)	36 (23.84%)		
IPSS Score			0.113	0.737
< 20	88 (65.67%)	102 (67.55%)		
≥ 20	46 (34.33%)	49 (32.45%)		

Note: NHT: Neoadjuvant Hormonal Therapy, BMI: Body Mass Index, RP: Radical Prostatectomy, PLND: Pelvic Lymph Node Dissection, ASA: American Society of Anesthesiologists Physical Status Classification System, PSA: Prostate-Specific Antigen, PSAD: Prostate-Specific Antigen Density, IPSS: International Prostate Symptom Score.

mean ± SD and compared between groups using independent-sample t-tests. Categorical variables were expressed as numbers and percentages and analyzed using chi-square tests, and ordinal variables were assessed using Wilcoxon rank-sum tests (reported as Z values). K-M survival analysis with log-rank tests evaluated 1- and 3-year survival outcomes. Cox regression models was applied to identify independent prognostic factors. The predictive accuracy of the model was evaluated using ROC curves. A two-sided $P < 0.05$ denoted statistical significance.

Results

Baseline clinical characteristics

Baseline characteristics were compared between the non-NHT and NHT groups in both the

Table 2. General baseline characteristics of non-NHT and NHT groups in the validation set

Item	Non-NHT Group (n = 42)	NHT Group (n = 44)	χ^2/t/Z	P
Age (years)	64.55±13.63	65.68±11.42	-0.419	0.676
BMI	25.01±4.26	25.53±4.47	-0.557	0.579
Surgical Approach			0.501	0.479
Robot-assisted RP+PLND	27 (64.29%)	25 (56.82%)		
Open RP+PLND	15 (35.71%)	19 (43.18%)		
Gleason Score			0.517	0.772
8	22 (52.38%)	24 (54.55%)		
9	15 (35.71%)	13 (29.55%)		
10	5 (11.90%)	7 (15.91%)		
ASA Classification			1.016	0.602
Grade I	28 (66.67%)	25 (56.82%)		
Grade II	9 (21.43%)	11 (25.00%)		
Grade III	5 (11.90%)	8 (18.18%)		
Clinical CT Stage			0.164	0.685
cT2c	23 (54.76%)	26 (59.09%)		
cT3a	19 (45.24%)	18 (40.91%)		
Clinical CN Stage			0.361	0.548
N0	32 (76.19%)	31 (70.45%)		
N1	10 (23.81%)	13 (29.55%)		
Diabetes Mellitus			0.361	0.548
No	32 (76.19%)	31 (70.45%)		
Yes	10 (23.81%)	13 (29.55%)		
Hypertension			0.432	0.511
No	33 (78.57%)	37 (84.09%)		
Yes	9 (21.43%)	7 (15.91%)		
Preoperative PSAD (ng/mL^2)	0.95 [0.62, 1.20]	1.08 [0.78, 1.29]	1.028	0.304
Preoperative PSA (ng/mL)	27.48 [20.69, 30.33]	25.60 [20.32, 30.05]	0.352	0.725
Urinary Flow Rate (mL/s)			2.508	0.285
≥ 15	28 (66.67%)	22 (50.00%)		
10-15	9 (21.43%)	15 (34.09%)		
< 10	5 (11.90%)	7 (15.91%)		
IPSS Score			0.742	0.389
< 20	29 (69.05%)	34 (77.27%)		
≥ 20	13 (30.95%)	10 (22.73%)		

Note: NHT: Neoadjuvant Hormonal Therapy, BMI: Body Mass Index, RP: Radical Prostatectomy, PLND: Pelvic Lymph Node Dissection, ASA: American Society of Anesthesiologists Physical Status Classification System, PSA: Prostate-Specific Antigen, PSAD: Prostate-Specific Antigen Density, IPSS: International Prostate Symptom Score.

validation and training sets. The results showed no significant differences between the two groups in terms of age, BMI, surgical approach, Gleason score, ASA classification, clinical stage, comorbidities (diabetes, hypertension), preoperative PSAD, PSA, urinary flow rate, or IPSS scores (all P > 0.05), confirming their comparability (**Tables 1**, **2**).

Analysis of perioperative and postoperative treatment outcomes in the training set

Comparison of postoperative outcomes between the two groups showed that the proportion of patients with postoperative Gleason score ≥ 8 was significantly higher in the NHT group than in the non-NHT group (78.81% vs.

