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**Relationship and interactions of curcumin with radiation therapy**

Verma V. Curcumin and radiotherapy

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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

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**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[20,21]. 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[22]. 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[23]. 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[23]. Hence, results of pre-RT curcumin intake leading to radiosensitization in murine rhabdomyosarcoma models are not surprising in light of suppressing NF-κB[24]. These results have been echoed in neuroblastoma cells in a high-quality study by Aravindan *et al*[25]. 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)[26]. 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[27]. Though RT is not the centerpiece of therapy for Burkitt’s lymphoma, there are data supporting radiosensitization in this otherwise aggressive lymphoma[28]. The same group did demonstrate another interesting mechanism of radiosensitization in non-Hodgkin’s lymphoma (which constitute large proportions of lymphomas treated with RT)[29]. 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[30], and hence great emphasis is placed on using high-fidelity imaging technology to guide RT planning/delivery[31,32]. 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*[33] postulated the mechanism to be related to NF-κB and found threefold fewer surviving PC3 cells when treated with both RT and curcumin[33]. 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[34].

Next, data is not limited to the male genitourinary system, with one report demonstrating increased reactive oxygen species formation in tumor cells with the addition of curcumin[35]. Similar to the aforementioned report on cell cycle arrest[29], 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[36]. 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 as delivered by Veeraraghavan *et al*[37]. 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[38]. 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[39,40]. 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[41]. 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[42]. 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[43-45]. One example of breast cancer radiosensitization with curcumin was shown by Calaf *et al*[46]. 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[47]. 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[48,49] for which screening has recently been instituted[50-52]. A radiosensitizer would therefore be a welcome addition to recently-developed and cutting-edge RT technologies used for treatment of some NSCLCs[53]. 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[54]. 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[55].

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[56,57]. However, cisplatin’s amplification of adverse RT toxicities beckons whether the lack thereof with curcumin could prove to be a helpful utility. Since an initial publication describing curcumin’s ability to radiosensitize head and neck tumor cells *in vitro* and *in vivo*[58], another demonstrated the mechanism to be NF-κB – consistent with mechanistic relationships of curcumin on multiple aforementioned neoplasms[59]. Next, it is also worth mentioning another study of curcumin in nasopharyngeal carcinoma, in which greater amounts of cleaved PARP were discovered[60]. This is consistent with results for malignant breast carcinoma cells in a previously discussed study[46]. However, the most thought-provoking results were published by Tuttle *et al*[61] 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[62], a major focus of upcoming trials has been to determine whether de-escalation of therapy is feasible for HPV+ tumors[63]. 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[64], other data has displayed synergism of curcumin with an anti-glioblastoma antibody, including sustained NF-κB suppression[65]. This is noteworthy because biologics are at the forefront of oncologic therapy, and are already approved for relapsed glioblastoma[66]. 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[67-72]. 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[73]

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*[74] 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[75]. 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[76]. 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[77-79]. Two studies demonstrating radioprotection against RT pneumonitis and its delayed sequela – pulmonary fibrosis – have already been discussed in the radiosensitization section[54,55] and corroborated by another report[80]. 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[81].

Two small studies examining central nervous system adverse effects of RT will now be addressed. Ozgen *et al*[82] 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[83]. 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[84]. 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)[85]. 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[86]. 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[87]. 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[88,89]. A Turkish study demonstrated that intestinal mucosa was protected to a greater degree in rats fed curcumin, as detected histopathologically[90]. 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[91]. In 2004, a publication demonstrated a clinically evident decrease in oral mucosal ulceration in rats fed curcumin[92]. However, this issue remained untranslated into the clinical realm until Indian researchers published a study in 2013[93]. 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*[94] 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[76], 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[95-97]. Several discussed studies[36,55], as well as undiscussed studies in other diseases[22], 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.

