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Phase III randomised trial

Paradoxical metastatic progression following 3 months of neo-adjuvant androgen suppression in the TROG 96.01 trial for men with locally advanced prostate cancer

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ABSTRACT

Purpose: In the TROG 96.01 trial 6 month neo-adjuvant androgen suppression (NAS) and radiotherapy (RT) for locally advanced prostate cancer prevented distant progressions (DPs) when compared to RT alone, but 3 months did not. We ask why?
Methods: Between 1996 and 2000, 802 men with T2-4 N0 M0 prostate cancers received RT alone (0 month NAS) to 66 Gy, 3 months or 6 months NAS before RT. Interval hazards and cumulative incidences of DP were compared using competing risks methodology.
Results: In the first 4 follow-up years 39, 40 and 26 DPs were diagnosed in subjects treated with 0, 3 and 6 month NAS, respectively. Compared with 0 month, significant reductions in PSA doubling time in subjects with DP occurred following 3 month NAS ($p = 0.01$), but a significant reduction ($p = 0.01$) and a near significant delay in DPs ($p = 0.06$) occurred after 6 month NAS. Subsequently 25, 20 and 11 DPs occurred in the three trial arms. After early secondary therapy for PSA or local progression 34, 19 and 12 DPs were diagnosed after median delays of almost 4 years.
Conclusions: The data are consistent with the failure of 3 month NAS to prevent the progression of sub-clinical metastatic deposits already present before treatment.
 Radiotherapy and Oncology 107 (2013) 123–128

The three arm TROG 96.01 trial for men with locally advanced prostate cancer produced a straightforward result. After 10 year minimum follow-up, distant metastatic progressions (DPs) were reduced by half in the 6 month neo-adjuvant androgen suppression (NAS) plus radiotherapy arm when compared with the radiotherapy alone and 3 month NAS plus radiotherapy arms.

Unfortunately only one other trial dataset has produced data that have a bearing on this hypothesis. This was the RTOG 86.10 trial in men with locally advanced prostate cancer which compared radiotherapy alone with the same radiotherapy commencing 2 months after a 4 month course of AS. Four month AS was found to reduce subsequent DPs by approximately 24% [1]. A subset analysis revealed that the reduction in DPs was restricted to men with Gleason score $\leqslant 6$ tumours where the reduction was 62% [1].

At first sight the TROG 96.01 trial result suggests that there is a threshold duration of NAS, somewhere between 3 and 6 months, above which a large proportion of sub-clinical metastatic deposits present before treatment is eradicated. The RTOG 86.10 trial indicates that this threshold is between 3 and 4 months in subjects with low grade cancers.

A second look at the TROG 96.01 trial data suggests that while this hypothesis may be correct, the influence of treatment on metastatic progression is more complex. When compared with the radiotherapy only arm, the 3 month NAS arm reduced local (prostatic) progression by 50% and the 6 month arm by 55%. Almost certainly these large reductions would have produced measurable reductions in metastases that originated after treatment from the uncontrolled primary tumour. Why, therefore, has 3 month NAS produced no overall reduction in DPs compared to the radiotherapy only arm? In this report we explore the reasons for this paradoxical finding.

Abbreviations: NAS, neo-adjuvant androgen suppression; LP, local progression; DP, distant progression; STI, secondary therapeutic intervention (aka "salvage therapy" or "secondary therapy"); PSADT, PSA doubling time.

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Methods

Subjects

Data for the present study came from the 802 eligible patients who participated in the TROG 96·01 trial, described in detail previously [2]. Between 1996 and 2000, men with T2b, T2c, T3 and T4 prostatic adenocarcinoma, after providing informed consent were randomised to one of three treatment arms. In the control arm radiotherapy (RT) alone to the prostate and seminal vesicles to a dose of 66 Gy was delivered in daily fractions of 2 Gy. In the two experimental arms neo-adjuvant androgen suppression therapy (NAS) using monthly goserelin 3·6 mg (AstraZeneca Pty Ltd., Sydney, Australia) subcutaneously and flutamide 250 mg (Schering-Plough Pty Ltd., Sydney, Australia) orally three times a day was administered before and during RT. NAS began 2 months before radiation in the 3 month NAS arm and 5 months before radiation in the 6 month NAS arm.