Table 3. Analysis of perioperative and postoperative treatment outcomes in non-NHT and NHT groups of the training set of patients

Item	Non-NHT Group (n = 134)	NHT Group (n = 151)	χ^2/t/Z	P
Postoperative Gleason Score			5.527	0.019
8-10	89 (66.42%)	119 (78.81%)		
≤ 7	45 (33.58%)	32 (21.19%)		
Perioperative Complications			3.003	0.083
None	107 (79.85%)	132 (87.42%)		
Present	27 (20.15%)	19 (12.58%)		
Long-term Complications			0.087	0.768
None	91 (67.91%)	105 (69.54%)		
Present	43 (32.09%)	46 (30.46%)		
Positive Surgical Margin			22.852	< 0.001
Negative	81 (60.45%)	129 (85.43%)		
Positive	53 (39.55%)	22 (14.57%)		
Operative Time (min)	148.00 [142.25, 154.00]	143.00 [137.00, 148.00]	5.580	< 0.001
Intraoperative Blood Loss (ml)	494.98±62.36	428.64±45.31	10.351	< 0.001
Hemoglobin Difference (ΔHB)	1.81 [1.50, 2.13]	1.73 [1.52, 1.91]	2.106	0.035
Postoperative Hospital Stay (days)	4.00 [3.00, 8.75]	5.00 [3.00, 10.00]	0.715	0.474
Gastrointestinal Function Recovery (days)	3.15 [2.90, 3.50]	3.00 [2.80, 3.20]	4.329	< 0.001

Note: HB: Hemoglobin, NHT: New Hormonal Therapy.

66.42%, P = 0.019), while the positive surgical margin rate was lower (14.57% vs. 39.55%, P < 0.001). The NHT group also exhibited shorter operative time (143.00 vs. 148.00 minutes, P < 0.001), less intraoperative blood loss (428.64±45.31 vs. 494.98±62.36 ml, P < 0.001), faster gastrointestinal function recovery (3.00 vs. 3.15 days, P < 0.001), and a slightly lower hemoglobin difference (ΔHB) with marginal significance (1.73 vs. 1.81, P = 0.035). There were no significant differences in perioperative and long-term complication rates or postoperative hospital stay between the two groups (all P > 0.05) (**Table 3**).

Correlation between PSA biochemical recurrence time and first recurrence PSA in patients with and without preoperative NHT

Analysis revealed that in the training set, the correlation coefficient between the time to first postoperative PSA elevation and the PSA value at the time of elevation was -0.65 (P < 0.001) for patients who received preoperative NHT treatment, indicating a significant negative correlation. For patients who did not receive preoperative NHT treatment, the correlation coefficient was -0.62 (P = 0.006), also demonstrating a significant negative correlation. Comparison of the absolute values of the correlation coefficients between the two groups shows no substantial difference in the correlation between the time to first PSA elevation and the corresponding PSA values for patients with and without preoperative NHT treatment, as illustrated in **Figure 1**.

Statistics on long-term complication types in training set patients undergoing two different surgical approaches

A comparison of long-term complications between robot-assisted RP+PLND (170 cases) and open RP+PLND (115 cases) showed that the robotic group had significantly lower incidences of urethral stricture (3.53% vs. 10.43%, P = 0.019), bladder neck contracture (1.76% vs. 8.70%, P = 0.007), and chronic pelvic pain (1.18% vs. 6.09%, P = 0.024) than the open group. There were no significant differences in the incidences of urinary incontinence, urine leakage, sexual nerve injury, intestinal obstruction, or adhesions between the two groups (all P > 0.05) (**Table 4**).

Comparison of 5-year OS, MFS, and BRFS between NHT and non-NHT groups

As shown in **Figure 1**, the NHT group demonstrated significantly higher 5-year OS (82.12%

