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Effect of Curcumin Supplementation During Radiotherapy on Oxidative Status of Patients with Prostate Cancer: A Double Blinded, Randomized, Placebo-Controlled Study

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ABSTRACT

Curcumin is an antioxidant agent with both radiosensitizing and radioprotective properties. The aim of the present study was to evaluate the effect of curcumin supplementation on oxidative status of patients with prostate cancer who undergo radiotherapy. Forty patients treated with radiotherapy for prostate cancer were randomized to the curcumin (CG, $n = 20$) or placebo group (PG, $n = 20$). They received curcumin (total 3 g/day) or placebo during external-beam radiation therapy of up to 74 Gy. Plasma total antioxidant capacity (TAC) and activity of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) were measured at baseline and 3 mo after radiotherapy completion. Analysis of covariance was used to compare the variables between groups following the intervention. Serum PSA levels and MRI/MRS images were investigated. In CG, TAC significantly increased ($P < 0.001$) and the activity of SOD decreased ($P = 0.018$) after radiotherapy compared with those at baseline. In CG, however, the activity of SOD had a significant reduction ($P = 0.026$) and TAC had a significant increase ($P = 0.014$) compared with those in PG. PSA levels were reduced to below 0.2 ng/ml in both groups, 3 mo after treatment, however, no significant differences were observed between the 2 groups regarding treatment outcomes.

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Introduction

Curcumin, the yellow pigment of popular Asian spice, turmeric, is a potent antioxidant agent. During recent decades many investigations have been performed on different aspects of curcumin and many beneficial effects of it have been reported (1). Most of these effects, at least to some extent, are attributable to the antioxidant properties of curcumin (2).

Radiotherapy is one of the most important methods for treatment of many cancers including prostate cancer. In addition to its direct effects, such as DNA damaging of the cells within its field, radiotherapy also has some indirect impacts. The ionizing radiation can produce active oxygen radicals such as hydroxyl radicals that may increase oxidative stress in the whole body of the patients who undergo radiotherapy (3). The oxidative stress is the main cause for the most of the side effects, which are experienced by the patients during and after radiotherapy (4).

Whether supplementation with antioxidant agents during radiotherapy or short after, should be encouraged or not still remains controversial; during the last few years, however, large body of evidence has supported the advantage of these supplementations (5,6).

We previously showed that curcumin supplementation can improve lower urinary tract symptoms in patients with prostate cancer who undergo radiotherapy (7). Radioprotective effect of curcumin has also been reported by other clinical trials (8) and in vivo studies (9,10). The most acceptable mechanism for the radioprotective effects of curcumin is its antioxidant features.

Although curcumin is a well-established antioxidant agent, like many other phenolic compounds it can serve as a prooxidant agent under some conditions (11,12). High concentrations (13), concomitance with copper (14), or radiation (15) are of these conditions. Some

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investigators have used this property of curcumin to justify its radiosensitizing effect on cancer cells (15). Because cancer cells have an increased basal oxidative stress, production of extra reactive oxygen species (ROS) by curcumin along with radiotherapy can increase its effectiveness (16,17). However, curcumin can radiosensitize tumor cells by more than 1 definite pathway. The increased radiosensitivity was possibly associated with the inhibition of radiation-induced elevation of growth factors, cytokines, cyclins, NF-κB, PKC, TNF-α, and inhibition of cell cycle at the G2 + M phase, increased apoptosis, and some other unknown mechanisms (18).

As a result, there is a possibility that curcumin can protect normal tissues against deleterious effects of ionizing radiation as an antioxidant while enhancing sensitivity of cancer cells to the radiation by above mentioned mechanisms (19).

Despite the potential benefit of curcumin for patients on oxidative stress, the net effect of curcumin supplementation on the oxidative status and treatment outcome of those who accede to radiation therapy is still unknown. The aim of the present study is to evaluate the effect of curcumin supplementation on oxidative status, the activity of antioxidant enzymes and treatment outcomes in patients with prostate cancer who undergo radiotherapy.

