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Perioperative effects of neoadjuvant androgen-deprivation therapy prior to radical prostatectomy: comparative study

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The objective: **to analyze effects of neoadjuvant androgen-deprivation therapy (NADT) prior to radical prostatectomy (RP) on perioperative outcomes with identification of it safety profile.**
Materials and methods**. From January 2015 to December 2021, we collected retrospective data of patients with prostate cancer (PCa) who underwent RP to assess perioperative and pathological outcomes. The data included age, body mass index (BMI), serum prostate-specific antigen (PSA) level, clinical stage, NADT usage, time of surgical intervention, estimated blood loss (EBL), perioperative complications, blood transfusion rate (BTR), length of hospital stay, pathological stage, Gleason score (GS) of the biopsy and pathological specimen, surgical margin and lymph node status.**
Results**. Of the 175 RP's performed, 84 (48%) were in NADT group and 91 (52%) were in comparison group. The time of surgical intervention, EBL, BTR, length of hospital stay did not differ statistically significantly between the groups. Nevertheless, rate of positive surgical margin (PSM) was statistically significant lower in NADT group (10.7 vs 52.7%, p < 0.001) rather than in comparison group.**
Conclusions**. NADT prior to RP did not increase the rate of perioperative complications and did not significantly impact perioperative outcomes. However, it was associated with improved pathological outcomes.**
Keywords: *prostate cancer, neoadjuvant androgen-deprivation therapy, radical prostatectomy, laparoscopic, endoscopic extraperitoneal, perioperative outcomes.*

Вплив неоад'ювантної андроген-деприваційної терапії перед радикальною простатектомією на періопераційний перебіг: порівняльне дослідження

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Мета: ціллю цього дослідження було проаналізувати вплив неоад'ювантної андроген-деприваційної терапії (нАДТ) перед радикальною простатектомією (РПЕ) на періопераційний перебіг та визначити профіль її безпеки.
Матеріали та методи. З січня 2015 по грудень 2021 року було зібрано ретроспективні дані від пацієнтів, хворих на рак передміхурової залози, яким проведено РПЕ для оцінки періопераційних та патологічних результатів. Зібрана інформація включала вік, індекс маси тіла, рівень простатоспецифічного антигену, клінічну стадію, застосування нАДТ, тривалість хірургічного втручання (ХВ), об'єм крововтрати (ОК), періопераційні ускладнення, частоту гемотрансфузій (ЧГ), тривалість стаціонарного лікування, патологічну стадію, індекс Глісону після біопсії та ХВ, статус хірургічного краю та лімфатичних вузлів.
Результати. У дослідження було включено 175 пацієнтів, яким виконано РПЕ: 84 (48%) були в групі нАДТ, а 91 (52%) – у групі порівняння. Час ХВ, ОК, ЧГ, а також термін перебування на стаціонарному лікуванні статистично вірогідно не відрізнялися між групами. Проте частота позитивного хірургічного краю була значно нижча в групі нАДТ (10,7 проти 52,7%, p < 0,001), ніж в групі контролю.
Висновки. НАДТ перед РПЕ не підвищує ризик інтраопераційних ускладнень та не впливає на загальні періопераційні результати, але знижує частоту несприятливих патологічних знахідок.
Ключові слова: *рак передміхурової залози, неоад'ювантна андроген-деприваційна терапія, радикальна простатектомія, лапароскопічна, ендоскопічна екстраперитонеальна, періопераційні результати.*

Prostate cancer (PCa) is a geographically variable disease, ranking as the most common cancer in men in some countries [1] and the second most common in others [2]. It is also the second leading cause of cancer-related death among men globally. In Ukraine, according to data from the National Cancer Registry, there were 7,220 newly diagnosed cases of PCa from 2021 to 2022, marking an 11.4% increase compared to 2020 [3]. Radical prostatectomy (RP) is the standard of care in the management of localized, and potential component of multimodal treatment strategy of locally-advanced PCa. This surgery can be performed through various approaches, including open radical prostatectomy (ORP), laparoscopic (LRP), endoscopic extraperitoneal (EERP) and robotic (RRP) techniques [4, 5].