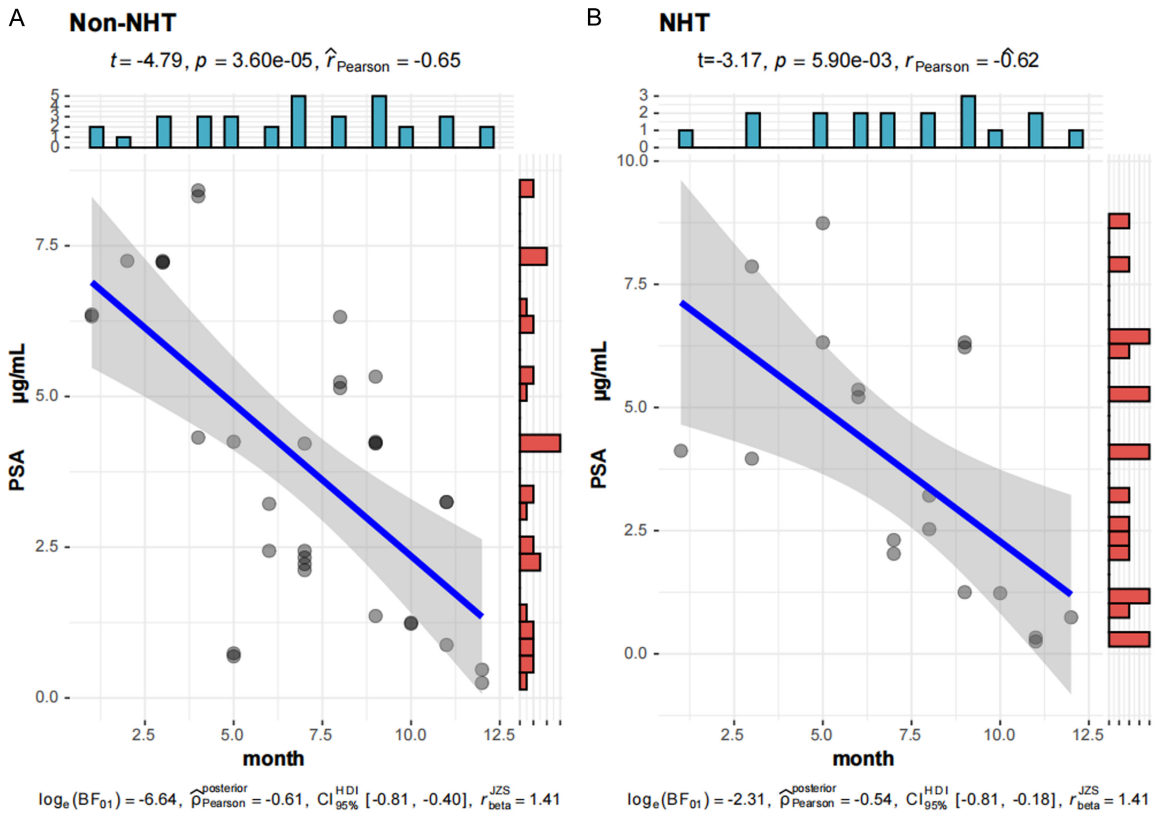


Figure 1. Correlation analysis of first PSA elevation time and postoperative PSA value in non-NHT (A) and NHT (B) groups. Note: PSA: Prostate-Specific Antigen, NHT: New Hormonal Therapy.

Table 4. Comparison of long-term complications between Robot-assisted (RARP) and Open (LRP) RP+PLND

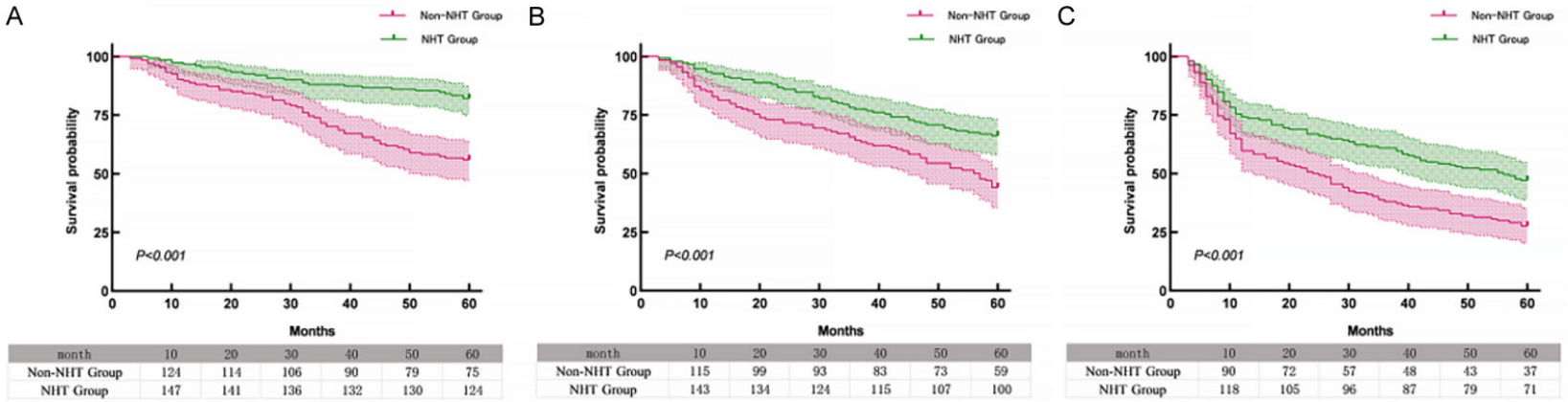
Item	Robot-assisted RP+PLND (n = 170)	Open RP+PLND (n = 115)	χ^2	P
Urinary Incontinence	18 (10.59%)	12 (10.43%)	0.002	0.565
Urine Leakage	4 (2.35%)	3 (2.61%)	0.015	0.596
Urethral Stricture	6 (3.53%)	12 (10.43%)	5.528	0.019
Bladder Neck Contracture	3 (1.76%)	10 (8.70%)	7.569	0.007
Sexual Nerve Injury	2 (1.18%)	2 (1.74%)	0.240	0.494
Intestinal Obstruction/Adhesions	1 (0.59%)	3 (2.61%)	2.024	0.182
Chronic Pelvic Pain	2 (1.18%)	7 (6.09%)	5.409	0.024