Follow-up, endpoints and quality control

Patients were followed up 2 months after radiotherapy, every 4 months for 2 years, and every 6 months thereafter for a further 3 years. If free of all signs of cancer patients were then followed annually. At each follow-up visit digital rectal examination and serum PSA estimation were performed.

Endpoints in the present study were PSA progression, local progression (LP) and DP. LP was defined as occurring at the time of first progression of malignant induration or confirmatory biopsy or trans-urethral resection $\geqslant$2 years after treatment. DP was defined as metastasis at anatomical sites outside of the prostatic region. PSA progression was determined using the Phoenix method (i.e. time from end of radiotherapy to a PSA rise of 2 ng/mL above the post-treatment nadir). Time to all endpoints was measured from randomisation. PSA doubling times (PSADTs) were estimated using the value prior to Phoenix progression up until STI or last follow-up. A spline fitting procedure allowed significant changes in PSADT to be detected [3].

Site monitoring visits were performed to verify source data. All relapse and mortality data were reviewed by a blinded Endpoints Committee.

Statistical methods

Cumulative incidence of competing risks methodology was used to compare DP in the three trial arms. The Fine and Gray method [4] was used to derive adjusted HRs and *p*-values for comparison of treatment arms. Adjusting factors were: age (<70 vs $\geqslant$70), Gleason score (2–6 vs 7 vs 8–10), initial PSA (<20 vs $\geqslant$20 μg/L), and stage (T2b vs T2c vs T3 and T4). Unless specified otherwise competing risk events were STI and death due to any cause. Life tables were used to derive 2 yearly interval hazards of DP from randomisation to illustrate their respective time-courses because the proportion of DPs was relatively small. Chi-square tests were used to compare categorical data, and the Wilcoxon rank-sum for continuous data.

A two-sided *p*-value <0·05 was considered significant because all analyses were exploratory. Stata Version 11·2 was used for all analyses.

Assumptions concerning the time-course of distant progression in interpreting the data

Our first assumption is that metastases originate from the primary, both prior to its treatment and after treatment if the primary tumour remains viable. Metastases originating before treatment are likely to be diagnosed at earlier timepoints after treatment than metastases originating after treatment. In the electronic supplement we discuss what is known of prostate cancer cellular kinetics [5–9] and its relevance to the duration of the sub-clinical growth phase of prostate cancer metastases, i.e. the time it takes for a single clonogenic metastatic cell to be diagnosed as a small metastasis. We then estimate that the shortest duration of this phase would be between 1.1 and 2.7 years but would apply to only the most rapidly growing cancers. The median duration, applying to most tumours, would be 1.9–13.8 years, and longest duration, associated with the most slowly growing tumours, would range between 4.9 and 32.4 years. In clinical terms this means that the great majority of DPs diagnosed in the first four years of follow-up in the present study will have originated from sub-clinical metastatic deposits present before treatment, though many will also be diagnosed at later timepoints. Our second assumption is that NAS could both have delayed and prevented the growth of sub-clinical metastases, but that secondary therapy with AS following PSA or local progression could have delayed but not prevented DPs. Our third assumption is that lack of clinical evidence of LP does not rule out the possibility that DPs can originate from uncontrolled primary tumours, because digital examinations underestimate the presence of viable cancer in irradiated prostates. These assumptions have enabled us to advance plausible explanations for the proportion of DPs that originate from sub-clinical metastases and the proportion of metastases "induced" by local progression.