Androgen-deprivation therapy (ADT) is an essential component of an alternative, equally effective option for initial local therapy in the form of external beam radiotherapy (EBRT) for treating both the aforementioned forms PCa [4–6], as well as in adjuvant and/or salvage approaches in cases of adverse pathological features and/or disease progression following RP [7].

Neoadjuvant androgen-deprivation therapy (NADT) prior to RP remains a controversial treatment option [8]. Previous studies have demonstrated improvements in surgical margin status and a reduction in the frequency of positive lymph nodes (PLN), however, these advantages have not been extrapolated to long-term oncological outcomes. Furthermore, prolonged use of ADT is associated with the development of side effects: metabolic syndrome, osteoporosis, gynecomastia, anemia, and an increased risk of cardiovascular mortality [9, 10]. Consequently, current clinical guidelines do not recommend the use of NADT prior to RP [4, 5].

Over the past decade, scientific literature has reported that cases of complete pathological response (pT0) under the influence of NADT are associated with improved progression-free survival and a reduced risk of cancer-specific mortality [11–15]. This has consequently increased scientific interest in studying this treatment option. Furthermore, due to Russia's full-scale invasion of Ukraine, many patients with PCa are unable to receive highly specialized medical care in a timely and comprehensive manner, further highlighting the relevance of studying the application of NADT prior to RP.

The objective: to analyze the impact of NADT prior to RP on perioperative outcomes and to determine the safety profile of its application.

MATERIALS AND METHODS

This study is a non-randomized, retrospective, single-center study conducted in accordance with the Helsinki Declaration of the World Medical Association on "Ethical Principles for Medical Research Involving Human Subjects" and approved by the Bioethics Committee of the SI "Academician O. F. Vozianov Institute of Urology of NAMS of Ukraine" (Protocol N 6 dated December 14, 2023).

A total of 994 medical records of patients with PCa who underwent RP at the SI "Academician O. F. Vozianov Institute of Urology of NAMS of Ukraine" between January 2015 and December 2021 were analyzed. Among them, 114 received NADT, and from this cohort, 84 patients who met the inclusion criteria were included in the study group. The comparative group consisted of 91 patients who did not receive neoadjuvant therapy and also met the inclusion criteria.

Androgen deprivation therapy

In this study gonadotropin-releasing hormone analogues such as leuprolide, goserelin and triptorelin were used for ADT. The choice for medication depended on the surgeon preference.

The duration of NADT varied from 1 to 12 months. The decision was made upon the discussion between patients and physicians. Since the specific criteria for selection have not been officially stated, we typically advise the NADT for those patients associated with high or very high risk of disease progression or patient hesitated in choosing a treatment method.

Inclusion criteria:

1. Confirmed diagnosis of clinical PCa with a stage of ≤ T4 prior to initial systemic and local treatment based on magnetic resonance imaging (MRI).
2. Availability of data before the initiation of primary therapy regarding:
   – Gleason score (GS) after biopsy;
   – Presence of data on prostate-specific antigen (PSA) levels;
   – Availability of data on prostate volume (PV) determined by MRI and/or transrectal ultrasound (TRUS).
3. Availability of data of PV after NADT determined by MRI and/or TRUS.
4. Availability of data on RP: method, duration, intraoperative estimated blood loss, hemotranfusion, and intraoperative complications.

Exclusion criteria:

1. Presence of oligometastatic and/or metastatic PCa.
2. Intermittent ADT prior to surgical treatment.
3. Radiation and/or systemic chemotherapy in the medical history prior to RP.
4. NADT with anti-androgen drugs in monotherapy mode.
5. Lack of or insufficient data in medical records.

