Does Neoadjuvant Androgen Deprivation Therapy Before Primary Whole Gland Cryoablation of the Prostate Affect the Outcome?

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OBJECTIVE To evaluate the effect of neoadjuvant androgen deprivation therapy (NADT) on the outcomes for primary whole gland prostate cryoablation (CRYO). NADT before CRYO has sometimes been used for prostate volume reduction, with some theoretical benefit toward improving disease control. NADT has been shown to be beneficial for biochemical disease-free survival (bDFS) with radiotherapy but not in conjunction with radical prostatectomy.

METHODS We retrospectively compared risk-stratified cohorts according to whether they had received NADT. bDFS was defined using the Phoenix criteria, and postoperative morbidity and complications were compared.

RESULTS A total of 1761 men had undergone NADT before CRYO and 2727 had not. No differences were found in the incidence of postoperative incontinence, pad use, potency, or fistula formation. The rate of urinary retention at 12 months was slightly lower for those who had not undergone NADT (0.8% vs 1.2%, $P = .015$). No difference was found in bDFS between the NADT and non-NADT men (66.9% vs 66.5% at 5 years). When stratified by risk, however, a statistically significant difference was found between the NADT and non-NADT men only in the intermediate-risk cohort (71.3% vs 65.9%; $P < .013$).

CONCLUSION bDFS was statistically similar between the NADT and non-NADT men, except in the intermediate-risk cohort, with slightly improved survival for those undergoing NADT. No significant difference was found in the complication rates. These data do not support the routine use of NADT for men undergoing primary whole gland cryoablation, although its use could be considered for men with larger prostates or men in the intermediate-risk category. UROLOGY 83: 379–384, 2014. Published by Elsevier Inc.

Despite recent controversies surrounding prostate-specific antigen (PSA) testing, it remains true that in the post-PSA era, more cases of prostate cancer (CaP) are being detected earlier and at a lower stage and grade, allowing the clinician and patient a wide array of treatment options.[1] Minimally invasive surgical techniques are becoming the standard for many diseases, and the treatment of localized CaP is no exception. Cryoablation of the prostate (CRYO) is 1 such option that has increased in use during the past several years.

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Since its recognition in 1996 by the American Urological Association as an acceptable treatment option, CRYO has become increasingly useful as a therapeutic modality for organ-confined disease. With current data showing promising biochemical disease-free survival (bDFS) and similar morbidity among all treatment options, CRYO can be an attractive option for select patients.[2,3]

Androgen deprivation therapy (ADT) has been enlisted in the treatment of both locally advanced and metastatic CaP in both neoadjuvant and adjuvant settings. One effect of ADT on the prostate gland itself includes volume reduction, a characteristic that has been useful primarily combined with radiotherapy (RT), for which it is believed that ADT sensitizes CaP to the effects of ionizing radiation.[4,5] Historically, ADT has been used in the neoadjuvant setting before CRYO for volume reduction of glands >40-50 g, although this has not been standardized. Randomized studies have shown that ADT before RT improves both cancer-specific and overall

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survival in men with localized, but high-risk, disease.[6-8] The same beneficial effect has not been shown to be evident for hormonal therapy before radical prostatectomy.[9,10]

We present a study based on data obtained through the Cryo On-line Database (COLD) regarding neoadjuvant ADT (NADT) before primary whole gland CRYO. CRYO is unique in its role in the treatment of localized CaP in that it is not extirpative nor is it RT. We postulated that NADT before CRYO would produce favorable outcomes similar to those for NADT before RT.