Materials and methods

Patients

The present randomized double-blinded placebo-controlled clinical trial was conducted between March 2011 and March 2013 (Clinicaltrials NCT01917890). All the patients with localized prostate cancer diagnosed at the Department of Oncology at Besat Hospital were assessed for eligibility. Patients referred to local curative radiotherapy with external beam radiation therapy were assigned to participate in the study. Inclusion criteria were histologically proven prostate cancer, life expectancy of 5 yr or longer, and no metastatic disease confirmed with physical examination, standard radiography such as computed tomography, and isotope bone scan. Exclusion criteria were prior androgen deprivation therapy, prior definitive local therapy, clinical local stage of T3 or T4, Gleason score of $\geq$ 8, and/or serum PSA levels of $\geq$20 ng/mL. Those with other malignancy; concurrent participation in another clinical trial that would require approval upon entry to this trial; gastrointestinal disorders such as inflammatory bowel disease, reflux, and peptic ulcers; and any adverse reaction to curcumin were also excluded. The study was approved by the Ethical Committee of National Nutrition and Food Technology Research Institute. All patients gave their written informed consent prior to participation. Forty-five of 78 eligible patients agreed to participate in, and 40 patients completed the study (Fig. 1).

EBRT was given as daily fractions of 2 Gy to achieve a total dose of 74 Gy (5 times a week for about 8 wk). Data were collected 1 wk prior to radiotherapy onset, at the same time as randomization and intervention onset, and 3 mo after radiotherapy and intervention completion.

Randomization

Patients were randomly assigned to either the curcumin group (CG, $n = 22$) or placebo group (PG, $n = 23$; Fig. 1). Randomization was performed by administrative personnel outside the research project in a double-blind fashion. Random assignment was based on a computer-generated randomization list obtained using blocks of size 4.

Intervention

Curcumin capsules (BCM95, Biocurcumin) and their placebos were obtained as a generous donation from Arjuna Natural Extracts Ltd. Kerela, India, in 500 mg capsule form. Each curcumin capsule contained curcuminoids of 440 mg (curcumin of 347 mg, desmethoxycurcumin of 84 mg, and bisdesmethoxycurcumin of 9 mg) and essential oil of turmeric of 38 mg, and each placebo capsule contained roasted rice flour of 500 mg.

Patients in each group took 3 grams of curcumin or placebo (as 6 $\times$ 500 mg capsules, 2 capsules with each meal) 1 wk before the initiation of radiotherapy until its completion. All patients were advised to avoid any changes in their usual dietary habits during intervention period. Compliance was assessed by capsule counts at each weekly study visit and adverse event information was recorded.

Study endpoints and the evaluation of patients

The endpoints were biochemical and clinical progression-free survivals (time frame: 1 yr, designated as safety issue), treatment outcomes evaluated by serum nadir levels and MRI/MRS images, and alterations in TAC and the activity of antioxidant enzymes following radiotherapy.

A complete history [pathologic confirmation of malignancy, disease staging, prior therapy/surgery, and prior response(s)] and a physical examination, as well as blood tests (including a complete blood count and PSA) were performed at baseline by a trained physician. Patients were weighed in light clothing and without shoes using a