**REFERENCES**

1 **Aggarwal BB**, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. *Adv Exp Med Biol* 2007; **595**: 1-75 [PMID: 17569205 DOI: 10.1007/978-0-387-46401-5\_1]

2 **Pari L**, Tewas D, Eckel J. Role of curcumin in health and disease. *Arch Physiol Biochem* 2008; **114**: 127-149 [PMID: 18484280 DOI: 10.1080/13813450802033958]

3 **Jurenka JS**. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. *Altern Med Rev* 2009; **14**: 141-153 [PMID: 19594223]

4 **Gupta SC**, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J* 2013; **15**: 195-218 [PMID: 23143785 DOI: 10.1208/s12248-012-9432-8]

5 **Singh S**, Aggarwal BB. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane) [corrected]. *J Biol Chem* 1995; **270**: 24995-25000 [PMID: 7559628 DOI: 10.1074/jbc.270.42.24995]

6 **Shehzad A**, Rehman G, Lee YS. Curcumin in inflammatory diseases. *Biofactors* 2013; **39**: 69-77 [PMID: 23281076 DOI: 10.1002/biof.1066]

7 **Cheng AL**, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, Ko JY, Lin JT, Lin BR, Ming-Shiang W, Yu HS, Jee SH, Chen GS, Chen TM, Chen CA, Lai MK, Pu YS, Pan MH, Wang YJ, Tsai CC, Hsieh CY. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res* 2001; **21**: 2895-2900 [PMID: 11712783]

8 **Aggarwal BB**, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res* 2003; **23**: 363-398 [PMID: 12680238]

9 **Duvoix A**, Blasius R, Delhalle S, Schnekenburger M, Morceau F, Henry E, Dicato M, Diederich M. Chemopreventive and therapeutic effects of curcumin. *Cancer Lett* 2005; **223**: 181-190 [PMID: 15896452 DOI: 10.1016/j.canlet.2004.09.041]

10 **Shishodia S**, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Curr Probl Cancer* 2007; **31**: 243-305 [PMID: 17645940 DOI: 10.1016/j.currproblcancer.2007.04.001]

11 **Anand P**, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett* 2008; **267**: 133-164 [PMID: 18462866 DOI: 10.1016/j.canlet.2008.03.025]

12 **Tuorkey MJ**. Curcumin a potent cancer preventive agent: Mechanisms of cancer cell killing. *Interv Med Appl Sci* 2014; **6**: 139-146 [PMID: 25598986 DOI: 10.1556/IMAS.6.2014.4.1]

13 **Shanmugam MK**, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed ME, Alharbi SA, Tan BK, Kumar AP, Sethi G. The multifaceted role of curcumin in cancer prevention and treatment. *Molecules* 2015; **20**: 2728-2769 [PMID: 25665066 DOI: 10.3390/molecules20022728]

14 **Thomas R**, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer--the U.K. NCRN Pomi-T study. *Prostate Cancer Prostatic Dis* 2014; **17**: 180-186 [PMID: 24614693 DOI: 10.1038/pcan.2014.6]

15 **Panahi Y**, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. *Phytother Res* 2014; **28**: 1625-1631 [PMID: 24853120 DOI: 10.1002/ptr.5174]

16 **Dhillon N**, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, Abbruzzese JL, Ng CS, Badmaev V, Kurzrock R. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res* 2008; **14**: 4491-4499 [PMID: 18628464 DOI: 10.1158/1078-0432.CCR-08-0024]

17 **Jagetia GC**. Radioprotection and radiosensitization by curcumin. *Adv Exp Med Biol* 2007; **595**: 301-320 [PMID: 17569217 DOI: 10.1007/978-0-387-46401-5\_13]

18 **Goel A**, Aggarwal BB. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. *Nutr Cancer* 2010; **62**: 919-930 [PMID: 20924967 DOI: 10.1080/01635581.2010.509835]

19 **Brown JM**. Sensitizers and protectors in radiotherapy. *Cancer* 1985; **55**: 2222-2228 [PMID: 2983876]

20 **O'Brien MM**, Donaldson SS, Balise RR, Whittemore AS, Link MP. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dose radiation and chemotherapy. *J Clin Oncol* 2010; **28**: 1232-1239 [PMID: 20124178 DOI: 10.1200/JCO.2009.24.8062]

