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RESEARCH ARTICLE

Peri-Adjuvant Androgen Deprivation Therapy for Patients with High-Risk Prostate Cancer Undergoing Radical Prostatectomy – The Concept Behind and Initial Outcomes

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ABSTRACT

Background: Radical prostatectomy (RP) is increasingly employed as part of a multimodal strategy for treating locally advanced and/or high-risk prostate cancer (LA-HR CaP), though its oncological adequacy alone is limited due to the risk of micrometastatic disease. While androgen deprivation therapy (ADT) with radiation remains the traditional standard, the optimal integration of ADT with RP is yet to be defined. This study introduces the concept of *periadjuvant ADT*, which combines neoadjuvant ADT, RP, and adjuvant ADT for a total duration of 18 months.

Methods: A retrospective study was conducted on 127 patients with LA-HR CaP who received neoadjuvant ADT (Degarelix ± Abiraterone/Apalutamide) for 3–6 months, followed by RP and continuation of ADT postoperatively. Treatment regimens were individualized based on patient preference and affordability. Data were collected on clinical, operative, pathological, and follow-up parameters. Kaplan-Meier analysis was used for survival outcomes.

Results: The majority (67.7%) of patients were staged as T3, with nodal involvement in 26%. Neoadjuvant therapy was well tolerated, with no significant intraoperative complications (99.2% complication-free). Positive surgical margins and nodal positivity were seen in 24.4% and 26.8% of patients, respectively. Adjuvant radiation was required in 29.1% of cases. At a median follow-up of 12 months, overall survival was 97.6%, with a cumulative Kaplan-Meier survival rate of 94.6%.

Conclusion: Periadjuvant ADT combining neoadjuvant and adjuvant hormonal therapy with RP is a feasible and safe approach for LA-HR CaP in a resource-limited setting. Early results suggest acceptable surgical morbidity and promising short-term oncological outcomes. Longer follow-up is warranted to evaluate survival benefits and refine treatment duration guidelines.

Introduction

Radical prostatectomy (RP) has now become the standard of care for patients with localized prostate cancer (CaP).[1] The procedure has been widely adopted since the advent of robotic surgery.[2] A better understanding of surgical techniques has allowed this surgery to be performed with minimal complications and excellent functional recovery.

Localized CaP is defined as a tumor confined to the prostate on digital rectal examination. The European Association of Urology (EAU) further subdivides localized cancer into three different risk groups—low, intermediate, and high-risk—based on PSA levels and Gleason scores.[3,4] Locally advanced and/or high-risk prostate cancer (LA-HR CaP) includes tumors that extend beyond the prostatic capsule (cT3, cT4, or N1 disease) or cases where PSA levels exceed 20 ng/mL, or the Gleason score is greater than 7.[3,4]

Although RP remains a standard treatment option for clinically localized high-risk prostate cancer, providing excellent local control, patients with high-risk disease remain at considerable risk for recurrence after surgery. Patients with LA-HR CaP have a higher risk of local and systemic recurrence due to possible microscopic disease in the local area or metastatic sites.[5] Hence, multimodal therapy for these patients aims to address both the primary tumor and microscopic disease.[6]

Traditionally, LA-HR CaP patients have been treated with multimodal therapy, which includes androgen deprivation therapy (ADT) along with radiation therapy (RT) to the prostate.[7] The duration of ADT in such patients is typically 2–3 years.[7,9] This approach has resulted in excellent overall survival (OS) and disease-free survival (DFS).[7,9]

However, patients with locally advanced CaP often experience troublesome local symptoms such as bladder outflow obstruction and ureteric obstruction, which frequently require additional operative procedures for symptom relief.[10,11] On the other hand, upfront RP for LA-HR CaP carries a risk of multifocal positive margins, necessitating additional therapy such as ADT or early salvage RT to the prostatic bed.[12,13] Limited expertise in performing RP in LA-HR CaP patients in the past contributed to ADT and RT becoming the standard of care for this cohort.[14,15]

According to EAU guidelines, RP can be considered for patients with locally advanced and/or high-risk CaP only as part of a multimodal therapy approach.[16] The components of multimodal therapy include the use of ADT and RT in appropriate circumstances.[17] However, the timing and duration of these treatments remain undefined.[18]

In the past, most studies have been conducted in patients with low-risk CaP, where the probability of extraprostatic microscopic disease is minimal.[19] Neoadjuvant ADT and RP have been tested recently in patients with high-risk CaP, demonstrating an improvement in negative surgical margins but not in OS.[20-23] This may be because of the fact that patients received neoadjuvant ADT and no additional treatment in the postoperative setting was contemplated. In comparison to patients undergoing RT for similar disease specifications, the ADT has not been continued in the postoperative period in patients undergoing RP.

