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**Original Article**

# Effect of Naturopathic and Nutritional Supplement Treatment on Tumor Response, Control, and Recurrence in Patients with Prostate Cancer Treated with Radiation Therapy

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## Abstract

***Objectives:*** Use of naturopathic and nutritional supplements (NNS) with antioxidant activity is controversial in patients receiving radiation therapy. The effects of concomitant use of NNS with antioxidant activity during radiation therapy for prostate cancer were investigated in terms of clinical tumor responsiveness, kinetics, and durability.

***Materials and methods:*** A retrospective investigation was done of 134 patients treated with curative intent for limited-stage prostate cancer by radiation therapy. Patients self-selected to receive NNS as part of their treatment and maintenance during an extended post-treatment interval of at least 2 years. The outcome measures were the following: prostate-specific antigen (PSA) nadir; ≥24 months post-treatment PSA; time to reach nadir; and time to last follow-up were compared across +NNS and −NNS.

***Results:*** Sixty-nine (69) patients elected to receive NNS while 65 did not. Seventy-seven (77) (+NNS 39, −NNS 38) patients received hormone therapy while 57 (+NNS 30, −NNS 27) did not. In the nonhormone cohort, median pretreatment PSA, nadir, post-treatment PSA, time to reach nadir, and time to follow-up were 5.5 ng/mL, 0.56 ng/mL, 0.61 ng/mL, 25 months, and 39.7 months for the −NNS group and 5.1 ng/mL, 0.32 ng/mL, 0.44 ng/mL, 27 months, and 50.1 months for the +NNS group, respectively ($p > 0.05$ for all). Similarly, no significant differences were observed between +NNS and −NNS in the hormone-receiving cohort.

***Conclusions:*** The clinical tumor response to radiation therapy in patients with limited-stage prostate cancer is not inhibited by concomitant NNS based on the magnitude of the PSA response, the velocity of the PSA nadir, and the duration of PSA normalization.

## Introduction

Naturopathic and nutritional supplements (NNS) are used by many patients with cancer.[1] Their use has been prompted by purported effects on general health and well-being, as well as amelioration of the morbid effects of cancer and its treatment.[2–5] In many instances, the positive effects of supplements have been attributed to their activity as antioxidants. Although antioxidants may play a role in the primary prevention of cancer in part by reducing the oxidative modification of DNA, the same action might be expected to be counterproductive against radiation therapy and chemotherapeutic agents that act solely or in part via the production of reactive oxygen species (ROS) and induction of apoptosis.[6] Thus, the use of NNS in conjunction with conventional cancer treatment remains controversial.

NNS use in most patients is unstructured, and the majority of published studies have been uncontrolled. Nevertheless, there are several well-controlled clinical trials that have investigated the effects of these treatments on clinical outcomes in cancer patients. For example, Bairati et al. performed a randomized, placebo-controlled trial in patients who had stage I–II head and neck cancer and who received radiation therapy with curative intent. Patients supplemented with $\alpha$-tocopherol and $\beta$-carotene showed increased primary tumor recurrence and secondary cancer development rates compared to placebo-treated patients during the 3-year supplementation period,[7] but reduced rates following cessation of supplements by 52 months' median follow-up. By the 8th year of follow-up, there was no difference between the 2 groups with respect to these parameters. Also, cause-specific mortality rates tended to be higher in the

Office of Clinical Research, Cancer Treatment Centers of America® (CTCA) at Midwestern Regional Medical Center, Zion, IL.

supplement arm than in the placebo arm.[2] Another article published by the same research group demonstrated a statistically significant reduction in acute adverse effects of radiation therapy in patients supplemented with α-tocopherol and β-carotene.[5] The most recent report by the same research group showed a significant risk of relapse positively associated with antioxidant use only in the subgroup who smoked cigarettes during radiation therapy.[8] In a similar study reported by Toma et al.,[9] patients who had radiated head and neck cancer and who received β-carotene for 3 years exhibited equivalent disease-free and overall survival and rates of secondary cancer occurrences at 5 and 10 years compared to patients not receiving supplements.

A less well-studied issue raised by patients with cancer is the effect of NNS use on treatment responses to discrete types of therapy. With respect to chemotherapy, many of the most commonly prescribed drugs generate ROS but do not, in general, depend on these mediators for therapeutic effects.[10] Clinical studies comparing NNS-treated and nontreated patients receiving the identical chemotherapy have shown equivalent tumor responses with some suggestion of benefit based on amelioration of side-effects.[5,11] There is substantially more controversy for the use of supplements during radiation therapy, since radiation therapy elicits ROS that play a major role in both therapeutic tumor responses and toxicity to normal tissues.[6,12,13] Treatment with antioxidants or other modalities that trap or neutralize ROS have at least a theoretical potential to interfere with ROS-mediated tumoricidal function. Thus, the use of supplements with antioxidant activity during radiation treatment is highly controversial, mandating further investigation.

