



## Retrospective Analysis of Curcumin in Cervical Cancer Patients Post Radiotherapy

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### Abstract

**Aim of the Study:** To Evaluate the Effect of Curcumin on Toxicity and Outcomes in Cervical Cancer patients Post Radiotherapy.

**Material and Methods:** 60 Cervical Cancer patients who received definitive Chemo radiation and Brachytherapy were selected for the study. Patients received External beam Radiotherapy by 3DCRT technique to a total dose of 45-50GY with concurrent Platinum based chemotherapy of 5cycles and Brachytherapy was delivered by HDR technique, limiting the Bladder and Rectal doses to 75-80GY and 70-75GY respectively.

Of these, 30 Patients received Tab. Curcumin 500mg BID for a minimum period of 3 months post Radiotherapy during Follow-up and were compared with patients of similar characteristics kept only under Observation. The toxicity and outcomes post Radiotherapy was analyzed. The incidence of Radiation Dermatitis, Radiation Cystitis and Radiation Proctitis was analyzed.

**Results:** At 3 months post Radiotherapy, Radiation Dermatitis was seen in 20 out of 30 patients in the observation arm with Grade I toxicity in 12 patients, Grade II toxicity in 6 patients and Grade III toxicity in 2 patients compared to 12 patients having Grade I toxicity who received Curcumin ( $p=0.038$ ) which was significant. Radiation Cystitis was seen in 21 patients in the observation arm with Grade I Toxicity in 16 Patients, Grade II Toxicity in 4 Patients and Grade IV Toxicity in 1 patient compared to 12 patients with Grade I Cystitis in Curcumin arm ( $p=0.0198$ ) which was significant. Radiation Proctitis was seen in 23 patients in the observation arm with Grade I toxicity in 14 Patients and Grade II Toxicity in 9 patients compared to 8 patients with Grade I proctitis and 1 patient with Grade II toxicity in Curcumin arm.

( $p=0.001$ ) which was significant. There was no evidence of disease in 25 patients and only 5 patients had Stable disease in Curcumin arm compared to 6 patients with Stable disease and 4 patients with Progressive disease and no evidence of disease was seen in 20 patients in Observation arm.

**Conclusions:** Radiation Dermatitis, Cystitis and Proctitis are well known complications of radiation treatment in Carcinoma Cervix patients. Early detection and treatment reduces the grade of toxicity and improves Quality of life. The use of Curcumin post radiation definitely reduces the side effects and thereby improves the therapeutic ratio. Better local control with Curcumin must also be proved with large randomized control trials addressing all the bias. With the advent of nano-curcumin there is better absorption and bio-availability for enhanced effects of curcumin and improving the quality of life. The optimal dosage and duration of curcumin post radiotherapy to be administered is still investigational.

**Keywords:** Curcumin, Dermatitis, Cystitis, Proctitis, Cervical Cancer, Radiotherapy.

## Introduction

Cervical Cancer represents the 4<sup>th</sup> most common malignancy among women worldwide<sup>[1]</sup>. But, it's the second most common cancer in India accounting for 22.86%. In Karnataka, it ranks number- 1 disease among women from rural areas, accounting for 23% of the cases being registered at our institute (HBCR KMIO- 2015)<sup>[2]</sup>. More than 60% of patients present to our Institute in advanced stage. Attaining good Local control rates and better Overall survival rates still remains a challenge even in this modern era of Advanced treatment.

Radiotherapy with concurrent Chemotherapy still remains the standard of care treatment for Locally advanced Cancer Cervix. Cervical Cancer is a potentially Radio curable disease. Our Institute's policy is to treat carcinoma cervix with Platinum based Chemotherapy during External beam radiotherapy (National Cancer Institute alert, publication February-1999), followed by Brachytherapy. The Brachytherapy is an integral component of Standard treatment protocol, incorporation of which along with External Beam radiotherapy has shown good local control with significant survival improvement. Minimizing the Bladder and Rectal doses and thereby reducing the incidences of toxicities remains a challenge even with 3D-Image based Radiotherapy.

In the Indian Culture, "Turmeric" plays a pivotal role in terms of customs and food habits. The usage of Turmeric dates back to Vedic period. Turmeric is used for a wide variety of ailments and conditions in our day to day Life, so it has become "Spice of Life". Curcumin is a pigment in

the rhizomes of turmeric, which gives yellow color and adds the flavor to dishes. It has anti-oxidant, anti-inflammatory, anti-viral, anti-bacterial, anti-fungal and anti-cancer effects. There are various chemical components in turmeric like Curcumin (Diferuloyl methane), D-Methoxy-Curcumin (DMC), Bis-D-Methoxy-Curcumin (BDMC), Tetrahydro Curcumin (THC) and Turmerones.

