Title

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Neoadjuvant androgen deprivation therapy (NADT) Leads to Immediate Impairment of Vitality/ Hormonal and Sexual Quality of Life: Results of a Multi-Center, Prospective Study

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Abstract

Objectives—To evaluate the immediate effects of neoadjuvant androgen depravation therapy (NADT) on health-related quality of life (HRQOL) among patients undergoing RT for newly diagnosed prostate cancer.

Methods—The Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) Consortium is a prospective, multi-institutional study. HRQOL is measured with the EPIC-26 questionnaire. Differences in patient reported HRQOL were observed between pre-

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treatment and 2 months after NADT start (and before definitive RT) with significant differences evaluated by paired t-test.

Results—From among 450 subjects who completed the EPIC-26 before and 2-months after NADT start, 71 received NADT prior to proceeding with definitive RT. Patients receiving NADT experienced significant impairment in vitality/hormonal ($p<0.0001$) and sexual ($p<0.0001$) HRQOL after NADT initiation. The mean ± standard deviation vitality/hormonal score fell from an average of 94.1 ± 9.7 before NADT to 78.7 ± 16.3 two months after NADT initiation; and sexual HRQOL fell from a mean of 51.7 ± 31.1 pre-treatment to 32.3 ± 26.1 after NADT initiation. Both of these HRQOL domain changes exceeded the thresholds for clinical significance. Patients receiving NADT also experienced a significant impairment in urinary continence ($p=0.024$), although this difference did not meet criteria for clinical significance.

Conclusions—In this analysis, patients receiving NADT experience significant impairment in sexual and vitality/hormonal HRQOL even before starting definitive radiation therapy. The significant impact of this therapy on HRQOL needs to be considered before initiating NADT in men where there is no clear evidence of clinical benefit.

Keywords

PROST-QA; neoadjuvant androgen deprivation therapy; quality of life; radiotherapy; prostate cancer

Introduction

Enthusiasm is emerging regarding the possible benefits of new androgen-suppressive therapies in the treatment of primary, early stage prostate cancer, as evidenced by various open clinical trials combining radiation therapy (RT) and novel neoadjuvant androgen deprivation therapy (NADT) strategies (1, 2). Because of this, there is a growing need to quantify the immediate impact on health related quality of life (HRQOL) of neoadjuvant androgen deprivation therapy (NADT). Understanding the effects of NADT will enable judicious evaluation of its sometimes overlooked harms.

NADT plays a critical role in the radiotherapeutic management of men with locally advanced and/or high-risk prostate cancer. In high-risk patients, several randomized clinical trials demonstrated that a combination of androgen deprivation therapy (ADT) and RT compared to RT alone, resulted in improved local control, biochemical disease free survival, cause specific survival and in some instances overall survival. (3–11) However, a systematic evaluation of ADT on HRQOL has not been a component of most of these trials. Some of these studies utilized brief or temporary hormone therapy initiated one to five months prior to the start of RT and continued for four to six months (3–5) while others utilized longer duration of ADT. The discontinuation of ADT, especially short-term ADT, should allow for testosterone recovery (12, 13) and minimize adverse hormone therapy side effects.

Since these clinical trials demonstrated that ADT benefits intermediate- and high-risk patients, with many patients receiving also receiving NADT prior to RT, it is important to evaluate the early short-term adverse consequences of ADT in order to counsel patients about the HRQOL impacts from these treatments.

The time course and severity of ADT side effects in men receiving definitive RT for prostate cancer has not been extensively characterized using validated, patient-reported HRQOL instruments like the Expanded Prostate Cancer Index Composite (EPIC) instrument. Searching in PubMed for the keywords “radiation” or “radiotherapy”, “EPIC” and “prostate cancer” results in no publication focusing on the short-term QOL effects from ADT. Most of

these publications focus on some form of hypofractionation (stereotactic body radiotherapy, high dose rate brachytherapy), brachytherapy, or surgery. In this study, we explore the impact of NADT on the sexual, hormonal and vitality domains occurring soon after the start of NADT.

Methods

Centers and subjects

The Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROST-QA) consortium is a multi-institutional prospective study conducted at nine university-affiliated clinical sites across the US. Patients with early stage prostate cancer were recruited between 2003–2006 from urologic surgery or radiation oncology departments affiliated with the University of Michigan, Cleveland Clinic, University of California-Los Angeles, M.D. Anderson Cancer Center, Washington University and the Beth-Israel Deaconess Medical Center (14). Each center had the study reviewed and approved by its local Institutional Review Board (IRB). Patients were ineligible for the study if they had received any prior therapy for prostate cancer. All patients signed informed consent to participate in this prospective study of HRQOL.