Baseline characteristics and preoperative parameters

The following data were collected from all patients: age, body mass index (BMI), PSA (ng/ml), clinical stage (TNM classification), GS after biopsy, and risk group classification (National Comprehensive Cancer Network (NCCN) classification).

Perioperative outcomes

Perioperative outcomes included: duration of surgery (minutes), estimated blood loss (EBL) (ml), perioperative complications, which included the rate of blood transfusions (RBT), damage to the bladder, rectum, ureter, intestine, or major vessels.

Pathological outcomes

All macroscopic specimens were examined by an experienced pathologist according to the clinical guidelines of the NCCN, reporting on pathological stage, GS, as well as surgical margin status and lymph nodes. A positive surgical margin (PSM) was defined as the presence of tumor cells extending beyond the surface of the examined macroscopic specimen.

Statistical analysis

A descriptive analysis of the data was conducted. The Mann–Whitney test was used to determine the statistically significant differences between the medians (interquartile range) of the parameters in the study groups. Categorical variables were analyzed using the χ^2 test (Pearson's criterion) and Two-Way ANOVA. Before performing the Two-Way ANOVA, Levene's test of equality of error variances was conducted. A p-value > 0.05 was considered indicative of homogeneity of variances. Statistical processing of the data was performed using IBM SPSS Statistics 22 software, with p values < 0.005 considered statistically significant.

RESULTS AND DISCUSSION

Demographic data and preoperative parameters are presented in Table 1. The NADT group and the comparison group did not statistically differ in median age (64.5 vs 65 years; p = 0.734), BMI (27.8 vs 27.2 kg/m^2; p = 0.202), clinical stage (x^2 = 7.1; p = 0.213), initial PSA level (20.9 vs 18.6 ng/ml; p = 0.258) and GS af-

ter biopsy ($x^2 = 7.2$; p = 0.217). No statistically significant difference was found between the studied groups regarding the risk stratification of individual patients ($\chi^2 = 7.2$; p = 0.125). However, the preoperative PV was statistically significantly smaller in the NADT group (36.1 [11.2–164.2] vs 43.2 [45–56.6] cm^3; p < 0.004), and there was a statistically significant difference between the two study groups regarding the techniques of RP ($\chi^2 = 16.2$; p < 0.001).

Perioperative results (Table 2) demonstrated that the duration of surgical intervention (200 vs 210 minutes; p = 0.553), EBL (200 vs 200 ml; p = 0.816), and complication rate (7.1 vs 4.4%; $\chi^2 = 0.612$; p = 0.324) did not significantly differ. No statistically significant differences were noted between the NADT group and the control group regarding the frequency of adjacent organ injury (2.4 vs 2.2%; $\chi^2 = 2.2$; p = 0.519) and the length of hospital stay (20 vs 19 days; p = 0.174).

Pathological results (Table 3) revealed that the pathological stage ($\chi^2 = 13.2$; p = 0.039) and the PSM rate (10.7 vs 52.7%; $\chi^2 = 35.1$; p < 0.001) were significantly lower in the NADT group than in the comparative group, while there was no statistically significant difference between the study groups regarding the pathological GS ($\chi^2 = 6.6$; p = 0.244) and the rates of positive lymphnodes (PL) (19 vs 23%; $\chi^2 = 0.425$; p = 0.321).

Subgroup analysis of perioperative results (Table 4) showed that EBL did not statistically significantly differ based on whether the PCa was localized or locally advanced, nor did the use of NADT. Specifically, the EBL for localized PCa was 277.7 ± 221.8 vs 323.30 ± 229.21, and for locally advanced PCa, it was 279.8 ± 175.3 vs 304.1 ± 209.5 respectively, with F = 0.99; p = 0.753. Similarly, surgery duration did not differ based of PCa form and NADT use (F = 0.086; p = 0.770).

