PSA doubling time post radiation: the effect of neoadjuvant androgen ablation

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Objective: *To determine whether men who relapse after neoadjuvant androgen ablation (NAA) and high-dose radiation therapy (RT) have faster PSA doubling times (PSAdt) than those who are treated with RT alone.*

Materials and methods: *From a prospective database of 1880 patients treated with RT for localized prostate cancer, patients were selected for further study if they had a rising PSA profile >1 ng/ml, and were treated with either no NAA, or prolonged NAA (defined as 3-12 months NAA) with a minimum 5 years follow-up. The PSAdt was calculated from the exponential line of best fit from the first post-nadir value >1 ng/ml to the last PSA prior to secondary intervention. Those patients with a rising PSA profile at 5 years of follow-up were further examined with linear regression to determine factors of possible independent adverse effect.*

Results: *There were 251 patients eligible with rising PSA profiles. Patients treated with NAA had higher pre-treatment Gleason scores ($p<0.001$), PSA ($p<0.001$), and T stage ($p<0.001$). Median duration of NAA was 5.1 months. Rising PSA profiles occurred in 78% of the RT-only group and 70% of the NAA group. In regression analysis, factors predictive of more rapid PSAdt were pre-treatment Gleason score ($p<0.001$), pre-treatment PSA ($p=0.025$), and T stage ($p=0.017$). The use of NAA ($p=0.4$) was not significant.*

Conclusion: *The use of prolonged NAA in men treated with RT does not itself cause a more rapid PSAdt when relapse occurs. Faster relapse observed in these men is due to intrinsically more aggressive tumors prior to treatment.*

Key Words: androgen ablation, prostate neoplasms, prostate specific antigen, radiotherapy

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Introduction

There is increasing evidence supporting the use of combined androgen ablation (AA) with radiotherapy (RT) in high-risk localized prostate cancer.[1-4] The EORTC trial demonstrated an advantage to 3 years of adjuvant androgen ablation after irradiation compared to irradiation alone in men who primarily had T3-T4 tumors. The RTOG 85-31, and 92-02 trials showed a better biochemical disease free survival in men treated with androgen ablation after irradiation, but a survival benefit was restricted to those with centrally reviewed high-grade tumors. The RTOG 86-

10 and 94-13 trials suggest that brief neoadjuvant androgen ablation may have a role in combination with pelvic irradiation in improving biochemical disease free survival. Furthermore animal models and retrospective studies,[5-7] suggest that neoadjuvant androgen ablation with irradiation may be useful. As a result of such evidence, there is increased use of adjuvant and neoadjuvant hormonal with irradiation.[8]

The BCCA is a centralized cancer care provider that is responsible for the provision of Radiation Therapy and other cancer services to the entire population (4 million) of British Columbia. With the evolution of evidence in support of AA along with RT over the last decade, the BCCA has developed a policy of offering AA along with RT to high-risk localized prostate cancer patients treated with curative intent RT. Such patients (Gleason >=7, PSA>15, or >=T3a) are now offered up to 3 years of AA (8 months of which is typically given as neoadjuvant androgen ablation (NAA)). The percentage of such high-risk patients receiving AA increased from 11% in 1994, to 86% in 2000.

Contrary to the benefits seen with neoadjuvant androgen ablation with irradiation, studies on the use of neoadjuvant androgen ablation prior to radical prostatectomy, have not demonstrated clear advantages in biochemical disease free survival.[9] In animal models, AA may select more malignant phenotype, (eg increased expression of BCL2).[10] Furthermore, others have suggested that NAA prior to radical prostatectomy leads to more aggressive subsequent relapses.[11]

As a result of these latter concerns, we have analyzed our results with combined NAA-RT compared with RT alone to see if those patients relapsing after combined therapy have more aggressive relapses. Our hypothesis is that those patients who relapse biochemically after NAA-RT have faster PSA doubling times (PSAdt) than those treated with RT alone. This hypothesis assumes that more rapid PSAdt's reflect more aggressive tumors at relapse.

