



A phase II randomized double blinded trial evaluating the efficacy of curcumin with pre-operative chemoradiation for rectal cancer

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Background: *In vivo* studies demonstrate that curcumin increases radioresponse of colorectal cancers. To demonstrate efficacy in humans, we performed a randomized double-blind study of locally advanced rectal cancer (LARC) patients receiving pre-operative chemoradiation therapy (CRT) ± curcumin. We used pathologic complete response (pCR) rate as a surrogate for clinical outcome.

Methods: From 2008–2010, LARC patients were randomized to placebo/curcumin in a 1:2 ratio. Patients received CRT [50.4 gray in 28 fractions; capecitabine (825 mg/m² twice daily)] followed by surgery. Curcumin (4 grams orally, twice daily) or placebo was given throughout CRT and 6 weeks afterward. Toxicity was monitored weekly. Blood samples taken pre- and 1-hour post-ingestion and tissue biopsies (both collected at CRT week 2) were analyzed for pharmacokinetics. The primary outcome was surgical pCR rate.

Results: Of 22 enrolled patients, 15 received curcumin. Median age was 61 years and the majority were male (n=13; 59%). The median serum curcumin concentrations before (3.04 ng/mL; range, 1.24–18.88 ng/mL) and 1 hour after (3.32 ng/mL; range, 0.84–5.36 ng/mL) curcumin intake did not differ significantly (P=0.33). Serum curcumin concentrations both increased and decreased 1-hour post-administration (range as percentage of baseline: 8.8–258.1%). Twelve curcumin patient tissue biopsies had median curcumin concentration of 33.7 ng/mg tissue (range, 0.1–4,765.7 ng/mg). Two placebo and 1 curcumin patient achieved pCRs (P=0.18). One grade 3 toxicity (infection) was experienced.

Conclusions: The addition of curcumin to CRT did not increase pCR rates for LARC patients. The unpredictable bioavailability of curcumin contributes to continued uncertainties regarding curcumin efficacy.

Trial Registration: ClinicalTrials.gov identifier: NCT00745134.

Keywords: Locally advanced rectal cancer (LARC); chemoradiation; curcumin

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Introduction

The standard of care treatment for locally advanced rectal cancer (LARC) was established as preoperative chemoradiation therapy (CRT) followed by surgical resection in 2004 by the German rectal cancer trial, which proved the benefit of preoperative *vs.* postoperative CRT in terms of improved local control (LC), sphincter preservation, and decreased toxicity (1). During this trial, patients received radiation therapy (RT) concurrent with 5-fluorouracil (5-FU), used as a radiation sensitizer, followed by surgical resection.

Since that time, one thrust of research has been to alter the sequence of treatments to preoperative chemotherapy and CRT before surgery (total neoadjuvant therapy). This approach addresses the concern that postoperative adjuvant chemotherapy has failed to reduce the incidence of distant metastases that is over twice the incidence of local and regional metastases. Preoperative chemotherapy affords the opportunity to target occult micrometastatic disease early, allows tumor downstaging, facilitates greater compliance with planned therapy, and permits early assessment of chemosensitivity. Early results suggest that this is indeed associated with improved overall outcomes, but the exact sequencing of neoadjuvant chemotherapy and CRT remains unclear (2-4).

A parallel research thrust seeks to improve the efficacy of CRT using radiation sensitizers like 5-FU to improve the current roughly 20% pathologic complete response (pCR) rate. Improved pCR rates are associated with longer progression-free survival (PFS) and overall survival (OS) (5-7). Response to pre-operative CRT may improve the chances of sphincter-preserving surgery (8,9), and a pCR to CRT may permit selected patients to undergo less extensive resections and potentially organ-preserving strategies, therefore further minimizing toxicity (10).

Another strategy has been to explore the convergence of these approaches where total neoadjuvant therapy is coupled with radiation sensitization. This approach is being tested currently in a multi-arm cooperative group study with no clear improvement thus far (11). Many have evaluated the substitution or addition of other systemic agents to the preoperative regimen (12-14), but none has shown a clear advantage over the regimen with 5-FU alone, especially

without increased toxicity (15). While most strategies to improve radiation response rates with concurrent systemic agents have focused on the inhibition of inherent or constitutive pro-survival pathway overexpression within tumor cells (16,17) redundant signaling pathways hinder success (18). Alternatively, many have identified the broad spectrum blockade of inducible pathways that drive pro-survival and anti-apoptotic signals as a promising method of improving tumor response to treatment.

Curcumin, a polyphenol and major component of the spice turmeric, has been implemented for anti-inflammatory medicinal purposes in India for centuries (19). More recently, this agent has been recognized for its potential as an anti-neoplastic or chemopreventive agent (20-22). It inhibits angiogenesis, induces apoptosis or cell cycle arrest, and causes regression of tumors in preclinical models (23-26). While safety has been established in multiple phase I trials, its benefit in terms of tumor response has not been established in colorectal cancer trials. The poor bioavailability of curcumin creates challenges for therapeutic use (27); however, this obstacle could possibly be circumvented when targeting gastrointestinal tract malignancies.