21 **Verma V,** Beethe AB, LeRiger M, Kulkarni RR, Zhang M, Lin C. Anesthesia complications of pediatric radiation therapy. *Pract Radiat Oncol* 2015; **31**: S1879-8500(15)00394-X [PMID: 26725960 DOI: 10.1016/j.prro.2015.10.018]

22 **Peddada KV**, Peddada KV, Shukla SK, Mishra A, Verma V. Role of Curcumin in Common Musculoskeletal Disorders: a Review of Current Laboratory, Translational, and Clinical Data. *Orthop Surg* 2015; **7**: 222-231 [PMID: 26311096 DOI: 10.1111/os.12183]

23 **Aggarwal BB**. Nuclear factor-kappaB: the enemy within. *Cancer Cell* 2004; **6**: 203-208 [PMID: 15380510 DOI: 10.1016/j.ccr.2004.09.003]

24 **Orr WS**, Denbo JW, Saab KR, Ng CY, Wu J, Li K, Garner JM, Morton CL, Du Z, Pfeffer LM, Davidoff AM. Curcumin potentiates rhabdomyosarcoma radiosensitivity by suppressing NF-κB activity. *PLoS One* 2013; **8**: e51309 [PMID: 23408929 DOI: 10.1371/journal.pone.0051309]

25 **Aravindan N**, Veeraraghavan J, Madhusoodhanan R, Herman TS, Natarajan M. Curcumin regulates low-linear energy transfer γ-radiation-induced NFκB-dependent telomerase activity in human neuroblastoma cells. *Int J Radiat Oncol Biol Phys* 2011; **79**: 1206-1215 [PMID: 21236599 DOI: 10.1016/j.ijrobp.2010.10.058]

26 **Veeraraghavan J**, Natarajan M, Herman TS, Aravindan N. Curcumin-altered p53-response genes regulate radiosensitivity in p53-mutant Ewing's sarcoma cells. *Anticancer Res* 2010; **30**: 4007-4015 [PMID: 21036715]

27 **Zhao Z**, Verma V, Zhang M. Anaplastic lymphoma kinase: Role in cancer and therapy perspective. *Cancer Biol Ther* 2015; **16**: 1691-1701 [PMID: 26529396 DOI: 10.1080/15384047.2015.1095407]

28 **Qiao Q**, Jiang Y, Li G. Inhibition of the PI3K/AKT-NF-κB pathway with curcumin enhanced radiation-induced apoptosis in human Burkitt's lymphoma. *J Pharmacol Sci* 2013; **121**: 247-256 [PMID: 23603894]

29 **Qiao Q**, Jiang Y, Li G. Curcumin enhances the response of non-Hodgkin's lymphoma cells to ionizing radiation through further induction of cell cycle arrest at the G2/M phase and inhibition of mTOR phosphorylation. *Oncol Rep* 2013; **29**: 380-386 [PMID: 23117293 DOI: 10.3892/or.2012.2091]

30 **Zaorsky NG**, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. *Radiother Oncol* 2015; **115**: 295-300 [PMID: 26028229 DOI: 10.1016/j.radonc.2015.05.011]

31 **Garsa AA**, Verma V, Michalski JM, Gay HA. Transperineal ultrasound-guided implantation of electromagnetic transponders in the prostatic fossa for localization and tracking during external beam radiation therapy. *Pract Radiat Oncol* 2014; **4**: 415-421 [PMID: 25407864 DOI: 10.1016/j.prro.2014.01.004]

32 **Verma V**, Chen L, Michalski JM, Hu Y, Zhang W, Robinson K, Verma S, Eschen L, Fergus S, Mullen D, Strope S, Grubb R, Gay HA. Evaluation of 3 T pelvic MRI imaging in prostate cancer patients receiving post-prostatectomy IMRT. *World J Urol* 2015; **33**: 69-75 [PMID: 24647879 DOI: 10.1007/s00345-014-1269-6]

