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Short report

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Quantitative assessment of quality of life in New Zealand prostate cancer survivors: the effect of androgen deprivation therapy

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Abstract

Men with prostate cancer experience many challenges to their quality of life (QOL). While some of these challenges reflect the direct effects of the cancer, additional side-effects and symptoms are also associated with common treatments especially androgen deprivation therapy (ADT). While several studies have examined the effects of ADT on the QOL of men with prostate cancer, much of this research is between 10-20 years old and was conducted in North America or Europe. This study therefore examined the effects of ADT on QOL in prostate cancer patients (survivors) in the Southern hemisphere. The registries of two New Zealand based hospitals were sourced to identify men with prostate cancer who were using ADT for at least six months (ADT group, n=205) and those who had never used ADT (non-ADT group, n=143). Participants in both groups were mailed a letter of invitation, the WHOQOL-BREF and three facets of the WHOQOL-OLD QOL questionnaire. Response rates of 41% and 40% were obtained for the ADT and non-ADT groups, respectively. QOL scores were generally similar between the groups, with the exception of physical QOL, which was significantly lower in the ADT group. Such results suggest that cancer clinicians, allied health professionals and cancer researchers should not just concentrate on the physical effect of ADT on their survivors' risk of developing osteoporosis, falls-related fracture and cardio-metabolic syndrome, but also devote time to ensure their survivors' perception of their physical QOL is not compromised.

Keywords: cancer survivorship; cancer therapy; hormonal therapy; quality of life; prostate cancer

Introduction

Prostate cancer is the most common form of cancer for men in many countries including New Zealand and Australia [1, 2]. As a result of high 5 year survival rates of 88% [2], 53,296 men are still alive 5 years post prostate cancer diagnosis in Australia. The high 5 year survival rates may reflect some combination of improvements in early detection and treatment modalities including surgical techniques, radiation therapy, chemotherapy and ADT [3].

Of these treatments, ADT is perhaps the most commonly prescribed, with ~50% of prostate cancer survivors likely to use ADT during their treatment [4, 5]. ADT reduces the cancer progression by blocking testosterone production, but this unfortunately contributes to many side-effects

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and symptoms. Such effects include significant changes in body composition (increased fat mass and reduced muscle and bone mass), reduced muscular strength, endurance, functional performance in activities of daily living and sexual function as well as increased levels of fatigue and rates of other chronic conditions including osteoporosis, falls-related fracture and metabolic syndrome [6, 8]. While men on ADT experience greater co-morbidity than their non-ADT peers, it is not completely clear how these ADT-related side-effects and symptoms affect their QOL, with several studies reporting relatively few significant differences in QOL between ADT and non-ADT prostate cancer survivors [9–11].

The relative lack of significant QOL differences, while perhaps a surprise due to the side-effects and symptoms associated with ADT may reflect several factors. The first is that the literature comprises studies that have compared prostate cancer survivors using ADT to prostate cancer survivors undergoing radiation therapy and radical prostatectomy [9] or active surveillance [9–12]. As ADT, radiation therapy and radical prostatectomy all have known side-effects and symptoms [7, 13], a lack of many significant differences in the QOL of men using these therapies is of little surprise. Secondly, all of these studies were conducted in North America or Europe, with the North America studies involving data from 1994 and 1995 [9, 10]. As ADT treatment protocols have changed considerably since that time and may also differ across countries [14, 16], newer studies in other non-North American and European countries may be needed to better quantify the contemporary effect of ADT on QOL in men with prostate cancer. Another issue with these studies may concern the QOL tools used, with the studies generally using the SF-36 [9–11] although one study used the EORTC-C30 and sexual behaviour questionnaires (SBQ) [12]. While all of these QOL tools have adequate psychometric properties, the WHOQOL tools [17] have the added advantage of providing excellent cross-cultural validity due to the way in which they were developed [18]. Scores on the WHOQOL tools, especially those pertaining to physical and psychological QOL, are generally found to be moderately correlated with related components of the SF-36 [19], although the SF-36 appears to be much more likely to yield floor and ceiling effects [20]. The WHOQOL also captures a very wide range of relevant QOL issues, such as social and environmental QOL, thus extending QOL assessment beyond factors that are restricted only to direct concerns about disease and symptoms [19]. The subjective elements that are assessed by the WHOQOL tools distinguish them from more objective instruments, such as the SF-36. This means, for example, that the WHOQOL is able to differentiate between two prostate cancer survivors who may experience similar side-effects and symptoms, but who may have very different perceptions on how these impairments affect their QOL [18].