The current study directly addresses the question of potential inhibitory effects of NNS with antioxidant activity on clinical tumor responses to radiation therapy for prostate cancer.

## Materials and Methods

### *Patient population*

The study population consisted of 134 patients diagnosed with localized adenocarcinoma of the prostate at the Midwestern and Southwestern Regional Medical Centers of Cancer Treatment Centers of America® between 2000 and 2004. All patients were followed up for a minimum period of 5 years post completion of therapy unless lost to follow-up or died. Patients who could not be contacted after a minimum follow-up period of 5 years were considered to be lost to follow-up. In those patients, the date of last contact or last known to be alive was considered the date of last follow-up. Similarly, in patients who had expired before a follow-up period of 5 years, the date of death was considered the date of last follow-up. In all other patients who were available after a follow-up period of 5 years, December 31, 2010 was considered the date of last follow-up for the purpose of this analysis.

There were 69 patients who elected to receive naturopathic/nutritional supplements (+NNS cohort: median age = 62.0 years; range = 46–81) and 65 patients who elected not to receive supplements (−NNS cohort: median age = 61.5 years; range = 48–81). Patients were stratified according to their pretreatment PSA level as being of low (range 4–10 ng), intermediate (range 10–20 ng), or high risk (>20 ng). In the +NNS cohort there were 52, 13, and 4 low, intermediate, and high-risk patients, respectively. In the −NNS cohort the corresponding numbers were 50, 10, and 5, respectively. Tumor staging for the +NNS population was T1c (39%); T2a (44%); T2b (10%); T2c (5%) with 1 T3b tumor. For the −NNS population, the corresponding frequencies were T1b (3%); T1c (46%); T2a (32%); T2b (12%); T2c (5%) with 1 T3a tumor.

### *Radiation therapy and hormone ablation treatment*

Conformal external beam radiation therapy or tomotherapy (4500–5000 cGy) in conjunction with high-dose-rate brachytherapy (600–650 cGy/fraction × 2–3 fractions) administered over a 6–8-week treatment course was given to 94.2% and 92.8% of +NNS and −NNS cohorts, respectively. The remaining patients received either high dose rate monotherapy, tomotherapy, or intensity modulated radiation therapy + tomotherapy.

Hormone ablation therapy with oral Casodex (bicalutamide) (50 mg/day) alone or in conjunction with leuprolide depot injection (generally 22.5 mg IM every 3 months) was administered as neoadjuvant or adjuvant therapy according to standard protocols to 39 (57%) patients in the +NNS cohort and 38 (58%) patients in the −NNS cohort.

### *Naturopathic and nutritional supplements*

Cancer Treatment Centers of America provides a fully integrated program of complementary and alternative medical therapy in conjunction with state-of-the-art conventional cancer care at all of its treatment centers. Patients elected to use them with the knowledge and consent of their attending radiation oncologist. Patients were seen at regular intervals by both their attending radiation therapist and members of the naturopathic and nutrition teams during their radiation treatment and throughout their clinical follow-up.

### *Statistical analysis*

Descriptive statistics for +NNS and −NNS cohorts were calculated for the following clinical tumor parameters: pretreatment PSA level; post-treatment PSA nadir; time in months to achieve PSA nadir; last recorded PSA level at or beyond 24 months post-treatment; and months of follow-up post completion of therapy. Tumor progression was declared as the time of biochemical failure as judged by a PSA level ≥2 ng/mL above the PSA nadir according to the Houston definition.[14] Descriptive statistics were also calculated for patients assessed according to the American Urological Association (AUA) instrument querying urinary and sexual performance. Differences between cohorts were tested by two-sample *t*-test and nonparametric Mann-Whitney *U* test as appropriate. All data were analyzed using SPSS version 17.0 (SPSS, Chicago, IL).

This study was approved by the Institutional Review Boards at Midwestern and Southwestern Regional Medical Centers.