33 **Chendil D**, Ranga RS, Meigooni D, Sathishkumar S, Ahmed MM. Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogene* 2004; **23**: 1599-1607 [PMID: 14985701 DOI: 10.1038/sj.onc.1207284]

34 **Li M**, Zhang Z, Hill DL, Wang H, Zhang R. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. *Cancer Res* 2007; **67**: 1988-1996 [PMID: 17332326 DOI: 10.1158/0008-5472.CAN-06-3066]

35 **Javvadi P**, Segan AT, Tuttle SW, Koumenis C. The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. *Mol Pharmacol* 2008; **73**: 1491-1501 [PMID: 18252805 DOI: 10.1124/mol.107.043554]

36 **Yallapu MM**, Maher DM, Sundram V, Bell MC, Jaggi M, Chauhan SC. Curcumin induces chemo/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth. *J Ovarian Res* 2010; **3**: 11 [PMID: 20429876 DOI: 10.1186/1757-2215-3-11]

37 **Veeraraghavan J**, Natarajan M, Lagisetty P, Awasthi V, Herman TS, Aravindan N. Impact of curcumin, raspberry extract, and neem leaf extract on rel protein-regulated cell death/radiosensitization in pancreatic cancer cells. *Pancreas* 2011; **40**: 1107-1119 [PMID: 21697760 DOI: 10.1097/MPA.0b013e31821f677d]

38 **Hsu FT**, Liu YC, Liu TT, Hwang JJ. Curcumin Sensitizes Hepatocellular Carcinoma Cells to Radiation via Suppression of Radiation-Induced NF-κB Activity. *Biomed Res Int* 2015; **2015**: 363671 [PMID: 26539482 DOI: 10.1155/2015/363671]

39 **Kunnumakkara AB**, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB, Krishnan S. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin Cancer Res* 2008; **14**: 2128-2136 [PMID: 18381954 DOI: 10.1158/1078-0432.CCR-07-4722]

40 **Sandur SK**, Deorukhkar A, Pandey MK, Pabón AM, Shentu S, Guha S, Aggarwal BB, Krishnan S. Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-kappaB activity. *Int J Radiat Oncol Biol Phys* 2009; **75**: 534-542 [PMID: 19735878 DOI: 10.1016/j.ijrobp.2009.06.034]

41 **Chambers AF**, Matrisian LM. Changing views of the role of matrix metalloproteinases in metastasis. *J Natl Cancer Inst* 1997; **89**: 1260-1270 [PMID: 9293916 DOI: 10.1093/jnci/89.17.1260]

42 **Barker HE**, Paget JT, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer* 2015; **15**: 409-425 [PMID: 26105538 DOI: 10.1038/nrc3958]

43 **National Comprehensive Cancer Network**. Breast Cancer. 2016-01-06. Available from: URL: http//www.nccn.org/professionals/physician\_gls/pdf/breast.pdf

44 **Vargo JA**, Verma V, Kim H, Kalash R, Heron DE, Johnson R, Beriwal S. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. *Int J Radiat Oncol Biol Phys* 2014; **88**: 285-291 [PMID: 24268787 DOI: 10.1016/j.ijrobp.2013.05.039]

45 **Shah C**, Khan A, Arthur D, Wazer D, Mantz C, Verma V, Vicini F. Regional Nodal Irradiation: Examining the Clinical Implications of Randomized Trials. *Am J Clin Oncol* 2016; **39**: 90-91 [PMID: 26600011 DOI: 10.1097/COC.0000000000000250]

46 **Calaf GM**, Echiburú-Chau C, Wen G, Balajee AS, Roy D. Effect of curcumin on irradiated and estrogen-transformed human breast cell lines. *Int J Oncol* 2012; **40**: 436-442 [PMID: 21993423 DOI: 10.3892/ijo.2011.1228]

47 **Curtin N**. PARP inhibitors for anticancer therapy. *Biochem Soc Trans* 2014; **42**: 82-88 [PMID: 24450632 DOI: 10.1042/BST20130187]

48 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]