We hypothesized that the addition of curcumin to the preoperative therapy regimen could improve outcomes when given with capecitabine (a 5-FU pro-drug) and RT. Therefore, we conducted a phase II randomized double-blinded study to evaluate the efficacy in terms of pCR rates of adding curcumin to preoperative CRT for LARC patients. We analyzed tumor downstaging, local regional/distant failure, and survival rates. To further explore the pharmacology of curcumin and validate observed effects, we also determined the serum and rectal tumor tissue levels to correlate with clinical response. We present the following article in accordance with the CONSORT reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-259/rc>).

Methods

Patient eligibility and study design

From 2008–2010, 22 patients with LARC (T3/T4 or

Table 1 Trial eligibility and exclusion criteria

Eligibility criteria

Clinical stage T3,4 N0,1,2 or T2N1,2 adenocarcinoma of the rectum

Staged using endorectal ultrasound, pelvic CT or MRI, and physical examination

Histology confirmed by the Department of Pathology at MD Anderson Cancer Center

No distant metastatic disease in the liver, peritoneum, lungs, or paraaortic lymph nodes

Performance status (Karnofsky scale) of 70% or greater

18 years of age or greater

ANC >1,200 cells/mm³, platelets >100,000/mm³, total serum bilirubin <2 mg/dL, BUN <30 mg/dL, creatinine <1.5 mg/dL or creatinine clearance >50 cc/min (estimated by Cockcroft-Gault equation)

Signed informed consent for investigational nature of study and voluntary participation

No use of additional herbal supplements during study

For women: amenorrhea for ≥12 months or use of reliable contraception (continued 30 days from last study drug administration)

For men: use of reliable contraception during study

Exclusion criteria

Prior complete course up to 5 Gy of radiotherapy to the pelvis

Pregnant or lactating woman (women/men of childbearing potential not using a reliable contraceptive method)

Treatment for other carcinomas within last 5 years, except cured non-melanoma skin and treated *in-situ* cervical cancer

Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or requiring IV antibiotics, cardiac disease NYHA class III or IV, unstable angina pectoris, unstable cardiac arrhythmia or tachycardia (heart rate >100 beats/minute), or psychiatric illness/social situations limiting compliance with study

Other serious uncontrolled medical conditions that might compromise study participation

Major surgery within 4 weeks of the start of study treatment

Prior unanticipated severe reaction to fluoropyrimidine therapy or known hypersensitivity to 5-FU, capecitabine, or curcumin

Concurrent use of therapeutic Coumadin

Concurrent use of cimetidine, allopurinol, or aluminium hydroxide and magnesium hydroxide-containing antacids

Sorivudine and brivudine use within 4 weeks of the start of study treatment

CT, computed tomography; MRI, magnetic resonance imaging; ANC, absolute neutrophil count; BUN, blood urea nitrogen; 5-FU, 5-fluorouracil.

T2 and node positive disease) treated at our institution were enrolled in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the MD Anderson Cancer Center institutional review board (protocol 2006-0644) (clinicaltrials.gov number NCT00745134). Informed consent was taken from all individual participants. Inclusion and exclusion criteria are shown in *Table 1*. The primary endpoint was pCR rate following definitive CRT with/without curcumin. The research staff at MD Anderson Cancer Center enrolled participants. Patients,

care providers, and the research team, including those assessing outcomes and toxicity, were blinded to treatment assignment. Patients were randomized to control and experimental treatment arms in a 1:2 ratio, with a planned enrollment of 15 placebo patients and 30 curcumin patients. Randomization was performed using a website created by the Department of Biostatistics and used by pharmacists. For patients randomized to curcumin, a two-stage design was employed with a significance level of 10% and 80% power (16 patients were to be treated in the first stage, and 14 were to be treated in second stage only if there were 3

or more patients with pCR in first stage). The null pCR rate was 18%, and the target pCR rate was 36% or more. There was a 0.43 probability of stopping the study after the first stage if the pCR rate was 18% and a 0.04 probability of stopping the study early if the pCR rate 36%. Secondary endpoints included patient downstaging at the time of surgery, LC, PFS, and OS. We also planned to determine curcumin serum and tissue levels. There were no significant changes to trial methods after commencement. The trial was stopped early because there was only one patient with pCR among the first 15 patients randomized to the curcumin arm.

Systemic therapy

Capecitabine was given orally twice daily 12 hours apart on the days of RT at 825 mg/m². Curcumin or placebo was given at 4 gm twice daily [dose based on prior studies (28,29)] during RT and for 6 weeks after completion of RT (for prosurvival signaling suppression until time of surgery). Curcumin was consumed approximately 1 hour before RT. Curcumin C3 complex and placebo were obtained from Sabinsa Corporation, Piscataway, NJ, USA.