In the PROST-QA trial, primary treatment could consist of radical prostatectomy, external beam RT or brachytherapy. The selection of primary treatment modality was left to the discretion of the treating physician and the patient. At the time of this analysis, 899 men with localized prostate cancer had been registered to the PROSTQA study. Of the 899 men, 449 (49.9%) had elected to undergo radical prostatectomy, 219 (24.4%) external beam RT, 215 (23.9%) brachytherapy, and another 16 (1.8%) patients received a combination of external beam RT with a brachytherapy boost.

The decision to administer NADT was left to the treating physician. Only 1 of the 449 radical prostatectomy patients received ADT prior to surgery. For this reason, we decided to focus this analysis on the 450 patients who were treated with definitive RT. Of the men receiving RT, 71 received NADT typically starting 2 months prior to initiation of their RT.

Measures

At registration, pre-treatment demographics, cancer severity, and treatment details were recorded. HRQOL was measured by the EPIC-26 instrument collected by computer assisted telephone interviews prior to NADT, and at 2 month, 6 month and annual intervals. The EPIC 26-item questionnaire has been validated (15) and measures prostate cancer-specific HRQOL (16). The questionnaire consists of four summary domains (urinary, bowel, sexual, and vitality/hormonal) as well as two urinary subscales (incontinence and irritative/obstructive). Each summary domain contains function and bother subscales. Patient responses to questions are transformed to a 0–100 scale where higher scores represent a better HRQOL. The EPIC-26 has been validated.

Not all changes in an HRQOL score have clinical significance. Norman et al. recommend that a clinically meaningful change in function is defined as a change of greater than one half the standard deviation in an HRQOL score. (17)

Statistical Analysis

Chi-square tests and t-tests determined differences in patient and disease characteristics between 71 patients who did and 379 patients who did not receive NADT. Paired t-tests determined significance in the difference of the mean scores between pre-treatment status

and those measured two months after initiation of NADT. All analyses were conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

Results

The characteristics of these patients are listed in Table 1. Patients receiving ADT were more likely to be older and have significantly higher clinical stage, Gleason grade, and pre-treatment PSA as compared to those treated with RT alone. When NADT was administered, it consisted of an LHRH agonist alone in 47 (66.2%), combined androgen blockade with an LHRH agonist and an antiandrogen in 23 (32.5%) and an antiandrogen alone in 1 (1.3%). Of the patients receiving external beam RT, brachytherapy or combined external beam RT with a brachytherapy boost, 26.0%, 5.1% and 18.8% received NADT, respectively.

The sexual and vitality/hormonal domains show significant declines as soon as two months after the start of NADT (Table 2). Prior to the start of NADT the mean ± standard deviation EPIC sexual score was 51.7 ±31.1, and following the initiation of NADT it dropped to 32.3 ± 26.1, $p<0.001$. Prior to the start of NADT the mean ± standard deviation EPIC vitality/hormonal score was 94.1 ± 9.7 and two months following the initiation of NADT it dropped to 78.7 ± 16.3, $p<0.001$. A slight decline in the urinary incontinence domain also reached statistical significance following two months of ADT. Using the definition of a clinically meaningful change in HRQOL, the sexual and vitality/hormonal changes meet clinical significance whereas the urinary incontinence difference (<5%) does not. There were no significant or clinically meaningful changes in the urinary irritative, obstructive or bowel domains related to the administration of NADT.

The biggest declines in the sexual domain were seen in erectile function and ability to have an orgasm or to function sexually (Table 3). Prior to starting NADT, 26% of men reported very poor to no erections compared to 59% two months after initiating NADT. Prior to NADT start, only 26% of men reported very poor to no ability to reach orgasm compared to 56% after hormone therapy. The smallest change in the sexual domain was the amount of sexual bother the men reported. Despite a decline in erections and ability to have an orgasm there was very little difference in the response to the question of how big a problem the sexual function created for men before (47.1%, no problem) and after (43.1%, no problem) ADT.

The biggest changes in the vitality/hormonal domains were associated with hot flashes, feelings of depression, lack of energy and change in body weight (Table 4). Ninety-three percent of men reported no problem at all with hot flashes prior to NADT compared to only 32% after two months of ADT. Prior to NADT 80.3% of patients described no problem with depression compared to 68.1% after 2 months of NADT. Lack of energy was no problem for 70.4% of the patients prior to NADT compared to 50.7% two months later. The percentage of patients reporting no problem with body weight fell from 91.4% to 69.4%.