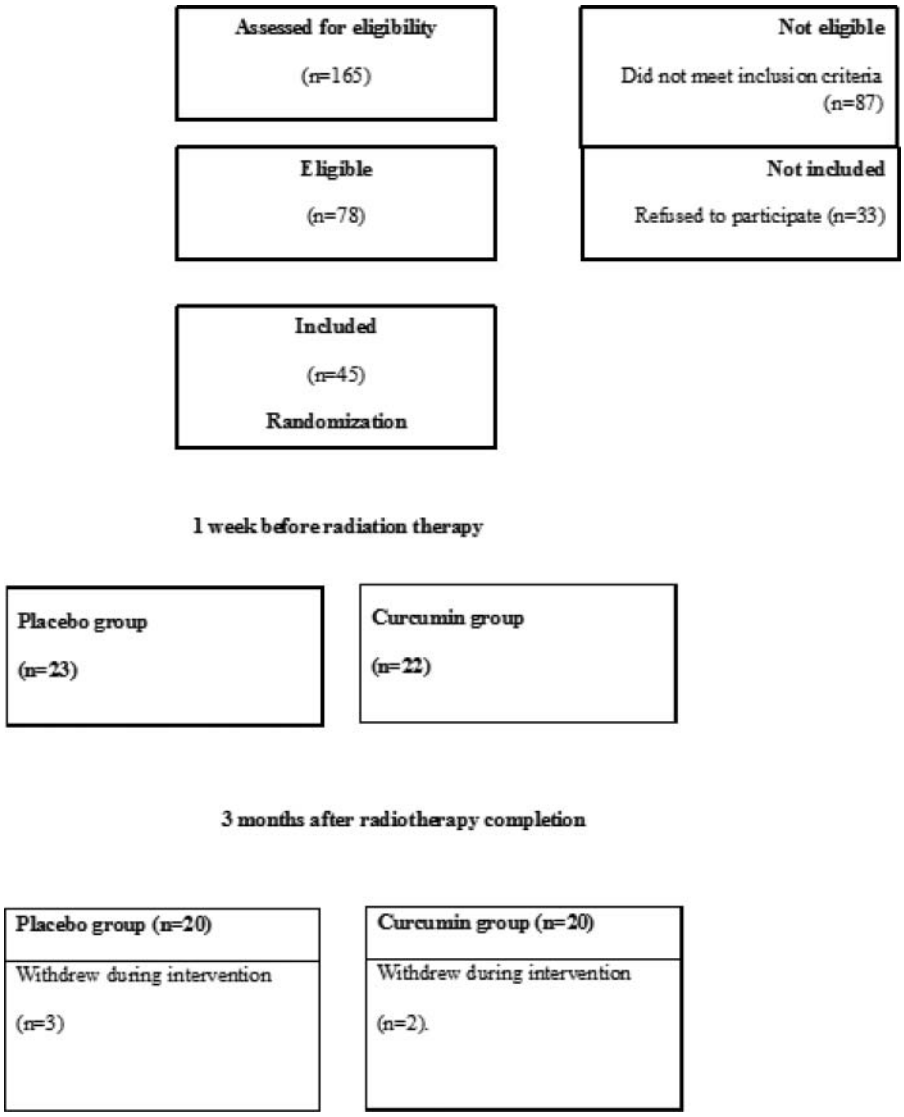

Figure 1. Flow of participants throughout trial.

scale (Seca, Hamburg, Germany) and their height, measured with a stadiometer (Holtain Ltd, Crymych, UK), was used to calculate body mass index (BMI).

Local disease extension and status were also assessed using magnetic resonance imaging/spectroscopy (MRI/MRS). All patients were independently referred to Babak imaging center for MRI/MRS. MRI/MRSI studies were performed on a 1.5 Tesla Siemens Avanto scanner (Erlangen, Germany) using a combined pelvic phased array and endorectal coil (Medrad, Indianola, PA). MRI/MRS data were obtained and processed using software developed at the University of California in San Francisco. In the present study, MRI/MRS was referred to just for ruling out disease progression/treatment failure following radiotherapy. Diagnostic criteria for treatment failure on MRI/MRS were emergence of new lesions, enlargement of primary foci, or the elevated choline to citrate ratio (20,21).

A validated semi-quantitative food frequency questionnaire (FFQ) (22) was used to evaluate dietary intake of patients. For the extraction of polyphenols intake from foods in FFQ, the phenol-Explorer database was used. The phenol-Explorer database contains data on the content of 502 polyphenols in 452 foods (23).

Biochemical tests

A venous blood sample for biochemical analyses was taken following a minimum of 8 h fast. The blood was maintained at 4°C, centrifuged, plasma distributed in aliquots, and stored at −80°C.

Plasma catalase activity was measured by a commercial catalase assay kit (Cayman Chemical, Ann Arbor, MI) which uses the catalase peroxidative function to determine enzyme activity based on the reaction between the enzyme and methanol in the presence of an optimum

concentration of hydrogen peroxide. Formaldehyde produced is measured spectrophotometrically using 4 amino-3-hydrazino-5-mercapto- 1,2,4-triazole as the chromogen.

Superoxide dismutase (SOD) activity was measured by the SOD assay kit (Cayman Chemical, Ann Arbor, MI) which measures the dismutation of superoxide radicals generated by xanthine oxidase and hypoxanthine. An important characteristic of the kit is the inclusion of a quality control standard for SOD. The standard curve generated using this enzyme enables the exact quantification of the enzyme under three assay conditions from which the 3 SOD types derive their description (Cu/Zn-, Mn-, and Fe-SOD).