49 **Verma V**, Talmon GA, Zhen WK. Intracardiac Metastasis From Non-Small Cell Lung Cancer. *Front Oncol* 2015; **5**: 168 [PMID: 26258073 DOI: 10.3389/fonc.2015.00168]

50 **Verma V**. Lung cancer: Implementing lung-cancer screening--oncological 'grey areas'. *Nat Rev Clin Oncol* 2015; **12**: 256-257 [PMID: 25850551 DOI: 10.1038/nrclinonc.2015.65]

51 **Verma V**, Beriwal S. Medicare Approves Coverage for Lung Cancer Screening: The Case for Symptomatic Screening. *JAMA Oncol* 2015; **1**: 1027-1028 [PMID: 26226384 DOI: 10.1001/jamaOncol2015.2165]

52 **Verma V**, Zhen W. Treatment Costs of Early-Stage Lung Cancers Detected by Low-Dose Computed Tomography Screening. *Int J Radiat Oncol Biol Phys* 2015; **93**: 207-208 [PMID: 26279036 DOI: 10.1016/j.ijrobp.2015.03.036]

53 **Verma V**. Stereotactic Radiotherapy Versus Surgery for Early-Stage Operable Lung Cancer: More Questions Than Answers. *J Natl Compr Canc Netw* 2015; **13**: 1293-1295 [PMID: 26483066]

54 **Lee JC**, Kinniry PA, Arguiri E, Serota M, Kanterakis S, Chatterjee S, Solomides CC, Javvadi P, Koumenis C, Cengel KA, Christofidou-Solomidou M. Dietary curcumin increases antioxidant defenses in lung, ameliorates radiation-induced pulmonary fibrosis, and improves survival in mice. *Radiat Res* 2010; **173**: 590-601 [PMID: 20426658 DOI: 10.1667/RR1522.1]

55 **Shi HS**, Gao X, Li D, Zhang QW, Wang YS, Zheng Y, Cai LL, Zhong RM, Rui A, Li ZY, Zheng H, Chen XC, Chen LJ. A systemic administration of liposomal curcumin inhibits radiation pneumonitis and sensitizes lung carcinoma to radiation. *Int J Nanomedicine* 2012; **7**: 2601-2611 [PMID: 22679371 DOI: 10.2147/IJN.S31439]

56 **Cooper JS**, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004; **350**: 1937-1944 [PMID: 15128893 DOI: 10.1056/NEJMoa032646]

57 **Bernier J**, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004; **350**: 1945-1952 [PMID: 15128894 DOI: 10.1056/NEJMoa032641]

58 **Khafif A**, Lev-Ari S, Vexler A, Barnea I, Starr A, Karaush V, Haif S, Ben-Yosef R. Curcumin: a potential radio-enhancer in head and neck cancer. *Laryngoscope* 2009; **119**: 2019-2026 [PMID: 19655336 DOI: 10.1002/lary.20582]

59 **Chiang IT**, Liu YC, Hsu FT, Chien YC, Kao CH, Lin WJ, Chung JG, Hwang JJ. Curcumin synergistically enhances the radiosensitivity of human oral squamous cell carcinoma via suppression of radiation-induced NF-κB activity. *Oncol Rep* 2014; **31**: 1729-1737 [PMID: 24503718 DOI: 10.3892/or.2014.3009]

60 **Pan Y**, Wang M, Bu X, Zuo Y, Wang S, Wang D, Liu Q, Su B, Xu T, Wang C, Claret FX, Yang H. Curcumin analogue T83 exhibits potent antitumor activity and induces radiosensitivity through inactivation of Jab1 in nasopharyngeal carcinoma. *BMC Cancer* 2013; **13**: 323 [PMID: 23815987 DOI: 10.1186/1471-2407-13-323]

61 **Tuttle S**, Hertan L, Daurio N, Porter S, Kaushick C, Li D, Myamoto S, Lin A, O'Malley BW, Koumenis C. The chemopreventive and clinically used agent curcumin sensitizes HPV (-) but not HPV (+) HNSCC to ionizing radiation, in vitro and in a mouse orthotopic model. *Cancer Biol Ther* 2012; **13**: 575-584 [PMID: 22441776 DOI: 10.4161/cbt.19772]

