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RESEARCH ARTICLE

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Randomized, double-blind, placebo-controlled phase II trial of nanocurcumin in prostate cancer patients undergoing radiotherapy

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Clinical potential of curcumin in radiotherapy (RT) setting is outstanding and of high interest. The main purpose of this randomized controlled trial (RCT) was to assess the beneficial role of nanocurcumin to prevent and/or mitigate radiation-induced proctitis in prostate cancer patients undergoing RT. In this parallel-group study, 64 eligible patients with prostate cancer were randomized to receive either oral nanocurcumin (120 mg/day) or placebo 3 days before and during the RT course. Acute toxicities including proctitis and cystitis were assessed weekly during the treatment and once thereafter using CTCAE v.4.03 grading criteria. Baseline-adjusted hematologic nadirs were also analyzed and compared between the two groups. The patients undergoing definitive RT were followed to evaluate the tumor response. Nanocurcumin was well tolerated. Radiation-induced proctitis was noted in 18/31 (58.1%) of the placebo-treated patients versus 15/33 (45.5%) of nanocurcumin-treated patients (p = 0.313). No significant difference was also found between the two groups with regard to radiation-induced cystitis, duration of radiation toxicities, hematologic nadirs, and tumor response. In conclusion, this RCT was underpowered to indicate the efficacy of nanocurcumin in this clinical setting but could provide a considerable new translational insight to bridge the gap between the laboratory and clinical practice.

KEYWORDS

curcumin, proctitis, prostate cancer, radiotherapy, randomized trial

1 | INTRODUCTION

Targeted radioprotection by curcumin, a natural polyphenol, is considered as a potential method to enhance therapeutic ratio of radiotherapy (RT; Chung, Smart, Chung, & Citrin, 2017; Kalman, Zhao, Anscher, & Urdaneta, 2017). The RT constitutes a mainstay of treatment for pelvic malignances including prostate cancer (Nicholas et al., 2017). Up to 75% of these patients develop symptoms associated with acute radiation-induced proctitis (Grodsky & Sidani, 2015). The management of gastrointestinal toxicity is a crucial part of clinical practice (Nicholas et al., 2017; Serrano, Kalman, & Anscher, 2017). Currently, there is no strong evidence to support the use of prophylactic or therapeutic agents to reduce RT-induced gastrointestinal toxicity (Lawrie et al., 2018).

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There is an increasing body of evidence exploring the potential role of curcumin as a promising natural product in preventing and/or mitigating radiation-induced toxicity (Goel & Aggarwal, 2010; Jagetia, 2007; Kalman et al., 2017; Verma, 2016). Interestingly, radiosensitizing property of curcumin in different tumor types including prostate, lymphoma, sarcoma, gynecologic, pancreas, liver, colorectal, breast, lung, head and neck, and glioma is also demonstrated (Verma, 2016). The dual function of curcumin as an oral radioprotective agent in healthy tissues and a radiosensitizer in cancer cells has led to development of extensive preclinical research (Goel & Aggarwal, 2010; Jagetia, 2007; Verma, 2016).

Despite multiple promising roles for the curcumin in preclinical models, clinical data are mixed and the recommendation for its clinical application remains controversial (Nelson et al., 2017). Poor oral bioavailability limits the systemic activity of curcumin and extremely high doses are required to show clinical efficacy (Hewlings & Kalman, 2017; Lao et al., 2006; Liu et al., 2016). Recently, curcumin nanoformulations have exhibited great potential as a novel strategy to reach enhanced bioavailability of curcumin (Gera et al., 2017; Liu et al., 2016; Lu, Inbaraj, & Chen, 2018; Mollaei & Babaei, 2017; Roointan, Sharifi-Rad, Badrzadeh, & Sharifi-Rad, 2016). SinaCurcumin® as a novel nanoformulation of curcuminoids has recently demonstrated considerable efficacy in different clinical settings. Some favorable results have been shown in patients with amyotrophic lateral sclerosis, multiple sclerosis, ulcerative colitis, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), type 2 diabetes, nonalcoholic fatty liver disease, and as well as infertile patients (Ahmadi et al., 2018; Alizadeh et al., 2018; Dolati, Aghebati-Maleki, et al., 2018; Dolati, Ahmadi, et al., 2018; Jazayeri-Tehrani et al., 2018; Masoodi et al., 2018; Mohammadi et al., 2017; Rahimi et al., 2016). The main underlying mechanisms included the modulation of some inflammatory factors, posttranscriptional activities, and total antioxidant capacity (Alizadeh et al., 2018; Dolati, Aghebati-Maleki, et al., 2018; Dolati, Ahmadi, et al., 2018). The importance of curcumin nanoformulation for optimizing its anticancer efficacy in prostate cancer was also described (Guan et al., 2017; Schmidt & Figg, 2016).