RT technique

The primary tumor and involved lymph nodes, determined by pre-operative computed tomography (CT) imaging [5 patients also had magnetic resonance imaging (MRI)] and/or colonoscopy, as well as the perirectal, presacral, and internal iliac ± external iliac nodes, were treated to 45 Gy in 25 fractions using standard rectal fields. An additional 5.4 Gy in 3 fractions was given as a boost to the primary tumor and involved lymph nodes with 2–3 cm margin including the presacral space and sacrum.

Evaluation of plasma/tissue curcumin levels

Biopsies for tissue curcumin levels and patient plasma samples were obtained during CRT week 2. Plasma levels were assessed pre- (1 hour prior) and post- (1 hour after) curcumin/placebo administration. Please see the [Appendix 1](#) for full methods of plasma and tissue sample analysis.

Toxicity assessment

Toxicity was assessed at weekly on-treatment visits at MD Anderson Cancer Center using the National Cancer

Institute Common Terminology Criteria for Adverse Events, version 3.0.

Patient follow-up and outcomes assessment

Patients were contacted by telephone approximately 1 month after completion of CRT and 6 weeks of maintenance therapy to evaluate toxicity. Patients then underwent surgery, usually within 1–3 weeks from this toxicity check. Pathologic response was determined by specialized gastrointestinal pathologists at our institution using the following tumor regression grading system: 1= pCR, 2= near pCR, 3= partial response, 4= no response, 5= progression.

Adjuvant chemotherapy after surgery and follow-up evaluations (including history and physical, endoscopy, and laboratory studies) were recommended at the discretion of the treating medical oncologist and generally performed at MD Anderson Cancer Center. Recurrence was defined as clinical or imaging findings consistent with disease recurrence, typically confirmed by biopsy or surgical resection. The trial was stopped early because there was only one patient with pCR among the first 15 patients randomized to the curcumin arm; otherwise, there were no changes to trial outcomes after commencement. Retrospective clinical chart review was performed until 2021 to update outcomes.

Statistical analysis

We compared the rate of pCR between treatment arms with Fisher's exact test. We estimated OS and PFS with the Kaplan-Meier method. OS was calculated from start of CRT to date of death, censored at last follow-up. PFS was calculated from start of CRT to date of disease progression or death, censored at last endoscopy/imaging evaluation. We used the methods of Fine and Gray (30) to estimate the cumulative incidence of time to local regional failure (TTLRF) and time to distant failure (TTDF) from start of CRT to date of failure as documented by endoscopy/imaging, with death as a competing event. Patients were censored at last follow-up. Comparisons of treatment arm patient/tumor characteristics (e.g., age, T stage) and treatment outcomes (e.g., pCR) were performed using Fisher's exact test and the Wilcoxon signed rank test as appropriate. One patient who did not undergo surgical resection was removed from analyses related to pathologic response outcomes; otherwise, there were no patient losses or exclusions.

Table 2 Patient and clinical tumor characteristics

Characteristics	All patients (n=22)	Curcumin (n=15)	Placebo (n=7)	P
Age (years), median [range]	60 [28–75]	69 [28–75]	50 [45–64]	0.02
Sex, n [%]				0.65
Male	13 [59]	8 [55]	5 [71]	
Female	9 [41]	7 [47]	2 [29]	
Clinical T stage, n [%]				1.00
2	4 [18]	3 [20]	1 [14]	
3	17 [77]	11 [73]	6 [86]	
4	1 [5]	1 [7]	0 [0]	
Clinical N stage, n [%]				0.56
0	6 [27]	3 [20]	3 [43]	
1	15 [68]	11 [73]	4 [57]	
2	1 [5]	1 [7]	0	
Tumor size (cm), median [range]	4.5 [2–8] [†]	4 [2–8]	5 [4–8]	0.39
Distance from anal verge (cm), median [range]	4 [1–10]	3 [1–9]	6.5 [2–10]	0.17
Tumor circumference (%), median [range]	50 [15–100] [†]	50 [15–100]	55 [40–75]	0.21
Pretreatment CEA (ng/mL), median [range]	1.6 [1.0–8.1]	1.3 [1–5.4]	2.4 [1.0–8.1]	0.62
Tumor differentiation, n [%]				1.00
Well	0 [0]	0 [0]	0 [0]	
Moderate	22 [100]	15 [100]	7 [100]	
Poor	0 [0]	0 [0]	0 [0]	

[†], one patient's tumor found in polyp—size and circumference not evaluable. T, tumor; N, nodal; CEA, carcinoembryonic antigen.

Results

Patient and clinical tumor characteristics are shown in *Table 2*. Of 22 randomized patients, 15 patients received curcumin and 7 patients received placebo (*Figure 1*). All patients received the intended treatment with few modifications as noted below. All patients were analyzed with no losses or exclusions after randomization. Median age was 60 years with curcumin patients older than placebo patients (69 vs. 50 years, median, $P=0.02$). Majority of patients were male (59%). Most patients had clinical T3 (77%) and N1 (68%) disease presentations. Tumors were similar size in the curcumin (4 cm) and placebo (5 cm) groups with a median distance from the anal verge of 3 and 6.5 cm, respectively ($P=0.17$). Median extent of involvement of lumen circumference was 50% for the entire cohort, with tumors ranging from 15% to 100% involvement of lumen circumference. All tumors were moderately differentiated

(grade 2).