62 **Ang KK**, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363**: 24-35 [PMID: 20530316 DOI: 10.1056/NEJMoa0912217]

63 **Chera BS**, Amdur RJ, Tepper J, Qaqish B, Green R, Aumer SL, Hayes N, Weiss J, Grilley-Olson J, Zanation A, Hackman T, Funkhouser W, Sheets N, Weissler M, Mendenhall W. Phase 2 Trial of De-intensified Chemoradiation Therapy for Favorable-Risk Human Papillomavirus-Associated Oropharyngeal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2015; **93**: 976-985 [PMID: 26581135 DOI: 10.1016/j.ijrobp.2015.08.033]

64 **Qian Y**, Ma J, Guo X, Sun J, Yu Y, Cao B, Zhang L, Ding X, Huang J, Shao JF. Curcumin enhances the radiosensitivity of U87 cells by inducing DUSP-2 up-regulation. *Cell Physiol Biochem* 2015; **35**: 1381-1393 [PMID: 25792385 DOI: 10.1159/000373959]

65 **Langone P**, Debata PR, Inigo Jdel R, Dolai S, Mukherjee S, Halat P, Mastroianni K, Curcio GM, Castellanos MR, Raja K, Banerjee P. Coupling to a glioblastoma-directed antibody potentiates antitumor activity of curcumin. *Int J Cancer* 2014; **135**: 710-719 [PMID: 24142484 DOI: 10.1002/ijc.28555]

66 **Vredenburgh JJ**, Desjardins A, Herndon JE, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007; **25**: 4722-4729 [PMID: 17947719 DOI: 10.1200/JCO.2007.12.2440]

67 **Verma V**, Johnson CP, Bennion NR, Bhirud AR, Li S, McComb RD, Lin C. Atypical teratoid rhabdoid tumor: long-term survival after chemoradiotherapy. *Childs Nerv Syst* 2015; **31**: 1393-1399 [PMID: 25939716 DOI: 10.1007/s00381-015-2723-5]

68 **Verma V,** Giri S, Manandhar S, Pathak R, Bhatt VR. Acute promyelocytic leukemia during pregnancy: a systematic analysis of outcome. *Leuk Lymphoma* 2015; **28**: 1-7 [PMID: 26110880 DOI: 10.3109/10428194.2015.1065977]

69 **Verma V**, Muttineni S, Kulkarni RR, Silva-Lopez E, West WW, Thompson RB. Enormous, rapidly growing breast mass. *BMC Cancer* 2015; **15**: 1008 [PMID: 26704076 DOI: 10.1186/s12885-015-2024-0]

70 **Badiyan SN**, Rao RC, Apicelli AJ, Acharya S, Verma V, Garsa AA, DeWees T, Speirs CK, Garcia-Ramirez J, Esthappan J, Grigsby PW, Harbour JW. Outcomes of iodine-125 plaque brachytherapy for uveal melanoma with intraoperative ultrasonography and supplemental transpupillary thermotherapy. *Int J Radiat Oncol Biol Phys* 2014; **88**: 801-805 [PMID: 24462385 DOI: 10.1016/j.ijrobp.2013.12.014]

71 **Verma V**, Mendenhall WM, Werning JW. Polymorphous low-grade adenocarcinoma of the head and neck. *Am J Clin Oncol* 2014; **37**: 624-626 [PMID: 23428952 DOI: 10.1097/COC.0b013e31827e5537]

72 **Verma V**, Patel K, Peregrin I, Brandes S, Zighelboim I. Occult transitional cell carcinoma and Lynch syndrome incidentally revealed after laparoscopic hysterectomy and cystoscopy during staging for endometrial cancer. *Gynecol Oncol Case Rep* 2012; **4**: 26-28 [PMID: 24371667 DOI: 10.1016/j.gynor.2012.12.005]

