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Original Article

The effect of neoadjuvant androgen deprivation therapy for prostate cancer on lower urinary tract symptoms: Could they be affected by prostate gland volume reduction?

David R. H. Christie[1,2,*] and Christopher F. Sharpley[2]

[1]Genesiscare, Inland Drive, Tugun, Qld 4224; [2]Brain-Behaviour Research Group, University of New England, Armidale, NSW, 2350, Australia.

ABSTRACT

Neo-adjuvant androgen deprivation therapy (NADT) is commonly undertaken for 3-6 months prior to radiotherapy for prostate cancer and causes shrinkage of the prostate gland. The changes in lower urinary tract symptoms and their relationship with the changes in the prostate gland volume as it shrinks have not been studied in detail. Urinary symptoms prior to radiotherapy predict for urinary problems during and after radiotherapy and reductions in them might reduce the risk of these occurring. Fifty consecutive patients with intermediate and high-risk prostate cancer were treated with six months of triptorelin prior to definitive radiotherapy. Urinary symptoms were measured using international prostate symptom scoring system (IPSS) scores. The volume of the prostate gland was measured using serial magnetic resonance imaging (MRI) scans. Volumes and symptoms were measured at the outset and every six weeks during the neoadjuvant component of the treatment. The mean IPSS score at the outset was 11.76 and reduced by a mean of 1.67 over the six-month period. Although the median prostate volume reduced over that time, there was no significant correlation between them, or between the IPSS and changes in prostate-specific antigen (PSA) or testosterone levels. Urinary symptoms were relatively stable during the treatment and were not associated with changes in the prostate gland volume. When those patients with more severe IPSS than the mean value were considered separately, an improvement by 5.31 points was noted. Neoadjuvant hormone therapy is unlikely to affect the ability of patients to complete their radiotherapy with any lowering of their risk of treatment interruption due to urinary toxicity or their risk of long-term urinary problems, unless they have relatively severe symptoms initially.

KEYWORDS: gonadotropin-releasing hormone, magnetic resonance imaging, prostate-specific antigen, testosterone, radiotherapy.

ABBREVIATIONS

LUTS	:	Lower urinary tract symptoms
PGV	:	Prostate gland volume
NADT	:	Neoadjuvant androgen deprivation therapy
RT	:	Radiotherapy
IPSS	:	International Prostate Symptom Scoring system
BPH	:	Benign prostatic hyperplasia
MRI	:	Magnetic Resonance Imaging
QoL	:	Quality of life
TE	:	Testosterone escape
TURP	:	Trans-urethral resection of the prostate
PSA	:	Prostate-specific Antigen

*Corresponding author: david.christie@genesiscare.com

INTRODUCTION

Enlargement of the prostate gland has been associated with lower urinary tract symptoms (LUTS), but the induction of shrinkage of the prostate gland volume (PGV) has had variable effects on these. The greatest reductions in PGV have been caused by hormone therapy and the most commonly studied form of hormone therapy in this setting has been neoadjuvant androgen deprivation therapy (NADT) prior to radiotherapy (RT). Of the studies which measure changes in PGV with NADT, several have noted changes in lower urinary tract symptoms (LUTS) during that time.

These changes have usually been studied using the international prostate symptom scoring system (IPSS) which was originally intended for use in patients suffering benign prostatic hyperplasia (BPH) [1]. It has been argued that the IPSS is not validated in prostate cancer populations; however it has been used in a wide variety of settings including prostate cancer and the difference in LUTS between benign and malignant prostatic enlargement do not appear significant [2, 3]. It includes questions that enable difficulties in storage of urine, voiding and overall quality of life (QoL) to be recorded, and the relationship between these sections of the survey has been investigated [4]. Changes of more than 3 units have been considered clinically meaningful [5].