Glutathione peroxidase (GPX) activity was measured in plasma aliquots using a commercial glutathione peroxidase assay kit (Cayman Chemical, Ann Arbor, MI), which directly measures the activity via a GSH reaction. Oxidized glutathione produced by GPX organic hydroperoxide reduction is recycled to its reduced state by GSH and NADPH. NADPH to $NADP^+$ oxidation is accompanied by a decreased absorbance at 340 nm, which is directly proportional to GPX activity in the sample.

Total antioxidant capacity (TAC) was determined in plasma aliquots using the commercial kit "Antioxidant Assay Kit" (Cayman Chemical, Ann Arbor, MI) which uses an antioxidant assay buffer, chromogen (2,2-azino-bis-[3-ethylbenzothiazoline-6-acid]), metmyoglobin, trolox (synthetic antioxidant; 6-hydroxy-2,5,7,8-tetramethylchroman- 2-carboxylic acid) and hydrogen peroxide.

The intra- and interassay coefficients of variation (CVs) of TAC, GPx, catalase, and SOD were 3.4% and 3.0%; 5.7% and 7.2%; 3.8% and 8.9%; 3.2% and 3.7%, respectively.

Statistical analyses

Statistical analyses were performed using SPSS 19.0. All analyses were conducted on an intention-to-treat basis. All *P*-values were 2-tailed and the level of statistical significance was set at $P < 0.05$. Between-group differences at baseline were analyzed using the independent *t*-test or Mann Whitney-U test. Analysis of covariance adjusting for baseline was used to evaluate the effect of the intervention on the antioxidant capacity and activity of antioxidant enzymes. Analyses for each biochemical test were performed in duplicate. Soft Max Pro program calculated the linear regression standard curve, where the absorbance is based on the final Trolox concentration.

Results and discussion

In both groups, compliance with the treatment protocol appeared to be very high and no side effects from the supplementation were reported. Twenty patients from each CG and PG group (87% and 91%, respectively) completed the study, and they comprised the final study groups. The characteristics of the patients are summarized in Table 1.

Table 1. Baseline characteristics of participants.

Baseline variables	CG ($n = 20$)	PG ($n = 20$)	*P*
Age (years)	69.58 ± 8.08	71.85 ± 8.33	0.394
Height (cm)	167.48 ± 6.09	167.63 ± 5.50	0.935
Weight (kg)	76.26 ± 10.79	75.53 ± 12.28	0.844
BMI (kg/m^2)	27.17 ± 3.37	26.81 ± 3.68	0.750
Married	18 (90)	19 (95)	0.548
PSA (ng/ml)	12.98 (1.18–20)	16.47 (2.8–20)	0.130
Gleason score (n(%))			
≤6	9 (45)	7 (35)	
7	11 (55)	13 (65)	
Clinical stage			
$T1_{a-c}$	0 (0)	1 (5)	
T2	20 (100)	19 (95)	
Calorie intake (Kcal)	2145.38 ± 584.5	2199.41 ± 442.62	0.744

CG = curcumin group; PG = placebo group; BMI = body mass index. Results presented as mean ± SD, median (range), or number of participants (percentage of participants).

The intake of antioxidant and prooxidant nutrients (vitamin E, vitamin C, zinc, selenium, iron, and copper) and nonnutrients components of foods such as phenolic compounds were evaluated in both groups (Table 2); there were no significant differences between intake of antioxidant or prooxidant agents between the 2 groups.

TAC and the activity of antioxidant enzymes including catalase, SOD and GPx were measured 1 wk before the initiation of radiotherapy and 3 mo after its completion (Table 3). The evaluated variables at baseline were similar between the 2 groups, except for TAC ($P = 0.045$).

In CG, 3 mo after completion of radiotherapy, TAC increased significantly ($P < 0.001$) and the activity of SOD decreased significantly ($P = 0.018$) compared with those at baseline. Regarding other variables, no significant changes were observed during the study period both in CG and PG. In CG, the activity of SOD had a significant reduction compared with PG, and this difference remained significant after adjusting for baseline values (Table 3). The posttreatment increase of TAC was greater in CG than on PG after adjusting for baseline values ($P = 0.014$).