We hypothesized that the exclusive properties of nanocurcumin could probably make it a proper radioprotector and/or radiosensitizer for prostate cancer patients undergoing RT. The purpose of this study was to investigate the clinical efficacy of nanocurcumin in patients undergoing RT for prostate cancer.

2 | MATERIAL AND METHODS

2.1 | Study design

This was a stratified, double-blind, placebo-controlled, parallel-group study conducted at the Shohada-e-Tajrish Medical Center as a tertiary referral Hospital in Tehran, Iran, from March 2016 to April 2017. Patients with histologically confirmed adenocarcinoma of the prostate and the performance status of 0–2 who were candidates for 3D conformal or intensity modulated radiotherapy (IMRT) were included in the study. Moreover, all patients had to have normal complete blood count at baseline. Patients with metastatic prostate cancer; kidney and liver dysfunction; gastrointestinal disorders such as inflammatory bowel disease, reflux, and peptic ulcers; and any adverse reaction to curcumin were excluded from the study. The protocol of this study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences and registered on ClinicalTrials.gov (Identifier: NCT02724618). All patients provided signed informed consent before inclusion in the study. Participants were randomly assigned to one of two parallel groups in 1:1 ratio to receive either nanocurcumin (120 mg/day) or placebo 3 days before and during the RT course. All patients were stratified by treatment schedule (hypofractionated IMRT vs. conventional 3D conformal RT). An Internet-generated randomization list of permuted blocks of sizes 4 or 6 was drawn up by an investigator with no clinical involvement in the trial to randomly assign patients to nanocurcumin or placebo. The nanocurcumin and placebo were in capsule form and identical in appearance. They were prepacked in sequentially numbered containers according to the randomization list. According to the protocol, a radiation oncologist had obtained the patient's informed consent and telephoned the researcher who was independent of the recruitment procedure. Each participant was assigned an order number and received the capsules in the corresponding numbered containers. All patients, health care providers, data collectors, and outcome assessors were blinded to treatment allocation.

2.2 | Sample size

Based on an expected incidence of 58% for the acute gastrointestinal toxicity in control group (Pollack et al., 2006) and an acceptable toxicity of 20% in nanocurcumin group, we calculated that we would need a sample size of 30 patients for each study group to give 90% power to detect a significant difference ($p < 0.05$) between the nanocurcumin and placebo. To compensate the expected exclusion of 5% of patients, we scheduled to enroll a total of 64 participants.

2.3 | Study endpoints

The primary endpoint was radiation-induced proctitis as assessed weekly during the treatment and once thereafter using the common terminology criteria for adverse events (CTCAE v.4.03; US Department of Health and Human Services, 2009; Table 1). As secondary outcomes, we evaluated radiation-induced cystitis, hematologic nadirs, and treatment response based on diffusion-weighed magnetic resonance imaging (MRI). The hematologic variables analyzed included neutrophils, lymphocytes, platelets, and hemoglobin assessed before, biweekly during the treatment, and once thereafter. The lowest level of these hematologic parameters obtained after initiation of the RT course was selected as the nadir. Moreover, patients underwent serum urea, liver enzymes, C-reactive protein, erythrocyte sedimentation rate, ferritin, and creatinine level before, during, and after the treatment. The tumor response was assessed as percentage of apparent diffusion coefficient (ADC) increase approximately 3 months after the RT course in IMRT-treated patients (Decker et al., 2014; Iannelli et al., 2016; Manal & Mohamed, 2015).

