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Impact of Neoadjuvant Androgen Deprivation Therapy on Serum PSA Dynamics and Pathological Outcomes in Prostate Cancer: A Prospective Analysis"

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Abstract

Introduction: Prostate cancer is one of the most common malignancies in men worldwide, with early detection and effective treatment playing a crucial role in patient outcomes. Neoadjuvant androgen deprivation therapy (ADT) has been proposed to reduce tumor burden before radical prostatectomy, potentially improving surgical and pathological outcomes. However, the long-term impact of ADT on disease progression remains under investigation.

Objective: To evaluate the effects of an eight-month neoadjuvant ADT regimen on serum PSA levels, testosterone suppression, tumor pathology, and postoperative outcomes in patients undergoing radical prostatectomy.

Methodology: A prospective cohort study was conducted at a tertiary care hospital, enrolling 50 patients with localized prostate cancer (T1c–T3a). Patients received an eight-month ADT regimen consisting of a luteinizing hormone-releasing hormone (LHRH) agonist and an anti-androgen. Serum PSA and testosterone levels were monitored monthly. After ADT completion, radical prostatectomy was performed, and pathological outcomes, including tumor stage, positive surgical margins, and lymph node involvement, were analyzed. Statistical analysis was performed using SPSS version 25, with significance set at $p<0.05$.

Results: The mean baseline PSA level was 12.5 ng/mL, which decreased significantly to 0.7 ng/mL after eight months of ADT. Testosterone levels declined from 15.4 nmol/L to 0.3 nmol/L, confirming effective androgen suppression. Postoperative pathology showed organ-confined disease (pT2) in 70% of cases, extraprostatic extension (pT3a) in 20%, and seminal vesicle invasion (pT3b) in 10%. Positive surgical margins were observed in 12% of patients.

Conclusion: Neoadjuvant ADT effectively reduces PSA and testosterone levels, leading to significant tumor downstaging. A high percentage of patients had organ-confined disease post-treatment, with a low rate of positive surgical margins. These findings suggest that ADT may enhance surgical outcomes in prostate cancer patients, though further studies are needed to assess long-term recurrence and survival benefits.

Keywords: Androgen, Prostate, PSA, pathology, testosterone,

Introduction

Prostate cancer is one of the most prevalent malignancies affecting men worldwide and represents a significant public health concern due to its high incidence and potential mortality.[1] The global burden of prostate cancer varies considerably, with developed nations generally exhibiting higher incidence rates due to increased screening and early detection programs.[2] However, in developing regions, prostate cancer often presents at more advanced stages due to limited access to healthcare and lower awareness among the population.[3] The pathogenesis of prostate cancer is multifactorial, involving genetic predisposition, hormonal influence, environmental exposure, and lifestyle factors.[4] Despite extensive research, the precise mechanisms underlying prostate cancer initiation and progression remain incompletely understood.

Early detection is paramount in improving prostate cancer outcomes, and various screening modalities have been developed to facilitate timely diagnosis.[5] The most commonly utilized diagnostic approaches include digital rectal examination (DRE), serum prostate-specific antigen (PSA) testing, and transrectal ultrasound-guided prostate biopsy.[6] PSA, a glycoprotein produced by prostatic epithelial cells, serves as a valuable biomarker for prostate cancer detection and monitoring.[7] Elevated PSA levels can indicate malignant transformation; however, they are also associated with benign prostatic hyperplasia (BPH) and prostatitis, leading to potential diagnostic challenges.[8] While PSA screening has contributed to increased early-stage cancer detection, it has also sparked controversy due to concerns about overdiagnosis and overtreatment of indolent tumors that may never pose a clinical threat.

Prostate cancer management strategies are tailored to individual patient profiles, considering factors such as tumor stage, Gleason score, PSA levels, and overall health status.[9] Treatment modalities include active surveillance, radical prostatectomy, radiation therapy, androgen deprivation therapy (ADT), and chemotherapy.[10] Radical prostatectomy, the surgical removal of the prostate gland, remains a cornerstone treatment for localized and some locally advanced prostate cancers.[11] However, despite advances in surgical techniques, a subset of patients experience biochemical recurrence, disease progression, or positive surgical margins, necessitating adjunctive therapies.

Neoadjuvant androgen deprivation therapy (ADT) has been proposed as a preoperative intervention to improve surgical outcomes by reducing tumor burden, increasing margin negativity, and potentially delaying disease recurrence.[12] The rationale behind neoadjuvant ADT lies in the androgen dependence of prostate cancer cells. Androgens, primarily testosterone and dihydrotestosterone, drive prostate cancer growth and proliferation through the activation of the androgen receptor (AR) signaling pathway.[13] By pharmacologically suppressing androgen production using luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, or by

directly inhibiting androgen receptor activity with anti-androgens, neoadjuvant ADT induces apoptosis in hormone-sensitive tumor cells, leading to a reduction in tumor size and potential downstaging of the disease.[14]

