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REVIEW

Relationship and interactions of curcumin with radiation therapy

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Abstract

Curcumin is widely reported to have remarkable medicinal - and antineoplastic - properties. This review details curcumin's relationship with radiotherapy (RT), principally as a radiosensitizer for various malignancies and a radioprotector for normal tissues. First, examples of radiosensitization are provided for various cancers: Pediatric, lymphoma, sarcoma, prostate, gynecologic, pancreas, liver, colorectal, breast, lung, head/neck, and glioma. It is not the purpose of this article to comprehensively review all radiosensitization data; however, high-quality studies are discussed in relationship to currently-controversial RT questions for many cancers, and thus the importance of developing a natural radiosensitizer. Attention is then shifted to radioprotection, for which supporting research is discussed for the following RT toxicities: Dermatitis, pneumonitis, cataractogenesis, neurocognition, myelosuppression, secondary malignancies, and mucositis/enteritis. Though there is fewer data for radioprotection, the overall quality of clinical evidence is higher, and small clinical trials implicating the efficacy of curcumin for RT toxicities (*vs* placebo/current therapies) are also detailed. Though the overall level of evidence for curcumin as a radiosensitizer and radioprotector is low, it must be recognized that risks of adverse effects are exceedingly low, and clinicians may need to judge the yet-unproven rewards with low toxicity risks.

Key words: Curcumin; Turmeric; Radiation therapy; Cancer; Radioprotection; Radiosensitization

Core tip: The Indian spice curcumin (turmeric) has been widely reported, largely in the preclinical realm, to offer many health - including antineoplastic - benefits. Though this article is not meant as a summative review of all studies of curcumin and radiotherapy, selected studies will be discussed that demonstrate curcumin to be a radiosensitizer of many types of tumor cells. Furthermore, data illustrating curcumin as a radioprotector of normal organs - including clinical studies - are also described. It is a sincere hope that these promising results can lead to curcumin use in cancer patients, either on or off a clinical protocol.

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INTRODUCTION

The Indian spice curcumin (also known as diferuloylmethane), extracted from the turmeric plant, has long held a role in Indian/Hindu rituals, traditions, customs, and cuisines. More recently, scientific evidence is mounting that curcumin offers innumerable health benefits (reviewed in multiple sources[1-4]), all stemming from the fundamental property of decreasing inflammatory mediators[5]. This leads hope to curb the unchecked progression of fundamentally inflammatory diseases[6], many of which are considered the scourge of medicine in the present day and age. Moreover, curcumin is a completely natural compound with essentially no side effects; tolerance in phase I clinical trials have shown no medically adverse effects for doses up to 8-12 g orally per day[7].

Cancer is a common conglomeration of diseases that can be termed as a "bane of healthcare" throughout the world, and affects hundreds of millions of persons throughout the world per year. Extensive work has been performed on curcumin's immense anti-cancer potential, which have been grossly underappreciated, largely owing to the notable roadblock of few clinical studies to date[8-13]. The phase I-II clinical trials that have been performed, however, have done nothing to dissuade further clinical study of this compound[14-16].

Primary management of cancer centers on various combinations of surgery, chemotherapy, and radiation therapy (RT). A comprehensive discussion of curcumin's effects on chemotherapy and surgical intervention is extremely broad and clearly beyond the scope of this article; rather, curcumin's interactions with RT will be evaluated. Additionally, though it is not the goal of this article to comprehensively and systematically detail all data of the curcumin-RT relationship[17,18], selected examples of curcumin's (1) radiosensitization ability and (2) radioprotective ability, will be enumerated in order to characterize the sheer breadth of curcumin's actions along with RT on cancer. The goal of this article, in turn, is to encourage clinicians to (1) commence clinical trials related to curcumin; and/or more importantly; (2) encourage their patients to routinely take curcumin for cancer therapy (despite a general dearth of solid data).