Curcumin exhibit the properties of Tumor Necrosis Factor (TNF) Blocker, Vascular Endothelial Growth Factor (VEGF) Blocker, Human Epidermal Growth Factor Receptor (h-EGFR) blocker. Of the components derived from turmeric, Curcumin was found to be the most active ingredient for its ability to suppress TNF-Alpha induced NF-k-beta activation. It also suppresses the proliferation of Leukemic, Prostate and Breast cancer cells. It also suppresses inflammatory pathways and cellular proliferation by NF-K beta, TNF-alfa, STAT-3 pathways<sup>[3]</sup>.

Curcumin is inhibitor of NF-k beta for treatment of human Myeloid ML1-alfa cells with TNF rapidly activated NF-Alfa beta, which consists of p50,p65 subunits and this activation was inhibited by curcumin. Activator protein-1(AP-1) binding factors were also found to be down-regulated by curcumin, whereas the SP-1 binding factor was unaffected. Besides TNF-Alfa, curcumin also blocked phorbol ester and hydrogen peroxide mediated activation of NF-k beta<sup>[4]</sup>.

Curcumin also inhibits Cox-2 and Cyclin-D1 protein expression in a dose dependent manner. It can be used from 1-6g/day and maximum ceiling dose of curcumin is not known. Curcumin inhibits

STAT3 (signal transducer and activator of transcription 3). It inhibits IL-6 induced STAT3 phosphorylation and consequent nuclear translocation. It also inhibits IF- $\alpha$  induced signal transducer and activator of transcription-1 phosphorylation. Curcumin inhibits TNF- $\alpha$ , which is a cell signaling cytokine, which is associated with systemic inflammatory process in the body. All the above effects of curcumin makes it a potent drug to minimize toxicities<sup>[5]</sup>.

### Pathogenesis

Radiation dermatitis is caused due to Pro-inflammatory cytokines(IL-3,5,6 and TNF- $\alpha$ ), Chemokines (exotaxin and IL-8), Receptor Tyrosine Kinase and Adhesion Molecules (ICAM-1, E-Selectin and Vascular Cell Adhesion proteins) which causes local inflammatory reaction, leading to tissue damage<sup>[6]</sup>.

The incidence of Radiation Cystitis is bladder dose dependent. Radiation causes double strand breaks resulting in DNA damage and cell death. The irreparably damaged DNA which is formed due to irradiation causes endarteritis obliterans and ischemia of the Bladder tissue resulting in reduced nutrition leading to fibrosis and necrosis. The time duration of this process is not precisely delineated because the damaged blood vessels can survive from months to years of injury, thus making it difficult to predict the time frame of early detection<sup>[7]</sup>.

Development of Radiation Proctitis is also dose dependent, which varies between 2-39% based on dose received to rectum and irradiation technique and brachytherapy techniques. Pathogenesis of radiation proctitis is found to be due to progressive epithelial atrophy, submucosal fibrosis, ischemia due to endarteritis leading to fragile neovascularization<sup>[8]</sup>.

### Material and Methods

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External beam Radiotherapy by 3DCRT technique to a total dose of 45-50GY with concurrent Platinum based chemotherapy of 5cycles and Brachytherapy was delivered by High dose rate (HDR) technique limiting the Bladder and Rectal doses to 75-80GY and 70-75GY respectively.

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### Results

Statistical analysis was done using Python 13.0 software. Proportion z-test was used for comparison between the two arms.

At 3 months post Radiotherapy, Radiation Dermatitis was seen in 20 out of 30 patients in the observation arm with Grade I toxicity in 12 patients, Grade II toxicity in 6 patients and Grade III toxicity in 2 patients compared to 12 patients having Grade I toxicity who received Curcumin ( $p=0.038$ ) which was significant. Radiation Cystitis was seen in 21 patients in the observation arm with Grade I Toxicity in 16 Patients, Grade II Toxicity in 4 Patients and Grade IV Toxicity in 1 patient compared to 12 patients with Grade I Cystitis in Curcumin arm ( $p=0.0198$ ) which was significant. Radiation Proctitis was seen in 23 patients in the observation arm with Grade I toxicity in 14 Patients and Grade II Toxicity in 9 patients compared to 8 patients with Grade I proctitis and 1 patient with Grade II toxicity in Curcumin arm ( $p=0.001$ ) which was significant. There was no evidence of disease in 25 patients and only 5 patients had Stable disease in Curcumin arm compared to 6 patients with Stable disease and 4 patients with Progressive disease and no evidence of disease was seen in 20 patients in Observation arm.