All patients received pre-operative CRT with capecitabine. Patients were treated with 3D conformal RT except for one patient who received intensity modulated RT (IMRT). All but two patients received 50.4 Gy in 28 fractions. One patient had clinically involved iliac lymph nodes which were treated to 63 Gy in 28 fractions due to questionable resectability; the primary rectal tumor received 50.4 Gy in 28 fractions. One patient's treatment was stopped early due to hospitalization and treatment for *Clostridium difficile* (*C. diff.*) colitis; she received 43.2 Gy in 24 fractions.

Two patients had dose reductions of capecitabine during treatment for hand-foot syndrome and paresthesias. Two patients had dose reductions of curcumin during CRT, one reduced dose to 2–3 tabs twice daily due to inability to tolerate 4 tabs twice daily and another refused curcumin

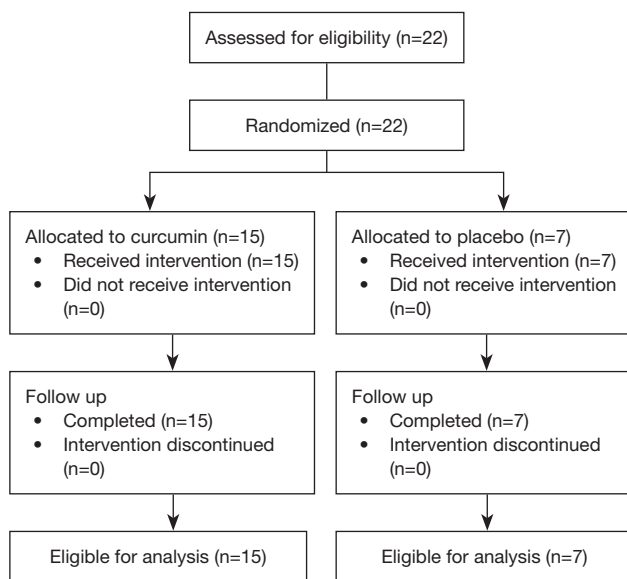


Figure 1 Participant flowchart with details on randomization, intervention, follow up, and analysis.

for the last 8 days of CRT due to diarrhea and dehydration later attributed to *C. diff*. Four patients discontinued post-CRT maintenance curcumin and one reduced the dose to 3 tabs twice daily.

Toxicities separated by grade are shown in *Table 3*. The most common grade 1 toxicities experienced by patients during CRT were anorexia (45%), diarrhea (59%), fatigue (86%), nausea (64%), and pain (59%). Nine patients experienced grade 2 radiation dermatitis (41%). One patient experienced a grade 3 toxicity. Near the end of treatment, this patient was diagnosed with *C. diff*. colitis, which required hospitalization and administration of intravenous antibiotics.

Patients underwent surgical resection at median 7.7 weeks after completed CRT as recommended by their surgical oncologist: low anterior resection (n=10), coloanal anastomosis (n=4), abdominoperineal resection (n=5), transanal excision (n=1), and total pelvic exenteration (n=1). Only one patient did not undergo surgery as he was found on first follow up imaging to have small pulmonary nodules increasing in size. He received systemic chemotherapy.

Pathologic response rates (reported in *Table 4*) included a pCR for 2 of 6 placebo patients and 1 of 15 curcumin patients (P=0.18). Tumor downstaging occurred in 7 of 15 curcumin patients and 4 of 6 placebo patients (P=0.64). There were no significant differences between curcumin and placebo patients in terms of pathologic tumor stage

Table 3 Toxicity during chemoradiation treatment

Toxicity	Toxicity grade, n [%]		
	I	II	III
Acne	1 [5]	-	-
Allergic rhinitis	1 [5]	-	-
Anorexia	10 [45]	-	-
Diarrhea	13 [59]	2 [9]	-
Dizziness	1 [5]	-	-
Dysuria	4 [18]	1 [5]	-
Elevated liver function tests	1 [5]	-	-
Fatigue	19 [86]	-	-
Hand foot syndrome	4 [18]	1 [5]	-
Hemorrhoids	1 [5]	-	-
Hypotension	1 [5]	-	-
Hypomagnesemia	1 [5]	-	-
Insomnia	1 [5]	1 [5]	-
Infection	1 [5]	-	1 [5]
Nausea	14 [64]	-	-
Neuropathy	1 [5]	-	-
Pain	13 [59]	3 [14]	-
Radiation dermatitis	7 [32]	9 [41]	-
Rash	1 [5]	-	-
Rectal bleeding	1 [5]	-	-
Testicular swelling	1 [5]	-	-
Urinary frequency	6 [27]	-	-
Vomiting	1 [5]	-	-

(P=0.34) or tumor regression grade (P=0.44). All patients who underwent surgery received adjuvant systemic therapy.