TABLE 1 Grading criteria for proctitis and cystitis according to the common terminology criteria for adverse events (CTCAE v.4.03)

Acute toxicity	Grade I	Grade II	Grade III	Grade IV
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood, or mucus); medical intervention indicated; limiting instrumental ADL[a]	Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL[b]	Life-threatening consequences; urgent intervention indicated
Cystitis	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia, or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective endoscopic, radiologic, or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated

[a]Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, and so on.
[b]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

2.4 | MRI examinations

All multiparametric-MRI (mp-MRI) examinations of prostate gland were performed using a 1.5 Tesla MRI machine (Magnetum Avanto, Siemens, Erlangen, Germany) with combination of endorectal and pelvic phased array coils. Each patient underwent two mp-MRI of the prostate gland, before and after the RT course. All mp-MRI examinations were done with the same protocol, represented as follows: axial, sagittal, and coronal turbo spin echo T2W images (slice thickness: 3 mm; interslice gap: 0.3 mm; repetition time (TR) range: 3,200–4,800; echo time (TE) range: 95–115; matrix: 320 × 256; field of view (FOV): 20 × 20 cm), axial turbo spin echo T1W images (slice thickness: 5 mm; interslice gap: 0.5 mm; TR range: 500–570; TE range: 15–20; matrix: 288 × 224; FOV: 28 × 28 cm), axial diffusion-weighted image (DWI) sequence using single-shot echo-planar imaging technique (slice thickness: 4 mm; interslice gap: 0.4 mm; b-values: 0, 400, 800, and 1,200 s/mm^2; TR range: 2,800–3,900; TE range: 78–99; number of excitation: 3; matrix: 320 × 256; FOV: 20 × 20 cm).

2.5 | Image analysis

All images were retrospectively analyzed by a radiologist with experience of interpreting more than 500 mp-MRI of the prostate gland examination, which was not aware of histologic findings of the patients. Initially, volume measurement of the prostate gland was done, with anteroposterior and mediolateral sizes acquired in axial images and craniocaudal dimension measured in midsagittal images. The localization of prostate cancer was done based on focal low signal areas on T2W images and ADC maps in peripheral zone. Tumor size was measured on axial, coronal, and sagittal T2W images, with respect to axial DWI sequence, in both pretreatment and posttreatment examinations. In case of nonvisualization of the lesion on posttreatment DWI sequence, no size measurement was performed. ADC maps were generated by using workstation software (Syngo MR D13). Subsequently, regions of interest were placed on ADC maps of visualized cancers, with care to exclude the neurovascular bundle and the urethra. For each lesion, multiple measurements were done in each slice where tumors were seen, and the average value was calculated. Afterward, ADC value of the contralateral normal peripheral zone was measured, using the same technique. These measurements were done for each visualized lesion, separately. Regions of interest placement was done in the same manner in posttreatment study, and the ADC value for both tumor lesions and normal contralateral side was measured, even in the absence of the lesion on posttreatment ADC map. In case of more than one lesion per patient, a mean ADC was calculated for the patient.

2.6 | RT schedule

The radiation therapy was delivered by Varian Clinac 600C (Varian Inc., California, USA) using the X-ray beam of 6 MV. Eligible patients with localized prostate cancer who were candidates for definitive RT received hypofractionated IMRT (70.2 Gy, 2.7 Gy/fraction, 50 patients) using a nine-field technique. The clinical target volume (CTV) in these patients was defined as the entire prostate gland and seminal vesicles. The planning target volume was defined by extending the CTV 0.6 cm posteriorly and 1 cm in all other directions. All patients who were candidates for postoperative RT received conventional 3D conformal RT (up to 70 Gy, 2 Gy/fraction, 14 patients) using a seven-field technique. Patients were asked to have a full bladder for the planning CT scan and each RT fraction. A CTV was contoured on CT and MRI slices. All patients received neoadjuvant hormone therapy. The supportive care was homogeneous in the two groups.

2.7 | Characteristics of nanocurcumin and administration

SinaCurcumin®, a commercially available dietary supplement, and placebo capsules were prepared by the Exir Nano Sina Company, Tehran, Iran. In a pharmacokinetic study on mice, the Cmax of SinaCurcumin® and free powder was 2,540.62 and 59.07, respectively. In this study, the bioavailability of SinaCurcumin® as a nanomicelle was estimated to be 59.2 times higher than its free form. Furthermore, the half-life of curcumin nanomicelle and free form was 1.44 and 0.48 hr, respectively (unpublished data). The percent of curcumin encapsulation in the nanomicelle was approximately 100%, and the sizes were about 10 nm. The purity of curcumin used was around 80%. Pharmacokinetic characteristics of SinaCurcumin® in cancer patients are currently under investigation.