73 **Tawfik SS**, Abouelella AM, Shahein YE. Curcumin protection activities against γ-rays-induced molecular and biochemical lesions. *BMC Res Notes* 2013; **6**: 375 [PMID: 24053347 DOI: 10.1186/1756-0500-6-375]

74 **Okunieff P**, Xu J, Hu D, Liu W, Zhang L, Morrow G, Pentland A, Ryan JL, Ding I. Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. *Int J Radiat Oncol Biol Phys* 2006; **65**: 890-898 [PMID: 16751071 DOI: 10.1016/j.ijrobp.2006.03.025]

75 **Jagetia GC**, Rajanikant GK. Acceleration of wound repair by curcumin in the excision wound of mice exposed to different doses of fractionated γ radiation. *Int Wound J* 2012; **9**: 76-92 [PMID: 21883936 DOI: 10.1111/j.1742-481X.2011.00848.x]

76 **Ryan JL**, Heckler CE, Ling M, Katz A, Williams JP, Pentland AP, Morrow GR. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res* 2013; **180**: 34-43 [PMID: 23745991 DOI: 10.1667/RR3255.1]

77 **Yorke ED**, Jackson A, Rosenzweig KE, Merrick SA, Gabrys D, Venkatraman ES, Burman CM, Leibel SA, Ling CC. Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2002; **54**: 329-339 [PMID: 12243805 DOI: http: ]

78 **Yorke ED**, Jackson A, Rosenzweig KE, Braban L, Leibel SA, Ling CC. Correlation of dosimetric factors and radiation pneumonitis for non-small-cell lung cancer patients in a recently completed dose escalation study. *Int J Radiat Oncol Biol Phys* 2005; **63**: 672-682 [PMID: 15939548 DOI: 10.1016/j.ijrobp.2005.03.026]

79 **Bradley JD**, Hope A, El Naqa I, Apte A, Lindsay PE, Bosch W, Matthews J, Sause W, Graham MV, Deasy JO. A nomogram to predict radiation pneumonitis, derived from a combined analysis of RTOG 9311 and institutional data. *Int J Radiat Oncol Biol Phys* 2007; **69**: 985-992 [PMID: 17689035 DOI: 10.1016/j.ijrobp.2007.04.077]

80 **Cho YJ**, Yi CO, Jeon BT, Jeong YY, Kang GM, Lee JE, Roh GS, Lee JD. Curcumin attenuates radiation-induced inflammation and fibrosis in rat lungs. *Korean J Physiol Pharmacol* 2013; **17**: 267-274 [PMID: 23946685 DOI: 10.4196/kjpp.2013.17.4.267]

81 **Palma DA**, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, Bradley JD, Kim TH, Ramella S, Marks LB, De Petris L, Stitt L, Rodrigues G. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2013; **85**: 444-450 [PMID: 22682812 DOI: 10.1016/j.ijrobp.2012.04.043]

82 **Ozgen SÇ**, Dökmeci D, Akpolat M, Karadağ CH, Gündüz O, Erbaş H, Benian O, Uzal C, Turan FN. The Protective Effect of Curcumin on Ionizing Radiation-induced Cataractogenesis in Rats. *Balkan Med J* 2012; **29**: 358-363 [PMID: 25207034 DOI: 10.5152/balkanmedj.2012.038]

83 **Dye NB**, Gondi V, Mehta MP. Strategies for preservation of memory function in patients with brain metastases. *Chin Clin Oncol* 2015; **4**: 24 [PMID: 26112810 DOI: 10.3978/j.issn.2304-3865.2015.05.05]

84 **Lim GP**, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J Neurosci* 2001; **21**: 8370-8377 [PMID: 11606625]

85 **Xie Y**, Zhao QY, Li HY, Zhou X, Liu Y, Zhang H. Curcumin ameliorates cognitive deficits heavy ion irradiation-induced learning and memory deficits through enhancing of Nrf2 antioxidant signaling pathways. *Pharmacol Biochem Behav* 2014; **126**: 181-186 [PMID: 25159739 DOI: 10.1016/j.pbb.2014.08.005]