Discussion

Although the initial report from the PROST-QA trial provided valuable insights into the HRQOL impact of radical prostatectomy, brachytherapy, or external-beam radiotherapy in prostate cancer patients (14, 18), there is surprisingly little data on the immediate adverse effects from ADT on men. To our knowledge, the only other study which addresses this question is a QOL analysis of the Medical Research Council RT01 trial, which delivered 3 – 6 months of NADT plus 64 Gy or 74 Gy in 2 Gy fractions. This study did not use the EPIC, but its predecessor, the UCLA-PCI, the Functional Assessment of Cancer Therapy core questionnaire with its additional prostate subscale, and the Short Form-36 Health Survey

questionnaire. The questionnaires were administered before NADT and before starting RT. The authors observed that sexual functioning deteriorated, urinary function did not change, and that there was a slight decline in physical well-being after 3 months of HT. Interestingly, overall QOL was not reported to be affected and patients indicated an improvement in attitude and satisfaction with treatment (19). Our study confirms the deterioration in sexual function with the validated EPIC-26, and provides new knowledge regarding the deterioration in the vitality/hormonal domain which the UCLA-PCI lacked.

Some of the limitations of this study are that 26.6 % of patients reported good or very good erections at baseline. If this percentage had been higher, the sexual impact of NADT would have been higher.

The National Comprehensive Cancer Network (NCCN) prostate cancer guidelines suggest considering 4 to 6 months of ADT in intermediate-risk patients undergoing external beam RT, and 2 to 3 years of ADT for high-risk patients undergoing external beam RT (20). Consequently, a large number of patients may undergo ADT as part of external beam RT which could have a significant impact on HRQOL. Due to the multi-institutional nature of this study, we believe that these results should be generalizable to most patients receiving NADT in the United States.

We compared the HRQOL prior to NADT with 2 months after NADT. Another comparison could have been made between the RT patients with and without NADT. Since patients who received RT alone likely had the 2 month evaluation closer to the end of RT, the comparison at 2 months would have been between NADT without RT and RT. This RT unbalanced comparison would confound the results since RT is known to cause fatigue among other acute side effects (21).

This prospective study demonstrates that the adverse effects on sexual HRQOL are observed as early as 2 months from the start of NADT. Several studies have also demonstrated that the negative effects on sexual function may last 2 or more years after treatment with NADT (22). Utilizing the EPIC in a group of 149 men undergoing external beam radiation therapy, Hollenbeck *et al.* reported that sexual function was adversely affected in the first two to three years after treatment with some improvement thereafter (22). Using the same instrument, they reported that of 114 men undergoing brachytherapy, the 43 men that received NADT had worse sexual HRQOL as compared to those treated with brachytherapy alone for at least 22 months after the brachytherapy implant (23).

In a series of 482 patients undergoing permanent interstitial brachytherapy, Potters *et al*. reported that 76% of the men undergoing brachytherapy alone had potency preserved compared to 56% receiving brachytherapy with external beam radiation, 52% receiving brachytherapy with NADT, or only 29% receiving all three modalities(24). Chen reported a worse sexual function with NADT at one year but the difference was not significantly worse. Patients getting NADT had worse baseline function. The authors did not describe duration of hormones and they did not have short term data at 2 months (25). In the PROST-QA series it was also recently demonstrated that the use of NHT not only influenced early HRQOL (as reported herein) but that these impacts upon sexual function persisted even out to 2-years (14).

Our series also shows that NADT has an immediate adverse effect on the vitality/hormonal HRQOL domains. Patients getting NADT frequently reported hot flashes, feelings of depression, lack of energy and change in body weight. The use of NADT was not randomized. In the present series, men with higher risk features were more likely to receive ADT, and it may be difficult to determine if the anxiety associated with higher risk disease

could account for some of the worse sexual function and vitality complaints after 2 months of ADT.

Herr *et al.* examined the short-term (6 and 12 month) effects of ADT in asymptomatic men with evidence of biochemical progression or risk of systemic failure (26). They demonstrated a significant reduction in physical function, fatigue and sexual problems using the EORTC prostate cancer quality of life questionnaire. Among 79 patients receiving ADT, there were significantly worse outcomes in physical functioning, fatigue and sexual problems and overall quality of health compared to 65 men not receiving ADT (26).

In contrast, a study of 300 patients undergoing brachytherapy, of whom 86 received 3-month NADT to downsize the prostate before treatment, the NADT group reported better global HRQOL, social and emotional functioning 1 year post-brachytherapy compared with baseline ($P < 0.05$) (27). If the baseline HRQOL was obtained after starting NADT, but before brachytherapy, one would expect an improvement in HRQOL as the effect of the short course NADT decreased a year later. Although the study reports that the baseline was obtained prior to brachytherapy, it does not specify if this was also prior to NADT (27). Our study is distinct from others like the previous one because our HRQOL baseline was before NADT, and we were able to detect the early effects of NADT.

Although our study and the previous study are not directly comparable, they suggest that the time point selected for comparison, and specific radiation treatment modality may influence the results obtained.

Conclusions

Neoadjuvant ADT has significant early negative effects on sexual, vitality/ hormonal HRQOL domains, and patients should be informed of the adverse effects of neoadjuvant ADT on their quality of life.