In the present study, the nanocurcumin 40 mg or placebo capsules were taken 3 times daily (120 mg/day), so 2 capsules were administered in the morning and another capsule at bedtime.

2.8 | Statistical analyses

Pearson's chi-square was used to compare the number of patients with acute toxicities in the two groups. Fisher's exact test was used to adjust chi-square probability values when cell frequencies were lower than the expected values. The baseline-adjusted hematologic nadirs were compared by analysis of covariance (ANCOVA) test. The duration of acute toxicities and percentage of ADC increase were compared between the two groups using Mann–Whitney U test. To compare the ADC of tumor and contralateral normal tissue pre- and post-RT, a paired *t* test was used. The statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, N.Y., USA). A p value < 0.05 (two-sided test) was considered significant.

3 | RESULTS

A total of 64 patients were included in the study (Figure 1). Nanocurcumin was well tolerated, and no serious drug-related adverse event was observed. The mean age of the patients was 70.28 years

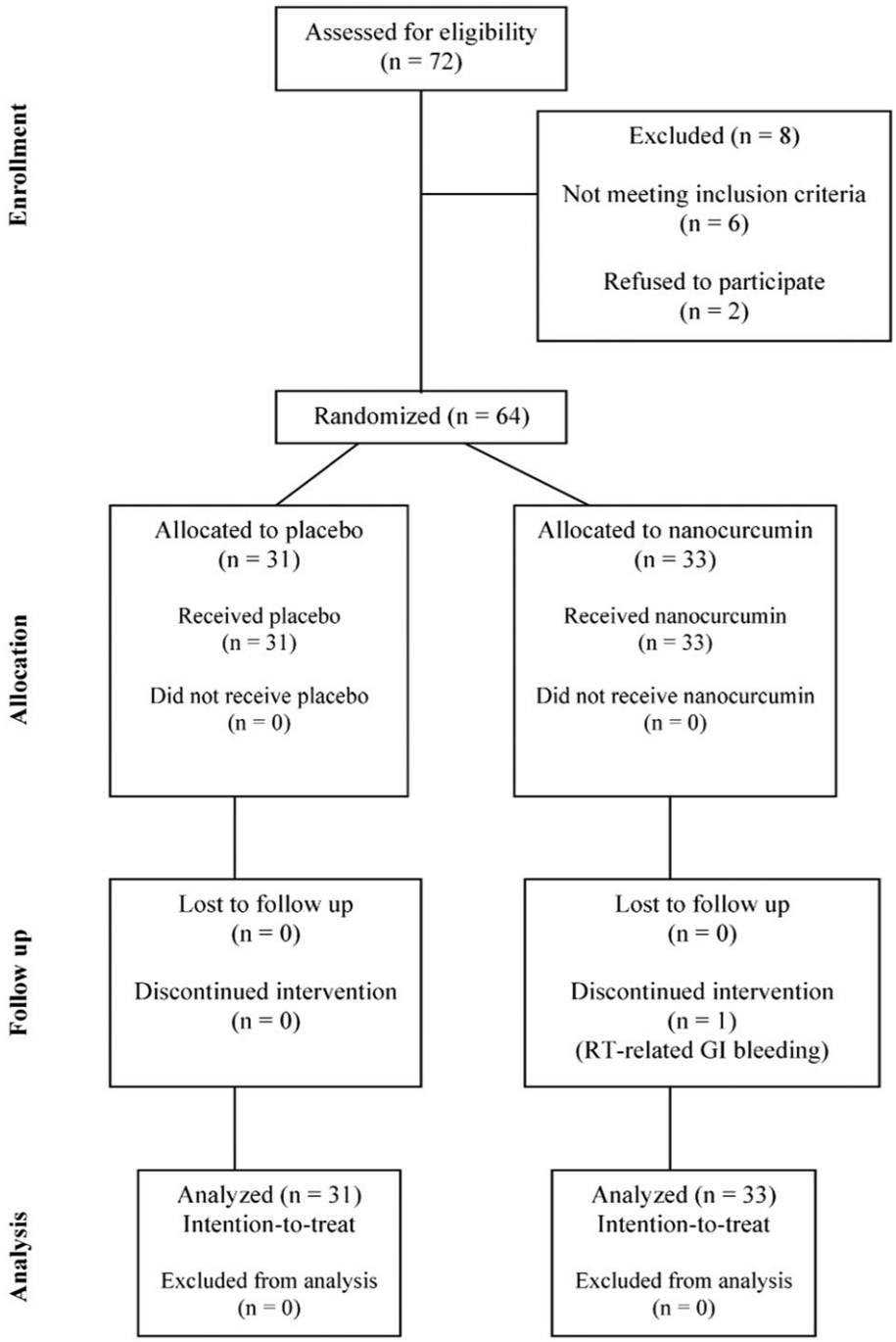

FIGURE 1 The CONSORT flow chart of patients

(range 51–82). The characteristics of the patients and treatment-related parameters in each group are shown in Table 2. All patients completed the RT course, except for one patient in the nanocurcumin group who developed grade III radiation-induced proctitis.

3.1 | Radiation-induced toxicities

Acute toxicities and hematologic nadirs were analyzed using an intention-to-treat approach. Acute radiation-induced toxicities were usually transient and mostly subsided after completion of the RT course. Except for one participant in the nanocurcumin group, no grade III or higher acute toxicity was occurred. The clinical endpoints related to radiation-induced toxicities are listed in Table 3. No significant reduction in the rate of proctitis was observed in the nanocurcumin compared with the placebo group. Radiation-induced proctitis (≥grade I) was noted in 18/31 (58.1%) of patients receiving placebo versus 15/33 (45.5%) of patient receiving nanocurcumin (p = 0.313). No significant difference was also found between the two groups with regard to ≥grade II proctitis, cystitis (≥grade I/II), and duration of radiation toxicities (Table 3).

3.2 | Hematologic nadirs