However, Table 5 showed that, the surgical technique of RP: ORP (372.2 vs 411.1 ml), LRP (260.3 vs 225.5 ml), EERP (244.2 vs 342.4 ml) had a significant effect on EBL. These differences were statistically significant (F = 5.7; p = 0.004). In contrast, the use of NADT did not have a statistically significant effect on this parameter (F = 1; p = 0.318).

Neoadjuvant systemic therapy before surgical intervention is standard in treating solid tumors of various localizations (breast, rectum, and bladder), which increases the resectability of tumors while reducing the rates of PSM, subsequently improving perioperative outcomes and distant oncological results [11].

Table 1

Demographic data and preoperative parameters of NADT and comparative groups

Demographic data	NADT group (n = 84)	Comparative group (n = 91)	p-value
Clinical parameters			
ORP, n (%)	29 (34.5)	9 (10.0)	< 0.001^{x2}
LRP, n (%)	29 (34.5)	49 (54.0)	
EERP, n (%)	26 (31.0)	33 (36.0)	
Age (years), median (range)	64.5 (48–78)	65 (51–77)	0.734*
BMI (kg/m^2), median (range)	27.8 (21.6–40.2)	27.2 (20.1–40.6)	0.202*
PSA (ng/ml), median (range)	20.9 (2.7–242.0)	18.6 (2.5–163.5)	0.258*
Prostate Volumes (cm^3), median (range)	36.1 (11.2–164.2)	43.2 (45.0–56.6)	0.004*
Clinical stage, n (%)			
T2a	5 (6.0)	4 (4.4)	0.213^{x2}
T2b	6 (7.0)	11 (12.1)	
T2c	43 (51.2)	52 (57.1)	
T3a	4 (4.8)	8 (8.8)	
T3b	24 (28.6)	16 (17.6)	
T4	2 (2.4)	0	
GS after biopsy, n (%)			
GS ≤ 6	28 (33.3)	30 (33.0)	0.217^{x2}
GS = 3 + 4 (7A)	25 (29.8)	33 (36.3)	
GS = 4 + 3 (7A)	13 (15.5)	6 (6.6)	
GS = 4 + 4 (8)	11 (13.1)	11 (12.0)	
GS = 4 + 5 (9A)	4 (4.8)	7 (7.7)	
GS = 5 + 4 (9B)	3 (3.5)	1 (1.1)	
GS = 5 + 5 (10)	0 (0)	3 (3.3)	
NCCN stratification group, n (%)			
Low	1 (1.2)	–	0.125^{x2}
Intermediate favorable	11 (13.1)	20 (22.0)	
Intermediate unfavorable	15 (17.8)	19 (20.9)	
High	21 (25.0)	28 (30.8)	
Very high	36 (42.9)	24 (26.3)	

Notes: * – comparison of groups by Mann–Whitney test; x^2 – comparison of categorical variables by x^2-test; ORP – open radical prostatectomy; LRP – laparoscopic radical prostatectomy; EERP – endoscopic extraperitoneal radical prostatectomy; NADT – neoadjuvant androgen-deprivation therapy; BMI – body mass index, PSA – prostate-specific antigen; GS – Gleason score.

Table 2

Perioperative parameters of NADT and comparative groups

Perioperative Parameters	NADT group, n = 84	Comparative group, n = 91	p-value
Operative time (min), median (range)	200 (105–435)	210 (120–420)	0.553*
Estimated blood loss (ml), median (range)	200 (50–1200)	200 (50–800)	0.816*
Hemotransfusion rate, n (%)	6 (7.1)	4 (4.4)	0.324^{x2}
Adjacent organ injury, n (%)			
Rectum Ureters Urinary bladder Major vessels	1 (1.2) 1 (1.2) – –	1 (1.1) – – 1 (1.1)	0.519^{x2}
Length of hospital stay (days), median (range)	20 (5–41)	19 (8–65)	0.174*

Notes: *– comparison of groups by Mann–Whitney test; x^2 – comparison of categorical variables by x^2-test; NADT – neoadjuvant androgen-deprivation therapy.