## Results

### *Patient follow-up*

There were 6 deaths prior to 5 years; 5 in −NNS cohort and 1 in +NNS cohort. There were 12 losses to follow-up prior to 5 years; 6 each in −NNS and +NNS cohorts. The median follow-up period postradiation therapy for the

Table 1. Clinical Tumor Response (Means and Standard Deviations) in Patients Receiving No Hormone Therapy ($N=57$)

| *Parameters* | *+NNS* (n=*30*) | *−NNS* (n=*27*) | *2-Sample* t-*test* p-*value* |
|---|---|---|---|
| Pretreatment PSA (ng/mL) | 7.4 (6.8) | 6.3 (2.7) | 0.43 |
| PSA Nadir (ng/mL) | 0.51 (0.50) | 0.88 (1.1) | 0.10 |
| Post-treatment PSA (ng/mL) | 1.1 (1.8) | 1.9 (2.9) | 0.21 |

NNS, naturopathic and nutritional supplements; PSA, prostate-specific antigen.

+NNS cohort was 79.2 months (range 14.8–130.8) and for the −NNS cohort was 71.1 months (range 21.6–107.5).

### *NNS treatment*

A total of 69 patients elected to receive NNS as prescribed by their naturopathic physician. All 69 patients received at least one antioxidant supplement (range = 1–7; mean ± standard deviation = 2.9 ± 1.7) daily during the entire 6–8-week course of radiation therapy. All supplement-treated patients continued on supplements for at least 24 months following the end of radiation therapy. The most frequent antioxidant naturopathic treatments included green tea extract (500–750 mg BID, standardized to 80% catechins), melatonin (20 mg daily at bedtime), vitamin C (500–1000 mg TID), and vitamin E (200–400 IU BID). All patients were questioned with respect to their NNS use, and this was monitored routinely for all patients by documenting that their prescriptions were filled as recommended. As a result, it is believed that compliance with the NNS recommendations was very high, and that patients took their NNS as prescribed during radiation treatment.

### *Clinical tumor response to curative radiation therapy in supplement-treated and nontreated patients who did not receive hormonal ablation*

Mean PSA levels for +NNS and −NNS cohorts who did not receive hormonal ablation are displayed in Table 1. The mean ± standard deviation values are provided at the pretreatment point, nadir, and ≥24 months post-treatment point (defined as the last PSA value obtained at or beyond 24 months following completion of therapy). There were no statistically significant differences in the PSA values at any time point for the two populations. Median PSA levels, median time to reach nadir PSA values, and the median duration of follow-up are provided in Table 2. There were no differences between supplement-treated and nontreated patients at either pretreatment, nadir, or ≥24 months follow-up time points.

Table 2. Clinical Tumor Response (Medians) in Patients Receiving No Hormone Therapy ($N=57$)

| *Parameters* | *+NNS* (n=*30*) | *−NNS* (n=*27*) | *Mann-Whitney* p-*value* |
|---|---|---|---|
| Pretreatment PSA (ng/mL) | 5.05 | 5.5 | 0.57 |
| PSA nadir (ng/mL) | 0.32 | 0.56 | 0.32 |
| Post-treatment PSA (ng/mL) | 0.44 | 0.61 | 0.91 |
| Time to reach nadir (months) | 27 | 25 | 0.48 |
| Follow-up (months) | 64.5 | 61.5 | 0.59 |

NNS, naturopathic and nutritional supplements; PSA, prostate-specific antigen.

Table 3. Clinical Tumor Response (Means and Standard Deviations) in Patients Receiving Hormone Therapy ($N=77$)

| *Parameters* | *+NNS* (n=*39*) | *−NNS* (n=*38*) | *2 sample* t-*test* p-*value* |
|---|---|---|---|
| Pretreatment PSA (ng/mL) | 8.1 (4.9) | 12.4 (17.5) | 0.14 |
| PSA nadir (ng/mL) | 0.10 (0.23) | 0.13 (0.32) | 0.63 |
| Post-treatment PSA (ng/mL) | 0.24 (0.36) | 0.28 (0.44) | 0.66 |

NNS, naturopathic and nutritional supplements; PSA, prostate-specific antigen.

When patients were grouped according to risk based on pretreatment PSA level and Gleason scores, no differences in nadir PSA, time to achieve nadir PSA, or ≥24 months post-treatment PSA level were seen for low, intermediate, and high-risk groups considered separately (data not shown). In the patients who did not receive hormonal ablation, there were two biochemical failures that occurred at 15 and 45 months in the +NNS group, and two biochemical failures that occurred at 14 and 59 months in the −NNS group. Collectively, these results show that neither the magnitude of the PSA response, the velocity of the nadir response, nor its durability for up to 61.5 months' median follow-up were different in supplement-treated and nontreated patients who had prostate cancer and who did not receive hormone ablation.