Studies reporting changes in the PGV during NADT were recently reviewed [6]. Most of these studies are retrospective and have significant limitations. Only two have assessed changes in PGV beyond 3 months and these indicate that shrinkage continues up to and beyond 6 months of NADT duration [7, 8]. As well as being frequently insufficient in duration, the studies also suffer from wide heterogeneity including the stages of the patients' cancers, the range of NADT agents, varying combinations of NADT with anti-androgens, irregular scan types taken at irregular intervals, and heterogeneous scanning. None of them have used the number of scans that would be required for a detailed mapping of the changes in PGV and LUTS. Very few have measured the PGV by MRI scanning, which was considered the most accurate method in a recent review [9]. As recent study has suggested most of the changes in PGV occurred during the first six weeks, we considered it important to include assessment of LUTS at that time [10]. We also aimed to extend the monitoring of urinary symptoms for six months to ensure any improvements were sustained.

Larger PGVs have been associated with greater urinary bother in prostate cancer patients prior to radiotherapy and greater acute and late urinary toxicity after radiotherapy, particularly for volumes greater than 50 cc [11-14]. The likelihood of acute grade 3 toxicity was doubled for every increase of 27 cc in one study [13]. Our aim was to perform the most detailed study correlating changes in LUTS with changes in PGV during NADT over six months.

MATERIALS AND METHODS

Ethics approval for this study was provided by the Uniting Care Health Human Research Ethics Committee (Registration number 2013.14.85). The study was initiated at GenesisCare sites on the Gold Coast, including the Southport and Tugun centres. Staff at the ICON Cancer Centre at the Gold Coast University Hospital were also invited to participate. The patients received six months of standard NADT, given with two 3-monthly depot injections of Diphereline™ (triptorelin embonate, hereafter triptorelin) prior to definitive treatment by RT.

It was estimated that 50 patients would provide reliable information. Consecutively-presenting prostate cancer patients between August 2013 and December 2016 were invited to participate. Patients were eligible if their cancers were previously untreated, biopsy-proven, indicated an intermediate or high risk of recurrence using conventional criteria, and were confined to the prostate as confirmed by staging bone and CT scans. Written, informed consent was obtained.

Assessments of the patients were made at baseline and at intervals of six to seven weeks during the six months of their NADT. LUTS were measured using the IPSS. Scores for each question, the total IPSS and the QoL score were recorded at baseline and at each assessment. IPSS subscores for voiding and storage were also generated [15]. Moderate LUTS were considered to be present when the total IPSS score was between seven and 19, and severe LUTS above 20.

Serum PSA and Testosterone levels were also examined using chemiluminescent assays. Other baseline factors recorded included age, risk category of the cancer, and Gleason scores. A 3-Tesla MRI scan was done without contrast in order to avoid the need for IV access, anti-spasmodic pre-medication, a laxative suppository or an endorectal coil. The PGV was measured from the MRI scan using a planimetric calculation.

After the baseline assessment, Diphereline treatment was initiated and further assessments were undertaken at intervals of six to seven weeks. At these times, the IPSS, PSA levels, testosterone levels and the PGV were reassessed. Most patients were expected to have reductions in their testosterone to castrate levels, but some were expected to have testosterone escape (TE) during these further assessments. Two definitions of TE are in current usage. Historically, testosterone levels above 1.7 nmol/L (50 ng/dL) were considered to indicate TE, but more recently levels above 0.7 nmol/L (20 ng/dL) have also been noted to be significant [16]. TE at these levels (TE1.7 and TE0.7) was recorded. PSA kinetics was also recorded. The rate of reduction in PSA was measured using the PSA halving time [17]. The PSA level taken at the final assessment was considered the pre-RT level, which has been shown to have prognostic significance, as recently reviewed [18].

After NADT, the patients were treated with definitive radiotherapy and further adjuvant hormonal therapy at the discretion of their treating radiation oncologist. Longer-term outcome data are not yet available.

Five analyses were undertaken:

1. Repeated measures analysis of variance (ANOVA) on each of the IPSS items, plus the IPSS V and IPSS S, and total IPSS, performed on the 5 observations of data collected at 6-7 week intervals.

2. Correlation between initial IPSS and the other baseline clinical factors.

The baseline factors assessed were patient age, prostate cancer risk category, Gleason score, baseline PGV, serum PSA and testosterone levels.

3. Correlation between baseline clinical factors and any changes in IPSS during NADT.

Any correlation between baseline factors and the magnitude of the changes in IPSS were assessed, to determine whether large changes in urinary symptoms could be predicted.

