Impact of Androgen Deprivation Therapy on Sexual and Hormonal Function in Patients Receiving Radiation Therapy for Prostate Cancer

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ABSTRACT: **Background:** Androgen deprivation therapy (ADT) added to radiation therapy (RT) in intermediate to high risk prostate cancer negatively impacts quality of life.

Objectives: To compare health-related quality of life (HR-QOL) in patients receiving combined RT with and without ADT.

Methods: The study population comprised patients treated with definitive RT for prostate cancer who completed the Expanded Prostate Cancer Index Composite-26 form between 3 and 24 months after completing RT. Covariance and a stepwise backward logistic regression model was used.

Results: Data were available for 143 patients who received RT+ADT and 70 who received RT alone. The sexual function and hormonal vitality scores of patients receiving RT+ADT were significantly lower than those receiving RT alone ($P < 0.0001$). Patients with only compulsory school education had significantly lower sexual function scores than patients with university level education ($P \leq 0.005$). Patients with depression had significantly lower hormonal vitality scores than those without depression ($P \leq 0.0001$).

Conclusions: The addition of ADT to RT is responsible for decrements in quality of life in the sexual and hormonal vitality domains, which is further compounded by depression and lack of education. This underlines the need to improve education, identify and treat depression, and develop strategies to improve the quality of life of patients receiving combination therapy.

IMAJ 2016; 18: 49–53

KEY WORDS: prostate cancer, androgen deprivation therapy (ADT), radiation therapy (RT), sexual function

Androgen deprivation therapy (ADT) in combination with RT is the standard of care in locally advanced and high risk prostate cancer [1,2]. Over the last 20 years, there has been ongoing debate regarding the role of ADT in combination with RT in intermediate risk disease [3]. Proponents of ADT in intermediate risk disease point to data showing an improvement in overall survival following the addition for 6 months of ADT to 70 Gy RT [4]. Opponents highlight the surgical experience where the addition of ADT had no impact on overall survival [5] and the many series using dose-escalated radiation therapy alone without ADT that have demonstrated excellent results [3]. The decision whether to offer ADT in intermediate risk prostate cancer is impacted by medical co-morbidities [6] and to a large extent patients' expectations and preference [7]. The latter is powerfully influenced by anxiety concerning a detrimental effect on quality of life, especially in the sexual domain.

Most of the randomized studies testing combinations of ADT and RT were funded, at least in part, by the pharmaceutical industry. Reports of the adverse effects of ADT on health-related quality of life (HR-QOL) come largely from population-based studies [8] as they were not adequately reported in the large randomized trials [9,10].

Advances in radiation therapy may also impact HR-QOL. Intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are developments that facilitate dose sparing around critical organs, thus potentially reducing radiation toxicity [11].

In the present study we compared HR-QOL of patients receiving RT alone vs. RT and ADT. The primary objective of this study was to identify significant differences in five domains of HR-QOL (urinary incontinence, urinary irritation, bowel function, sexual function, hormonal vitality) between RT alone and RT+ADT. Secondary objectives were to determine the impact of total radiation dose, technique, duration of ADT, and time since completion of RT on HR-QOL domains.

PATIENTS AND METHODS

This was a retrospective study comparing men with prostate cancer referred for RT to a tertiary university hospital. Since 2005, men referred to our department for curative radiotherapy for prostate cancer are asked to complete the Expanded

*Recipient of Best Nursing MA Thesis Award at the Henrietta Szold Hadassah-Hebrew University School of Nursing, 2014

Prostate Cancer Index Composite Short Form-26 (EPIC-26) as part of data collection for an institutional review board-approved clinical database [12]. Informed consent was not required for the study and patient privacy was respected by anonymization. EPIC is a HR-QOL instrument developed at the University of Michigan for the purpose of measuring HR-QOL outcomes in men undergoing treatment for localized prostate cancer. EPIC has undergone extensive testing, validation and item reduction analysis to the abbreviated EPIC-26 [13]. A validated Hebrew language translation and cultural adaptation of EPIC was used for this study [14]. EPIC-26 measures five domains of HR-QOL: urinary incontinence (four items), urinary irritation (four items), bowel function (six items), sexual function (six items) and hormonal vitality (five items). The patients were asked to report symptoms over the previous 4 weeks, with answers graded by a Likert scale. The Likert scale was converted to a linear scale from 0 to 100, the latter reflecting the best outcome.