Individual changes in TAC and SOD from baseline, 3 mo after radiotherapy, is presented in Fig 2. Treatment outcomes were evaluated by serum PSA levels and MRI/MRS images. The treatment was successful in both groups. Mean PSA levels at baseline were 12.98 ± 7.09 ng/ml and 16.47 ± 5.94 ng/ml in CG and PG, respectively. PSA levels were reduced to 0.12 ± 0.16 ng/ml and 0.13 ± 0.06 ng/ml 3 mo after completion of radiotherapy, respectively, and they were similar between the 2 groups ($P = 0.78$).

Table 2. Intake of antioxidant and prooxidant components of diet at baseline.

Baseline variables	CG ($n = 20$)	PG ($n = 20$)	P
Vitamin E(mg)	9.44 ± 3.18	11.09 ± 3.92	0.186
Vitamin C (mg)	149.1 ± 79.74	178.27 ± 132.88	0.430
Zinc (mg)	10.94 ± 4	11.44 ± 3.15	0.699
Selenium (mcg)	115.1 ± 69.5	108 ± 30.1	0.724
Iron (mg)	23.19 ± 12.9	29.67 ± 20.52	0.256
Copper (mcg)	1592 ± 695	1613 ± 502	0.924
Total polyphenol (mg)	3315.27 ± 2019.38	2925.63 ± 1065.67	0.539
Flavonol (mg)	905.4 ± 582.9	850.8 ± 378.7	0.743
Flavon (mg)	155.9 ± 98.1	149.3 ± 57.0	0.806
Anthocianides (mg)	69.3 ± 242.2	23.7 ± 27.8	0.414
Isoflavonoids (mg)	6.93 ± 20.0	4.7 ± 7.6	0.650

Results presented as mean ± SD.

Regarding the results of MRI/MRS imaging, there was also no significant differences between the 2 groups; 2 patients in CG and 4 patients in PG refused MRI/MRS. At the baseline, the ratio of choline to citrate was high in all patients, which was suggestive of the presence of prostate cancer (Fig. 3A). Three months after the completion of radiotherapy, the choline/citrate ratio remains high in a small fraction of the patients, which may possibly be associated with failure in treatment [3 in CG (16%) and 2 in PG (12%)].

The present study showed that curcumin can increase TAC and decrease SOD activity in the plasma of patients with prostate cancer receiving radiotherapy; these observations are thought to be possibly brought about by the antioxidant effect of curcumin. To our knowledge, this double-blinded, randomized, placebo-controlled clinical trial is the first to evaluate the effect of curcumin supplementation on oxidative stress, which is induced by radiation therapy.

Application of ionizing radiation, along with its direct effect such as DNA damage of the cells in its field, has some indirect impacts such as radiolysis of water and production of free radicals represented by hydroxyl ions as well (24). These ROS can cause the adverse reactions immediately after radiation, by breaking chemical bonds and promoting lipid peroxidation which explains, at least to some extent, the side effects that are induced by radiotherapy (4). In a previous study on the authors' radioprotective effects of curcumin, supplementation in patients with prostate cancer has been investigated and it was shown that patients in the curcumin group experienced much milder urinary symptoms compared with the placebo group although the differences between the 2 groups in terms of other radiation induced side effects (bowel symptoms, sexual function, etc.) was not significant (7). In the present study curcumin as a potent antioxidant agent has increased the antioxidant capacity of plasma and it is plausible that the observed reduction in the severity of radiotherapy related urinary symptoms in CG is because of this increment in TAC. A significant inverse relationship is observed between the increment of TAC levels and urinary symptoms, 3 mo after radiation therapy completion ($r = -0.354$, $P = 0.047$); however the relationship between activity of antioxidant enzymes and urinary symptoms did not reach statistical significance.

In the present study, patients in PG also showed an insignificant increase in their TAC, 3 mo after radiotherapy completion, which may be of note considering the production of large amount of free radicals during

Table 3. Oxidative stress-related markers.