Median follow-up for all patients was 9.2 years. *Figure 2* depicts TTLRE, TTDF, PFS, and OS. Five-year cumulative incidence of local regional failure was 14.3% [95% confidence interval (CI): 0 to 42%] and 6.7% (95% CI: 0 to 19.7%) and 5-year cumulative incidence of distant failure was 28.6% (95% CI: 0 to 65.0%) and 33.3% (95% CI: 8.5% to 58.2%) for placebo and curcumin groups, respectively. Five-year PFS was 71.4% (95% CI: 44.7% to 100%) (placebo) and 66.7% (95% CI: 46.6% to 95.3%) (curcumin) and 5-year OS was 85.7% (95% CI: 63.3% to 100%) (placebo) and 85.7% (95% CI: 69.2% to 100%) (curcumin).

Table 4 Response to treatment at time of surgical resection

Characteristics	All patients (n=21) [†]	Curcumin (n=15)	Placebo (n=6) [†]	P
Pathologic T stage, n [%]				0.34
0	1 [5]	1 [7]	0 [0]	
1	4 [19]	2 [13]	2 [33]	
2	6 [29]	5 [33]	1 [17]	
3	7 [33]	6 [40]	1 [17]	
4	3 [14]	1 [7]	2 [33]	
Tumor downstaging, n [%]				0.64
Yes	11 [52]	7 [47]	4 [66]	
No	10 [48]	8 [53]	2 [33]	
pCR, n [%]				0.18
Yes	3 [14]	1 [7]	2 [33]	
No	18 [86]	14 [93]	4 [66]	
Tumor regression grade [‡] , n [%]				0.44
1	3 [14]	1 [7]	2 [33]	
2	3 [14]	2 [13]	1 [17]	
3	5 [24]	4 [27]	1 [17]	
4	10 [48]	8 [53]	2 [33]	
5	0 [0]	0 [0]	0 [0]	

[†], one patient did not undergo surgery; [‡], tumor regression grade (1= pCR, 2= near pCR, 3= partial response, 4= no response, 5= progression). T, tumor; pCR, pathologic complete response.

Plasma and tissue concentrations of curcumin are presented in *Figure 3*. Plasma concentrations for patients receiving curcumin varied widely both in terms of absolute plasma levels 1 hour after administration and the relative change when compared to baseline (*Figure 3A,3C*). The median serum curcumin concentrations before (3.04 ng/mL; range, 1.24–18.88 ng/mL) and 1 hour after (3.32 ng/mL; range, 0.84–5.36 ng/mL) curcumin intake did not differ significantly ($P=0.33$). Serum curcumin concentrations increased in some curcumin patients ($n=4$), while they decreased or remained constant 1 hour after administration in others ($n=8$) (range, as percentage of baseline: 8.8–258.1%). Twelve curcumin patients had analyzable tissue biopsies with a median curcumin concentration of 33.7 ng/mg tissue (range, 0.1–4,765.7 ng/mg) (*Figure 3B,3C*). Three placebo patients had analyzable tissue biopsies with a median curcumin concentration of 0.0 ng/mg tissue (range, 0.0–0.0 ng/mg). There was no association between tissue

curcumin concentration and TTLRF ($P=0.23$) or pCR ($P=0.17$).

Discussion

In this phase II randomized study, we did not observe a benefit from the addition of curcumin to long course preoperative CRT for LARC patients. Unfortunately, we again demonstrate that the poor bioavailability of curcumin remains a challenge that prevents the true assessment of any potential benefit of this agent.

There is considerable interest in improving the current standard of care regimen for LARC patients. Many studies have reported an association between increased pathologic response to CRT and improved survival outcomes. Furthermore, a significant increase in pCR rates may afford the patient a non-operative treatment option with watchful waiting or a limited surgical procedure like a wide local