Given the recent trend toward surgical management of LA-HR CaP, long-term outcomes and guideline recommendations on ADT dosage and duration in this subset remain loosely defined. Although the impact of ADT has primarily been observed in margin status rather than overall oncological outcomes, ongoing studies highlight the need to address this gap before establishing definitive guideline recommendations regarding the dosage, duration, and timing of ADT in combination with RP for LA-HR CaP patients.

On the other hand, as mentioned above, combining systemic ADT with local therapy (RT) has improved overall survival in these patients. However, this approach fails to address issues related to local symptoms.[24] Furthermore, in patients with long life expectancy, addressing both the local and micrometastatic components using RP and ADT, respectively, may be more beneficial, as the long-term side effects of radiation therapy become more pronounced after a decade.[25]

In recent years, significant advancements have been made in ADT with the introduction of androgen receptor pathway inhibitors (ARPIs) such as Abiraterone acetate, Enzalutamide, and Apalutamide.[26] These drugs have been well-established in the metastatic setting.[26]

Ongoing trials are evaluating the role of these drugs (in addition to standard ADT) in the neoadjuvant setting.[28] ADT for LA-HR CaP can be administered in the form of luteinizing hormone-releasing hormone (LHRH) agonists (e.g., Goserelin, Leuprolide) or LHRH antagonists.[29,30]

We propose the introduction of a new term, Periadjuvant ADT, for patients undergoing RP. This regimen would include neoadjuvant ADT for 3–6 months, followed by RP, with the continuation of ADT as adjuvant therapy for a total duration of 18 months. This study aims to assess the safety and short-term oncological efficacy of periadjuvant therapy, which includes neoadjuvant and adjuvant ADT (with or without ARPI), in patients undergoing radical prostatectomy for locally advanced high-risk prostate cancer.

Materials and Methods

A retrospective study was conducted following ethics committee approval (AMH-C-S-023/03-23). Data were collected from a prospectively maintained database that included details of all patients with locally advanced and/or high-risk CaP. As this was a preliminary study in a resource-limited setting, patients were offered Degarelix, Degarelix + Abiraterone, or Degarelix + Apalutamide, with treatment selection based on preference and affordability.

All included patients had their diagnosis confirmed via transrectal ultrasound (TRUS)-guided biopsy, and staging was performed using PSMA PET MRI. Disease status was assessed through clinical and radiological evaluation, with imaging and pathology reviewed by a single radiology and pathology team for consistency, as per routine practice.

Periadjuvant therapy, which combines neoadjuvant therapy (3–6 months), RP and adjuvant ADT for a total of 18 months, was initiated after obtaining informed consent. Patients were allocated to one of the treatment arms based on their choice. Collected data included demographics, pre-treatment cancer status, operative and post-operative outcomes, pathology, functional and oncological follow-up, and the need for further treatment.

STATISTICAL ANALYSIS

Data were tabulated in Microsoft Excel and analyzed using SPSS (IBM, version 28.0). Categorical variables were presented as frequency (percentage), continuous variables as Mean ± SD, and skewed data as Median (IQR). Kaplan-Meier survival analysis was performed to assess survival probabilities.

Results

A total of 127 patients were included in the study. The majority (48.8%) were in the 61–70 years age group, with 30.7% aged above 70 years. Comorbidities were present in 70.1% of patients, and all cases (100%) were histologically confirmed as adenocarcinoma (Table 1).

Table.1: Demographic factors

Parameters	**(n=127), n (%)**
Age (In years)	
51 – 60	26 (20.5)
61 – 70	62 (48.8)
>70	39 (30.7)
Co-morbidities	
Yes	89 (70.1)
No	38 (29.9)
Biopsy results	
Adenocarcinoma	127 (100.0)

Preoperative evaluation showed that 31.5% had PSA levels ≥40 ng/mL, while 22.8% had PSA <10 ng/mL. PSMA with MRI staging classified 67.7% as T3, with nodal involvement in 15% and distant metastasis in 7.1%. Preoperative biopsy-based Gleason grading (GG) identified 29.1% as GG5, with similar distributions for GG2 (23.6%), GG3 (21.3%), and GG4 (21.3%) (Table 2).