Note: RP: Radical Prostatectomy, PLND: Pelvic Lymph Node Dissection.

vs. 55.97%), MFS (66.23% vs. 44.03%), and BRFS (40.02% vs. 27.61%) rates than the non-NHT group (all P < 0.001), as depicted in **Figure 2**.

Univariate analysis of independent risk factors for 5-year mortality

Patients were divided into a mortality group (86 cases) and a survival group (199 cases) based on 5-year survival status. Univariate analysis showed that the mortality group had a significantly higher proportion of patients without NHT (68.60% vs. 37.69%, OR = 0.343, P < 0.001), open surgery (58.14% vs. 32.66%, OR = 2.344, P < 0.001), clinical stage cT3a (74.42% vs. 27.64%, OR = 0.193, P < 0.001), CN1 stage (44.19% vs. 20.10%, OR = 2.504, P < 0.001), and postoperative Gleason ≤ 7 (51.16% vs. 16.58%, OR = 0.263, P < 0.001). Additionally,



month	10	20	30	40	50	60
Non-NHT Group	124	114	106	90	79	75
NHT Group	147	141	136	132	130	124

month	10	20	30	40	50	60
Non-NHT Group	115	99	93	83	73	59
NHT Group	143	134	124	115	107	100

month	10	20	30	40	50	60
Non-NHT Group	90	72	57	48	43	37
NHT Group	118	105	96	87	79	71

Figure 2. 5-year OS (A), MFS (B), and BRFS (C) in NHT and non-NHT groups. Note: NHT: New Hormonal Therapy, OS: Overall Survival, MFS: Metastasis-free Survival, BRFS: Biochemical Recurrence-free Survival.

Table 5. Univariate analysis of risk factors significantly associated with 5-year mortality

Item	Mortality Group (n = 86)	Survival Group (n = 199)	OR	95% CI	P
Age (years)	65.19±11.22	64.91±13.14	1.003	0.987-1.020	0.711
BMI	25.61±4.22	24.91±4.27	1.031	0.981-1.084	0.225
NHT Exposure			0.343	0.217-0.541	< 0.001
Yes	27 (31.40%)	124 (62.31%)			
No	59 (68.60%)	75 (37.69%)			
Surgical Approach			2.344	1.526-3.600	< 0.001
Robot-assisted RP+PLND	36 (41.86%)	134 (67.34%)			
Open RP+PLND	50 (58.14%)	65 (32.66%)			
Clinical CT Stage			0.193	0.119-0.341	< 0.001
cT2c	22 (25.58%)	144 (72.36%)			
cT3a	64 (74.42%)	55 (27.64%)			
Clinical CN Stage			2.504	1.636-3.899	< 0.001
N0	48 (55.81%)	159 (79.90%)			
N1	38 (44.19%)	40 (20.10%)			
Urinary Flow Rate (mL/s)			1.597	0.888-2.873	0.205
≥ 15	55 (63.95%)	105 (52.76%)			
10-15	17 (19.77%)	48 (24.12%)			
< 10	14 (16.28%)	46 (23.12%)			
Hypertension			0.859	0.511-1.444	0.572
No	68 (79.07%)	162 (81.41%)			
Yes	18 (20.93%)	37 (18.59%)			
Postoperative Gleason Score			0.263	0.172-0.401	< 0.001
8-10	42 (48.84%)	166 (83.42%)			
≤ 7	44 (51.16%)	33 (16.58%)			
Preoperative PSAD	0.96 [0.64, 1.23]	1.03 [0.72, 1.29]	1.496	0.925-2.418	0.103
Preoperative PSA	30.08 [28.94, 36.97]	25.63 [22.09, 29.65]	1.187	1.135-1.242	< 0.001
Operative Time (min)	146.00 [142.00, 153.00]	144.00 [139.00, 150.50]	1.029	1.005-1.054	0.018
Intraoperative Blood Loss (ml)	490.69±65.54	446.50±57.53	1.010	1.006-1.013	< 0.001
Hemoglobin Difference (ΔHB)	1.71 [1.49, 2.06]	1.75 [1.52, 2.04]	0.939	0.520-1.695	0.835