4. Correlations between the reductions in PSA, testosterone, PGV and the reductions in the IPSS. Changes in the PSA level were measured using the PSA halving time and the significance of TE was determined.

5. ANOVA to assess whether patients with worse than average initial symptoms or greater than average baseline PGV were more likely to be affected by NADT in terms of their improvement on the total-IPSS.

Statistical analysis

The sample size was calculated by GPower 3.1. Since we were primarily interested in the association between changes in IPSS and changes in the PGV, the data regarding reductions in PGV was used to determine sample size. Reductions of approximately 30% in PGV, as previously reported, equate to a robust significant effect, ($p < 0.0001$), and this may be seen to equate to a large effect size in analysis of variance (ANOVA) [7]. Therefore, taking these results as a possible expected outcome, and translating this to a large effect size (f) of 0.2 within a one-way Repeated Measures ANOVA with an $\alpha = 0.05$ and $1-\beta = 0.95$, the required sample size was determined to be 48, rounded to 50 to allow for incomplete data in some cases [19]. The mean percentage reduction in IPSS was calculated by subtracting the mean of each assessment from its predecessor, and the mean of the last assessment (at 6 months) from the mean of the first assessment. In addition, repeated measures ANOVA was used to detect if the changes in IPSS were significant over time for the entire sample. The significance of the correlations between baseline factors and the baseline IPSS was determined by Linear Regression of the baseline clinical factors listed above (i.e. age, risk category, Gleason score and PGV). The significance of correlations between PSA or testosterone and changes in IPSS was also tested by Linear Regression of the same baseline clinical factors. The analysis of the subgroups with greater initial IPSS and baseline PGV was undertaken using separate ANOVA analyses.

RESULTS

The study closed to patient registration when the sample size was achieved. Patients were entered from both GenesisCare (44 patients) and ICON Cancer Centre (6 patients). All patients recruited to the study successfully completed all their required investigations and NADT injections. There were no serious adverse events or toxicities elating to either the scans or treatment. No patients developed urinary retention, required any catheterisation, trans-urethral resection of the prostate (TURP) or any other intervention for LUTS.

The IPSS data and the results of analysis 1 are shown in Table 1. The mean IPSS total score improved from 11.76 at baseline to 10.09 at six months. Of the seven questions, the first six of these followed a similar slightly downward pattern, while question 7 (nocturia) became slightly worse. The subscale score for voiding (IPSS V) trended slightly downwards, while storage symptoms (IPSS S) showed neither an upward nor downward trend and the QoL score showed slight improvement. Overall the changes were minimal for all of the parameters tested, as evidenced by the results of the repeated measures ANOVAs shown in the last two columns. Although some of these reached traditional statistical significance (0.05), the family-wise error rate of multiple tests such as this reduced the acceptable p value to 0.05/11 = 0.004. The number of patients that experienced an improvement in their scores by three or more points was 14 (28%) and was almost identical to the number that experienced deterioration by the same amount (16 patients, 32%).

Table 2 shows the results of the second and third analyses. There were no significant correlations between any of the baseline clinical variables and neither the baseline IPSS scores, nor any changes in these over time. Table 3 shows the results of the fourth analysis; there were no significant correlations between the changes in testosterone or PSA levels and the changes in IPSS scores, including the occurrence of testosterone escape or the pre-RT PSA level.

In the fifth analysis, patients with higher than average baseline IPSS (more than 11.76) had an improvement in their score by a mean of 5.32, while the remaining patients noted minimal change (-0.67). The difference between these two groups was significant ($p = 0.007$, $F(1,48) = 8.050$).

For patients with greater than average PGV, the improvement was 3.45, while in the remainder there was also minimal change (0.29). This difference was not significant ($p = 0.203$, $F(1,43) = 1.673$)

DISCUSSION

To compare our results with other similar studies describing comparable effects of hormone therapy on the urinary symptoms of prostate cancer patients, we have included previously published data in Table 4. As most previous reports have reported changes at 12 weeks, this time point was chosen for comparison. Studies were selected if they included an assessment of the PGV, reported changes in the PGV and reported the total IPSS at that time. Two of the four studies were randomised trials, providing a total of six data sets. Regarding the PGV, the initial measures and the changes in it over 12 weeks were similar with ranges of 35-55 mL and 35-40% respectively. Our data are included in the table to show that they were towards the lower end of both of those ranges, but not at the lower limit. Regarding the IPSS, the corresponding figures were 8.5-14.3 and -4.4 to 0.1, in which our data were reasonably central. Our data were thus similar to that reported by others, but our report adds detail by including interim data every 6-7 weeks, and extends upon previous reports by taking measurements for six months in total. Collectively the data show relatively little improvement in urinary symptoms and any change is of doubtful clinical significance.