Table 2: Clinical factors

Parameters (Pre operative)	**(n=127) n (%)**
PSA	
<10	29 (22.8)
10 – 19	31 (24.4)
20 – 29	19 (15)
30 – 39	8 (6.3)
≥40	40 (31.5)
PSMA with MRI	
T2	35 (27.6)
T3	86 (67.7)
T4	6 (4.7)
N	
0	108 (85.0)
1	19 (15.0)
M (Oligometastatic disease)	
0	118 (92.9)
1	9 (7.1)
Gleason grading (Pre operative biopsy)	
GG1	6 (4.7)
GG2	30 (23.6)
GG3	27 (21.3)
GG4	27 (21.3)
GG5	37 (29.1)

The mean operative time was 248.9 ± 57.9 minutes, with a median docking time of 180 minutes (IQR: 150–225). Blood loss was <250 mL in 93.7% of cases, and intraoperative complications were rare (0.8%) (Table 3).

Table 3: Intra-operative factors

Parameters	**(n=127), n (%)**
Operative time (In Mins)	
Mean ± SD	248.9 ± 57.9
Range	120 – 480
Dock time (In Mins)	
Mean ± SD	192.9 ± 52.7
Median (IQR)	180 (150 – 225)
Range	100 – 375
Blood loss	
<250 ml	119 (93.7)
>250 ml	8 (6.3)
Complications	
No	126 (99.2)
Yes	1 (0.8)

Final histopathology revealed that 65.35% had T3b disease, with nodal metastasis in 26%. Postoperative GG showed 30.0% as GG5, and 31.5% exhibited treatment-related histologic effects. Surgical margins were positive in 24.4% of cases, while 26.8% had positive lymph nodes (Tables 4–6).

Table 4: Post-operative factors

Parameters	**(n=127), n (%)**
HPE Results	
T0	1(0.8)
T2	22(17.32)
T3a	19(14.96)
T3b	83(65.35)
T4	2(1.57)
N	
N0	94(74.0)
N1	33 (26.0)
Gleason grading (post operative) *	
GG1	2 (1.6)
GG2	14 (11.0)
GG3	14 (11.0)
GG4	19 (15.0)
GG5	38 (30.0)
Not available due to ADT effect	40 (31.5)

*Post operative GG was assigned in cases that were possible to be determined by the pathologist for the purpose of the study.

Table 5: Margin

Margin	**(n=127), n (%)**
Margin positivity (multifocal)	
Yes	31 (24.4)
No	96 (75.6)

Table 6: Tumor

Tumor	**(n=127), n (%)**
Nodes positivity	
Yes	34 (26.8)
No	93 (73.2)

Regarding preoperative treatment, 63.8% received Degarelix alone, and 30.7% received Degarelix with Abiraterone. The majority (85.7%) were on an 18-month Degarelix regimen. Radiation therapy was administered to 29.1% of patients, with 22.8% receiving prostate bed radiation (Table 7). Although all the patients were advised a 18-month course of ADT, based on the tumor board recommendations, in patients (n=18) who had excellent response, ADT was discontinued in 12 months.

Table 7: Pre operative treatment

Parameters	**(n=127), n (%)**
Treatment given (Pre operative)	
Degarelix	81 (63.8)
Degarelix + Abiraterone	39 (30.7)
Degarelix + Apalutamide	7 (5.5)
Duration of Degarelix	
12 Months	18 (14.2)
18 Months	109 (85.7)
Radiation therapy	
Yes	37 (29.1)
No	90 (70.9)
Radiation therapy	
RT metastatic site	8 (6.3)
RT Prostate bed	29 (22.8)
Not given	90 (70.9)
Last follow-up (In months)	
Median (IQR)	12 (6 – 48)
Range	4 – 60