Compared with the baseline values, a significant reduction for the main hematologic values (i.e., neutrophils, lymphocytes, hemoglobin, and platelets) was observed during the RT course in both nanocurcumin and placebo groups (p < 0.001). Radiation-induced hematologic nadirs in the two groups after adjustment for the baseline values are summarized in Table 4. No significant differences were seen in the nadir levels between the two groups.

3.3 | Tumor response

A per protocol approach was used for assessment of the tumor response, and only patients who completed the MRI procedure pre- and post-IMRT were considered for the response analysis (38 lesions from 26 patients). Thus, patients without mp-MRI examination pre- and/or post-IMRT were excluded from the analysis. After the RT course, a significant increase in the ADC values of tumor lesions (an endpoint for assessment of tumor response to RT) was seen in both groups. The mean tumor ADC increase for nanocurcumin and placebo group was 269 (95% CI [149, 389]; p < 0.001) and 228 (95% CI [63, 392]; p = 0.011), respectively. There was no significant difference between pre- and post-RT values of contralateral normal tissue ADC (p = 0.390). No significant difference in the percentage of tumor ADC increase (as a secondary endpoint) was observed between the two groups (p = 0.574). The mean percentage of ADC increase in the nanocurcumin and placebo groups was 48.4% and 33.8%, respectively. The mean between-group difference was 14.6% (95% CI [−52.4, 23.1]).

4 | DISCUSSION

The radioprotective property of a large number of agents has been studied but, disappointingly, hardly any drug has so far entered into clinical practice (Hosseinimehr, 2007; Mishra & Alsbeih, 2017). Previous trials have shown that different routes of amifostine administration (i.e., intravenous, intrarectal, and subcutaneous) can reduce the incidence and severity of radiation-induced rectal toxicity in patients undergoing pelvic RT; however, several amifostine-related toxicities were also reported in these studies (Dunst, Semlin, Pigorsch, Muller, & Reese, 2000; Koukourakis et al., 2000; Koukourakis et al., 2013; Kouloulias et al., 2004; Kouvaris et al., 2003). In addition, the necessity of using the topical or injection route of administration and monitoring of blood pressure was another limitation. The easy route of daily administration (preferably oral route) is one of the most important requirements that a clinical radioprotector should be met