Most previous studies of the effects of medications on urinary function have involved the use of alpha adrenoceptor blocking agents in the treatment of BPH [20, 21]. In this setting, improvements in the IPSS score between 3 and 10 over 4-6 weeks are commonly reported. Prostate cancer tends to cause fewer LUTS than BPH as it affects the peripheral part of the gland. NADT agents are not usually used for BPH as they have more side effects and are more expensive. Our data showed trends towards lower LUTS with NADT for some of the questions, but these did not

Table 1. Mean (Standard Deviation) for IPSS and QoL scores, plus Repeated Measures ANOVA results.

	Possible Range	**1st reading (Baseline)**	**2nd reading**	**3rd reading**	**4th reading**	**5th reading (6 months)**	**Repeated measures ANOVA (Wilks' Lambda)**	
							F	*p*
Q1 Incomplete emptying	0-5	1.60 (1.54)	1.24 (1.30)	1.18 (1.38)	1.44 (1.46)	1.04 (1.13)	1.960	0.118
Q2 Frequency	0-5	1.90 (1.45)	2.38 (1.48)	1.78 (1.56)	1.88 (1.70)	1.84 (1.52)	3.145	0.023
Q3 Intermittency	0-5	1.68 (1.65)	1.60 (1.36)	1.48 (1.46)	1.33 (1.38)	1.29 (1.38)	1.285	0.291
Q4 Urgency	0-5	1.70 (1.56)	1.70 (1.49)	1.58 (1.37)	1.47 (1.57)	1.53 (1.42)	0.243	0.912
Q5 Stream	0-5	2.16 (1.71)	1.68 (1.36)	1.64 (1.43)	1.63 (1.60)	1.39 (1.57)	2.826	0.036
Q6 Straining	0-5	0.62 (1.11)	0.60 (0.95)	0.60 (0.97)	0.55 (0.84)	0.55 (0.96)	0.202	0.936
Q7 Nocturia	0-5	2.10 (1.17)	2.32 (1.20)	2.26 (1.31)	2.39 (1.17)	2.45 (1.34)	0.915	0.464
IPSS total	0-35	11.76 (7.59)	11.52 (6.23)	10.52 (7.35)	10.69 (7.80)	10.09 (7.13)	1.284	0.291
IPSS V (1,3,5,6)	0-20	6.06 (5.12)	5.12 (4.07)	4.90 (4.68)	4.95 (4.68)	4.27 (4.28)	1.041	0.397
IPSS S (2,4,7)	0-15	5.70 (3.19)	6.40 (3.29)	5.62 (3.57)	5.74 (3.90)	5.82 (3.66)	1.073	0.381
QoL score	0-6	2.34 (1.51)	2.06 (1.34)	2.10 (1.56)	1.84 (1.62)	1.92 (1.55)	1.471	0.226
Moderate to severe LUTS	% with IPSS > 7	66.0	66.0	54.0	51.0	51.0		

Table 2. Correlations between clinical factors and Baseline urinary symptoms.

Clinical factors (units or subcategories)	Number of pts / Mean value	Range	Correlation[1] between baseline factors and baseline IPSS	Correlation[1] between baseline factors and change in IPSS over 6 months
Patients age (Years)	76 yr	58-89 yr	r = -0.029	r = -0.204
Risk group (Intermediate or high risk)	50	Int. = 17 High = 33	ρ = -0.088	ρ = -0.143
Gleason score (6-10)	8.0	6-9	ρ = -0.018	ρ = 0.049
Baseline PSA levels (ng/mL)	10.4	1.6 - 57	r = 0.023	r = -0.125
Baseline testosterone levels (nmol/L)	10.6	1.3 - 54.1	r = -0.174	r = 0.040
Baseline Prostate gland volume (cc)	38.6	17.3 - 92.5	r = 0.293	r = 0.171
Baseline IPSS total	11.76	0 - 31		

[1]Pearson (r) or Spearman (ρ) values, all p =/> 0.05, unless otherwise specified.