Therefore, the purpose of this study was to use a cross-sectional design to examine the effects of current ADT usage on prostate cancer survivors' QOL as assessed by the WHOQOL. Based on the prostate cancer QOL literature and the direct effects of ADT, it was hypothesised that the ADT group would exhibit reduced QOL across some domains, with the most likely difference being for physical QOL.

Methods

Design

This study was a cross-sectional comparison of the QOL of prostate cancer survivors currently on ADT for a minimum of six months and those who have never been on ADT. All individuals who met these inclusions criteria were mailed a letter of invitation, with no individuals with bone metastasis excluded. The inclusion of men with metastases was done as national registry data suggests that 5% of men on ADT are diagnosed with metastatic cancer within 18 months of starting ADT [21] and 12% of all prostate cancer survivors will have metastatic disease by 2 years post-diagnosis [22]. The results reported here compares the new data for prostate cancer survivors not using ADT (non-ADT group) to previously published data for those using ADT (ADT group) [23]. The same data collection procedures were used for the non-ADT group and the previously published ADT group [23]. Both components of this study had approval from the Auckland Regional Ethics Review Board (formerly known as Northern Y Ethics Committee).

Participants and procedures

Non-ADT group: Using the database of the North Shore Hospital in New Zealand, all prostate cancer survivors who were not currently, and have never been, on ADT were sent a letter inviting them to participate in the present study. Of the 143 survivors who were identified and sent an invitation letter, 57 agreed to participate and returned a questionnaire, yielding a response rate of 40%. The initial letter of invitation included a cover letter that explained the study and how they could participate. One week later, another letter was sent including an information sheet, the WHOQOL-BREF and WHOQOL-OLD questionnaires and a stamped return-addressed envelope. In an attempt to improve the response rates [24], another letter package including the WHOQOL-BREF and WHOQOL-OLD was dispatched 2-4 weeks later thanking those who had responded and encouraging those who had not returned the questionnaires to do so. The mean age of this group was 67.9 years (SD=8.7).

ADT Group: Of the 205 survivors who were identified as being on ADT for longer than six months and sent an invitation letter to participate in the study, 84 men returned the questionnaire, resulting in a response rate of 41% [23]. This group had a mean age of 78.4 years (SD=8.2).

Measures

WHOQOL-BREF: The WHOQOL-BREF is the brief version of the World Health Organisation's QOL instrument,

with items contributing to a score on the following QOL domains: physical (7 items), psychological (6 items), social (3 items), and environmental (8 items). The WHOQOL-BREF has been validated for use in older adults [25] and for the New Zealand population [26].

WHOQOL-OLD: The WHOQOL-OLD is an optional add-on module to other WHOQOL measures to assess facets of QOL that are pertinent to older adults [27]. The original scale contains six facets of four items each. However, to minimize response burden, only items that were judged by the researchers as being most relevant were included. These were three of the six WHOQOL-OLD facets, namely *autonomy, social participation,* and *death and dying*. Only three of the four items of the facet death and dying were used in the present study to minimise participant burden. Prior to statistical analyses, these items were reverse coded so that a higher score represented elevated QOL, consistent with the other facets.

Statistical analyses

All data analyses were conducted using the program Statistics Package for the Social Sciences (SPSS) v.19. In total, 0.01 of all responses were missing. Given the sample size, missing items on the WHOQOL-BREF were imputed by the mean score on the other items that the participant rated on the same domain. To maintain the ordinal structure of the scale, imputed scores were rounded. Missing items were not imputed when more than half of the items on the sub-scale were missing, in which case no sub-scale score was calculated for that respondent.

Differences between the ADT and non-ADT groups in terms of the WHOQOL-BREF domains and the three WHOQOL-OLD facets were tested using a MANCOVA, controlling for age and time since diagnosis. A significant difference in one of the domains was then followed up by an additional analysis that included an ageand gender matched general population sample collected one year earlier [26]. This reference group was further divided into participants who self-identified as unwell and well, thus yielding a total of four groups to be compared (non-ADT, ADT, general population Well, and general population Unwell). Because no WHOQOL-OLD scores were available for the Unwell and Well groups, and there was no variable *time since diagnosis* for these groups, this comparison was made using an ANCOVA, controlling for age, and followed up with *post-hoc* tests. To minimize inflation of Type-1 error, the ANCOVA was only conducted to explore differences in the WHOQOL-BREF domain that yielded a significant difference in the above MANCOVA. The mean ages of the Well and Unwell groups were 65.2 years (SD=9.6) and 70.2 years (SD=10.1), respectively. The minimum age was 51 years for the Well, Unwell, and non-ADT groups, and 58 years for the ADT group.