Table 3

Pathological outcomes of NADT and comparative groups

Pathological Parameters	NADT Group, n = 84	Comparative Group, n = 91	p-value
Pathological Stage, n (%)			
T_0 T_{2a} T_{2b} T_{2c} T_{3a} T_{3b} T_4	1 (1.2) 7 (8.3) 8 (9.5) 36 (42.8) 5 (6.0) 26 (31.0) 1 (1.2)	– 2 (2.2) 4 (4.4) 35 (38.5) 17 (18.7) 33 (36.2) –	0.039^{x2}
Pathological GS, n (%)			
GS ≤ 6 GS = 3 + 4 (7A) GS = 4 + 3 (7A) GS = 4 + 4 (8) GS = 4 + 5 (9A) GS = 5 + 4 (9B) GS = 5 + 5 (10)	26 (30.9) 31 (37.0) 16 (19.1) 4 (4.7) 3 (3.6) 4 (4.7) –	21 (23.0) 32 (35.2) 20 (22.0) 10 (11.0) 7 (7.7) 1 (1.1) –	0.244^{x2}
Positive surgical margin, n (%)	9 (10.7)	48 (52.7)	$< 0.001^{x2}$
Positive lymph node, n (%)	16 (19.0)	21 (23.0)	0.321^{x2}

Notes: *– comparison of groups by Mann–Whitney test; x^2 – comparison of categorical variables by x^2-test; NADT – neoadjuvant androgen-deprivation therapy; GS – Gleason score.

Table 4

Estimated blood loss and operative time according to PCa form in NADT and comparative groups

NADT group, n = 84		Comparative group, n = 91		p-value
Localized PCa, n = 54	Locally advanced PCa, n = 30	Localized PCa, n = 67	Locally advanced PCa, n = 24	
Estimated Blood Loss (ml), mean (± SD)				
277.7 ± 221.8	323.30 ± 229.21	279.8 ± 175.3	304.1 ± 209.5	0.753^{A}
Operative time (min), mean (± SD)				
209.7 ± 56.5	205.1 ± 39.4	212.6 ± 53.2	213.1 ± 50.1	0.770^{A}

Notes: ^{A} –comparison of NADT and comparative groups according to disease form by Two-Way ANOVA test; PCa – prostate cancer; NADT – neoadjuvant androgen-deprivation therapy.

Table 5

Estimated blood loss according to variant of surgical approach and NADT usage

Surgical approach	Estimated blood loss (ml) mean (± SD)		p-value
	NADT group, n = 84	Comparative group, n = 91	
ORP	372.2 ± 202.9	411.1 ± 116.6	0.318^{A1}
LRP	260.3 ± 264.7	225.5 ± 151.4	0.004^{A2}
EERP	244.2 ± 176.8	342.4 ± 210.3	0.157^{A3}

Notes: ^{A} – the significance of the impact of treatment measures on expected blood loss was assessed by Two-Way ANOVA test (^{A1} – neoadjuvant androgen-deprivation therapy usage; ^{A2} – variant of surgical approach; ^{A3} – sum impact of neoadjuvant androgen-deprivation therapy usage and variant of surgical approach); ORP – open radical prostatectomy; LRP – laparoscopic radical prostatectomy; EERP – endoscopic extraperitoneal radical prostatectomy; NADT – neoadjuvant androgen-deprivation therapy.

The use of ADT causes biological changes in prostate tumors that contribute to reduced oncocell progression and survival. This is accompanied by metabolic changes, particularly the atrophy of intact prostate tissue, apoptosis of tumor cells, and a decrease in PSA levels. Clinically, these effects are confirmed by the smaller prostate volume in the NADT group (36.1 vs 43.2 cm^3; $p < 0.005$) compared to the comparative group in this study.