Table 3. Correlation (Pearson's r) between changes in IPSS and PSA kinetics, testosterone escape and PGV over the 6 months of NADT.

Responding clinical factors	Correlation with change in IPSS[1]
Total change in Testosterone	0.052
Testosterone escape (TE1.7)	-0.166
Testosterone escape (TE0.7)	-0.197
Total change in PSA	0.024
Pre-RT PSA level	0.012
PSA halving time	0.026
PGV	0.140

[1]All p > 0.05.

reach statistical significance, except for those with worse than average symptoms at the outset. Although a more sensitive test or a larger study might indicate that the differences for the whole group are statistically significant, they seem unlikely to be clinically meaningful. Neoadjuvant hormone therapy is therefore unlikely to affect the ability of patients to complete their radiotherapy with any lowering of the risks of treatment interruption due to urinary toxicity or long-term urinary problems. Patients with LUTS prior to radiotherapy may need to consider employing other methods to avoid those problems, such as alpha-adrenoceptor blocking agents.

Table 4. Examples from selected series studying 12-week reductions in PGV and IPSS in patients treated exclusively by hormone therapy.

Surname of first author, year of publication	Number of pts	Hormonal therapy	PGV assessment	Initial PGV (mL)	PGV reduction (%)	Initial IPSS	Reductions in IPSS	Pts with IPSS reduction by >3 (%)	Comments
Axcrona 2012 (RCT) (refs)	81	Degarelix	TRUS	55	37	14.3	-4.4	61	Younger age and higher BMI, IPSS decreased more
	93	Goserelin	TRUS	50	39 (ns)	13.4	-2.7 (ns)	44 (ns)	
Mason 2013 (RCT)	164	Degarelix	TRUS	51	36	9.5	-1.7	37	Excluded pts if PGV < 30 mL
	57	Goserelin and bicalutamide	TRUS	52	35 (ns)	8.5	0.1 (sig)	27 (ns)	
Washino 2018	32	Goserelin and bicalutamide	TRUS	35	40	11.7	-2.4	NS	Also assessed at 24 weeks, minimal further change
Present series	50	Diphereline	MRI	39	36	11.8	-1.2	28	Also assessed at 24 weeks, minimal further change

Abbreviations: PGV – prostate gland volume, pts – patients, RCT – randomised controlled trial, TRUS – trans rectal ultrasound, ns – no statistically significant difference between trial arms, sig – statistically significant, PGV – prostate gland volume, NS – not stated.

Mean or median values, numbers rounded up to whole numbers except columns 7 and 8.

Our study had some limitations. Firstly, we did not use multiparametric MRI techniques to assess the PGV, and therefore we could not assess changes within individual gland zones, nor in the cancer volume, and we could not assess BPH or urethral volumes. The relation between these sub-volumes and LUTS is yet to be explored. Secondly we did not perform any other measures of gland volume, such as a digital rectal examination at each visit; however it has been shown that this is less reliable as a measure of PGV than an MRI scan [22]. Thirdly, we did not record the use of medications that could act on LUTS, the discontinuation of which could mask the effect of changes in PGV. Fourthly, we did not use any other measures of urinary function such as flow rates or residual urinary volumes. In the experience of the authors none of these limitations seem likely to affect the findings of the study.

CONCLUSIONS

Our study was more detailed than any previous study addressing the correlation between PGV and LUTS in that we used more accurate methods of assessing the PGV and did so more frequently through the 6 months NADT time period. We found no evidence of any clinically significant effect of NADT on LUTS and no correlation with decreasing PGV, except that patients with worse than average IPSS at the outset showed significant improvement.

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CONFLICT OF INTEREST STATEMENT

Ipsen provided financial support for the statistical analysis but had no role in the design of the study or the publication of the results.