Results

Of the 802 eligible men, 519 had experienced progression by data close-out on 31 August 2010. Of these, 244 (47.0%) had PSA progressions without evidence of clinical progression; 275 (53.0%) had clinical progression diagnosed before secondary therapeutic intervention (STI); 114 occurred in the prostate alone ("LP only"), and 109 at metastatic sites alone ("DP only"). A smaller group of subjects had evidence of local and DPs ("LP/DP", $n = 52$). In the majority of these subjects ($n = 46$) DP was diagnosed at the time of LP or afterwards. STI was commenced in 88 subjects experiencing LP only before DP could be diagnosed. Ultimately DP was diagnosed after STI in 31 of these subjects. STI was also commenced in 123 subjects with PSA progression without CP. In 34 of these subjects DP was diagnosed after STI.

Time-course of diagnosed distant progressions

The time-course of the hazards of DPs occurring before STI is presented by treatment arm in Fig. 1. During the first two years

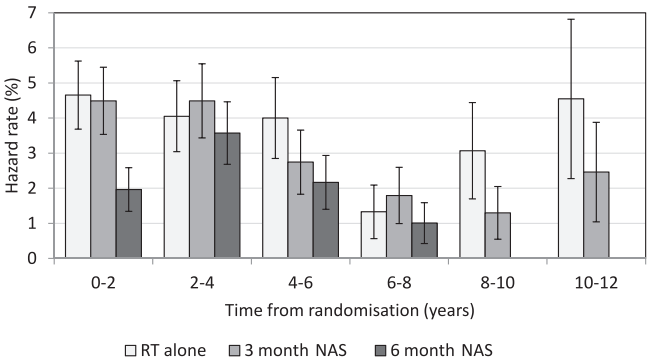
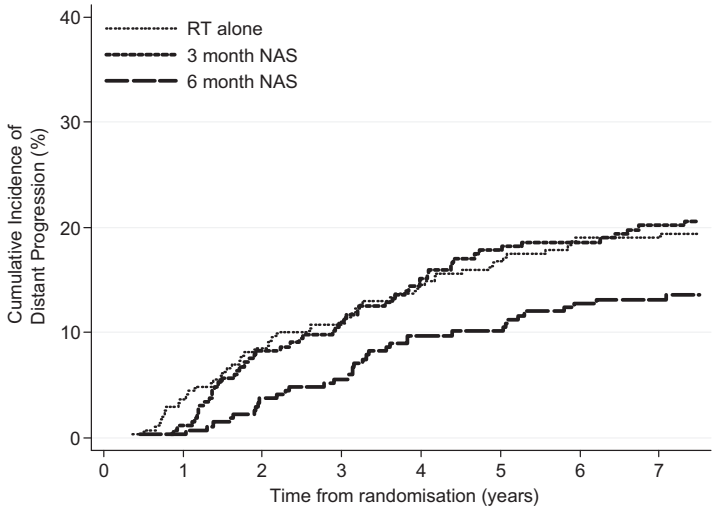


Fig. 1. Hazard rates of distant progression before secondary therapeutic intervention by treatment arm.



Number of events*

RT alone	10	13	6	10	6	6	0	1
3 month NAS	3	19	7	11	7	2	4	1
6 month NAS	1	9	5	11	1	7	1	1

Fig. 2. Cumulative incidence of distant progression occurring in the first 7.5 years of follow-up by treatment arm. *Abbreviations:* RT, radiotherapy; NAS, neo-adjuvant androgen suppression therapy. *Number of distant progression diagnosed before secondary therapeutic intervention.