86 **Sebastià N**, Montoro A, Hervás D, Pantelias G, Hatzi VI, Soriano JM, Villaescusa JI, Terzoudi GI. Curcumin and trans-resveratrol exert cell cycle-dependent radioprotective or radiosensitizing effects as elucidated by the PCC and G2-assay. *Mutat Res* 2014; **766-767**: 49-55 [PMID: 25847272 DOI: 10.1016/j.mrfmmm.2014.05.006]

87 **Inano H**, Onoda M. Radioprotective action of curcumin extracted from Curcuma longa LINN: inhibitory effect on formation of urinary 8-hydroxy-2'-deoxyguanosine, tumorigenesis, but not mortality, induced by gamma-ray irradiation. *Int J Radiat Oncol Biol Phys* 2002; **53**: 735-743 [PMID: 12062620 DOI: 10.1016/S0360-3016(02)02794-3]

88 **Classen J**, Belka C, Paulsen F, Budach W, Hoffmann W, Bamberg M. Radiation-induced gastrointestinal toxicity. Pathophysiology, approaches to treatment and prophylaxis. *Strahlenther Onkol* 1998; **174 Suppl 3**: 82-84 [PMID: 9830465]

89 **Elhammali A**, Patel M, Weinberg B, Verma V, Liu J, Olsen JR, Gay HA. Late gastrointestinal tissue effects after hypofractionated radiation therapy of the pancreas. *Radiat Oncol* 2015; **10**: 186 [PMID: 26337917 DOI: 10.1186/s13014-015-0489-2]

90 **Akpolat M**, Kanter M, Uzal MC. Protective effects of curcumin against gamma radiation-induced ileal mucosal damage. *Arch Toxicol* 2009; **83**: 609-617 [PMID: 18754102 DOI: 10.1007/s00204-008-0352-4]

91 **Verma V**, Liu J, Eschen L, Danieley J, Spencer C, Lewis JS, Diaz J, Piccirillo JF, Adkins DR, Nussenbaum B, Thorstad WL, Gay HA. Pre-radiotherapy feeding tube identifies a poor prognostic subset of postoperative p16 positive oropharyngeal carcinoma patients. *Radiat Oncol* 2015; **10**: 8 [PMID: 25572866 DOI: 10.1186/s13014-014-0314-3]

92 **Rezvani M**, Ross GA. Modification of radiation-induced acute oral mucositis in the rat. *Int J Radiat Biol* 2004; **80**: 177-182 [PMID: 15164799 DOI: 10.1080/09553000310001654693]

93 **Rao S**, Dinkar C, Vaishnav LK, Rao P, Rai MP, Fayad R, Baliga MS. The Indian Spice Turmeric Delays and Mitigates Radiation-Induced Oral Mucositis in Patients Undergoing Treatment for Head and Neck Cancer: An Investigational Study. *Integr Cancer Ther* 2013; **13**: 201-210 [PMID: 24165896 DOI: 10.1177/1534735413503549]

94 **Patil K**, Guledgud MV, Kulkarni PK, Keshari D, Tayal S. Use of Curcumin Mouthrinse in Radio-Chemotherapy Induced Oral Mucositis Patients: A Pilot Study. *J Clin Diagn Res* 2015; **9**: ZC59-ZC62 [PMID: 26436049 DOI: 10.7860/JCDR/2015/13034.6345]

95 **Holder GM**, Plummer JL, Ryan AJ. The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. *Xenobiotica* 1978; **8**: 761-768 [PMID: 726520]

96 **Ireson C**, Orr S, Jones DJ, Verschoyle R, Lim CK, Luo JL, Howells L, Plummer S, Jukes R, Williams M, Steward WP, Gescher A. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Res* 2001; **61**: 1058-1064 [PMID: 11221833]

97 **Hassaninasab A**, Hashimoto Y, Tomita-Yokotani K, Kobayashi M. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. *Proc Natl Acad Sci USA* 2011; **108**: 6615-6620 [PMID: 21467222 DOI: 10.1073/pnas.1016217108]

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