Note: NHT: New Hormonal Therapy, BMI: Body Mass Index, RP: Radical Prostatectomy, PLND: Pelvic Lymph Node Dissection, PSA: Prostate-Specific Antigen, PSAD: Prostate-Specific Antigen Density, IPSS: International Prostate Symptom Score.

the mortality group had higher preoperative PSA levels (OR = 1.187, P < 0.001), longer operative time (OR = 1.029, P = 0.018), and more intraoperative blood loss (OR = 1.010, P < 0.001). Age, BMI, urinary flow rate, hypertension history, preoperative PSAD, and hemoglobin difference showed no significant association with mortality (all P > 0.05) (**Table 5**).

Multivariate analysis of independent risk factors for 5-year mortality

As shown in **Tables 6**, **7**, Cox regression analysis identified non-NHT treatment (β = 2.019, P < 0.001, OR = 7.528), open RP surgery (β = 1.522, P < 0.001, OR = 4.581), higher clinical CT stage (β = 1.309, P < 0.001, OR = 3.701), higher clinical CN stage (β = 0.648, P = 0.006, OR = 1.912), higher postoperative Gleason score (β = 1.34, P = 0.001, OR = 3.818), and higher preoperative PSA (β = 0.137, P < 0.001, OR = 1.147) as independent risk factors affecting 5-year survival. However, operative time and intraoperative blood loss had no significant impact on survival (both P > 0.05).

A Nomogram risk prediction model was constructed based on risk factors for mortality in the training set

As shown in **Figure 3**, the nomogram for predicting 5-year mortality risk was constructed based on the identified independent risk factors in the training set. Each predictor was assigned a point value according to its regression coefficient, with the total score corresponding to the estimated probability of mortality. The results revealed that NHT and preop-

Table 6. Variable assignment table

Variable	Type	Coding
NHT Exposure (X)	Categorical	No = 0, Yes = 1
Surgical Approach (X)	Categorical	Robot-assisted = 0, Open = 1
Clinical CT Stage (X)	Categorical	cT2c = 0, cT3a = 1
Clinical CN Stage (X)	Categorical	N0 = 0, N1 = 1
Postoperative Gleason Score (X)	Categorical	≤ 7 = 0, 8-10 = 1
Operative Time (X)	Categorical	≥ 38.5 = 3, < 38.5 = 4
Intraoperative Blood Loss (X)	Categorical	≥ 10.5 = 4, < 10.5 = 5
Preoperative PSA (Y)	Categorical	≥ 20 = 1, ≤ 20 = 0

Note: PSA: Prostate-Specific Antigen.

Table 7. Multivariate analysis of independent risk factors for 5-year mortality

Variable	B	Std. Error	P	95% CI		OR
				Lower	Upper	
NHT Exposure	2.019	0.366	< 0.001	3.674	15.423	7.528
Surgical Approach	1.522	0.28	< 0.001	2.646	7.932	4.581
Clinical CT Stage	1.309	0.312	< 0.001	2.008	6.82	3.701
Clinical CN Stage	0.648	0.234	0.006	1.21	3.021	1.912
Postoperative Gleason	1.34	0.288	0.001	2.17	6.717	3.818
Operative Time	0.012	0.014	0.375	0.985	1.041	1.012
Intraoperative Blood Loss	0.002	0.002	0.296	0.998	1.007	1.002
Preoperative PSA	0.137	0.032	< 0.001	1.077	1.222	1.147

Note: NHT: New Hormonal Therapy, PSA: Prostate-Specific Antigen.