of follow-up, when virtually all DPs would have been due to the progression of sub-clinical metastases present at the time of treatment, similar numbers of subjects in the 3 month NAS arm ($n = 22$), and in the control (RT alone) arm ($n = 23$) had DPs, but the number of subjects in the 6 month NAS arm was considerably smaller ($n = 10$). The cumulative incidence of DP plots in Fig. 2 indicate that DP diagnosis occurred at a more rapid rate in the 3 month NAS arm, particularly in the second year of follow-up. This observation led us to compare the PSADT of subjects experiencing DPs in the first 7.5 years of follow up i.e. when a large proportion of DPs would have arisen from sub-clinical metastases (see electronic supplement). This was to find out whether testosterone recovery following NAS could have accelerated metastatic tumour progression, particularly in subjects receiving 3 month NAS. Table 1 indicates that PSA doubling time (PSADT) was more rapid in the 3 month NAS arm ($p = 0.01$) and that this phenomenon was most common in DPs occurring in the first five follow-up years. These findings are explored in the electronic supplement (Figs. S1 and S2). Fig. S1 presents the absolute frequencies of PSADT in subjects developing DPs in their first 7.5 years of follow-up; it shows that the number of subjects receiving 3 month NAS with PSADTs $\leqslant$3 months was markedly increased compared to those receiving RT alone ($p = 0.01$). Fig. S2 presents the relative frequencies of PSADTs and confirms the relative increase in rapid PSADTs in subjects receiving 3 month NAS. However it also suggests a relative increase in rapid PSADTs in subjects treated with 6 month NAS. While this could mean that PSADTs were shortened in the 6 month NAS arm, it could also mean that 6 month NAS eradicated substantial numbers of sub-clinical metastases present at diagnosis associated with PSADTs >3 months. Whether these rapid PSADT failures increased the rapidity of metastatic progression, however, is unclear. This is because the data in Table 1 and Figs. 1 and 2 suggest that the timing of DPs in the two NAS arms is more compatible with delays in the DP process rather than accelerations. When compared with the RT alone arm, the DP timing data in the 6 month arm are compatible with a delay in the diagnosis of some metastatic progressions ($p = 0.06$), particularly from follow-up years 1–2 until years 3–4, and the prevention of progression in a large number of others (Grays $p < 0.01$). However in the 3 month NAS arm where the prevention of metastatic progressions did not occur, delays in progression were shorter. Fig. 2 suggests that DPs which were likely to have occurred in the first follow-up year in subjects receiving 3 month NAS instead occurred in the second.

For these reasons the number of DPs diagnosed in the third and fourth years, which most likely arose from sub-clinical metastases present before treatment (see electronic supplement), was similar in the three trial arms. The PSADT data presented in Table 1 indicate that PSADTs in subjects experiencing progressions in both NAS treatment arms were still more rapid than in progressing subjects receiving RT alone. However, as pointed out above, this does not necessarily indicate an induced shortening of PSADT occurred in subjects on the 6 month NAS arm.

In follow-up years 5.0–7.5 when some of the DPs could have originated from uncontrolled primary tumours (i.e. LP induced metastases [see electronic supplement]), DPs were somewhat fewer in the 6 month NAS arm ($n = 10$) than in the 3 month NAS ($n = 14$) and RT alone arms ($n = 13$). The PSADTs associated with metastases occurring in this period provide no suggestion that any treatment related reductions in PSADT persisted beyond five years (Table 1).

From 7.5 years onwards the interval hazards data (Fig. 1) suggest the presence of a second (late) "wave" of DPs as described by Morgan et al. [10], in the radiotherapy only and 3 month NAS arms. Although the number of DPs in this "late wave" was small ($n = 19$) a greater number were seen in men treated by RT alone ($n = 12$) than by 3 month NAS ($n = 6$). Table 2 suggests some interesting differences between the earlier (<7.5 years) and the late wave of DPs. Tumours giving rise to the second wave of DPs were of lower T stage (<0·001) and Gleason score ($p = 0·03$), and had longer times to PSA progression ($p < 0·001$), and PSADTs ($p < 0·001$). Bony metastases were less frequent in this group ($p = 0·006$). In 10 of these 19 subjects, PSADTs became much more rapid in the months prior to the diagnosis of metastases and 3 had puzzling periods of PSA stability at levels of 10 ng/mL or more during their PSA rises (Figs. S3 and S4 in the electronic supplement). However caution needs to be exercised in interpreting

Table 1
Distribution of PSA doubling times by trial arm according to time to distant progression from randomisation.