RADIOSENSITIZATION BY CURCUMIN

There is a well-charted history of radiosensitizers, defined as molecular compounds that act to functionally amplify radiation-induced DNA and cellular damage, regardless of whether the compounds cause damage individually[19]. Though several radiosensitizers are used in cancer care today, such as platinum-based chemotherapeutic agents, the focus of this section is to describe many examples of curcumin as a radiosensitizer. The reader is first cautioned that nearly all evidence of radiosensitization comes from laboratory data, and clinically-apparent benefits of curcumin as a radiosensitizer are yet to be determined.

First, attention will be paid to pediatric, lymphoma, and musculoskeletal cancers. Why are these important? Clinically speaking, the fields of pediatric and lymphoma RT have undergone - and are undergoing - dramatic decreases in RT doses, so as to minimize secondary malignancy risk and ancillary procedures in the younger population[20-22]. The presence of a radiosensitizing agent, if proven clinically efficacious, would certainly aid the movement to de-escalate RT doses in this population. Sarcomas (many of which occur in children) are a logical extension for curcumin therapy, given its success in musculoskeletal inflammatory-based disorders[23]. As previously mentioned, inhibition of the transcription factor NF-κB is a primary mode of action of curcumin, which act to mediate various anti-inflammatory effects for various diseases[24]. However, what is often an overlooked fact between inflammatory diseases and cancer is that NF-κB has been widely implicated in both tumorigenesis and radioresistance[24]. Hence, results of pre-RT curcumin intake leading to radiosensitization in murine rhabdomyosarcoma models are not surprising in light of suppressing NF-κB[25]. These results have been echoed in neuroblastoma cells in a high-quality study by Aravindan *et al*[26]. However, the diverse pathways of curcumin's actions are not limited to this transcription factor; the same group studied mutant p53 Ewing's sarcoma cells, and radiosensitivity was found to be associated with other p53-response genes (despite the p53-mutated nature of the studied cells)[27]. There are also data to support the NF-κB suppression theory as means for radiosensitization in lymphomas, which are important in light of resistance to biologic therapies for some types of lymphomas[28]. Though RT is not the centerpiece of therapy for Burkitt's lymphoma, there are data supporting radiosensitization in this otherwise aggressive lymphoma[29]. The same group did demonstrate another interesting mechanism of radiosensitization in non-Hodgkin's lymphoma (which constitute large proportions of lymphomas treated with RT)[30]. The authors found that cell cycle arrest in the G2-M checkpoint was associated with curcumin administration, which is a normal effect of irradiating tumor cells and is hence presumably augmented by curcumin.

Shifting to genitourinary cancers, dose-escalation for prostate cancer (the most common genitourinary malignancy) is strongly proven to associate with improved outcomes[31], and hence great emphasis is placed on using high-fidelity imaging technology to guide RT planning/delivery[32,33]. Radiosensitization for these tumors could thus allow for "functional dose escalation", providing even greater tumor doses while

keeping a constant prescribed RT dose. Two convincing preclinical studies demonstrated the radiosensitizing effects of curcumin on the human prostate cancer cell line PC3. Chendil *et al*[34] postulated the mechanism to be related to NF-κB and found threefold fewer surviving PC3 cells when treated with both RT and curcumin. However, another report found another novel pathway of action, downregulation of the MDM2 oncogene (a p53-independent pathway), which provide encouragement that spontaneous mutagenesis in cancer cells could be less likely to cause multi-drug resistance affecting curcumin[35].

Next, data is not limited to the male genitourinary system, with one report demonstrating increased reactive oxygen species formation in cervical cancer cells with the addition of curcumin[36]. Similar to the aforementioned report on cell cycle arrest[30], this is a normal effect of RT that curcumin seems to augment. Lastly, though RT is not routinely utilized for ovarian neoplasms, a group at the University of South Dakota conjugated curcumin nanoparticles to an ovarian cancer-specific antibody and elicited both chemo- and radiosensitization phenomena[37]. Though the issue of curcumin delivery is beyond the scope of this review, it will briefly be addressed in the final section, and this study's use of nanoparticles is hence quite noteworthy.