TABLE 2 Patient characteristics and treatment-related parameters

Characteristics	Placebo (n = 31)	Nanocurcumin (n = 33)
Age		
Mean (*SD*), years	71.5 (7.3)	69.0 (8.6)
T Category, *n* (%)		
T2	11 (35.5)	16 (48.5)
T3	13 (41.9)	13 (39.4)
T4	0 (0.0)	1 (3.0)
Unknown	7 (22.6)	3 (9.1)
Biopsy Gleason Score, *n* (%)		
≤6	7 (22.6)	5 (15.2)
7	14 (45.2)	13 (39.4)
≥8	8 (25.8)	13 (39.4)
Unknown	2 (6.4)	2 (6.0)
Pre-RT PSA value		
Median (range), ng/ml	0.4 (0.03–15.6)	0.4 (0.05–12.3)
RT type, *n* (%)		
Definitive RT	25 (80.7)	25 (75.8)
Postoperative RT	6 (19.3)	8 (24.2)
PTV dose (Gy)		
Mean (*SD*)	70.0 (0.9)	69.5 (1.1)
% of rectum volume at 65 Gy		
Mean % (*SD*)	16.6 (15.4)	14.7 (7.2)
% of bladder volume at 65 Gy		
mean % (*SD*)	23.8 (13.1)	28.8 (16.9)

Note. PTV: planning target volume; PSA: prostate specific antigen; RT: radiotherapy; SD: standard deviation.

TABLE 3 Radiation-induced clinical toxicities

Endpoint	Placebo group (n = 31)	Nanocurcumin group (n = 33)	p value
Acute toxicity, *n* (%)			
Proctitis ≥ Grade I	18 (58.1)	15 (45.5)	0.313
Proctitis ≥ Grade II	3 (9.7)	5 (15.2)	0.709
Cystitis ≥ Grade I	23 (74.2)	29 (87.9)	0.161
Cystitis ≥ Grade II	8 (25.8)	14 (42.4)	0.162
Duration of toxicity, mean weeks (*SD*)			
Proctitis	1.3 (1.4)	1.2 (1.5)	0.651
Cystitis	2.5 (2)	3.3 (1.6)	0.309

TABLE 4 Hematologic nadirs after adjustment for baseline values

Hematologic parameter	Nadir value, mean (*SE*)		Between-group difference, mean [95% CI]	*p* value
	Placebo	Nanocurcumin		
Neutrophils	2.89 (0.14)	2.88 (0.13)	0.008 [−0.36, 0.38]	0.968
Lymphocytes	1.01 (0.06)	1.06 (0.05)	0.051 [−0.22, 0.11]	0.546
Platelets	160.77 (5.77)	159.59 (5.50)	1.180 [−14.79, 17.15]	0.883
Hemoglobin	11.93 (0.13)	11.77 (0.13)	0.159 [−218, 0.535]	0.403

Units of the hematologic values: neutrophils, lymphocytes, and platelets (10^9/L); hemoglobin level (g/dl).

(Hosseinimehr, 2007). In our previous study of 36 prostate cancer patients undergoing RT, we demonstrated the potential efficacy of oral famotidine in reduction of radiation-induced rectal toxicity as well as lymphocytopenia but not other hematologic and urinary toxicity (Razzaghdoust, Mozdarani, & Mofid, 2014; Razzaghdoust, Mozdarani, Mofid, Aghamiri, & Heidari, 2014).

Radiation triggers different cellular signaling pathways that lead to activation of proinflammatory cytokines and thus development of inflammatory responses (Dent et al., 2003; Farhood et al., 2018; Najafi et al., 2018; Stone, Coleman, Anscher, & McBride, 2003). Targeting of inflammation for radioprotection is a remarkable approach (Farhood et al., 2018; Kalman et al., 2017; Yahyapour et al., 2017). Cellular and molecular mechanisms by which the curcumin exerts its radioprotective effects are thought to be inhibition of nuclear factor-κB signaling pathway, reducing expression of inflammatory factors and DNA damage, scavenging the free radicals, and enhancing the expression of antioxidant enzymes (Ak & Gulcin, 2008; Biswas, McClure, Jimenez, Megson, & Rahman, 2005; Iqbal, Sharma, Okazaki, Fujisawa, & Okada, 2003; Nishinaka et al., 2007; Shi et al., 2012).