PSADT (mths)[a]	Time to distant progression from randomisation (years)					
	<2	2–4	4–5	5–7.5	>7.5	Total
RT alone						
<3	10 (16.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (16.1%)
3–4	3 (4.8%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.5%)
4–6	5 (8.1%)	5 (8.1%)	3 (4.8%)	0 (0.0%)	1 (1.6%)	14 (22.6%)
6–9	2 (3.2%)	9 (14.5%)	1 (1.6%)	3 (4.8%)	0 (0.0%)	15 (24.2%)
9–12	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.5%)	1 (1.6%)	5 (8.1%)
>12	1 (1.6%)	1 (1.6%)	2 (3.2%)	0 (0.0%)	10 (16.1%)	14 (22.6%)
Total	21 (33.9%)	16 (25.8%)	6 (9.7%)	7 (11.3%)	12 (19.4%)	62 (100.0%)
3 month NAS						
<3	16 (26.7%)	5 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (35.0%)
3–4	3 (5.0%)	4 (6.7%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	8 (13.3%)
4–6	2 (3.3%)	5 (8.3%)	3 (5.0%)	0 (0.0%)	0 (0.0%)	10 (16.7%)
6–9	1 (1.7%)	4 (6.7%)	4 (6.7%)	3 (5.0%)	1 (1.7%)	13 (21.7%)
9–12	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.3%)	2 (3.3%)	4 (6.7%)
>12	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	3 (5.0%)	14 (6.7%)
Total	22 (36.7%)	18 (30.0%)	7 (11.7%)	7 (11.7%)	6 (10.0%)	60 (100.0%)
6 month NAS						
<3	8 (23.5%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (32.4%)
3–4	0 (0.0%)	3 (8.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	4 (11.8%)
4–6	0 (0.0%)	7 (20.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	9 (26.5%)
6–9	0 (0.0%)	2 (5.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	3 (8.8%)
9–12	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.8%)	1 (2.9%)	4 (11.8%)
>12	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.8%)	0 (0.0%)	3 (8.8%)
Total	8 (36.7%)	15 (44.1%)	7 (11.7%)	9 (26.5%)	1 (2.9%)	34 (100.0%)

Abbreviations: PSA, prostate-specific antigen; PSADT, PSA doubling time; RT, radiotherapy; NAS, neo-adjuvant androgen suppression therapy.
[a] PSA doubling times in subjects diagnosed with distant progressions (DPs) prior to secondary therapeutic intervention according to the timing of DP in the three trial arms. In 4 subjects DPs were diagnosed in the absence of PSA progression. PSADT could not be estimated in another subject.

Table 2
Distribution of primary tumour characteristics according to the timing of distant progression.

Primary tumour characteristics		Distant progression within 7.5 years of treatment[d] (n = 142)		Second wave of distant progression[e] (n = 19)		p Value
Gleason score	2–6	32	(22.5%)	7	(36.8%)	0.03[a]
	7	69	(48.6%)	10	(52.6%)	
	8–10	41	(28.9%)	2	(10.5%)	
T stage	2b	18	(12.7%)	8	(42.1%)	<0.001[a]
	2c	42	(29.6%)	7	(36.8%)	
	3,4	82	(57.7%)	4	(21.1%)	
Pre-treatment PSA (ng/mL)	<10	30	(21.1%)	6	(31.6%)	0.05[a]
	10–19.9	38	(26.8%)	7	(36.8%)	
	⩾20	74	(52.1%)	6	(31.6%)	
PSA progression kinetics (median)	Time to progression (years)		1.5		5.7	<0.001[b]
	PSA doubling time (months)		4.8		15.6	<0.001[b]
Sites of clinical progression	Local	48	(33.8%)	6	(31.6%)	0.85[c]
	Nodal	50	(35.2%)	10	(52.6%)	0.14[c]
	Bony	122	(85.9%)	11	(57.9%)	0.006[c]

Abbreviations: PSA, Prostate-specific antigen.
[a] Trend test (one-tailed).
[b] Wilcoxon rank sum test.
[c] Pearson's chi-square test (two-tailed).
[d] Distant progression occurs less than 7.5 years after randomisation.
[e] Second wave of distant progression 7.5 years or later after randomisation.