Results

A description of the two cancer samples is given in Table 1. Both groups were similar in ethnicity and time since diagnosis, although the ADT group were significantly older and had a higher prostate specific antigen (PSA) level.

Table 1 Demographic and clinical descriptors of the two groups of participants

	ADT (n=81)	*Non-ADT (n=57)*
Age (yrs) *	78.4 (8.2)	67.9 (8.7)
Ethnicity	70 (84%)	47 (82%)
European other	11 (16%)	10 (18%)
PSA (ng/mL)*	9.2 (22.1)	2.4 (6.6)
Time since diagnosis (yrs)	5.5 (3.8)	5.5 (2.9)
Duration of ADT (yrs)	3.9 (3.6)	0.0 (0.0)
Average number of comorbidities	0.7 (0.9)	0.6 (0.5)

Except for ethnicity, all values shown in parentheses are standard deviations
*significant difference between the two groups

Table 2 shows the mean scores of the four WHOQOL-BREF domains as well as the WHOQOL-OLD facet scores *autonomy, social participation,* and *death and dying*. A multivariate analysis of co-variance, comparing the ADT with the non-ADT group on all of the seven dependent variables shown in Table 2 and controlling for age and time since diagnosis, revealed no significant group effect overall ($F(7, 110)=0.36$, $p>.05$). However, the difference on physical QOL was significant ($F(1, 116)=5.86$, $p<.05$). This difference was not driven by a limited number of items, but the ADT group had lower scores on every item of the physical domain. This difference was also significant, when PSA levels were controlled for instead of time since diagnosis ($F(1, 106)=5.21$, $p<.05$). Only the ADT and non-ADT groups had data for all seven dependent variables in Table 2, and therefore the Well and Unwell groups were not included in the above MANCOVA. To provide a comparison with the Well and Unwell groups, a subsequent univariate analysis of co-variance with age as a co-variate was conducted to explore group

differences on the physical QOL domain. The group effect was significant ($F(1, 299)=20.24$, $p<.001$). Except for the comparison between the non-ADT versus reference Values Well, all Bonferroni-corrected post-hoc analyses yielded a significant result (Table 2).

Table 2 Mean scores for WHOQOL-BREF domains and the WHOQOL-OLD facets *autonomy, social participation,* and *death and dying*

	ADT (n=81)	*non-ADT (n=57)*	*Reference Values Well (n=40)*	*Reference Values Unwell (n=128)*
WHOQOL-BREF				
Physical*	24.67 (4.91)	27.39 (4.38)	27.80 (3.83)	21.98 (5.85)
Psychological	23.21 (3.51)	23.47 (3.45)	23.43 (3.76)	21.00 (3.73)
Social	11.38 (2.72)	11.93 (2.26)	11.77 (2.04)	10.83 (2.02)
Environmental	32.58 (4.51)	32.60 (4.20)	32.59 (4.19)	30.53 (4.53)
WHOQOL-OLD				
Autonomy	16.01 (2.86)	16.02 (2.42)		
Social Participation	14.18 (3.68)	14.63 (2.66)		
Death and Dying	12.01 (3.39)	11.98 (3.07)		

Values in parentheses are standard deviations. For two reference values groups (age and gender matched data from the New Zealand general population, divided into self-identified Well versus Unwell; Krägeloh et al. [26] only domain scores were available. *$p<.05$ (MANCOVA, ADT vs non-ADT); the results from an ANCOVA, including all four groups and with physical QOL as the dependent variable, yielded the following significant post-hoc comparisons: $p<.01$ (ANCOVA, ADT vs non-ADT); $p<.01$ (ANCOVA, ADT vs Well); $p<.05$ (ANCOVA, ADT vs Unwell); n.s. (ANCOVA, non-ADT vs Well); $p<.01$ (ANCOVA, non-ADT vs Unwell); $p<.01$ (ANCOVA, Well vs Unwell).

Discussion

Due to the very high 5 year survival rates for a number of cancers including that of the prostate [2], a greater amount of research is now focusing on the wider issues of cancer survivorship rather than just how to reduce mortality rates. A major focus of this survivorship research is concerned with gaining an insight into the effect of long-term usage of common treatments on various aspects of QOL and how traditional and complementary therapies may offset these treatment-related issues. This study extends some of the literature in this area as the mean duration of ADT usage in this study of ~4 years was substantially greater than the durations of 0.5-2 years ADT cited previously.