In the conducted study, no improvements regarding the duration of surgical intervention ($p = 0.553$), EBL ($p = 0.816$), or complication rates ($p = 0.324$) were demonstrated. However, it is worth noting that the number of ORP procedures was performed more frequently in the NADT group (34.5 vs 10%; $p < 0.001$), and the EBL in this type of surgery was higher (372.2 vs 411.1 ml; $p = 0.004$), which explains the absence of improvements regarding this parameter. Moreover, literature data suggest that the use of NADT can improve perioperative outcomes, including the duration of surgical intervention, EBL, and complication rates. For example, Sun et al. reported a reduction in the duration of intervention (108.9 vs 118.5 minutes; $p = 0.007$) and EBL (110.7 vs 138.2 ml; $p < 0.001$), Sangkum et al. reported 185 vs 195 minutes ($p < 0.018$) and 300 vs 500 ml ($p < 0.001$), and Hu et al. reported 115 vs 145 minutes ($p < 0.005$) and 50 vs 100 ml ($p = 0.0263$) respectively [16–18]. The length of hospital stay also did not differ significantly between the two study groups. Additionally, this parameter in this study differ from those published by Sangkum et al. – 6 days and Wallerstedt et al. – 3.3 days [17, 19], long hospital stay in this study caused by the fact that in the institution where the study was conducted, discharge from hospital occurs after a full rehabilitation period.

Analysis of pathological outcomes did not reveal statistically significant differences between study groups regarding the pathological GS. However, literature data suggests that the use of NADT either results in no differ or even higher values for this parameter [17, 20]. It is important to note that the use of ADT in this cohort of patients results in changes in cellular structure, which may prevent adequate assessment of the GS and consequently reduce its prognostic potential as a predictor of subsequent disease progression [21]. Moreover, our study revealed a statistically significant difference in pathological stage ($p < 0.05$) between the study groups, primarily due to its reduction in the NADT group. Additionally, in one patient from the NADT group, no tumor cells were found, indicating complete pathological response [13, 14], which according to literature data is a predictor of favorable progression-free survival following radical prostatectomy [22].

One of the first documented improvements due to NADT is a reduction in the frequency of PSM. Some researchers report a decrease in its frequency in the NADT group [8, 12, 16, 18], while others show different results regarding PSM but note a reduction in the frequency of PL [23]. In this study, the PSM rate in the NADT group was significantly lower (10.7 vs 52.7%; $p < 0.001$) than in the comparative group; however, no statistically significant difference was noted in the frequency of PL ($p = 0.321$). Therefore, PSM are an unfavorable pathological feature that significantly increases the risk of biochemical recurrence following RP. However, it should be noted that the morphological changes in the prostate caused by ADT do not allow for definitive conclusions regarding the influence of this parameter in the context of NADT on the further course of the disease.

It is important to note that the studied patient groups were homogeneous not only concerning clinical parameters (except prostate volume) but also regarding their stratification into risk groups. A satisfactory safety profile of NADT prior to RP creates the conditions for the formulation of an expanded design for further studies on this issue, with adequate evaluation of distant oncological outcomes and the development of individualized approaches to this type of therapy.

This study has some limitations. One of them is its retrospective design. The second limitation is the lack of a unified approach to prescribing ADT, which was done solely based on the decision of individual physicians, usually outside the facility where the surgical interventions were performed. The third no less important point is that the surgical interventions were performed by different surgeons, which increases the possibility of discrepancies in the assessment of results.

CONCLUSIONS

This study demonstrated that the use of NADT prior to RP does not increase the risk of intraoperative complications and does not significantly affect the perioperative course. Moreover, the application of neoadjuvant therapy potentially reduces estimated blood loss, leads to a reduction in tumor volume in the prostate with a subsequent decrease in pathological stage, improves tumor resectability, and reduces the frequency of positive surgical margins. Further prospective studies aimed at detailing the impact of the type and duration of ADT are necessary to evaluate the true influence of NADT not only on the perioperative course but also on distant oncological outcomes in general.

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