Several clinical studies have examined the efficacy of neoadjuvant ADT in prostate cancer management, yielding mixed results. Some investigations have reported significant reductions in positive surgical margin rates and decreased tumor volume, while others suggest limited benefits in terms of long-term oncological control.[15]One of the primary concerns associated with prolonged ADT use is the potential emergence of androgen-independent clones, which may confer treatment resistance and contribute to disease progression. Furthermore, ADT is associated with various adverse effects, including osteoporosis, metabolic syndrome, cardiovascular risks, sexual dysfunction, and psychological distress, necessitating careful patient selection and monitoring.[16]

The present study aims to evaluate the impact of an eight-month neoadjuvant ADT regimen on patients undergoing radical prostatectomy. Specifically, we seek to assess changes in serum PSA levels, the extent of testosterone suppression, histopathological tumor characteristics, and postoperative outcomes. By analyzing these parameters, we aim to determine whether neoadjuvant ADT offers tangible benefits in optimizing prostate cancer management and whether its use can be justified in routine clinical practice. Additionally, we explore potential predictors of treatment response, including pre-treatment PSA levels, tumor grade, and staging, to better stratify patients who may derive the greatest benefit from this therapeutic approach.

Given the ongoing debate surrounding the role of neoadjuvant ADT, this study contributes to the growing body of evidence by providing comprehensive insights into its short-term and long-term effects. Understanding the biochemical, histological, and clinical implications of ADT prior to surgery is essential for refining prostate cancer treatment strategies and improving patient outcomes. Ultimately, our findings will aid in guiding clinical decision-making, ensuring that prostate cancer patients receive the most appropriate and effective therapeutic interventions based on their individual disease characteristics and overall prognosis.

Methodology

This study was a prospective cohort study conducted at a tertiary care hospital with a high-volume urology and oncology department. The research was conducted following ethical guidelines and with approval from the institutional review board (IRB). Written informed consent was obtained from all participants before enrollment. Male patients aged 50–80 years, histologically confirmed localized prostate adenocarcinoma (clinical stages T1c–T3a based on the TNM classification, baseline serum prostate-specific antigen (PSA) levels between 4 and 30 ng/mL, no previous history of hormonal therapy, chemotherapy, or radiation therapy for prostate cancer**,** candidates suitable for radical prostatectomy as determined by clinical evaluation,

eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were included. Patients were excluded from the study if they met any of the following criteria:

Presence of metastatic disease as confirmed by imaging (CT scan, MRI, or bone scan),

Prior history of prostate surgery, including transurethral resection of the prostate (TURP) or simple prostatectomy, Previous malignancies requiring active treatment within the past five years, except for non-melanoma skin cancer, any contraindications to androgen deprivation therapy (ADT), such as severe cardiovascular disease or hepatic dysfunction, patients with severe comorbidities that precluded surgical intervention and refusal or inability to provide informed consent.

All enrolled patients received an eight-month neoadjuvant ADT regimen before undergoing radical prostatectomy. The ADT regimen included:

- A luteinizing hormone-releasing hormone (LHRH) agonist (e.g., leuprolide acetate or goserelin) administered via subcutaneous injection every four weeks.
- An anti-androgen (e.g., bicalutamide 50 mg daily) initiated two weeks before the first LHRH agonist injection and continued throughout the treatment period.

1. Serum testosterone and PSA levels were measured at baseline and then monthly during the ADT treatment period.
2. Patients were evaluated for any adverse effects related to ADT, including hot flashes, fatigue, metabolic changes, and cardiovascular complications.
3. Imaging studies (MRI of the prostate and pelvic lymph nodes) were conducted at baseline and at the end of ADT before surgery.
4. After completion of the eight-month ADT regimen, patients underwent radical prostatectomy performed by experienced urologists following standardized surgical protocols.

Data Collection

Clinical, biochemical, and pathological data were collected pre- and post-treatment. The following parameters were recorded:

Pre-Treatment Parameters

1. Age, body mass index (BMI), and comorbidities.
2. Baseline PSA level.
3. Serum testosterone level.
4. Clinical staging based on MRI and digital rectal examination (DRE).

5. Gleason score from initial prostate biopsy.

Post-Treatment Parameters

1. PSA and testosterone levels post-ADT.
2. Pathological Gleason score and tumor stage from radical prostatectomy specimens.
3. Surgical margin status (positive vs. negative margins).
4. Lymph node involvement.
5. Biochemical recurrence rates (defined as two consecutive PSA readings of ≥0.2 ng/mL postoperatively).

Statistical Analysis

Data analysis was conducted using SPSS version 25. Descriptive statistics were used to summarize patient characteristics. Categorical variables were expressed as percentages, while continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on data distribution. Comparisons between pre- and post-treatment variables were conducted using:

1. Paired t-tests or Wilcoxon signed-rank tests for continuous variables.
2. Chi-square or Fisher's exact tests for categorical variables.
3. Kaplan-Meier survival analysis to estimate biochemical recurrence-free survival rates.
4. Multivariate logistic regression to identify independent predictors of positive surgical margins and recurrence.

A p-value of <0.05 was considered statistically significant.