REFERENCES

1. Barry, M. J., Fowler, F. J. Jr., O'Leary, M. P., Bruskewitz, R. C., Holtgrewe, H. L. and Mebust, W. K. 1992, J. Urol., 148, 1549-1557, discussion 1564.
2. Dowrick, A. S., Wootten, A. C., Murphy, D. G. and Costello, A. J. 2015, Urology, 85, 1304e1311.
3. Bhindi, A., Bhindi, B., Kulkarni, G. S., Hamilton, R. J., Toi, A., van der Kwast, T. H., Evans, A., Zlotta, A. R., Finelli, A. and Fleshner, N. E. 2017, Can. Urol. Assoc. J., 11(1-2), 41-46.
4. Sountoulides, P., van Dijk, M. M., Wijkstra, H., De La Rostte, J. J. M. C., Michel, M. C., 2010, World J. Urol., 28, 3-8.
5. Barry, M. J., Williford, W. O., Chang, Y., Machi, M., Jones, K. M., Walker-Corkery, E. and Lepor, H. 1995, J. Urol., 154, 1770-1774.
6. Jethwa, K. R., Furutani, K. M., Mynderse, L. A., Wilson, T. M., Choo, R., King, B. K., Bergstrahl, E. and Davis, B. J. 2016, J. Contemp. Brachytherapy, 8(5), 371-378.
7. Langenhuijsen, J. F., van Lin, E. N., Hoffmann, A. L., Spitters-Post, I., Witjes, A., Kanders, J. H. and Mulders, P. F. 2011, Urol. Oncol., 29, 52-57.
8. Faruya, R., Hisasue, S., Faruya, S., Saitoh, N., Ogura, H., Takahashi, S. and Tsukamoto, T. 2008, Urology, 72, 417-421.
9. Christie, D. R. H. and Sharpley, C. S. 2019, Prostate Cancer, Article ID 6932572, 12 pages.
10. Christie, D. R. H., Sharpley, C. F., Mitina, N., MacAteer, E., Jackson, J. E. and Lunn, D. 2020, J. Med. Imaging Radiat. Oncol., 64, 287-292.
11. Pinkawa, M., Fischedick, K., Asadpour, B., Gagel, B, Piroth, M. D., Nussen, S. and Eble, M. J. 2008, Int. J. Radiat. Oncol. Biol. Phys., 70(1), 83-89.
12. Chevli, C., Narayan, R., Rambarran, L., Kubicek, G., Chevli, K. K. and Duff, M. 2013, Res. Rep. Urol., 5, 29-37.
13. Aizer, A. A., Anderson, N. S., Oh, S. C., Yu, J. B., McKeon, A. M., Decker, R. H. and Peschel, R. P. 2011, Int. J. Radiat. Oncol. Biol. Phys., 79, 379-384.
14. Mazzola, R., Fersino, S., Fiorentino, A., Ricchetti, F., Gij Levra, N., Di Paola, G., Sicignano, G., Naccarato, S., Ruggieri, R. and Alongi, F. 2016, Clin. Transl. Oncol., 18, 317-321.

15. Jiang, Y. H., Lin, V. C., Liao, C. H. and Kuo, H. C. 2013, PLOS One, 8, e59176.
16. Crawford, E. D., Moul, J. W., Sartor, O. and Shore, N. D. 2015, Expert Opin. Drug Metab. Toxicol., 11(9), 1465-1474.
17. Foo, M., Lavieri, M. and Pickles, T. 2013, Int. J. Radiat. Oncol. Biol. Phys., 85(2), 385e392.
18. Zilli, T., Dal Pra, A., Kountouri, M. and Miralbel, R. 2016, Cancer Treat. Rev., 46, 35-41.
19. Cohen, J. 1988, Statistical Power Analysis for the Behavioural Sciences, 2nd Edition. Hillsdale, N.J.: Lawrence Erlbaum.
20. Jiwrajka, M., Yaxley, W., Ranasinghe, S., Perera, M., Roberts, M. J. and Yaxley, J. 2018, Aust. Prescr., 41, 150-153.
21. Wang, X. H., Wang, X., Shi, M. J., Li, S., Liu, T. and Zhang, X. H. 2015, Asian J. Androl., 17, 1022-1032.
22. Christie, D. R. H., Windsor, J. and Sharpley, C. F. 2019, J. Clin. Urol., 12(5), 361-370.