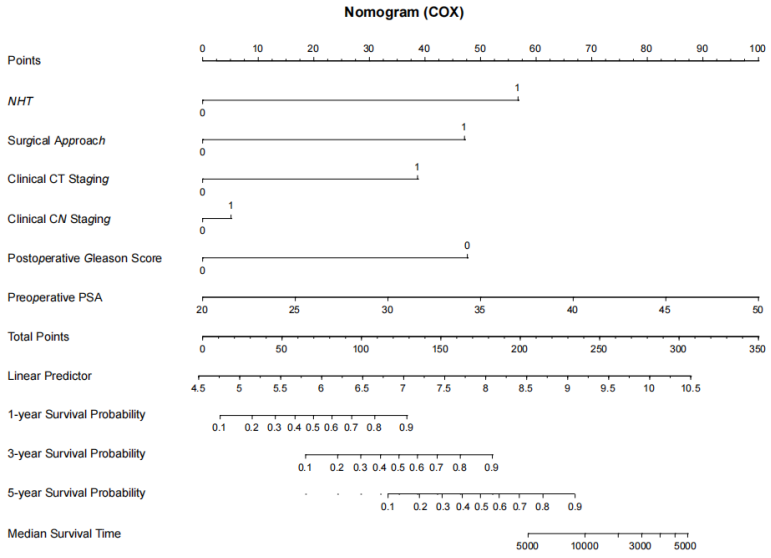


Figure 3. Nomogram for predicting 5-year mortality. Note: NHT: New Hormonal Therapy, PSA: Prostate-Specific Antigen.

erative PSA demonstrated the strongest associations with mortality risk, exhibiting a wide scoring range and substantial contributions to the total risk score. Surgical approach, clinical CT stage, and postoperative Gleason score were also correlated with mortality risk. In contrast, Clinical CN staging showed minimal score variation, indicating a weaker association with risk.

Validation of mortality risk factor model performance

The ROC curves for the training and validation cohorts are shown in **Figure 4**. The model achieved an AUC of 0.816 (95% CI: 0.784-0.881, P < 0.001) in the training set and 0.857 (95% CI: 0.801-0.914) in the validation set, indicating excellent discriminative ability. Calibration curves (**Figures 5**, **6**) demonstrated high consistency between predicted and actual probabilities in both the validation and training sets (training set: χ^2 = 2.217, P = 0.727; validation set: χ^2 = 0.784, P = 2.774). Meanwhile, the optimal cutoff values were determined using Youden's J statistic maximization method (J = sensitivity + specificity - 1) combined with clinical considerations. The optimal threshold was 0.32 for the training set (sensitivity: 82.44%, specificity: 79.01%) and 0.35 for the validation set (sensitivity: 80.25%, specificity: 81.39%). Considering clinical applicability, a final threshold of 0.35 was selected, providing high sensitivity to minimize missed diagnoses, while maintaining an acceptable false-positive rate (approximately 20%), which aligns with practical requirements for preoperative risk stratification in prostate cancer. These results indicate that the model

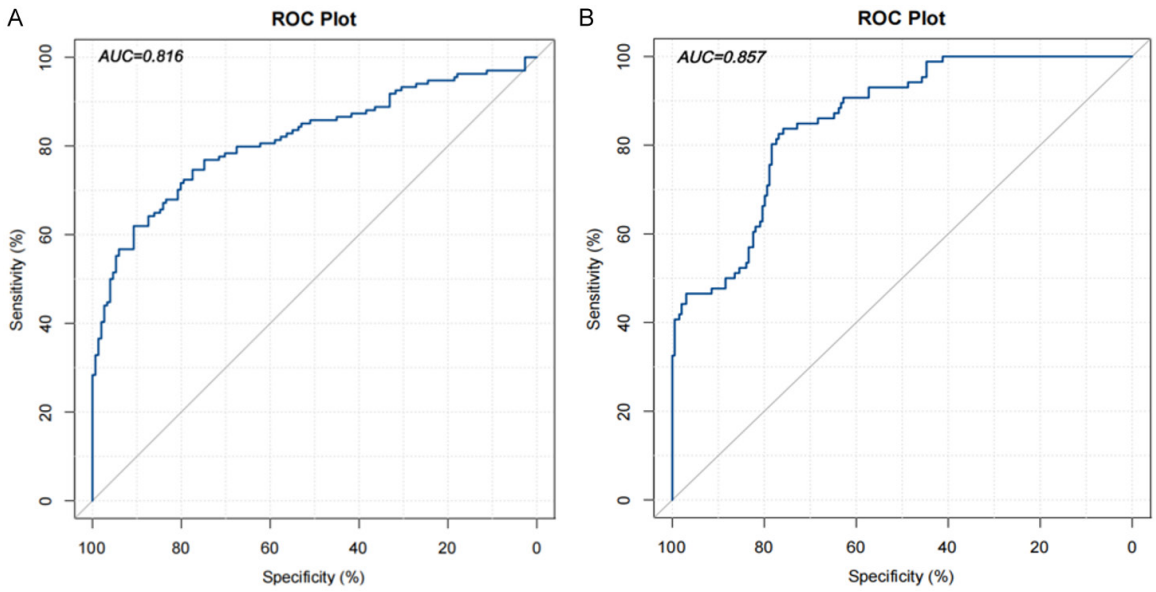


Figure 4. ROC curves for the model's predictive performance in training (A) and validation (B) sets.