Materials and methods

Since 1994, the BCCA had maintained a prospective database of prostate cancer patients treated with curative intent RT between June 1994 and January 2001. The only criterion for entry into the database has been the willingness of patients to attend regular follow up at one of the three mainland BCCA cancer centers. The database contains information on patient factors (e.g. age, co-morbidity, etc), tumor factors (e.g. initial PSA, stage, grade, etc) and treatment factors (e.g. use and duration of AA, radiation dose etc). At present more than 1800 patients have been entered and followed according to a standardized follow-up: visits at 6 weeks post RT, then every 6 months for 3 years then annually. At each visit a history and physical are performed, along with a PSA, testosterone, tumor control and toxicity scoring. All radiation treatment was given with curative intent with 66 to 70 Gy in 2 Gy fractions, or 52.5 to 55 Gy in 2.62 to 2.75 Gy fractions, and CT planning was utilized. Androgen ablation was given with LHRH agonists along with lead in oral anti-androgen, although in the early years of the cohort low dose diethylstilbesterol and cyproterone were used.

We selected patients from this dataset who had a rising PSA profile above a level of 1 ng/ml, and who had either received no NAA, or 3-12 months of NAA, and no adjuvant androgen ablation. We were particularly concerned about possible bias due to temporal changes of utilization of NAA during the time frame of the study, and a possible artefactual effect on PSA relapse and/or PSA velocity that might be observed in those treated with NAA. In order to minimize such potential biases we selected patients who were treated with radiation in 1996 and 1997 only, thus giving a potential maximum PSA follow-up of 5-6 years, as the data cut-off was February 2003. Patients treated in earlier years were not selected as the use of NAA was minimal (see below), and more recently treated patients would have inadequate follow-up. The intent was to create a "5-year snapshot" of the patients PSA status; those who had a rising PSA profile were selected only if the level of 1

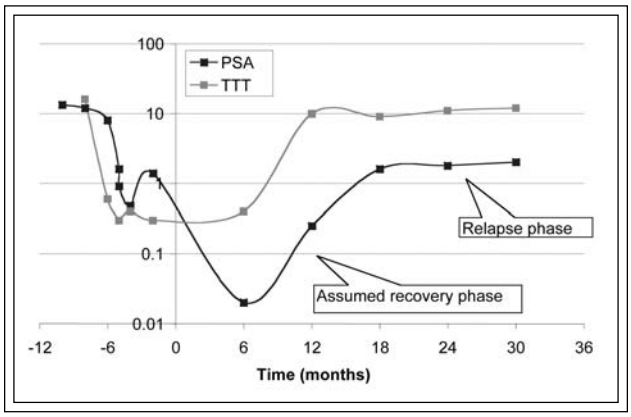

Figure 1. Example of PSAdt and testosterone recouvery after NAA-RT. Note the rapid PSA velocity between 6 and 18 months as the testosterone level recovers to normal following cessation of NAA, compared to the much slower PSA rise from 18-30 months indicative of eventual clinical relapse. F-PSA is free PSA. TTT is total testosterone.

TABLE 1. **Patient numbers by group**

	RT-only			NAA-RT*		
Total #	**#**	**No PSA rise**	**PSA Rise**	**#**	**No PSA rise**	**PSA Rise**
330	240	52	188 (78%)	90	27	63 (70%)

* NAA-RT: 3-12 months of neoadjuvant androgen ablation prior to radiation

ng/ml was breached before the 5-year time point, and those who did not have a rising PSA profile had to have been followed with serial PSA results for at least 5 years. A patient who developed a rising PSA profile in year 6, would thus be scored as a non-riser at the 5-year time point.

PSAdt was calculated by the exponential line from the post-nadir PSA > 1 ng/ml to the last PSA prior to a second intervention. The exponential line of best fit was calculated using the least squares method. The fit started from a PSA > 1, because PSA recovery after NAA is biphasic Figure 1. The initial rapid rise reflects testosterone recovery, while the delayed second progressive rise reflects relapse.

Stage, grade, initial PSA level, and treatment groups were then assessed for significance of effect on PSA doubling time by linear regression. PSAdt and PSA were logged to provide normal distributions for statistical analysis.

In order to examine whether the effect of NAA could arise as a result of prevention or delay of relapse among the persons with less aggressive disease we also compared the doubling time of the NAA relapsers with those in the non-NAA group who had the fastest relapse times.