### *Clinical tumor response to curative radiation therapy in supplement-treated and nontreated patients who did receive hormonal ablation*

Mean PSA levels for +NNS and −NNS cohorts who received hormonal ablation are displayed in Table 3. Once again, there were no statistically significant differences in the PSA values at any time point for the two populations. Median PSA levels, median time to reach nadir PSA values, and the median duration of follow-up are provided in Table 4. There were no differences between supplement-treated and nontreated patients who received hormonal ablation therapy at pretreatment, nadir or ≥24 months' follow-up time points.

There was one biochemical failure that occurred at 29 months in the +NNS cohort with no biochemical failures in the −NNS cohort to date. Neither the magnitude of the PSA response, the velocity of the nadir response, nor its durability for up to 84.1 months median follow-up were different in supplement-treated and nontreated patients who had prostate cancer and who received hormone ablation therapy.

Median nadir PSA values, the time to achieve nadirs, and the ≥24 months PSA levels for cohorts receiving hormone ablation therapy differed from the values determined for

Table 4. Clinical Tumor Response (Medians) in Patients Receiving Hormone Therapy ($N=77$)

| *Parameters* | *+NNS (n=39)* | *−NNS (n=38)* | *Mann-Whitney p-value* |
|---|---|---|---|
| Pretreatment PSA (ng/mL) | 6.8 | 6.9 | 0.84 |
| PSA nadir (ng/mL) | 0.03 | 0.03 | 0.68 |
| Post-treatment PSA (ng/mL) | 0.12 | 0.11 | 0.69 |
| Time to reach nadir (months) | 4.3 | 3.6 | 0.55 |
| Follow-up (months) | 84.1 | 81.6 | 0.75 |

NNS, naturopathic and nutritional supplements; PSA, prostate-specific antigen.

patients who did not receive hormonal therapy, reflecting the rapid effects of androgen ablation on PSA level (Table 5).

### *Urinary and sexual function*

This analysis was conducted in patients who received hormone therapy ($N=77$). The urinary performance as assessed by the AUA score for supplement-treated and non-treated cohorts is summarized in Table 6. Based on AUA score at pretreatment, 12 months, and 24 months following treatment, there is no statistically significant difference between the groups for either urinary or sexual function based on the Mann-Whitney test of ranks.

A higher percentage of patients reported adequate sexual potency prior to radiation therapy in the non-supplement-treated cohort (66%) compared to the supplement-treated cohort (51%), but this difference was not different statistically based on the $\chi^2$ test. The percentage of patients with adequate sexual potency declined to 38% ($p=0.06$) and 34% ($p=0.035$) at 12 months and 24 months following radiation therapy in the non-supplement-treated patients. The corresponding values were 42% ($p=0.60$) and 31% ($p=0.18$) for the supplement-treated population.

## Discussion

The results of this study demonstrate that NNS with antioxidant activity do not interfere with the effectiveness of radiation therapy as a definitive treatment for limited-stage prostate cancer. Using PSA level as a surrogate for clinical tumor response and control, there were no differences between +NNS and −NNS patients with respect to the magnitude, kinetics, or durability of the PSA response. This was true for patients who did not receive hormonal therapy wherein the PSA response is an excellent surrogate for the direct tumor killing effects of the radiation therapy. It was also true in patients who received hormone ablation therapy wherein the PSA response in the early post-treatment interval is a reflection of the effects of androgen deprivation, but the long-term follow-up PSA level is an excellent surrogate for continued tumor control. Finally, the results also demonstrate that NNS with antioxidant activity do not negatively impact the incidence of biochemical failures in patients with limited-stage prostate cancer for at least 24 months post-treatment.

Table 5. Clinical Tumor Response (Medians) Stratified by Hormone Therapy ($N=134$)

| *Parameters* | *Hormone therapy (n=77)* | *No hormone therapy (n=57)* | *Mann-Whitney p-value* |
|---|---|---|---|
| Pretreatment PSA (ng/mL) | 6.8 | 5.4 | 0.02* |
| PSA nadir (ng/mL) | 0.03 | 0.50 | <0.001* |
| Post-treatment PSA (ng/mL) | 0.12 | 0.56 | <0.001* |
| Time to reach nadir (months) | 4.0 | 25 | <0.001* |
| Follow-up (months) | 84.1 | 61.5 | <0.001* |

*$p$-value <0.05.
PSA, prostate-specific antigen.