Though gastrointestinal tumors are inherently very heterogeneous and diverse, brief examples for several tumor types are united by the overarching theme of NF-κB suppression by curcumin, despite any rises that could occur after a RT fraction. Again, this transcription factor is widely purported to relate to radioresistance, and the studies discussed hereafter in this paragraph will demonstrate sustained cellular killing, potentially as a result of decreased radioresistance. First, though pancreatic cancer is one of the deadliest known neoplasms, data have shown enhanced cell killing with five-fraction RT[38] especially as delivered by Veeraraghavan *et al*[39]. However, it is important to be skeptical of results insofar as questioning whether curcumin administration could be a panacea for a disease with dismal prognosis from aggressive tumor biology and high metastatic proclivity. The same criticism is true for similar results recently published on hepatocellular carcinoma, which also demonstrated NF-κB downregulation as a putative mechanism[40]. Lastly, curcumin may be a relatively good candidate to clinically sensitize colorectal cancer (the most common gastrointestinal malignancy) to RT. Two high-impact publications from M.D. Anderson Cancer Center also implicated NF-κB modulation - although its expression rises after RT - as an effector of curcumin[41,42]. There were several additional effects of note as measured by the authors. First, not only were proliferation markers downregulated, angiogenesis was decreased as well. Though this effect could result in decreased nutrients feeding the tumor (thus augmenting cell killing), potential decreases in tumor oxygenation could be problematic, as this is strongly related to tumor radioresistance. Importantly, this study also demonstrated decrease in matrix metalloproteinase (MMP) expression. This enzyme is thought to be a gateway for metastasis, by dissolving bonds to extracellular matrix (an "anchor" preventing dissemination) as well as promoting an overall microenvironment for growth and spread[43]. Hence, after RT the upregulation (presumably nonsustained) in NF-κB and MMP lead to some degree of increased risk for radioresistance (persistent growth) and spread[44]. Curcumin may hence act to decrease this risk, and it would certainly be helpful to examine tumor growth and metastasis from a clinical perspective to examine whether decreased NF-κB and MMP expression translate into "clinical gains".

Moving to neoplasms of the thorax, breast cancer is the most common noncutaneous cancer in the United States; RT is a major part of management, including several different techniques and RT modalities[45-49]. One example of breast cancer radiosensitization with curcumin was shown by Calaf *et al*[50]. The most important observation of this study was increased amounts of cleaved (inactive) PARP-1, a protein known to repair DNA after RT damage and thus attenuate RT damage[51]. There is an enormous amount of current research being done on PARP inhibitors, including multiple phase Ⅱ and Ⅲ clinical trials. If further results can corroborate the association between cleavage/inactivation of PARP by curcumin, these could have substantial implications on this burgeoning field.

Lung cancer, most commonly non-small cell lung cancer (NSCLC), is another common and deadly tumor[52,53] for which screening has recently been instituted[54-56]. A radiosensitizer would therefore be a welcome addition to recently-developed and cutting-edge RT technologies used for treatment of some NSCLCs[57]. Two important studies in NSCLC will be highlighted. A group from the University of Pennsylvania claimed a survival improvement with dietary curcumin administration along with RT, although there are several methodological flaws precluding reliability of these data[58]. More importantly, however, that dietary curcumin was able to cause clinical effect in the murine model is encouraging, because bioavailability remains a challenge of curcumin (further discussed in a subsequent section). In light of this fact, another research group utilizing liposomal curcumin was able to demonstrate potentiated NSCLC cell apoptosis with the presence of curcumin, and additionally found greater evidence of post-RT microvascular change, which (though uncorroborated) could be a surrogate marker for greater tumoral RT damage[59].

Regarding the diverse head and neck cancers, more common in Southern and Eastern Asia than the United States, treatment centers are on RT for the vast majority. Furthermore, cisplatin (administered concurrently with RT in select patients) has proven to be a radiosensitizer, increasing local tumor control in large randomized trials[60,61]. However, cisplatin's amplification of adverse RT toxicities beckons whether