**Table I:** Stage wise Distribution of Patients

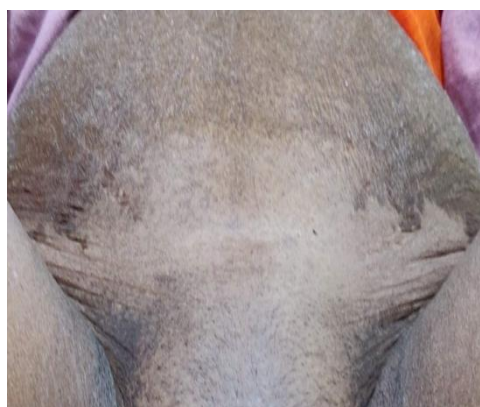
STAGE(FIGO- 2018)	NUMBER OF PATIENTS (NO)	PERCENTAGE OF PATIENTS (%)
I	-	-
II	27	45
III	27	45
IV	6	10
TOTAL	60	100

**Table II:** Radiation Therapy Oncology Group (RTOG): BASED TOXICITY (3-months Post-Radiotherapy)

TOXICITY GRADING	DERMATITIS		CYSTITIS		PROCTITIS	
	WITH CURCUMIN	WITHOUT CURCUMIN	WITH CURCUMIN	WITHOUT CURCUMIN	WITH CURCUMIN	WITHOUT CURCUMIN
1	12	12	12	16	8	14
2	-	6	-	4	1	9
3	-	2	-	-	-	-
4	-	-	-	1	-	-
TOTAL	12	20	12	21	9	23

**Table III:** OUTCOMES OF TREATMENT Post-Radiotherapy

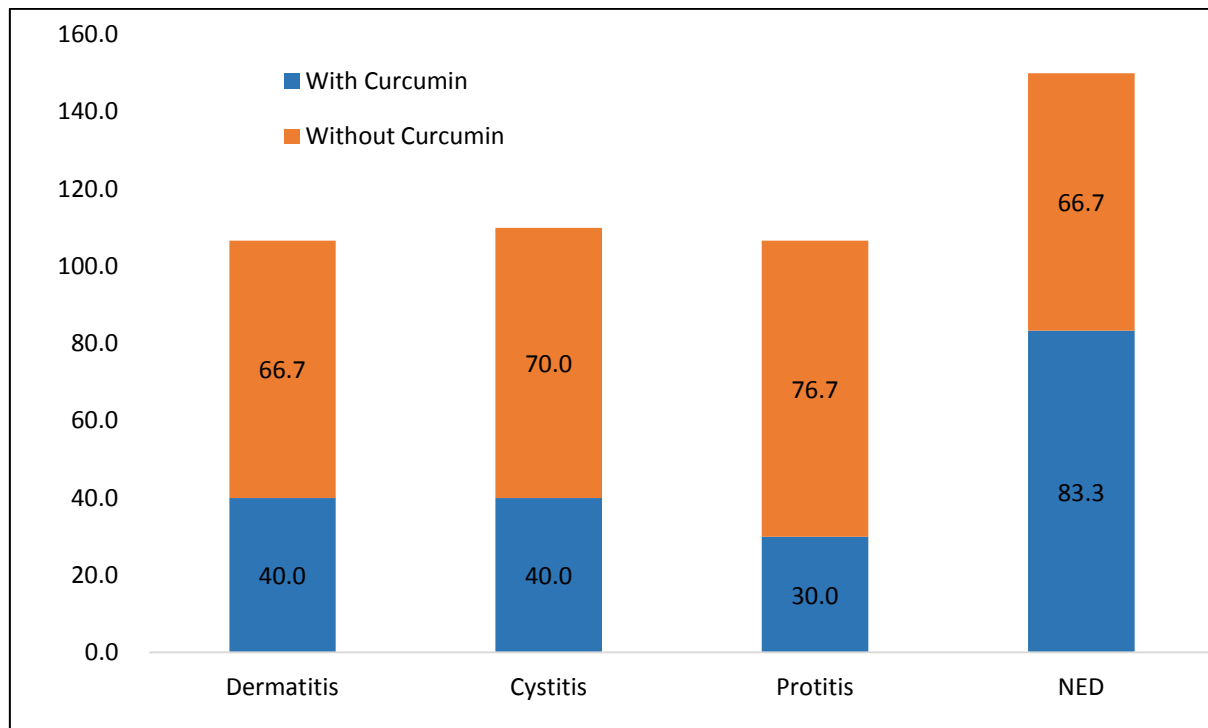
DISEASE STATUS	WITH CURCUMIN	WITHOUT CURCUMIN
NO EVIDENCE OF DISEASE (NED)	25	20
STABLE DISEASE	5	6
PROGRESSIVE DISEASE	-	4
TOTAL	30	30