To be included in this study, men had to have filled out the EPIC-26 at least once between 3 months and 2 years after completion of RT. This interval was chosen to capture the late effects of RT that typically occur in this interval. For patients completing more than one survey, the last survey was used for this analysis.

Additional information recorded was RT technique, total dose of RT, National Comprehensive Cancer Network (NCCN) risk group, date of completion of RT, interval between completion of RT and survey completion, and use and duration of ADT.

STATISTICAL METHODS

To test the hypothesis that patients who receive ADT differ from those who do not in the five domains of HR-QOL, we employed tests of variance using a covariance matrix. The mediator was the time interval between the completion of RT and the performance of the QOL instrument. The same method was used to test the hypothesis that HR-QOL domains would differ with RT technique. Regression analysis was used to test the hypotheses that longer duration of ADT and longer interval between completion of RT and survey completion would be associated with QOL outcomes. In order to test for the impact of demographic variables and co-morbidities a stepwise backward logistic regression model was used. Statistical significance for all tests was defined as $\alpha = 0.05$.

RESULTS

Between 2005 and 2012, 765 patients were treated for prostate cancer and completed EPIC-26. The study population comprised 213 patients who completed EPIC surveys 3 months to 2 years following completion of RT, thereby fulfilling the inclusion criteria. Patients' demographic and treatment characteristics are presented in Tables 1 and 2. The mean interval between completion of RT and survey completion was 10.6 months. Mean age ± SD was 70.7 ± 6. years. Most patients lived with spouses (88%) and were pensioned (57%). Most were non-smokers (92%) and approximately one-third (34%) had higher education. A combination of RT+ADT was delivered to 143 patients (67%). The median duration of ADT was 11.2

Table 1. Patient characteristics and co-morbidity

	No.	%
Age (years) (mean ± SD)	70.7 ± 5 (51–84)	
Relationships		
Lives with spouse	186	88
Significant relationship	7	3
Single	20	9
Employment		
Employed	97	41
Unemployed seeking work	4	2
Pensioned	121	57
Smoking		
Non-smoker	197	92
Smoker	16	8
Education		
Primary school only	20	9
High school	94	45
College (no degree)	26	12
BA	40	19
MA/PhD	33	15
Co-morbidity		
Diabetes mellitus	59	28
Myocardial infarction	43	20
Stroke	8	4
Peptic ulcer, irritable bowel	32	15
Asthma	13	6
Depression	13	6
Alcoholism/Drug addiction	0	

Table 2. Disease and treatment characteristics

	No.	%
Risk group*		
Low (T1T2 Gleason 6, PSA < 10 ng/ml)	38	18
Intermediate (Gleason 7 or PSA 10–20)	64	30
High (T3 or Gleason 8 or PSA > 20)	111	52
RT modality		
3D conformal	51	24
IMRT	61	29
VMAT	101	47
RT only	70	33
RT+ADT**	143	67
Treatment for erectile dysfunction		
None	166	78
Intracavernous injection	1	0.5
Prosthesis	1	0.5
Phosphodiesterase-5 inhibitors	42	20
Other	3	1

*National Comprehensive Cancer Network risk stratification

**Mean duration of ADT 11.2 ± 7.4 months

PSA = prostate specific antigen, RT = radiation therapy, ADT = androgen deprivation therapy, IMRT = intensity-modulated radiation therapy, VMAT = volumetric arc radiation therapy

± 7.4 months. Intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) was delivered to 162 patients (76%). The mean total dose of RT was 77.4 Gy. Diabetes mellitus was reported in 28% of subjects and a history of myocardial infarction in 20%. Treatment for erectile dysfunction was reported by 22%.