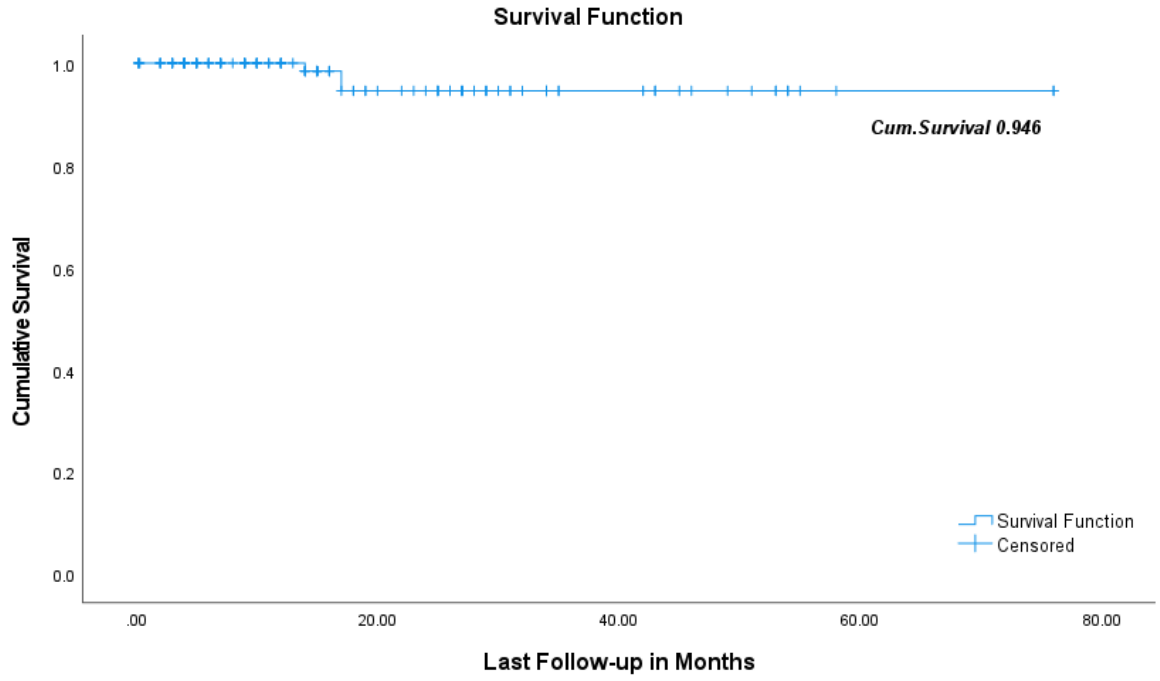
At a median follow-up of 12 months (IQR: 6–48 months), overall survival was 97.6%, with three deaths recorded—two due to neuroendocrine small cell carcinoma and one due to stroke (Table 8).

Table 8: Outcome

Parameters	**(n=127), n (%)**
Survival status	
Alive	124 (97.6)
Expired	3 (2.4)
Reason for death	
Neuroendocrine small cell carcinoma	2 (1.6)
Stroke	1 (0.8)
Last follow-up (In months)	
Median (IQR)	12 (6 – 48)
Range	4 – 60

The Kaplan-Meier survival curve (Figure 1) demonstrates a cumulative survival rate of 94.6% at the last follow-up, indicating favourable overall survival outcomes with a gradual decline over time.

Figure 1: Kaplan-Meier Survival Curve for Overall Survival



Discussion

The treatment landscape for LA-HR CaP is evolving, with an increasing emphasis on multimodal strategies. While ADT with RT has been the traditional standard of care,[7,9] RP is now being reconsidered for its role in local tumor control and symptom relief.[30] However, RP alone is often inadequate for oncological control due to the high risk of microscopic extraprostatic disease, necessitating systemic therapy to optimize outcomes.[5,6]

Our study introduces the novel concept of periadjuvant ADT, which integrates neoadjuvant therapy (3–6 months), RP, and adjuvant ADT (total of 18 months). This structured approach aims to maximize oncological control by addressing both local and micrometastatic disease.[16,17] Neoadjuvant ADT can downstage tumors, improve surgical margin status, and reduce tumor burden, facilitating a better surgical outcome.[19-23] Post-RP adjuvant ADT aims to suppress residual microscopic disease, potentially delaying recurrence.[18] The combination of RP and ADT thus offers a more comprehensive treatment strategy compared to either modality alone.[34,35]