**Fig 1:** Represents the Grade I Dermatitis and completely healed Skin 1 month post RT



**Fig 2:** Represents the Grade III Dermatitis and completely healed Skin 3 month post RT.



**Fig 3:** Diagram represents the Toxicity and Disease status in both arms post Radiotherapy.

### Discussion

Radiotherapy in cancer cervix is a “Double Edged sword” in terms of achieving good local control and improving Overall survival, which comes along with complications, contributing to compromised Quality of life. There is a Dose response relationship between dose to Point-A and Local Control, between Bladder dose and Cystitis and between Rectal dose and Proctitis. There is no fixed time duration for development of Radiation Cystitis and Radiation Proctitis. Several factors are associated with complications like Age, Stage, Comorbidities, Modalities of treatment used and Dose received to Bladder and Rectum. Most of the patients being treated need supplements because they have low levels of Vitamins, micronutrients in their body and even their dietary intake is compromised because of complications.

Radiation Dermatitis is the most common side effect of Radiotherapy regardless of site of irradiation. Randomized and double blinded trial of oral curcumin versus placebo in breast cancer patients post radiotherapy. This study favored the usage of curcumin with p value 0.008 along with decreased moist desquamation, which was significant<sup>[9]</sup>.

Roa S et al studied the effect of curcumin on oral mucositis in Head and Neck Cancer patients receiving radiotherapy and found that it was effective in preventing and reducing radiation induced mucositis. The use of Curcumin as mouth rinse is also beneficial to patients in preventing oral mucositis who receive Chemoradiation in Head and Neck cancer cases.<sup>[10,11]</sup>

Chendil et al, studied the mechanism of NF-KB pathway and found 3 times lesser surviving prostate cancer cells due to sustained cellular killing and reduced radio resistance, when treated with both Radiotherapy and curcumin<sup>[12]</sup>.

A Turkish study demonstrated that intestinal mucosa was protected to greater degree in rats fed with curcumin, which was proven histopathologically. Bowel toxicity resulting from irradiation during Gynaecologic, Prostate, Gastro-intestinal, Pediatric Cancers can be alleviated by the use of curcumin<sup>[13]</sup>.

Montana GS et al evaluated 527 Cancer cervix patients, who received Radiotherapy and found dose response relationship between bladder dose and cystitis. Risk of cystitis was 3-12% in patients receiving radiation dose ranging from 50 - 80Gy. The study also showed dose response

relationship between rectal dose and proctitis. Risk of Proctitis was 2-18% in patients receiving radiation dose ranging from 50 -80Gy<sup>[14]</sup>.

During irradiation of the bone marrow in Gynecological malignancy patients, Curcumin protects lymphocytes, the most Radiosensitive blood cell. Thus decreasing Hematological Toxicities. The role of Intensity modulated Radiotherapy has been well established in post operative Cervical cancer cases<sup>[15]</sup>.

MDACC also studied NF-KB modulation – although its expression raises after RT. This study also showed that there is decrease in matrix metalloproteinase expression (MMP). This is the enzyme found to be the gateway for metastasis by dissolving bonds of extracellular matrix and also promoting micro environment for growth and spread of cancer cells<sup>[16]</sup>.

Curcumin has good and potent anti-inflammatory effects, which can benefit from Dermatitis, Mucositis, Pneumonitis, Cataractogenesis, Neurocognition, Myelosuppression and Secondary tumors, which are the adverse effects of Radiotherapy<sup>[17,18]</sup>.

### Conclusions

Radiation Dermatitis, Cystitis and Proctitis are well known complications of radiation treatment. Early detection and treatment reduces the grade of toxicity and improves Quality of life. Curcumin is a leading armament in naturopathic oncology, which is being used since ages in India. The use of curcumin post radiation definitely mitigates the side effects and thereby improves the therapeutic ratio. The optimal dosage and duration of curcumin post radiotherapy to be administered is still investigational. With the advent of nano-curcumin there is better absorption and bio-availability for enhanced effects of curcumin and improving the quality of life.

The usage of curcumin during radiotherapy is controversial, though it has Radio sensitization effect. Role of prophylactic administration of Curcumin before the onset of disease needs to be answered. Future large randomized trials is

required for conclusive evidence for better clinical outcomes. The usage of special formulations like liposomal, conjugated, intravenous and other molecular analogues must also be investigated for better management and control of post radiotherapy complications.

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