	1 wk before radiation therapy onset				3 mo after radiation completion				Adjusted group differences in mean change over 20 ks				
	CG		PG		CG		PG						
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	95% CI		P^*	P^{**}
TAC(U/mL)	10.7‡	2.0	9.1	2.3	12.8‡	2.1	10.6	1.3	−0.8	−2.4	0.8	0.342	**0.014**
SOD (U/L)	226.1†	143.1	195.2	43.1	189.4†	115.4	215.2	83.5	52.3	9.2	95.3	**0.019**	**0.026**
GPx(U/mL)	123.4	15.4	125.9	17.1	125.6	13.4	126.8	12.0	−1.3	−12.6	10	0.813	0.998
Catalase (U/L)	139.7	110.2	134.4	62.7	111.2	80.9	134.8	60.2	33.1	−17.8	84.1	0.193	0.151

CG = curcumin group; PG = placebo group; ANCOVA = analysis of covariance; CI = confidence interval.
*Between-group change by Independent *t*-test or Mann Whitney-U.
**Between-group change by ANCOVA adjusted for baseline values.
†Difference between before and after intervention values significant at $P < 0.05$ level.
‡Difference between before and after intervention values significant at $P < 0.001$ level.

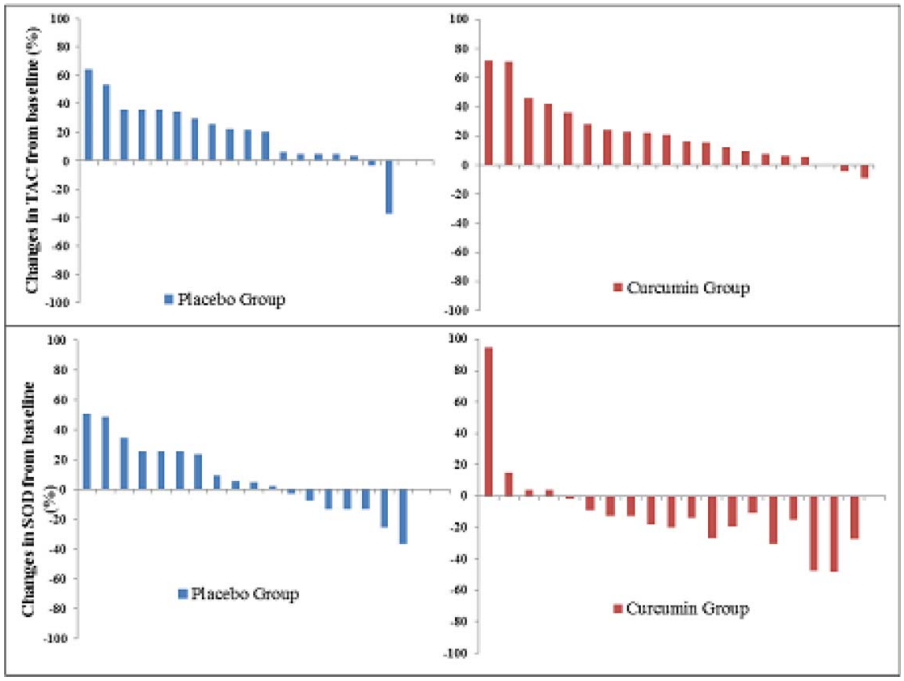

Figure 2. Waterfall plot showing plasma total antioxidant capacity (TAC) and activity of superoxide (SOD) posttherapy changes from baseline.

radiotherapy. In a study by Chevion on 14 patients who underwent total body irradiation prior to bone marrow transplantation, TAC was reduced by 36% short after radiotherapy, but after 4 mo recovered to a level 22% higher compared with that before the treatment (25). The authors concluded that the antioxidant system of body can compensate the increment of oxidative stress after this period. This mechanism possibly accounts for the mentioned observation in PG.

The activity of antioxidant enzymes, SOD, catalase, and GPx, were also investigated in the present study. The activity of SOD was significantly reduced in CG ($P = 0.018$) 3 months after radiotherapy completion, whereas no significant increase was observed in the activity of SOD in PG during the same period, and in terms of SOD activity a significant difference was observed between the 2 groups. Regarding catalase activity, although the differences between the 2 groups and between the beginning and end of the study did not reach a statistical significance, a similar trend with SOD was observed. These results suggest that the catalase activity was decreased in CG and increased in PG. GPx activity did not change significantly during the study period, and no significant difference was observed in terms of GPx activity between the 2 groups.