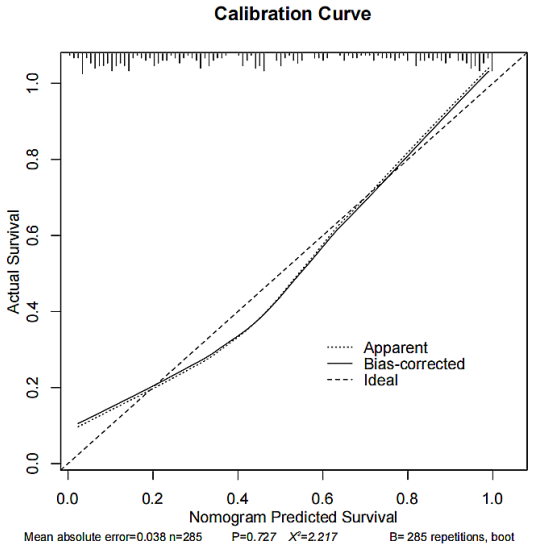


Figure 5. Calibration curve for the predictive model in the training set.

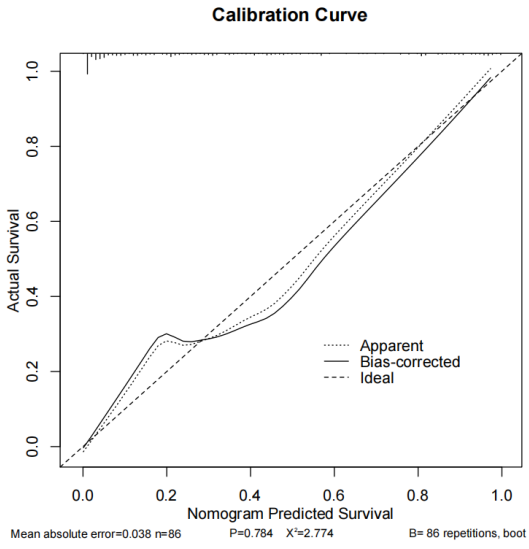


Figure 6. Calibration curve for the predictive model in the validation set.

is statistically robust and exhibits excellent discrimination and calibration performance.

Discussion

This study demonstrate that preoperative NHT could significantly reduce the positive surgical margin rate, shorten the operation time, and decrease the intraoperative blood loss. In addition, the clinical benefits of NHT in high-risk prostate cancer are primarily dependent on its remodeling of the tumor microenvironment (TME) and regulation of anti-tumor immunity [24, 25]. Mechanistically, by blocking the AR signaling pathway, NHT inhibits the activation of cancer-associated fibroblasts (CAFs), reduces the secretion of pro-invasive factors such as MMPs, and decreases the adhesion between tumors and surrounding tissues [26, 27]. This is directly associated with the significantly lower positive surgical margin rate in the NHT group (14.57% vs. 39.55%) observed in this

study. Meanwhile, NHT downregulates vascular endothelial growth factor (VEGF), inhibits tumor angiogenesis, reduces intraoperative blood loss (428.64±45.31 ml vs. 494.98±62.36 ml), and blocks the nutrient supply to micrometastases. In terms of immune regulation, NHT abrogates the immunosuppressive effect of androgens, promotes the activation of $CD8^+$ T cells, induces the polarization of tumor-associated macrophages (TAMs) toward the M1 phenotype, and reduces the secretion of immunosuppressive factors. Additionally, it downregulates the expression of PD-L1 and the infiltration of regulatory T cells, thereby reversing immune escape [24, 25]. These mechanisms synergistically improve surgical outcomes, eliminate residual tumor cells, and enhance 5-year survival rates. Moreover, the individual differences in these mechanisms provide a basis for precise stratification guided by molecular markers.