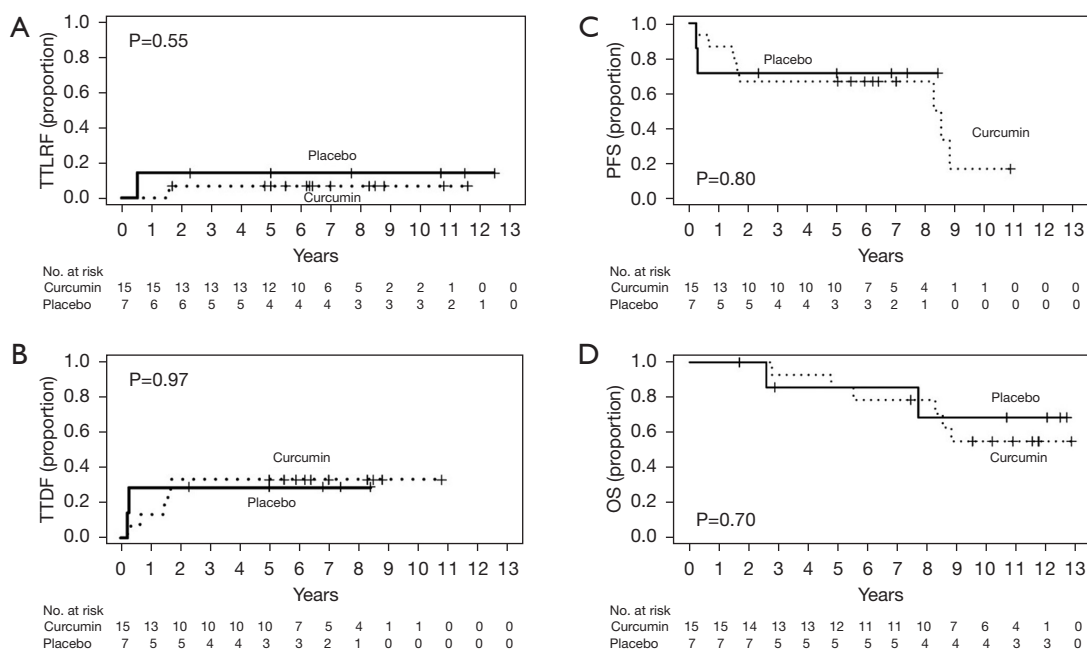


Figure 2 TLLRF (A), TTDF (B), PFS (C), and OS (D) for curcumin and placebo patients. TLLRF, time to local regional failure; TTDF, time to distant failure; PFS, progression-free survival; OS, overall survival.

excision. By omitting the more extensive resections involved in total mesorectal excision, this subset of patients may avoid the morbidity of surgery and potentially have a better quality of life. To improve outcomes and possibly decrease morbidity, alternative concurrent chemotherapeutic agents such as oxaliplatin have been investigated in many trials. Although some of these have resulted in improved pCR rates, this was accompanied by increased grade 3–4 toxicity. A recent meta-analysis concluded that the benefit of adding oxaliplatin to 5-FU-based neoadjuvant CRT with adjuvant chemotherapy for this population remains controversial (31). As noted previously, the evaluation of promising radiosensitizers in the total neoadjuvant therapy setting has been explored in a large cooperative group setting but the agents tested to date (veliparib, pembrolizumab) have not improved pathologic response rates significantly (11,32,33). Novel compounds with the potential to increase the pathologic response of rectal tumors during CRT without added toxicity are still needed.

Curcumin, a component of the spice turmeric, was initially popularized for its potential role in the prevention of gastrointestinal tract malignancies (22). However, there is also considerable interest in curcumin as a novel anti-neoplastic agent, based on the numerous mechanisms by which it has been shown to overcome uncontrolled cell

growth (21,25,26,34). It is likely that curcumin provides a multi-faceted blockade of pathways that drive pro-survival signals, as it has been proven to interrupt proliferative pathways involving epidermal growth factor receptor (35,36), multiple tyrosine kinases (35,36), peroxisome-proliferator-activated receptors (37), and many others. It also has immunomodulatory effects mediated via activation of host macrophages and natural killer cells and modulation of lymphocyte-mediated function (38,39).

Tumors with constitutive expression of pro-survival signaling are well-characterized as more resistant to RT, and these pathways have been targets for radiosensitization strategies. Some radioresistance pathways are inducible, transiently upregulated in response to sublethal doses of radiation. Preclinical studies have demonstrated that the NF- κ B pathway constitutes one such pro-survival, anti-apoptotic signal that can be transiently activated to protect cells from radiation-induced apoptosis and that curcumin suppressed this radiation-induced NF- κ B activation via several mechanisms (40). As with other promising preclinical findings with curcumin for cancer therapy, including combination treatments with cytotoxic chemotherapy, targeted therapy, and immune checkpoint inhibitors (41), therapeutic success in clinical studies has been limited. The safety of curcumin has been established