Table 6. Median American Urological Association Scores in Hormone Therapy Patients Stratified by Naturopathic and Nutritional Supplements ($N=77$)

| *Parameters* | *+NNS (n=39)* | *-NNS (n=38)* | *Mann-Whitney p-value* |
|---|---|---|---|
| AUA pretreatment | 6 | 5 | 0.59 |
| AUA 12 months | 8 | 6 | 0.30 |
| AUA 24 months | 6 | 7 | 0.92 |

An exploratory analysis of treatment related-morbidities using the AUA self-assessment showed equivalent effects of radiation treatment in the NNS-treated and nontreated groups with respect to urinary performance. With respect to sexual potency, both groups showed a decline in the relative numbers of patients with adequate function at 12 and 24 months following the end of treatment, with the incidence of patients with adequate sexual function declining significantly in the −NNS cohort but not in the +NNS cohort. Taken together, the results demonstrate that NNS, integrated into radiation therapy treatment programs for early-stage prostate cancer, are clinically safe and appropriate.

This study differs from other studies in the literature in several important ways. First, the study elucidates the impact of NNS treatment with antioxidant activity on the direct tumor response to radiation therapy rather than overall effects on survival. While overall and disease-free survival are the most important benchmarks for any cancer therapy program, the tumor treatment response is a more immediate and quantifiable measure that would be expected to indicate untoward effects, if any, of antioxidant supplements on the effectiveness of radiation therapy. This study, given its retrospective uncontrolled design, provides preliminary evidence that NNS with antioxidant activity do not interfere with the capacity of radiation therapy to kill prostate cancer *in vivo* in patients.

The fact that complementary and alternative medicine (CAM) supplements had no effect on either the magnitude or the velocity of the PSA response to radiation treatment, in both hormone-treated and nontreated patients with prostate cancer indicates that antioxidants do not alter the sensitivity of tumor tissues to radiation therapy. This in turn suggests that supplements neither inhibited nor amplified the generation of ROS or the effectiveness of ROS-mediated oxidation reactions on the growth and survival of prostate cancer

tissues *in vivo*. While this result may not validate the use of supplements as an adjunct to radiation therapy in prostate cancer, it does provide support and reassurance for their use in patients who wish to take them.

Another important distinction between the current study and most others is the heterogeneity of the NNS provided to the patients in this investigation. Supplements taken by patients in this study were not consistent across the population with respect to either their chemical nature or their mechanism of action. Thus, their *in vivo* effects are expected to be complex, with multiple physiologic processes affected. Nevertheless, all patients were treated with at least one supplement with significant antioxidant activity, while the majority received two or more antioxidants continuously during the course of their radiation therapy and 2+ years of follow-up. However, it is possible that different supplements might demonstrate different trends toward tumor response, which might be lost when data showing opposing effects are aggregated. As a result, future studies with larger sample sizes and a detailed description of the number and type of NNS used by patients are needed to unravel such trends.

The use of NNS in patients with cancer has been advocated by proponents as a means of diminishing the toxic effects of treatment. In the current study, it is relevant to note that sexual potency was diminished following treatment in both supplement-treated and nontreated patients. Although the decline reached statistical significance only in the non-supplement-treated population, analysis of the variance in levels of potency at equivalent points post-therapy failed to reveal a significant difference between the populations. The same was found for urinary performance based on the AUA score. Thus, it was not possible to demonstrate a beneficial effect of supplements on urinary or sexual morbidities associated with prostate cancer and its treatment in the current study.

Most studies suggesting differential sensitivity of malignant and normal cells to supplement-mediated oxidative metabolic changes have been conducted with squamous epithelial cells of the skin and of the oral cavity.[15–17] Comparable studies have not been performed with malignant glandular epithelium of the prostate as yet. The principal finding of the current study does not address this question directly, although the results would be consistent with differential effects. This issue warrants investigation, given the prevalence of cancers of the glandular epithelium and the likelihood that patients afflicted with these malignant diseases may choose to employ NNS with antioxidant activity. Indeed, several recent studies have found a significant increase in vitamin and mineral supplement use in patients following a diagnosis of cancer, with little to no supervision in most cases.[1,18,19] While the current study suggests that this is not likely to hamper their tumor response to radiation therapy, the use of such therapies without the knowledge and consent of the attending physician, and where possible, a naturopathic physician, should be discouraged.

## Conclusions

It is concluded that NNS with antioxidant activity can possibly be taken during radiation therapy for localized prostate cancer without negatively affecting treatment response or outcome.

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## Disclosure Statement

There are no potential conflicts of interest.

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