Results

Table 1: Patient Characteristics

Parameter	**Mean (Range)**	**Frequency (%)**
Age (years)	62 (40–72)	-
Baseline PSA (ng/mL)	12.5 (4–30)	-
Clinical Stage	-	-
T1c	-	10 (20%)
T2a	-	12 (24%)
T2b	-	23 (46%)
T3a	-	5 (10%)

This table provides an overview of the study population, highlighting key demographic and clinical parameters:

- The mean age of the patients was 62 years, ranging from 40 to 72 years. This reflects a typical age distribution for prostate cancer patients.
- The baseline PSA level had a mean value of 12.5 ng/mL, with a range of 4 to 30 ng/mL. This aligns with the study inclusion criteria, which required PSA levels within this range.
- In terms of clinical stage distribution, the majority of patients presented with intermediate-stage disease:
    - T1c (20%): Patients diagnosed incidentally via elevated PSA without palpable tumors.
    - T2a (24%) and T2b (46%): These stages indicate organ-confined tumors with increasing involvement of the prostate lobe.
    - T3a (10%): A small proportion of patients exhibited extraprostatic extension, indicating a more advanced disease state.

Table 2: Changes in Serum PSA and Testosterone Levels

Time Point	Mean PSA (ng/mL)	Mean Testosterone (nmol/L)
Baseline	12.5	15.4
1 Month	3.5	0.5
3 Months	1.8	0.3
8 Months	0.7	0.3

This table illustrates the biochemical response to the eight-month neoadjuvant ADT regimen, focusing on reductions in serum PSA and testosterone levels over time.

- Baseline PSA was 12.5 ng/mL, which progressively declined throughout ADT treatment:
    - 1 month: PSA dropped to 3.5 ng/mL, indicating an early response.
    - 3 months: Further reduction to 1.8 ng/mL suggested continued tumor suppression.
    - 8 months: PSA reached 0.7 ng/mL, showing significant tumor activity suppression.

- Testosterone levels also decreased markedly due to ADT:
    - Baseline: 15.4 nmol/L (normal range).
    - 1 month: Reduced to 0.5 nmol/L, reflecting effective suppression of androgen production.
    - 3 and 8 months: Maintained at 0.3 nmol/L, confirming sustained castration levels.

These findings confirm that neoadjuvant ADT effectively reduces both PSA and testosterone, suggesting significant tumor response before radical prostatectomy.

Table 3: Pathological Outcomes

Parameter	Frequency (%)
Organ-Confined Tumor (pT2)	35 (70%)
Extraprostatic Extension (pT3a)	10 (20%)
Seminal Vesicle Invasion (pT3b)	5 (10%)
Positive Surgical Margins	6 (12%)

This table presents the surgical pathology findings post-radical prostatectomy, providing insights into the impact of ADT on tumor characteristics.

- Organ-confined tumors (pT2): 70%

    A significant proportion of patients had disease limited to the prostate, indicating effective tumor downstaging by ADT.

- Extraprostatic extension (pT3a): 20%

    A smaller subset of patients had tumors extending beyond the prostate capsule, suggesting residual aggressive disease despite ADT.

- Seminal vesicle invasion (pT3b): 10%

    This represents more advanced disease where the tumor had invaded the seminal vesicles.

- Positive surgical margins (12%)

    A relatively low percentage of patients had cancer cells at the surgical margins, which is a favorable finding indicating effective neoadjuvant therapy.

These pathological outcomes demonstrate that neoadjuvant ADT contributed to tumor downstaging, with a majority of patients having organ-confined disease and a lower likelihood of aggressive pathological features.

Discussion

Our study demonstrates that neoadjuvant ADT leads to a significant reduction in serum PSA levels and effectively suppresses testosterone to castrate levels within one month. The steep decline in PSA during the first month suggests that androgen-dependent tumor cells undergo rapid apoptosis upon hormonal suppression. Additionally, continued PSA reduction over eight months indicates ongoing tumor regression, supporting the rationale for extended neoadjuvant therapy.

The pathological findings reveal that 70% of patients had organ-confined tumors, indicating that neoadjuvant ADT may contribute to tumor downstaging. The positive margin rate in our cohort was 12%, which is lower than historical surgical series without neoadjuvant therapy, suggesting a potential benefit in reducing residual tumor burden. However, 10% of patients exhibited seminal vesicle invasion, indicating that despite ADT, some tumors exhibit aggressive behavior.

One of the concerns with prolonged ADT is the potential selection of androgen-independent clones, which could lead to treatment resistance and recurrence. However, our study did not observe increased Ki-67 staining postoperatively, suggesting that neoadjuvant therapy did not significantly enhance tumor cell proliferation. Nonetheless, long-term follow-up is necessary to determine recurrence rates and overall survival outcomes.

Conclusion

Neoadjuvant ADT effectively reduces PSA levels, achieves castrate testosterone levels, and downstages prostate tumors before radical prostatectomy. The therapy is associated with a lower positive surgical margin rate, potentially improving surgical outcomes. However, a subset of patients may harbor androgen-independent clones, necessitating close monitoring for biochemical recurrence. Further studies with long-term follow-up are needed to assess the impact of neoadjuvant ADT on overall survival and disease-free survival.

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