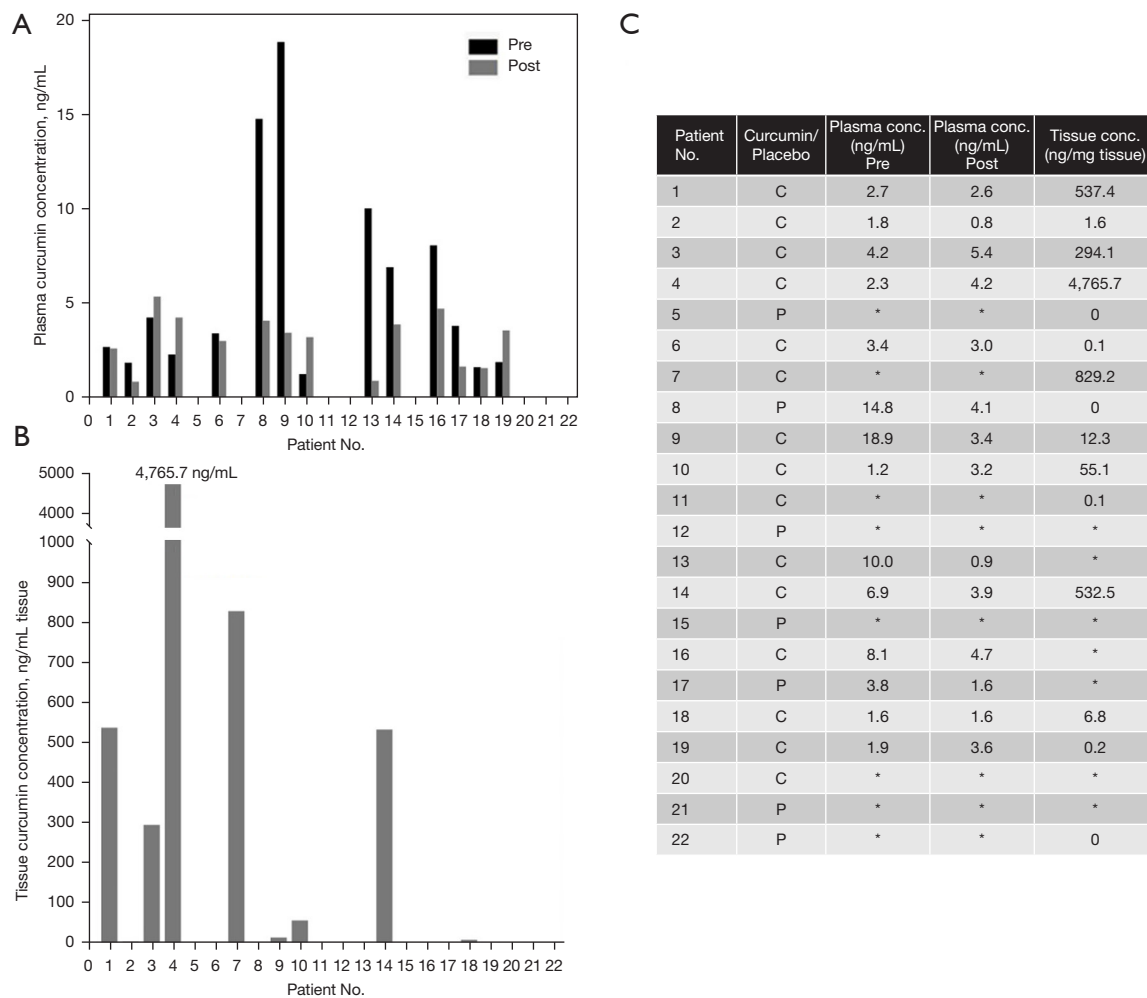


Figure 3 Curcumin levels in plasma (A) and tissue (B) for all available patients displayed in graphical and tabular formats (C). *, indicates sample not available. Conc., concentration.

through multiple phase I trials (28,42). A phase I study at the University of Leicester in England included 15 subjects with advanced colorectal cancers who orally consumed curcumin doses up to 3.6 gm daily for up to 4 months. There was no dose-limiting toxicity observed. Curcumin consumed at 3.6 gm levels generated detectable levels of the parent compound and conjugates in plasma and urine, demonstrating bioavailability outside the gastrointestinal tract and caused inhibition of prostaglandin E2 production in blood leukocytes (measured *ex vivo*) (43,44). A recent systematic review that examined the clinical effect of curcumin in enhancing cancer therapy concluded that curcumin reduces the toxicities of chemotherapy and RT; some included studies reported increased OS duration and decreased tumor marker levels (45). A phase IIa

study of metastatic colorectal cancer patients found that curcumin was a safe and tolerable addition to the FOLFOX (5-FU, leucovorin, and oxaliplatin) chemotherapy regimen; however, there was no significant difference in survival outcomes (46).

Unfortunately, a number of clinical studies have now demonstrated the poor and unpredictable bioavailability of this agent, with erratic and sometimes undetectable plasma levels after curcumin administration to humans (19). *In vitro* cell-based studies have shown that the concentration of curcumin needed to exert effects is in the 5 to 50 μ M range (47). In our study, plasma concentrations ranged from 1.2–18.9 ng/mL, equivalent to 0.003–0.05 μ M, far below the expected efficacious concentration range. In addition to these plasma studies, tissue concentrations of curcumin

after oral administration have also been reported (29). Twelve patients received oral curcumin at 0.45, 1.8, or 3.6 g per day for 7 days prior to surgery. Concentrations of curcumin in normal and malignant tissue for patients consuming 3.6 g per day were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively. With these concentrations, the authors detected significantly lower levels of the oxidative DNA adduct M₁G, suggesting that 3.6 g curcumin achieves efficacious levels in the colorectum. Despite the twice daily dosing schedule used in our study, we observed tissue concentrations ranging from 0.1–4,765.7 ng/mg tissue (equivalent to 0.04–1,753.8 nmol/g). Six of the 12 analyzable tissue biopsies had curcumin levels below the levels others have postulated to be sufficient for biological efficacy (47).

The cause for curcumin's unpredictable pharmacokinetics and documented poor bioavailability is multifactorial and includes low water solubility, inefficient absorption, and rapid metabolism (48). Alternative promising delivery mechanisms, including liposomes, nanoparticles, phospholipid formulations, and synthetic analogs have been developed (41). Studies have also shown increased efficacy of curcumin derivatives, which furthers interest in the development of curcumin analogs with improved bioavailability and potency (49). Various lesion-oriented delivery methods have also been explored (50).