the lack thereof with curcumin could prove to be a helpful utility[62]. Since an initial publication describing curcumin's ability to radiosensitize head and neck tumor cells *in vitro* and *in vivo*[63], another demonstrated the mechanism to be NF-κB - consistent with mechanistic relationships of curcumin on multiple aforementioned neoplasms[64]. Next, it is also worth mentioning another study of curcumin in nasopharyngeal carcinoma, in which greater amounts of cleaved PARP were discovered[65]. This is consistent with results for malignant breast carcinoma cells in a previously discussed study[50]. However, the most thought-provoking results were published by Tuttle *et al*[66] who illustrated that curcumin offers radiosensitization to head and neck malignancies that were human papillomavirus (HPV)-negative but not HPV^+. Ever since it was published in 2010 that HPV^+ oropharyngeal cancers had substantially better prognoses[67], a major focus of upcoming trials has been to determine whether de-escalation of therapy is feasible for HPV^+ tumors[68]. Though it is counterintuitive that curcumin did not radiosensitize HPV^+ tumors - they are vastly more sensitive to RT - it is in fact important that the HPV-negative neoplasms (worse prognosis) could be favorably addressed by curcumin and RT, if proven clinically efficacious.

Lastly, application of curcumin radiosensitization in gliomas will be briefly touched upon. Although a report posited G2-M cell cycle arrest as a mechanism[69], other data has displayed synergism of curcumin with an anti-glioblastoma antibody, including sustained NF-κB suppression[70]. This is noteworthy because biologics are at the forefront of oncologic therapy, and are already approved for relapsed glioblastoma[71]. Though it may be unlikely that simple administration of curcumin could curb the aggressive spread of glioblastoma, it rather provides hope that a clinical difference could be gleaned with curcumin for less aggressive neoplasms.

In summary, there is a great breadth of corroboratory data for many different tumor types available that demonstrate the radiosensitizing potential of curcumin. It is likely that other untested tumor types could likely show similar radiosensitization in laboratory models[72-77]. Though there has been no documentation to date in patients, encouragement does exist that there could be small observed differences in outcomes (with appropriate sample sizes), and even if there are no changes in survival parameters, recurrence rates and local control (a prime marker of radiosensitization) could be affected if eventually tested in the clinic.

RADIOPROTECTION BY CURCUMIN

Though radiosensitization is important to enhance tumor death, equally important is toxicity minimization of normal tissues, the pursuit of which is one of the most prime goals of radiation oncology. Though the evidence for curcumin's radioprotection is less diverse/broad as compared to radiosensitization, the overall quality and applicability of data to human patients is noticeably greater. In this section, focus will be on curcumin's benefits against the following common RT toxicities: Dermatitis, pneumonitis, cataractogenesis, neurocognition, myelosuppression, secondary tumors, and mucositis/enteritis. Many of these toxicities are inflammatory in nature, so it intuitively follows that curcumin's potent anti-inflammatory effects[1,3,4,6] could lessen these inflammatory toxicities, likely through decreased inflammatory molecule production[5] as well as increasing the balance of antioxidants to oxidants[78].

RT dermatitis is one of the most common adverse effects of RT regardless of anatomic area, and two high-quality studies are as follows. Okunieff *et al*[79] documented reduction in both acute and chronic RT dermatitis in mice. This correlated with decreased levels of proinflammatory cytokines as well as subsequently-released fibrogenic cytokines such as TGF-β. Though a criticism of the study is the utilization of a single 50 Gray RT dose (extremely rare in humans), the radioprotection was consistent with another study that showed improved irradiated wound healing with curcumin[80]. The second major piece of evidence is a randomized and double-blinded trial of oral (2.0 g thrice daily) curcumin tablets (n = 14) *vs* placebo (n = 16) in breast cancer RT[81]. Patients were equal in terms of demographics, receipt of chemotherapy, surgery type, stage, RT dose, and baseline skin and pain assessment. A RT dermatitis standardized scale was the primary endpoint and favored curcumin (P = 0.008) along with decreased moist desquamation in the curcumin group (P = 0.002). There were largely no differences in patient-reported pain scores. This trial provides the highest level of evidence offering real hope that curcumin can have clinically significant impact on radiotoxicity, and it should secondarily not be discounted that the study was able to obtain statistically significant differences between groups despite randomizing only thirty patients.