this "second wave" of DPs as a single metastatic phenomenon. Six of the 19 subjects had LPs diagnosed between 0 and 4.6 years prior to their DPs. Their tumours tended to have lower Gleason scores and T stage than the remaining 13 subjects without diagnosed LP. These six subjects also tended to have shorter PSADTs and experienced progression in lymph nodes more frequently than bone. However there were no trial arm related differences between these two small subgroups. Twelve of the 19 "late wave" DPs occurred in the RT only arm, 6 in the 3 month NAS arm and only 1 in the 6 month NAS arm. These DPs could therefore have arisen prior to treatment or from recurrent primary tumours (see electronic supplement). If the former is true then some of these metastatic deposits may have spent time in a dormant state. This is certainly possible in up to 6 subjects where PSA levels stabilised for periods of between 1.8 and 5.5 years before and during their PSA ascents.

Distant progressions diagnosed after STI or remaining undiagnosed

DPs were diagnosed after STI in 65 subjects. Thirty one of these had LP before STI and 34 had PSA progressions alone. The interval between local and PSA progression only and DP was approximately 4.5 years longer in those having STI soon after progression was diagnosed than in those in whom STI was delayed until after DP.

As discussed in the electronic supplement, the origin of the metastatic process in these two groups of subjects is not an easy determination. Nevertheless minimum, maximum and reasonable likelihood estimates for the proportions of DPs that arose from LPs and sub-clinical metastases have been derived for subjects treated by radiation alone as at trial closeout in electronic supplement. The minimum estimate for sub-clinical metastases in this group of 98 subjects is 41.8%, the maximum is 61.2% and a "reasonable" estimate is 52%. The corresponding estimates for LP induced DPs are 38.8%, 58.2% and 48%.

The number of subjects with DPs that were not diagnosed is also estimated in the electronic supplement. The minimum and maximum likelihood estimates are 37 and 122 subjects (i.e. 14.1–34.9% of all DPs).

Discussion

The DP time-course data in this study suggest that approximately 52% (42–61%) of DPs in men with locally advanced, but non-metastatic prostate cancers who have received 66 Gy alone to the prostate arose from sub-clinical metastases present at diagnosis. The remaining DPs originated from viable foci of cancer in the prostate that remained after 66 Gy. The study indicates that 3 month NAS was less effective in preventing DPs than 6 month NAS largely because it failed to prevent the progression of sub-clinical metastatic deposits present prior to treatment that were destined to be diagnosed as DPs within the first 7.5 years of follow-up. During these years DPs were diagnosed just as frequently in the 3 month NAS trial arm ($n = 54$) as in the RT alone arm ($n = 52$), but almost 1.5 times more frequently than in the 6 month NAS arm ($n = 36$). However 3 month NAS was more successful in preventing DPs diagnosed 7.5 years or more after randomisation. When compared to the RT alone arm, in which 12 DPs were diagnosed, DPs were reduced to 6 in the 3 month NAS arm and 1 in the 6 month NAS arm. It is probable that 3 month NAS achieved this reduction by preventing local progression, which it did almost as efficiently as 6 month NAS. This suggestion is highly compatible with the theory advanced by Morgan et al. [10] that this belated surge in DPs, which they dubbed the "late wave" of metastases originated from LPs. However the possibility that some late appearing DPs in all three trial arms could have evolved from sub-clinical deposits present already at diagnosis cannot be ruled out.

The implications of these findings for routine clinical practice are twofold. For men with "high-risk" localised prostate cancers, (where sub-clinical metastatic deposits are likely to be present at diagnosis in $\geqslant$20%), adjuvant AS will remain necessary because radiation dose escalation will not prevent these metastatic deposits from progressing. However in men at lower risk of sub-clinical metastases the need for adjuvant AS is much more limited and in low-risk patients radiation dose escalation is likely to prevent the majority of DPs. However, our time-course data suggest that this approach is unlikely to cause significant reductions in prostate cancer specific mortality until 15 years of follow-up has been undertaken.