The scores of the five dimensions are presented in Table 3 and exhibit robust internal validity. There were no significant differences in urinary or bowel scales between the groups. Sexual QOL scores were significantly reduced in men receiving RT+ADT vs. RT only (39.2 vs. 16.9, $P < 0.0001$). Covariance analysis with the time of survey completion as a mediator demonstrated a coefficient of determination, indicating that 17% of the difference observed was due to the addition of ADT. The ability to obtain a "reasonable or better" erection was 29% for RT vs. 10% for RT+ADT ($P < 0.001$) and this comprised a major problem for 39% of men receiving combination therapy. Similarly, satisfactory or better orgasm was achieved in 40% vs. 12%, respectively ($P < 0.001$). In the entire cohort, patients with only compulsory school education had significantly lower sexual function scores than patients with university level education (16.6 ± 5.8 vs. 41.8 ± 5.3, $P \leq 0.005$).

Hormonal vitality scores were inferior for RT+ADT vs. RT only (77.4 vs. 92.2, $P < 0.0001$). The coefficient of determination indicated that 13% of the difference observed was due to the addition of ADT. One-third of men receiving RT+ADT reported hot flashes as a medium to major problem versus no patients in the RT only group ($P < 0.001$). Patients with depression had significantly lower hormonal vitality scores than those without depression (57.7 ± 4.6 vs. 86.9 ± 1.3, $P \leq 0.0001$).

The modality of radiation therapy did not impact outcomes except for urinary irritation, which was moderately improved among patients treated with IMRT and VMAT vs. 3D conformal (83.1, 82.1 vs. 73.9 respectively, $P = 0.02$, $r^2 = 4.5\%$).

Regression analysis demonstrated a positive relationship between the hormonal vitality score and the interval between completion of RT and QOL survey completion ($P < 0.05$), most probably due to amelioration of treatment-induced fatigue over time; however, no significant changes were seen in other domains. There was no relationship between the duration of ADT and the domains of HR-QOL. Although ADT adversely affects sexual and hormonal vitality scores, this was not worsened with longer duration of ADT.

Smokers reported improved bowel function compared to non-smokers (93.2 ± 4.7 vs. 83.3 ± 1.8, $P \leq 0.04$). Patients with a history of peptic ulcer or irritable bowel disease had reduced bowel function (84.5 ± 3.8 vs. 92.0 ± 2.5, $P \leq 0.03$).

Table 3. Health-related quality of life domains of the Expanded Prostate Cancer Index-26

	Mean EPIC**domain scores (95% confidence interval)			Internal consistency***
	All (n=213)	RT (n=70)	RT+ADT (n=143)	
Urinary incontinence	88 (85.4–90.7)	90 (85.8–94.2)	87 (83.6–90.4)	0.8
Urinary irritation	80.4 (77.6–83.1)	80.9 (76.2–85.5)	80.2 (76.9–83.4)	0.69
Bowel function	86.6 (84.1–89.2)	87.4 (83.2–91.6)	86.2 (83.1–89.4)	0.83
Sexual function	24.2 (20.8–27.7)	39.2* (32.1–46.4)	16.9* (13.7–20)	0.88
Hormonal vitality	82.2 (79.6–84.8)	92.1* (89.1–95.1)	77.4* (74.1–80.7)	0.66

*$P < 0.0001$ for the sexual and hormonal domains

**The Expanded Prostate Cancer Index domains are reported on a linear scale from o to 100, the latter reflecting the best outcome