Radiation pneumonitis has been extensively studied and well-validated to several RT dose-volume parameters; hence, it is a major focus of RT treatment planning especially because severe RT pneumonitis can be fatal[82-84]. Two studies demonstrating radioprotection against RT pneumonitis and its delayed sequela - pulmonary fibrosis - have already been discussed in the radiosensitization section[60,61] and corroborated by another report[85]. All three studies have shown, mechanistically, that curcumin's action is due to decreasing oxidative stress, proinflammatory cytokines, NF-κB expression, and fibrogenic cytokines - all of which tend to occur both simultaneously and sequentially. Undoubtedly, the presence of a lung radioprotector, if clinically proven, would be of great use to the ubiquitous NSCLC patients, many of which have risk factors for RT pneumonitis such as baseline lung disease and receipt of concurrent carboplatin-paclitaxel[86].

Two small studies examining central nervous system adverse effects of RT will now be addressed. Ozgen *et al*[87] examined cataractogenesis, a late toxicity that was hastened in the study by giving high single-

fraction doses to the lens (a relatively uncommon clinical scenario). Irradiation with curcumin lowered the cataract rate from 100% to 40%, correlating with lower levels of oxidative stress. Next, substantial ongoing research (and clinical trials) in radiation oncology relates to whether patients with primary or secondary brain tumors that undergo brain irradiation could be spared of its resulting memory/cognitive decline[88,89]. Curcumin is widely thought to be neuroprotective; its high consumption is associated with minimal rates of several neurodegenerative diseases in India, which is backed by convincing experimental evidence of such[90]. Pre-RT administration of curcumin was able to improve results in post-RT spatial/memory functional tests (Morris water maze) in mice administered carbon ion RT (high biologically effective dose owing to the heavy particle size)[91]. Furthermore, histologically-apparent neuropathological changes were also present between both groups. Hence, if other research can confirm these results, it will not be difficult to design clinical trials examining learning/memory tests in patients undergoing whole-brain RT with or without curcumin.

Curcumin can also protect lymphocytes, the most RT-susceptible blood cell, especially when radiating bony lesions (marrow) in patients[92]. The authors postulated that curcumin's actions could consist of radiosensitization or radioprotection, with the latter observed in non-cycling cells (in G0 phase) and the former in cycling cells (G2 transitioning to M phase), which is a theory that could sum up all the radioprotective and radiosensitizing data in this entire review.

Japanese researchers published an impactful article in 2002 demonstrating that rats undergoing whole body irradiation (dose of 9.6 Gray) - simulating a natural disaster such as Chernobyl - produced lower levels of an oxidant metabolite if fed curcumin pre- and post-RT, as compared to control rats[93]. Furthermore, post-exposure implantation of the carcinogen diethylstilbestrol led to significantly more secondary tumors in rats not having been administered curcumin. The results lead to query as to whether curcumin could directly prevent further mutations, but data for this is scant at best. Nevertheless, there is more evidence to support that curcumin lowers circulating reactive oxygen species (oxidative stress), which are normally known to cause DNA mutations (*i.e.,* how ionizing radiation causes DNA damage in cancer cells).

Lastly, owing to the relatively high proliferative index of mucosal cells, any mucosal surface is particularly sensitive and susceptible to acute and chronic RT-induced damage[94-96]. A Turkish study demonstrated that intestinal mucosa was protected to a greater degree in rats fed curcumin, as detected histopathologically[97]. These results, especially if validated, are important for three major reasons: (1) bowel toxicity is relatively common and may occur at any point of the RT course (even well-below the bowel tolerance dose); (2) parts of the bowel receive RT dose for several common (*e.g.,* prostate, gastrointestinal, gynecologic, and some palliative/pediatric) cancers; and (3) because curcumin is poorly absorbed in the gastrointestinal tract, it remains in direct contact with intestinal mucosa and hence could directly act on mucosal cells.