Results

Of the 1880 patients in the database, 689 were treated with radiation in 1996 -1997. Of these patients, 415 received no hormone therapy, and 164 short-term NA therapy as defined in the methods section. From these 579 men, 330 were followed sufficiently according to the criteria above (240 RT-only, and 90 NAA-RT), and had a median follow-up of 56 months. Two hundred forty received no NAA (or adjuvant androgen ablation) and formed the RT-only group, and 90 received 3-12 months NAA (and no adjuvant androgen ablation) and form the NAA-RT group. From the total of 251 men with a rising PSA, 188 were

TABLE 2. **Risk Factors for patients treated with RT-only and NAA-RT who had a rising PSA profile >1 ng/ml**

Factor	**RT-only**	**NAA-RT**	**P value**
n	188	63	
Follow-up prior to secondary intervention (median)	53 months	35 months	
Time to rising PSA >1 ng/ml (median)	22 months	19 months	
Duration of NAA (median)	0	5.1 months	
Pre-treatment PSA (median)	11 nmol/L	27 nmol/L	p<0.0001
Gleason score (median)	6	7	p<0.0001
Gleason score 2-5	36.6%	14.3%	
Gleason score 6	29.8%	25.4%	
Gleason score 7	23.6%	30.2%	
Gleason score 8-10	10%	30.1%	
T stage (median)	T2b	T3a	p<0.0001
T1-2	80.2%	20%	
T3-4	19.8%	80%	
Risk - Low	12%	1.6%	
- Intermediate	54%	6.5%	
- High	34%	92%	p<0.0001

Low-risk: All of PSA<10nmol/l, £T2a, Gleason 6
Intermediate-risk: Not low or high risk
High-risk: Any of PSA>20, Gleason ≥8 or Stage ≥T3a

in the RT-only group, and 63 in the NAA-RT group.

The breakdown of patients is shown in Table 1. According to the follow-up schedule, 2970 follow-up PSA measurements would have been expected, and 2810 were actually measured. Patients in the NAA-RT group had higher risk tumors compared to the RT-only group Table 2. Therefore patients with a rising PSA were analyzed with logistic regression to account for the known risk factors, stage, grade and pre-treatment PSA.

In the NAA-RT group the mean and median duration of NAA was 5.6 and 5.1 months respectively. Twenty seven percent of those in the NAA-RT group had continuation of NAA during the entire course of radiation.

In those patients with a PSA above 1 ng/ml, after a median follow-up of 20 months after radiation, rising PSA profiles were seen in 78% and 70% of the RT-only and NAA-RT groups respectively. It should be noted that this does not reflect the biochemical relapse rate of all patients, which for the entire cohort is 15%, 30%, 50%, at 5 years for low, intermediate and high risk by Canadian consensus risk groups as described elsewhere.[16]

The PSAdt was faster in those patients relapsing in the NAA-RT group compared to the RT-only group Figure 2. The median PSAdt was 17 months in the RT-only and 9.4 months in the NAA-RT group (p=<0.001).

In regression analysis, factors predictive of more rapid PSAdt was pre-treatment Gleason score (p=<0.0001), PSA (p=0.025) and T stage (p=0.017). The use of NAA was not significant (p=0.4). We then compared the doubling time of the NAA relapsers with those in the RT-only group who had the fastest relapse times, assuming that a proportion of the NAA treated patients had not yet relapsed because of the prior NAA. To do so we compared the fastest 168 of the 188 rising PSA's in the RT-only group (being the 70% proportion of men with rising PSA's in the NAA-RT group, applied to the 240 men total in the RT-only group) to all the NAA relapsers, and found the effect of prior NAA remained non-significant on logistic regression between these groups (p=0.9).

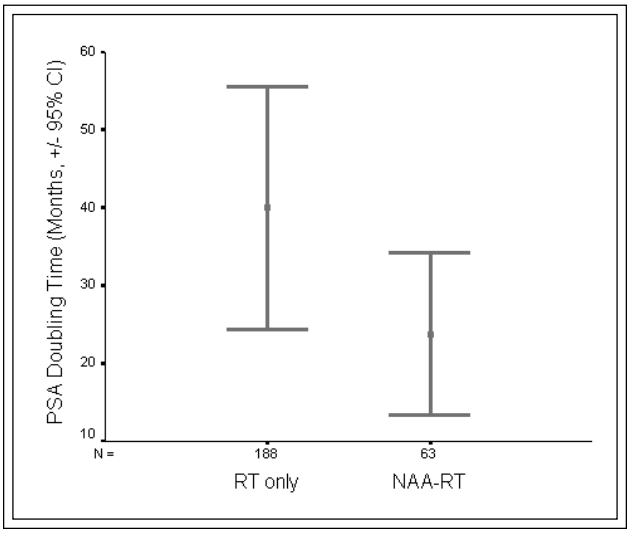

Figure 2. PSA Doubling time with and without AA. The median PSAdt in the RT-only group was 17 months and was 9.4 months in the NAA-RT group (p<0.001), but was not significantly different on linear regression (see text).