Among the strengths of the study was the strong translational component that enabled a careful analysis; however, this study also had limitations. The small number of participants prohibited robust statistical analyses. With these small numbers, there was no observed benefit to the addition of curcumin to preoperative CRT with capecitabine. However, given the known challenges of poor bioavailability of curcumin and the erratic and low plasma and tissue levels seen in this study, it is likely that curcumin was not present at consistent and therapeutic levels at the time these patients received RT. As numerous metabolites of curcumin have been identified (49), it is possible that the plasma and tissue levels measured in our study were not reflective of the levels of active compound metabolites. These studies would be challenging to perform given the number and varied distribution of each compound. Regardless of the erratic measurements of curcumin levels, there was no overall improved effect seen in this small patient cohort.

Although observational and cancer prevention studies have shown benefits from the simple ingestion of curcumin (22), it is possible that the mechanism of action for curcumin to

effect colorectal tumor response or improve conventional treatment efficacy requires more than local contact during digestion in the gastrointestinal tract. If curcumin is further evaluated as a clinical radiosensitizer, studies should examine formulations with proven biodistribution profiles.

Conclusions

In conclusion, we conducted a phase two randomized double-blind study to evaluate the efficacy of curcumin with preoperative CRT for LARC patients. We saw no improvement in pCR rates of rectal tumors at the time of surgery. Additionally, we saw no improvement in tumor downstaging, TTLRF, or survival endpoints. On analysis of both plasma and tissue levels of curcumin, we observed low and variable levels of curcumin. This variability is a source of significant concern for the clinical utility of native curcumin as a therapeutic anti-cancer agent; future studies should evaluate curcumin formulations with proven bioavailability.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-259/rc>

Trial Protocol: Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-259/tp>

Data Sharing Statement: Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-259/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-259/coif>). JRG reports unrelated funding from RSNA, honoraria from the Osler Review and Maryland Boards courses, and leadership roles in ROECSG and ILROG. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the MD Anderson Cancer Center institutional review board (protocol 2006-0644). Informed consent was taken from all individual participants.

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Appendix 1

Plasma sample analysis

Patient plasma samples were stored at $-80\text{ }^{\circ}\text{C}$. Samples were prepared for analysis by thawing on ice followed by a centrifugation step to remove insoluble plasma components, 50 μL of plasma was removed from the sample and deproteinated using an equal volume of ice cold acetonitrile. The deproteinated sample was diluted with 100 μL of 0.1% formic acid in water and the sample centrifuged at 15K rpm to remove all insoluble materials. The sample was analyzed for curcumin using a Waters Xevo TQS mass spectrometer coupled to a Waters Acquity UPLC with a Phenomenex Kinetex PFP 2.6 μm 50 \times 2 mm analytical column. Curcumin was detected using electrospray positive ionization in selected reaction monitoring mode (m/z 369.1 \rightarrow 177.05). Quantification was performed by comparing the sample curcumin peak area to a regression curve prepared from peak area of known concentrations of curcumin in protein precipitated human plasma to match the patient plasma sample matrix.

Mass spectrometry instrument conditions

MS conditions

Capillary voltage: 2.43 kV;

Cone voltage: 44 V;

Collision energy: 22 eV;

Source temperature: 150 $^{\circ}\text{C}$;

Desolvation temperature: 200 $^{\circ}\text{C}$.

LC conditions

Mobile phase A: 0.1% formic acid in water;

Mobile phase B: 80:20 (acetonitrile: methanol);

Sample temperature: 10 $^{\circ}\text{C}$;

Column temperature: 60 $^{\circ}\text{C}$;

Injection volume: 10 μL ;

Gradient (linear): see *Table S1*;

Curcumin retention time: 2.22 \pm 0.1 minutes.

Tissue extraction procedure

The tissue extraction procedure was similar to previous reports (51). Samples were reconstituted and then injected into an Agilent 6460 triple quadrupole liquid chromatograph/mass spectrometer for quantitative analysis. Curcumin was separated on a Phenomenex Luna C18 column (3 μM , 2 \times 100 mm). Curcumin was eluted with mobile phase A 0.1% formic acid in water and mobile phase B 0.1% formic acid in acetonitrile using a gradient, delivered at a flow rate of 0.3 mL/min. The total run time was 15 min (31). Ionization was determined using electrospray in the positive ionization mode. Curcumin was monitored in the multiple reaction monitoring (MRM) mode. The MRM transition for curcumin was m/z 369 \rightarrow 285. Concentrations of metabolites were quantified using an authentic standard curve and normalized to the protein concentration of the homogenate.

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Table S1 Gradient (linear)

Time (min)	Flow rate (mL/min)	%A	%B
Initial	0.350	75	25
0.25	0.350	75	25
1.50	0.350	2	98
3.00	0.350	2	98
3.50	0.350	75	25
5.00	0.350	75	25