MATERIAL AND METHODS

The COLD registry is a secure web-based data collection and management tool designed specifically for CRYO. It has been sponsored by an unrestricted research grant from Endocare, and the data are held and analyzed by the independent research company, Watermark, under the direction of an independent physician board.[2] Data are sent to the registry from >40 sources in the United States, including information such as patient demographics, PSA level before and after treatment, Gleason score, disease stage, and complication reports. We used this registry to collect data on men who had undergone CRYO as their initial treatment of localized CaP in the United States and stratified them into 2 groups according to whether they had received NADT. All patients who had received only postoperative adjuvant hormonal therapy were excluded from the present analysis. Each group was then further stratified into 3 cohorts according to the D'Amico risk criteria.[11] Historically, biochemical recurrence after RT has been defined using 1 of 2 criteria. The American Society for Radiation Oncology criteria are defined by 3 consecutive increases greater than a PSA nadir, each separated by 3 months, backdated to the midpoint between the first and second increase.[12] The Phoenix criteria define biochemical recurrence as the nadir PSA level plus 2 ng/mL ≥6 months after treatment.[13] For the purposes of the present study, we used the latter. All statistical analyses of the data were performed by the Indianapolis-based privately owned company Watermark Research Partners. Statistical analysis of the demographic data between the 2 groups was performed using Student's *t* test. We analyzed bDFS at 6 and 12 months and then annually ≤5 years after surgery for the NADT and non-NADT men and for each risk-stratified cohort within the 2 major groups. Kaplan-Meier curves were constructed, and log-rank testing was performed to compare the bDFS rates between the 2 major groups and between each risk-stratified cohort. To determine whether NADT had any effect on postoperative complications after CRYO, we compared the rates of incontinence, pad use, potency, urinary retention, and postoperative rectourethral fistulas at 12 months after surgery using chi-square analysis.

RESULTS

Of the 4488 men included in the present study, 1761 had received ADT before prostate CRYO and 2727 had not. The average follow-up period was 961 days in the NADT group and 979 days in the non-NADT group. The patient and disease characteristics are outlined in Table 1. Patient age and Gleason score were similar, except for the incidence of Gleason score 8 and 9, which was greater for the NADT group. More men in the NADT group vs the non-NADT group presented with a higher clinical stage (stage T2b or higher in 42% vs 23%, $P < .0001$), higher PSA level (10-20 ng/mL in 21% vs 14%, and >20 ng/mL in 11% vs 5%, $P < .0001$), and higher D'Amico risk (high risk 42% vs 23%, $P < .0001$). These men were categorized as low (n = 981), intermediate (n = 2135), and high (n = 1372) risk. The men in the NADT group had larger glands than their non-NADT counterparts across all risk groups (40.19 vs 31.97 overall, 40.50 vs 32.53 low, 43.51 vs 32.06 intermediate, and 36.85 vs 31.15 high, $P < .0001$). Overall, no differences were found between the NADT and non-NADT groups in terms of postoperative incontinence (1.6% vs 1.7%, $P = .9159$), pad use (3.4% vs 3.6%, $P = .0598$), urinary retention, potency, and fistula formation at 12 months after surgery (Table 2). A small, but statistically significant, trend was seen toward lower urinary retention at 12 months postoperatively, favoring the non-NADT group (0.8% vs 1.2%, $P = .0150$). For men potent at baseline, no difference in the ability to achieve erections sufficient for intercourse with or without assistance was found at 12 months postoperatively between the NADT and non-NADT groups (30.4% vs 33.8%, $P = .1949$). Finally,

Table 1. Patient demographics

Variable	Non-NADT (n = 2727)	NADT (n = 1761)	*P* Value
Mean age (y)	70.3	69.9	.3235
Gleason score			<.0001
<6	469 (17)	330 (19)	
6	1040 (38)	621 (35)	
7	774 (28)	446 (25)	
8	208 (8)	213 (12)	
9	81 (3)	85 (5)	
10	9 (0.3)	7 (0.3)	
Missing	146 (5)	59 (32)	
Clinical stage			<.0001
<T2b	2105 (77)	1016 (58)	
≥T2b	622 (23)	745 (42)	
PSA at baseline (ng/mL)			<.0001
<4	434 (16)	267 (15)	
4-<10	1744 (64)	911 (52)	
10-<20	386 (14)	371 (21)	
≥20	125 (5)	198 (11)	
Missing	38 (1)	14 (1)	
Risk*			<.0001
Low risk	682 (25)	299 (17)	
Intermediate risk	1408 (52)	727 (41)	
High risk	637 (23)	735 (42)	
Prostate volume (cm^3)			<.0001
Overall	31.97	40.19	
Low risk	32.53	40.50	
Intermediate risk	32.06	43.51	
High risk	31.15	36.85	

NADT, neoadjuvant androgen-deprivation therapy; PSA, prostate-specific antigen.

Data presented as n (%); column percentages determined by the number of subjects identified at the top of the column.

* Low-risk, PSA <10 ng/mL, Gleason score <7, and stage <T2b; moderate-risk, not low or high risk; high-risk, PSA >20 ng/mL, Gleason score >7, or stage >T2b.