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Table 1

Patient and disease Characteristics of 450 men planned to undergo radiation therapy for localized prostate cancer, according to use of neoadjuvant ADT therapy.

		Treatment Group		
		No NADT (n=379)	**NADT (n=71)**	**p value**
Age (years)	Mean (±sd)	66.4 (±7.7)	70.2 (±7.5)	<0.001
Race	White	83.4%	88.4%	
	African American	15.2%	11.6%	0.444
	Other	1.3%	0%	
Clinical Stage	T1	81.8%	57.8%	<0.001
	T2	18.2%	42.2%	
Gleason Score	2–6	70.9%	18.3%	
	7	28.3%	46.5%	<0.001
	8–10	0.8%	35.2%	
PSA (ng/ml)	0–4	19.0%	14.1%	
	4–10	69.6%	50.7%	<0.001
	>10	11.4%	35.2%	
	Mean (sd)	6.2 (±3.4)	12.8 (±16.0)	

Table 2

HRQOL domain specific mean scores before and after the start of NADT among 71 men planned to undergo radiation therapy for localized prostate cancer.

Domain-specific prostate cancer HRQOL, EPIC summary scores	Mean EPIC HRQOL domain score (± standard deviation)		
	Before **NADT Start**	**2 months *After* NADT Start**	**p-value***
Sexual	51.7 (±31.1)	32.3 (±26.1)	<0.001
Vitality/Hormonal	94.1 (±9.7)	78.7 (±16.3)	<0.001
Urinary Incontinence	92.2 (±14.4)	88.1 (±17.2)	0.024
Urinary	87.6 (±13.9)	84.8 (±16.5)	0.173
Irritative/Obstruction			
Bowel/Rectal	95.4 (±8.4)	92.3 (±15.2)	0.082

* paired t-test

Table 3

Distribution of 71 patient responses to EPIC Sexual HRQOL items before and 2 months after initiation of NADT

How would you rate each of the following during the last 4 weeks?	Very poor to none	Poor	Fair	Good	Very good
Your ability to have an erection?					
Prior to Hormones:	26.1%	23.2%	20.3%	18.8%	11.6%
After 2 months NADT:	59.4%	14.1%	12.5%	7.8%	6.2%
Your ability to reach orgasm (climax)?					
Prior to Hormones:	25.8%	16.7%	15.2%	27.3%	15.2%
After 2 months NADT:	55.7%	13.1%	18.0%	8.2%	4.9%
How would you describe the usual QUALITY of your erections during the last 4 weeks?	None at all	Not firm for sexual Activity	Firm enough masturbation or foreplay	Firm enough for intercourse	
Prior to Hormones:	24.6%	20.3%	13.0%	42.1 %	
After 2 months NADT:	45.9%	21.3%	16.4%	16.4 %	
How would you describe the FREQUENCY of your erections during the last 4 weeks?	Never	Less than half the time wanted	About half the time wanted	More than half the time wanted	Whenever wanted
Prior to Hormones:	29.4%	10.3%	11.8%	20.6%	27.9%
After 2 months NADT:	56.9%	15.5%	8.6%	8.6%	10.3%
Overall, how would you rate your ability to function sexually during the last 4 weeks?	Very poor	Poor	Fair	Good	Very good
Prior to Hormones:	30.9%	13.2%	20.6%	26.5%	8.8%
After 2 months NADT:	55.9%	17.0%	13.6%	8.5%	5.1%
Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?	No Problem	Very small problem	Small problem	Moderate problem	Big problem
Prior to Hormones:	47.1%	18.6%	12.9%	8.6%	12.9%
After 2 months NADT:	43.1%	15.4%	15.4%	12.3%	13.9%

Table 4

Distribution of 71 patient responses to EPIC Hormone/Vitality items before and 2 months after initiation of NADT

How big a problem during the last 4 weeks, if any, has each of the following been for you?	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
Hot flashes					
Prior to Hormones:	92.9%	2.9%	2.9%	1.4%	0.0%
After 2 months NADT:	32.4%	14.1%	26.8%	19.7%	7.0%
Breast tenderness/enlargement					
Prior to Hormones:	100.0%	0.0%	0.0%	0.0%	0.0%
After 2 months NADT:	87.5%	4.3%	2.8%	5.6%	0.0%
Feeling depressed					
Prior to Hormones:	80.3%	8.5%	8.5%	2.8%	0.0%
After 2 months NADT:	68.1%	12.5%	8.3%	8.3%	2.8%
Lack of energy					
Prior to Hormones:	70.4%	15.5%	5.6%	5.6%	2.8%
After 2 months NADT:	50.7%	9.9%	19.7%	15.5%	4.2%
Change in body weight					
Prior to Hormones:	91.4%	4.3%	1.4%	1.4%	1.4%
After 2 months NADT:	69.4%	8.3%	12.5%	8.3%	1.4%