The results showed that the proportion of patients with high postoperative Gleason scores (≥ 8 points) in the NHT group did not decrease significantly, which may be related to the selective survival of tumor cells and treatment pressure. NHT mainly kills androgen-dependent cells by blocking the androgen receptor signaling pathway, while tumor cells with high Gleason scores often have a certain degree of androgen independence and are more likely to survive and enrich relatively during treatment [28]. In addition, although NHT reduces tumor volume and lowers the positive surgical margin rate (14.57% vs. 39.55%), it may lead to changes in tumor histological characteristics, such as the aggregation of poorly differentiated cells, rather than reducing the inherent malignant degree. Meanwhile, the sampling difference between preoperative biopsy and postoperative pathological evaluation may also affect the statistics of score proportion. This suggests that NHT focuses on improving surgical conditions, but has limited regulatory effect on the malignant grading of tumor cells [29]. The analysis also showed that regardless of whether NHT was administered or not, the time to first PSA elevation was significantly negatively correlated with the corresponding value, and the correlation coefficients of the two groups were similar, which was consistent with previous studies [31]. This indicates that although NHT may delay the time to PSA recurrence or reduce the PSA value at recurrence, it does not change the inherent correlation pattern between the two. It shows that NHT mainly delays disease progression by inhibiting the proliferation of androgen-dependent tumor cells, but has limited effect on changing the biological characteristics of tumor cells (such as proliferation rate and invasiveness) [30, 32].

A study involving patients with high-risk localized prostate cancer showed that the 5-year MFS, BRFS, and OS rates in patients who underwent NHT combined with radical prostatectomy were all superior to those in the non-NHT group [33], consistent with the conclusion of this study. Mechanistically, this is closely related to the role of NHT in reducing tumor stage and eliminating micro-metastases [34]. Preoperative ADT can induce tumor cell cycle arrest and reduce angiogenesis, thereby lowering the risk of postoperative recurrence and metastasis [35]. In addition, NHT may regulate the tumor microenvironment and enhance the body's immune surveillance, further improving the prognosis [36]. The results of this study support the use of NHT as a preoperative adjuvant treatment strategy for patients with high-risk prostate cancer, and the survival benefit is more significant especially for patients with high Gleason scores and advanced clinical stages.

Robot-assisted laparoscopic RP+PLND showed significantly lower long-term complication rates of urethral stricture, bladder neck contracture, and chronic pelvic pain compared to open surgery, which correlates with the advantages of robotic surgery including 3D vision, flexible robotic arm manipulation, and precise tissue suturing [37, 38]. Although oncological outcomes (e.g., positive surgical margin rate) between the two surgical procedures were not directly compared in this study, discrepancies in complication profiles may indirectly reflect patients' postoperative quality of life and their tolerance to subsequent therapeutic interventions.

Univariate and multivariate analyses identified non-NHT treatment, open surgery, high clinical stage, high postoperative Gleason score, and high preoperative PSA as independent risk factors for 5-year mortality. This highlights the need for closer follow-up and intensified thera-

py for patients with these characteristics. The constructed Nomogram model demonstrated good predictive efficacy, with NHT and preoperative PSA demonstrating the strongest association, providing a quantitative tool for individualized risk assessment. The nomogram constructed in this study exhibited distinct advantages and complementary value compared with the MSKCC model [39]. The MSKCC model incorporates pathological indicators such as PSA and Gleason score and has shown stable predictive performance (AUC 0.78-0.82) in prostate cancer patients who have not undergone NHT. However, it does not include NHT and robotic surgery, leading to a decreased AUC to 0.69 in high-risk NHT populations. The model in this study, for the first time, integrates preoperative NHT and data from novel surgical approaches, achieving an AUC of 0.816/0.857 in the training/validation sets. These findings indicate that the model is well suited for high-risk patients receiving NHT and effectively addresses an important gap in existing predictive tools.

Notably, this study has certain limitations. First, it is a single-center retrospective study, which inherently carries the risk of selection bias. Second, the duration of NHT (with a median of 4-6 months) and its discontinuation timing (2-4 weeks prior to surgery) were determined based on clinical experience alone, without the support of dose-effect analyses to validate their rationality. To address these gaps, future multicenter prospective randomized controlled trials (RCTs) are warranted. Such trials should aim to explore the optimal treatment cycle of NHT; concurrently, they should integrate molecular markers (e.g., DNA repair gene variations, tumor microenvironment characteristics) for precise patient stratification, thereby identifying subgroups of patients who are most likely to derive clinical benefits from NHT. Meanwhile, dynamic monitoring of circulating tumor cells (CTC) or cell-free tumor DNA (ctDNA) may serve as a viable approach to assess NHT efficacy in real time, providing more precise evidence to guide the formulation of personalized treatment strategies.

Conclusion

This study confirms that preoperative NHT improves surgical outcomes and long-term survival in high-risk prostate cancer patients without increasing perioperative risks. The consistent negative correlation between PSA recurrence time and value in both NHT and non-NHT groups suggests its potential as a universal indicator for recurrence risk assessment.

Disclosure of conflict of interest

None.

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