The main findings of the current study were that the ADT and non-ADT groups had very similar QOL. Of the four WHOQOL-BREF domains (Psychological, Social and Environmental) and three WHOQOL-OLD facets (*autonomy, social participation* or *death and dying*), the only significant difference was that the ADT group had significantly reduced physical QOL compared to the non-ADT and general population Well groups. The significantly reduced physical QOL for the ADT group was consistent with older North American [11] and European [12] studies' findings and likely reflects the significant physical side-effects and symptoms seen with prolonged ADT usage [6–8].

In contrast to the results for physical QOL, no significant differences in other three QOL domains and three facets were observed between the ADT and all other groups. While such a result is consistent with several other studies [9–11], it appeared substantially different to van Andel and Kurth [12] who observed significant reductions in several EORTC-C30 (emotional function and global QOL) and SBQ domains (erectile dysfunction, sexual interest, sexual activity, sexual pleasure) QOL domains as well as increase in fatigue and hot flushes for the ADT group. However, the EORTC-C30 and some domains of the SBQ may be criticised as being more of a symptom checklist than a true assessment of an individual's perceptions of their QOL [28]. Therefore it is quite possible that since the ADT group had been on ADT for a mean of approximately 4 years that they may have become accustomed to these side-effects and symptoms, so that they no longer perceived them as reducing their QOL, but that they were a regular part of their everyday life. Such a view is consistent with Potosky et al. [29] who observed that men with prostate cancer who were 2 years post-radical prostatectomy or external beam radiotherapy had significant differences in several symptoms but no significant differences in QOL. Collectively, these results further support the contention of QOL researchers that assessing symptoms does not necessarily correlate to individuals' perceptions of their QOL, especially if such symptoms have existed for an extended period of time.

The significant loss of physical but no other QOL domains and facets in the ADT group suggest that cancer clinicians and allied health professionals should monitor and regularly devote some time to discussing issues affecting

physical QOL with their patients on ADT [30]. While considerable research has focused on improving chemo-radiation, surgical and pharmacological techniques to reduce side-effects and symptoms and/or maintain physical QOL in prostate cancer survivors on ADT [31, 32], cancer patients and survivors may also benefit from research examining complementary therapies focusing on increasing physical activity levels or improving nutritional intake. Physical activity programs, especially those involving resistance training show much promise in improving various domains of QOL as well as body composition and physical function, thereby reducing the risk of osteoporosis, falls related fracture and cardio metabolic syndrome [33].

This study is not without its limitations. Its sample size per group was moderate in comparison to the literature, being considerably greater than some studies [11, 12] but substantially less than others [9, 10]. However, as these larger studies involved North American data sets from 1994 and 1995, the applicability of their results to how ADT is currently used in the southern hemisphere is somewhat unclear. This potential lack of applicability of these older studies to the current situation in the southern hemisphere may reflect changes in ADT procedures over this period of time, potential northern vs southern hemisphere difference in treatment approaches as well as differences in cultural attitudes between these countries. As with other survey based studies, the issue of how representative this sample of prostate cancer survivors are of the population is always some concern. However, the responses rates of ~40% in the current study were comparable to other studies in this area [13, 34]. Further, as a cross-sectional comparison, it is not possible to determine causation, so that these differences in QOL may have been influenced by differences in these groups' perceptions of their QOL prior to the cancer diagnosis and/or treatment. Additionally, the ADT and non-ADT were not matched according to disease characteristics such as prevalence of bone metastases, and comparisons therefore relied on statistical control of covariates.

Conclusions

Overall, the results of this study suggest that cancer clinicians and allied health professionals should strive to routinely monitor and discuss issues affecting the physical QOL of their prostate cancer patients on ADT as well as the more common outcomes including bone mineral density, PSA levels and risk of cardio-metabolic syndrome. While the lack of significant differences in the other QOL domains and facets was contrary to our hypothesis, it may reflect a combination of several factors. These could potentially include: (1) reduced side-effects of contemporary compared to historical ADT practices; (2) the men on ADT had become accustomed to ADT's side-effects and symptoms over several years and therefore did not feel it affected many aspects of their QOL; or (3) the challenges of using quantitative questionnaires to assess QOL in clinical populations. Future research may wish to use longitudinal research designs involving mixed-method data collection approaches to better understand the effect of ADT on QOL in prostate cancer survivors and to examine the effect of traditional oncological and complementary therapies on improving their physical QOL and reducing the risk of developing additional comorbidities.

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Conflict of interest

The authors wish to express that they have no conflict of interest.

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