Studies about the effect of radiotherapy on the activity of antioxidant enzymes in patients with prostate cancer have been quite limited. In a study by Wozniak et al., the activity of antioxidant enzymes were investigated in the plasma of 60 patients with prostate cancer 1.5 mo, 3 mo, and 2 yr after radiotherapy, and no significant changes were observed between the activity of SOD and catalase (26). Our findings in PG are in line with their observation regarding the activity of these enzymes after radiation therapy.

Several in vivo studies have investigated the effect of ionizing radiation on activity of plasma antioxidant enzymes. In some studies, the activity of antioxidant enzymes such as SOD, catalase, and GPx significantly decreased after radiation, and curcumin supplementation could halt this effect and even in some cases had increased the activity of these enzymes in animal models (27,28). The investigators have concluded that curcumin confers its radioprotective effect through incretion of these enzymes because some of these enzymes such as SOD are considered as radioprotective enzymes (4). However in the present study curcumin not only did not increase the activity of these enzymes but also could reduce the activity of SOD significantly.

A probable mechanism for this finding is that enzymes such as SOD are components of body's defending system against free radicals and when the oxidative stress goes higher the expression of these enzymes increase to maintain body's oxidative status. Curcumin is an antioxidant agent and as it is shown in the present study, it increases TAC thus it seems quiet rational that in the presence of curcumin there is no need for increased expression of SOD. In a study on a murine

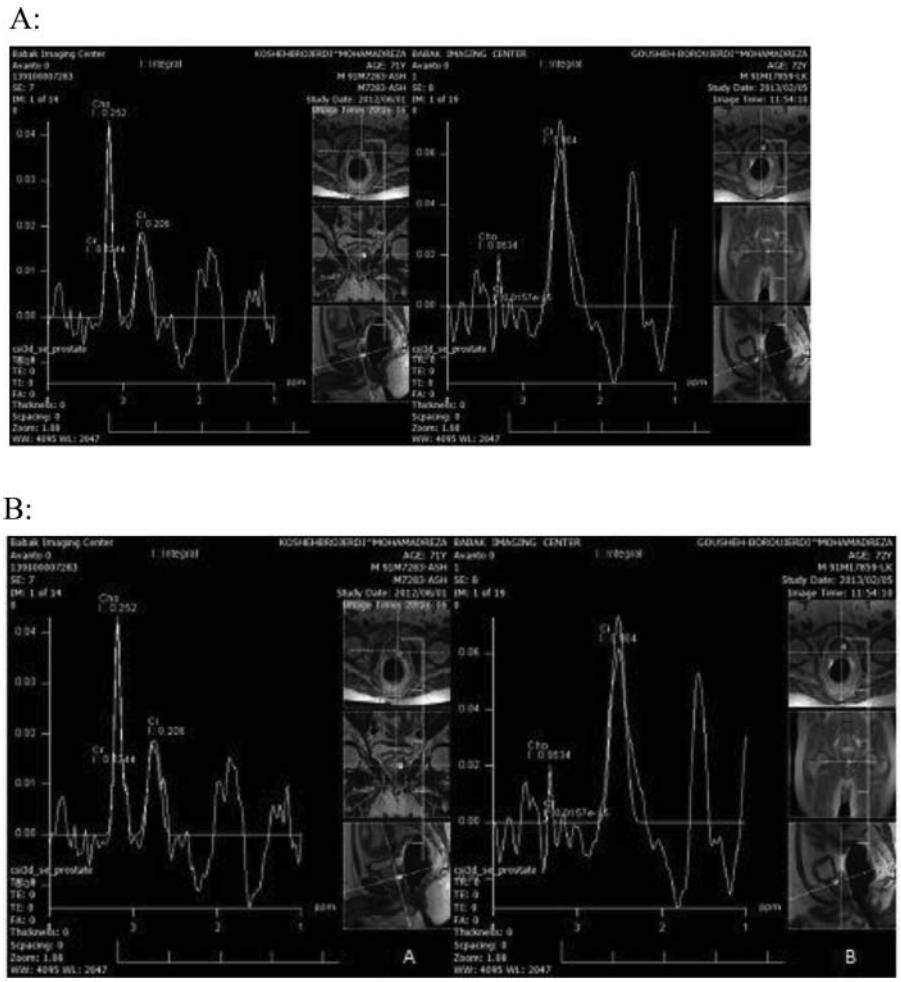

Figure 3. MRS image of patient number 23, 1 wk before (a) and 3 mo after radiotherapy (B). A: High choline to citrate ratio is indicative of cancer. B: Low choline to citrate ratio is indicative of successful treatment.

model of hyperthyroidism, it has been shown that curcumin could reduce the activity of SOD in rat brain (29).