***Cronbach's alpha

RT = radiation therapy, ADT = androgen deprivation therapy

DISCUSSION

This study focused on men in the first 2 years following completion of RT for localized prostate cancer and demonstrated a significant negative impact of ADT on HR-QOL in the sexual function and hormonal vitality domains in men receiving combination RT+ADT versus men who received RT alone. In this study, the use of ADT concomitantly with radiation was associated with a major reduction in the sexual domain, with three-quarters of the patients not achieving erection. Others have confirmed that radiation alone has less negative impact on sexual function [15]. In the study by van der Wielen et al. [16], radiation alone was associated with a gradual decrease in sexual function in 27% of patients in the first year post-RT and increased to 36% in year 2 [16]. The mechanism of sexual dysfunction as a result of radiation therapy is not fully understood yet appears distinct from dysfunction associated with ADT. While the former is associated with changes in the endothelium leading to sub-acute and late effects of radiation therapy in the cavernous tissue, the latter is due to the immediate effects of chemical castration on the erectile tissue as well as to decreased libido [17]. Phosphodiesterase-5 inhibitors have been shown to improve erectile dysfunction in patients treated with RT alone; however, the benefit in patients receiving concurrent short-term ADT has been minor [18]. Thus, it is important not only to demonstrate the difference in sexual outcomes associated with the addition of ADT but also to appreciate the possibility of effective sexual rehabilitation following RT as compared to the combination of RT+ADT.

Interestingly, in this study, patients with higher education had better sexual function than those with school level education only. Others have found that sexual function is improved in patients with higher income [15]. While multiple explanations may be offered, it is likely that both increased knowledge and access to sexual counseling and therapy are responsible for the disparity.

The hormonal vitality scale was significantly reduced in

the combination RT+ADT cohort. Twenty percent of men receiving RT+ADT complained of weight gain as a worrisome problem compared to 4% receiving RT alone. Breast tenderness occurred in 10% vs. 1%, respectively. These findings concur with other reports. Fatigue, weight gain, hot flashes and gynecomastia are all more common when ADT is added to RT and contributed to reduced hormonal vitality scores in a longitudinal prospective study [19].

An important finding of this study was reduced hormonal vitality scores in men reporting depression. There is some overlap, as "feeling depressed" is an item on the hormonal vitality scale and it is not clear whether depression preceded ADT or the contrary; however, depression has been described as an undesirable side effect of ADT [20,21]. A thorough history regarding pre-existing depression or mood changes should be elicited before prescribing ADT, and coping strategies such as active treatment of depression as well as alternative treatment options should be discussed with the patient.

This study has some limitations. It was a retrospective study with a moderately sized cohort; there were fewer patients in the RT-only arm but the sample for the intervention under investigation was a good size. The timing of the QOL assessment was not uniform and ranged between 3 months and 2 years after completion of RT; nevertheless, this interval captures the range when the impact of ADT is greatest and late effects of RT are most prevalent. We also accounted for the time interval by analysis of covariance and demonstrated causality in the sexual and hormonal domains.

The findings of this study highlight the negative impact of adding ADT to radiation therapy. Patients referred for combined ADT and RT require education regarding the expected side effects and how to best cope with and possibly avoid much of the negative influence on quality of life. Interventions directed towards correct nutrition and adequate physical activity and exercise contribute to the reduction of obesity, muscle weakness and osteoporosis, and improve energy and vitality [20,22,23]. Similarly, early detection of decreased sexual quality of life can facilitate referral for sexual counseling and possibly improve sexual function [24]. This study has highlighted the complex association between depression and effects of ADT and hopefully will motivate caregivers to follow patients more closely in this regard and refer them for intervention if necessary. The decision to recommend the addition of ADT therapy to RT is associated with multiple effects, requiring comprehensive assessment, education and guidance in order to achieve a favorable therapeutic result.

Future research using validated HR-QOL measures such as EPIC would provide important information for both patients and caregivers. In particular, obtaining specific pre-treatment baseline QOL measurements followed by a longitudinal measurement over time is extremely useful to tailor patients' expectations and is a powerful tool to direct caregivers towards what needs to be improved when delivering curative treatment for prostate cancer. A comprehensive approach which, in addition to QOL measures, would include tracking of functional status and symptoms of depression would facilitate early referrals to interventions that have been shown to benefit prostate cancer survivors.

Acknowledgments

Supported by an unrestricted grant from the Leroy Schecter Foundation

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"I myself have never been able to find out precisely what feminism is: I only know that people call me a feminist whenever I express sentiments that differentiate me from a doormat"

Rebecca West (1892-1983), British author, journalist, literary critic and travel writer