Our recent animal findings indicated that the oral administration of SinaCurcumin® 5 days before lethal irradiation effectively improves the survival of irradiated mice (data not shown). Based on the growing body of evidence from animal studies, the curcumin administration as an oral radiomodulator is a promising idea (Goel & Aggarwal, 2010; Jagetia, 2007; Kalman et al., 2017; Verma, 2016). However, translating the paradigm into clinical practice has proven to be challenging (Nelson et al., 2017). Negative results play an important role as the crucial building block in development of translational research (Teixeira da Silva, 2015). The present study describes the first clinical experience of nanocurcumin in prostate cancer patients and provides insight into future clinical directions. Technically, this study was underpowered to indicate the efficacy of nanocurcumin in this special clinical setting. However, because "absence of proof" is not "proof of absence," a larger randomized trial with a modified administration protocol can serve to provide some guidance.

A possible component involved in the nanocurcumin failure in this randomized trial is the duration of its pretreatment before the RT course initiation. Recently, several clinical trials on SinaCurcumin® have had favorable results for the clinical application of curcumin after long-term administration (Ahmadi et al., 2018; Alizadeh et al., 2018; Dolati, Aghebati-Maleki, et al., 2018). Based on these randomized trials, we assumed that a longer duration of supplementation seems to produce a better outcome. In human, targeted radioprotection (via regulation of antioxidant enzymes and inflammatory genes) by nanocurcumin may require long-term pretreatment, for example, several weeks or months before the RT course. Fractionated RT could result in a rapid reduction in cell numbers and consequently an immediate suppression of cell production in the first week of the RT course (Dorr, Hamilton, Boyd, Reed, & Denham, 2002). Although the clinical presentation of radiation injury may not become apparent for weeks after RT initiation, the pathological processes begin immediately after radiation exposure (Stone et al., 2003). Hence, the lack of rectal and bladder sparing in this study might be associated with short-term supplementation (3 days) before the initiation of cellular and molecular process of radiation injury. A future trial of nanocurcumin with a long-term pretreatment may yield positive results. Recently, in a microRNA profiling study of SinaCurcumin® in patients with multiple sclerosis, the anti-inflammatory effect of nanocurcumin has been shown after 6 months of treatment. Another double-blind randomized trial using this nanoformulation (SinaCurcumin®) has demonstrated the efficacy and safety of nanocurcumin in patients with amyotrophic lateral sclerosis after long-term supplementation. Furthermore, in a randomized trial conducted in infertile men, 10 weeks administration of SinaCurcumin® resulted in a slight but statistically significant improvement in plasma levels of total antioxidant capacity and inflammatory factors. These trend results raise an interesting question whether short- or long-term nanocurcumin pretreatment may contribute to the different findings. In addition, nanocurcumin administration within a period of 1 or 2 hr before exposure to daily radiation may result in a better radioprotective efficacy.

In a recent double blind randomized placebo-controlled trial, Wolf et al. (2018) examined the radioprotective effect of oral curcumin in 686 breast cancer patients undergoing RT. In this multicenter trial, in agreement with our study, the curcumin did not significantly reduce the radiation-induced dermatitis in comparison with placebo. It should be noted that despite large body of preclinical evidence exploring the beneficial role of curcumin, "the dark side of curcumin" has also been described in the literature (Burgos-Moron, Calderon-Montano, Salvador, Robles, & Lopez-Lazaro, 2010; Nelson et al., 2017).

The single-center design of this trial could be considered as a critical limitation. Patients recruited in a single center are not completely representative of the entire population. The fairly small number of patients recruited is another limitation, and this trial is underpowered to accept or reject the study hypothesis. It seems that the 90% power used in the methodology to calculate sample size was chosen based on an ideal effect size (i.e., reaching the expected incidence of 20% in the nanocurcumin group as an acceptable toxicity). Because the actual effect of the experiment was smaller than this ideal effect size, this study does not have enough power to accept or reject the hypothesis. The lack of statistical significance in the percentage of

the ADC increase is possibly due to large amounts of missing data as a consequence of incomplete imaging procedures for some patients. All the limitations could be addressed in a subsequent pivotal trial.

In conclusion, this RCT failed to demonstrate the efficacy of nanocurcumin for concurrent therapy in prostate cancer patients undergoing RT but could have a major role to bridge the gap between experimental and clinical studies on nanocurcumin. Further studies with a large number of patients and long-term nanocurcumin pretreatment will clarify whether this phytochemical acts as a radioprotector and/or radiosensitizer in the RT setting.

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CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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