Next, another large area of morbidity in irradiated patients is mucositis of the soft tissues of the head and neck, some of which can be so severe that it necessitates feeding tube placement due to lack of oral feeding[98]. In 2004, a publication demonstrated a clinically evident decrease in oral mucosal ulceration in rats fed curcumin[99]. However, this issue remained untranslated into the clinical realm until Indian researchers published a study in 2013[100]. In this single-blinded and randomized trial, patients with mostly oral cavity/pharyngeal neoplasms undergoing RT (with or without surgery and chemotherapy) were given oral rinses of turmeric (n = 40) or povidone-iodine (n = 39) to take six and two times per day respectively. Tumor characteristics and treatment interventions (including RT dose and chemotherapy receipt) were balanced between groups. The group receiving curcumin was less likely to receive treatment breaks in the initial (< 4 wk) period (P < 0.01) and displayed decreased weight loss (P < 0.001). Though incidence of overall mucositis did not differ between groups, the curcumin group experienced lesser intolerable mucositis (P < 0.0001) as well as decreased severity of overall mucositis as per Radiation Therapy Oncology Group criteria (P < 0.003). Though povidone-iodine is uncommonly used for RT mucositis, similar agents (*e.g.,* lidocaine, chlorhexidine) used more often are likely no different because they are designed to treat symptoms rather than causative molecular inflammatory agents as curcumin does.

Another recent clinical protocol by Patil *et al*[101] will now be expounded upon. Twenty patients, mostly with oral cavity/pharyngeal cancer that received concurrent chemoradiation, received either chlorhexidine (n = 10) or 0.004% curcumin oral rinse (n = 10) thrice daily during RT. Patient and tumor characteristics, including chemotherapy receipt and RT dose, were underreported but equivalent between groups. Outcomes included a prespecified numerical pain score, oral mucositis assessment scales for erythema and ulceration, and the World Health Organization (WHO) mucositis scale. Most of these parameters were favorable for the curcumin group (P < 0.001 for pain, P = 0.05 for erythema, P < 0.001 for ulceration, and P = 0.003 for WHO mucositis). Though the methodology of this trial was less sound as compared to the aforementioned dermatitis trial[81], it should again be mentioned that a statistically significant difference was found despite the comparison of only ten patients in each group.

Taken together, there are greater clinical data available to support the use of curcumin as a radioprotector of normal tissues, especially epithelial tissues, potentially owing to direct contact with at-risk surfaces. Curcumin's mechanisms seem associated with decreased

oxidative stress in normal tissues.

CONCLUSION

A substantial volume of evidence exists that curcumin is a radiosensitizer of multiple cancers as well as a radioprotector of several normal tissues. However, the overall quality of evidence is low; there is no clinical evidence of radiosensitization and a few low-volume clinical trials of radioprotection published thus far. However, there is certainly something to be said about the sheer volume of corroborative positive data, particularly in radioprotection.

What do the aforementioned litany of laboratory and clinical studies mean for the clinician? On one hand, clinical evidence is weak, and there is no guarantee curcumin would provide a clinical difference in outcomes (*e.g.,* survival, local/regional recurrence). On the other hand, as previously discussed, curcumin administration has exceedingly low chances to produce adverse effects; empiric administration without solid clinical evidence will likely not harm the patient whatsoever.

Further research is greatly needed to strengthen curcumin's major weakness - poor gastrointestinal absorption leading to low oral bioavailability. After absorption in the gastrointestinal tract *via* a liposomal mechanism, four double bonds are reduced, followed by glucuronidation/sulfation and excretion through bile[102-104]. Several discussed studies[37,59], as well as undiscussed studies in other diseases[23], have used special formulations (*e.g.,* liposomal, intravenous, molecular analogs, and conjugated forms such as Meriva® and Theracurmin®) which could become more mainstream in the future with more research.

A subsequent question, then, is whether to administer curcumin therapeutically as in these studies, or preventatively - long prior to any therapy - or even prophylactically prior to any disease onset. These questions should likely be addressed after basic clinical efficacy/utility issues, so as to provide more solid footing on curcumin use. Although not the purpose of this article to provide recommendations of curcumin administration to clinicians, it is certainly encouraged to consider that in light of immature but still broadly corroborative data (including clinical studies), curcumin is extremely safe and not harmful to the cancer patient undergoing radio(chemo)therapy.

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