Our findings suggest that periadjuvant ADT is safe and feasible, with no major adverse effects related to Degarelix-based neoadjuvant therapy.[29,30] Importantly, there were no intraoperative complications, reaffirming that neoadjuvant ADT does not compromise the surgical field or increase technical difficulty.[12,13] Postoperative outcomes demonstrated acceptable morbidity, supporting the viability of RP in this subset of patients.[31] There was one patient who developed a postoperative pelvic hematoma and was managed conservatively. The pathological outcomes, including margin and nodal status, further validate the oncological safety of this approach.[32,33] With the advent of new robotic platforms and the increasing use of robotic surgery for complex oncological procedures, surgical expertise has improved. Consequently, the trend of LA-HR CaP through surgery is expected to rise in the future. Therefore, the oncological management protocol with ADT needs to be better defined and standardized.[34-36]

Compared to conventional strategies, periadjuvant ADT offers several advantages. RP alone, while effective in controlling local symptoms, does not adequately address micrometastatic disease, which remains the principal driver of recurrence.[5] Conversely, ADT with RT, though oncologically effective, does not offer the same degree of symptom relief in patients with significant obstructive symptoms.[10,11] Integrating ADT before and after RP within a periadjuvant framework bridges this gap, ensuring both local and systemic control.[16] Furthermore, with ARPI agents such as Abiraterone and Apalutamide demonstrating survival benefits in metastatic settings,[26,27] their incorporation into earlier disease stages within a periadjuvant framework may further enhance oncological control.[28] In this study, the Kaplan-Meier survival analysis demonstrated a cumulative survival rate of 94.6% at the last follow-up, reflecting favorable overall survival outcomes with a gradual decline over time (Figure 1). These findings support the potential role of intensified periadjuvant therapy in optimizing disease control and long-term survival in high-risk prostate cancer patients.

Despite its promise, our study has certain limitations. Being a retrospective study and a lack of a control arm limits direct comparison to standard treatments such as ADT + RT or RP alone.[14,15] The short follow-up duration prevents definitive conclusions on long-term survival outcomes, and the heterogeneous treatment selection based on patient preference and affordability introduces potential selection bias. Additionally, as guidelines on ADT in the surgical setting remain undefined, the optimal duration and intensity of ADT in combination with RP require further investigation.[18]

The findings from this study support the safety and feasibility of periadjuvant ADT, but its long-term oncological impact remains to be fully understood. Larger prospective, randomized trials are essential to validate its effectiveness and refine its role in treatment guidelines.[17] Future studies should focus on defining the ideal duration and intensity of ADT, evaluating the role of ARPIs in this setting, and identifying biomarkers for patient selection.

Periadjuvant ADT represents a paradigm shift in the management of LA-HR CaP, offering a structured, multimodal strategy that maximizes oncological control while preserving the benefits of RP.[16,17,37,38] Our preliminary findings indicate that this approach is safe and feasible, with the potential to redefine standard treatment protocols for high-risk prostate cancer. However, further long-term studies are warranted to establish its definitive role in clinical practice.[17,18]

Conclusion

Periadjuvant ADT with RP for LA-HR CaP is a viable and safe option, demonstrating promising short-term oncological and functional outcomes. The absence of significant perioperative complications and acceptable morbidity suggests its feasibility in clinical practice. However, long-term follow-up and randomized controlled trials are essential to validate its oncological benefits and define its optimal role in treatment protocols for LA-HR CaP.

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SUPPLEMENTARY MATERIAL

Peri Adjuvant Androgen Deprivation Therapy for prostate cancer

Indications:

1. High risk prostate cancer [PSA > 20 / T3a / T3b /T4 bladder neck involvement/ N1 pelvic nodes]
2. Oligometastatic prostate cancer

Drugs & its usage :

1. Degarelix / Firmagon 240 mg loading dose & monthly maintenance for 18 months
2. One of the following drugs can be used in addition to above
3. Abiraterone 1gm - 1 hour before coffee for 18 months & Wysolone 5mg once after food for 18 months/ Apalutamide 60mg 1-0-1 for 18 months
4. After the 4th month of the therapy patient can be considered for the surgery
5. If the patient has node positive disease /oligometastatic disease it would be better to do a reimaging before considering surgery.

Post surgery planning

1. All patients will complete 18 months of above therapy
2.Additional radiation to prostatic bed and lymph nodes will be considered (after Tumour Board recommendation and patient's consent) for those with

a. Multi-margin positivity
b. Perinodal spread
c. > 1 node positive

Special Circumstance:

In patients with oligometastatic disease additional Metastasis Directed Therapy (MDT) will be advised with SBRT covering the bone mets. This can be done at any point of time during the patient treatment journey.