More over curcumin may have direct suppressive effect on the activity of antioxidant enzymes with mechanisms which are not clear yet. In a study by Javvadi et al., on squamous carcinoma cells, treatment of the cells with curcuimin could inhibit the activity of thioredoxin reductase-1 (TxnRd1), an important antioxidant enzyme (30). Using this observation and findings of other investigators regarding the prooxidant feature of curcumin under some condition and in some specific cells, the authors concluded that curcumin confers its radiosensitizing effect by both increasing oxidative stress inside the cancer cells and inhibiting the antioxidant enzymes which neutralize this effect (30). In the present study we have failed to observe any radiosensitizing or prooxidant feature for curcumin in the prescribed dose; however the reduction in the activity of SOD and catalase may be explained by the same manner which is explained by Javvadi et al. for TxnRd1.

A concern about the use of antioxidant supplements, such as curcumin, during or short after radiotherapy is that these agents can have deleterious effects on the treatment outcomes. In the present study, there were no intergroup differences in serum PSA levels and choline to citrate ratio in MRS images, thus suggesting no adverse effect of curcumin on treatment outcomes, although verification with a large study may be needed.

Monitoring posttreatment serum PSA levels is the most common method to evaluate the efficacy and outcomes of radiotherapy (31). In the present study, serum PSA levels were favorably reduced in both CG and PG following treatment, and no difference was observed between the 2 groups. Overall 37 out of 40 patients (92.5%) had PSA levels below 2 ng/ml 3 months after radiotherapy. In a study by Schmitz et al., PSA levels in 89.5% of patients reached below this cut-off point after 3 mo (32), which is similar to our finding.

However, PSA does not necessarily reflect the true treatment endpoint (33); 3 consecutive increases in PSA

are possibly regarded as leading to treatment failure (34). Promising diagnostic modalities, which can more accurately predict survival outcomes after radiotherapy, are thus required. MRS is a recently developed technique, which expands the diagnostic assessment of prostate cancer beyond the anatomic information provided by MRI through functional imaging with the detection of cellular metabolites. It provides biochemical and metabolic information associated with tumor growth and development (35). In a meta-analysis of the accuracy of prostate cancer studies that use MRS as a diagnostic tool, Wang et al. (2008) concluded that as a new method in the diagnosis of prostate cancer, MRS has a better applied value compared to other common modalities (36). Several studies have evaluated the treatment outcome of radiotherapy by MRS and have reported very promising results (37,38). Some of these studies have shown that the accuracy of MRS in the prediction of recurrence is even higher than biopsy (38). The basis for MRS is that malignant tissues have higher choline concentration (probably because of higher turnover rate in the cell membrane phospholipids) (39) whereas benign tissues have higher citrate concentration. As a result, the ratio of choline (+ creatine) to citrate can be considered as a valuable marker for response of malignant cells to radiotherapy (40, 41). Between the 2 studied groups in the present study, no significant difference was observed regarding this ratio, which indicates that curcumin does not have any beneficial or adverse effect on the treatment outcomes.

Controversies still persist regarding the advantage of antioxidant supplements during radiotherapy, and large-scale randomized trials are thus warranted. Most of the comprehensive reviews have concluded that dietary antioxidants do not conflict with the use of radiotherapy in the treatment of a wide variety of cancers and may significantly mitigate its adverse effects (5,6).

Conclusions

The present study showed that curcumin, an antioxidant agent, can increase the TAC while it decreases the activity of antioxidant enzymes such as SOD in patients with prostate cancer receiving radiotherapy. It was also showed that curcumin improves the antioxidant status of them without compromising the therapeutic efficacy of radiotherapy.

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