Our report is not the first to document more rapid PSADTs in men receiving NAS. Shorter PSADTs have been reported in PSA progressions following 3 month NAS in radiotherapy and surgical series [11–13]. So far as we are aware however, no attempts have been made to determine whether the phenomenon is related to an acceleration of the metastatic process. Because PSADTs associated with DPs were significantly more rapid in the 3 month NAS arm than in the RT alone arm (Table 1) we feel it is reasonable to accept the possibility that testosterone recovery following 3 month NAS has induced more rapid PSADT in surviving sub-clinical metastatic deposits. However our DP time-course data (Figs. 1 and 2) are more compatible with delays in the progression of sub-clinical metastases due to androgen suppression itself than to accelerated progressions from testosterone recovery. In the 6 month NAS arm a relative reduction in short PSADTs was observed. However, because there was no increase in short PSADT DPs compared to the RT alone arm we feel the data are more compatible with the prevention of a large number of DPs with PSADT >3 months by 6 month NAS (Table 1) than a genuine induction of short PSADTs in surviving sub-clinical deposits. Fortunately the clinical implications of the acceleration in PSADT seen in subjects receiving 3 month NAS in this study is likely to be limited if confirmed in prospective studies. Although 3 month NAS remains a commonly used neo-adjuvant regimen in many countries, most men with high risk localised cancers already receive more prolonged courses of AS due to the varying benefits demonstrated by large scale trials [14–17].

Five limitations of this study need to be highlighted. The first is that only 161 DPs were diagnosed prior to STI and 65 afterwards. This limited the power of the study to recognise treatment arm related differences in both the time-courses of DP and associated PSADTs. The second is that DPs could have occurred more frequently and earlier than described for two reasons: Firstly due to competing risks such as infirmity, loss to follow-up and death occurring prior to diagnosis and secondly, due to the less sensitive imaging technology in use. Our likelihood estimates indicated that the proportion of subjects who had "missed" or yet to be diagnosed DPs was between 14% and 35% sometime after 7.5 years. The third limitation related to our LP data. Unfortunately local progression is difficult to diagnose reliably by digital examination and the magnitude of the reductions found is open to doubt. In RTOG 94.06 and two Canadian randomised controlled trials where prostatic biopsies were planned to occur 24 months after radiation, persistent cancer was found in as many as 65% of men treated by radiation alone, 14–28% in men treated with 3 or 4 month NAS and 5–9% of men treated with 8 or 9 month NAS [18–20]. Had biopsy and MRI data been available the frequency and timing of our LP estimates could have been more reliable. These, in turn, could have informed better estimates of the proportions of LPs that lead directly to subsequent DPs and ruled out dormant SCM as an explanation for their origins. In spite of these caveats the proportion of DPs thought to have originated from LPs would not have been seriously underestimated because LP was not assumed to be absent in subjects without LP diagnoses. The fourth is that "immortal time biases" could have influenced the characterisation of subjects with late appearing DPs [3,21]. Comparison of this group with subjects experiencing earlier DPs therefore should be viewed cautiously. The fifth limitation of this study is the sparsity of data regarding the characterisation and the duration of the sub-clinical growth phase of prostate cancer metastases. Better data would have enabled us to interpret our results with greater precision.

Conflict of interest statement

Allison Steigler – financial support from AstraZeneca to attend a meeting.

David Lamb – financial support from AstraZeneca to attend meetings.

David Joseph – honoraria associated with membership of AstraZeneca's Breast Cancer Medical Advisory Board.

Nigel Spry – honoraria associated with AstraZeneca and Schering Plough.

Keen-Hun Tai – FROGG-AstraZeneca education grant in 2003 and support by AstraZeneca to attend two Casodex Investigators Meetings in 2001 and 2004.

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The study sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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Appendix Supplementary. data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.03.025.

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