Discussion

There is an increasing role of androgen ablation in combination with radiotherapy both for localized prostate cancer patients.[12] Neoadjuvant androgen ablation is commonly used for men with large tumors[13] and prolonged androgen ablation is indicated for those with locally advanced or high-risk.[14,15]

The ASTRO consensus definition of biochemical relapse[16] has been used as the standard definition for biochemical relapse, however other definitions may be more sensitive and specific to a subsequent clinical relapse or death from prostate cancer than the ASTRO definition.[17-19] Whatever definition of biochemical relapse is used, a true biochemical relapse will be characterized by a trend to a continuously rising PSA in the long run. The rate of the PSA rise predicts for the time to clinical progression, whether this is ultimately metastatic or local.[20] Therefore a relapse characterized by a more rapidly rising PSA (i.e. a shorter PSAdt), would be expected to be associated with a worse outcome (i.e. a shorter clinical disease free survival, or a lower disease specific survival). There has been some debate in the literature as to whether a PSA relapse after irradiation predicts for a worse outcome,[21-23] however, in our analysis of the BCCA experience, reported elsewhere, we did find an effect of biochemical relapse on survival.[24] A more rapid PSAdt may also be associated with a worsening overall quality of life if it leads to patients starting on androgen ablation sooner, or if they develop symptoms from disease progression.

Rabbani et al[11] have suggested that a biochemical relapse is more rapid after NAA prior to radical prostatectomy, compared to radical prostatectomy alone. They used a different methodology in their study and it may be that this alone would account for

the different finding. However there may also be a difference in case mix between their study and ours. Patient treated with radical prostatectomy would generally be expected to be younger and their tumors lower risk than those treated with radiotherapy. There may also be differences in the threshold for using androgen ablation in their study, such that those patients treated with androgen ablation may have higher risk features than those treated with surgery alone. It may also be possible that the adverse features induced by androgen ablation are counteracted by radiotherapy but not with surgery.

Shipley et al[25] has reported that the relapses seen after neo-adjuvant androgen ablation prior to irradiation are not more resistant to subsequent salvage androgen ablation than those treated with radiation alone. This study updated the results of the RTOG 86-10 trial[13] which randomized patients with larger but localized tumors to 2 months NAA and 2 months concurrent androgen ablation with radiotherapy versus radiotherapy alone. More patients had biochemical relapse in the radiotherapy-alone arm; however, of those patients who relapsed and were treated with salvage androgen ablation there was no difference in the subsequent biochemical response or survival between patients in the initial study arms. Furthermore, Hanlon et al, noted that those patients relapsing after RT preceded by NAA had slower PSAdt and better overall survival compared to those relapsing after RT alone.[26]

There are limitations to our study. We compared two non-randomized groups and therefore there is potentially uncontrolled imbalance between the two groups. We attempted to address this possibility by controlling for the imbalance of known prognostic factors using multivariate analysis. Our study is also relatively small and therefore may be under-powered to detect a small, but clinically significant difference in PSAdt between the two groups. Furthermore, the duration of follow-up is relatively short and late differences in relapse may yet evolve. In addition, although patients are actively followed independent of health state, some patients may be lost to follow-up due to patient choice, migration, and illness. However it is unlikely that there is a large difference in rapid relapses that would be of significant clinical relevance in the first few years after therapy based on our data. Furthermore, it may be possible that the prior use of NAA had delayed relapse in the NAA group, such that a subgroup of patients destined to relapse had not yet done so. We did attempt to account for this possibility by repeating the regression analysis using only the equivalent proportion of the most aggressive relapsers in the RT-only group, however, it is possible that such an approach would not have accounted for all potential patients destined to relapse with longer follow-up.

NAA prior to radiation is used more frequently in those patients with adverse risk factors, on the basis of sound evidence. Patients treated with NAA-RT have a similar proportion with a rising PSA profile after RT compared to those treated with RT-only, in spite of having worse pre-treatment prognostic factors. As the patients included in our study were mainly high risk patients, we are unable to comment as to whether the same effect would be seen in low or intermediate risk patients treated with NAA.

Conclusions

Those patients with a rising PSA after NAA-RT have more rapid PSAdt compared to those treated with RT-only. However, in multivariate analysis, this effect is found to be due to the NAA patients having higher initial PSA, Gleason score and stage. The use of NAA does not appear to be causally related to more rapid PSAdt in those patients who relapse. □

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