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A Prospective Study to Evaluate the Toxicity and Efficacy of EGCG in Preventing Acute Radiation Dermatitis

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A B S T R A C T

Background: Nearly 75% of all solid cancer patients have to undergo radiation therapy as a part of their treatment of these patients, 95% of patients encounter the problem of radiation dermatitis either during, or after the completion of radiation treatment. Often, this is also associated with patient reported symptoms such as pain at local site and tightness of the skin. There are no topical or oral agents that has shown promise in prevention of radiation dermatitis. Our primary objective of this study was to look into the safety and efficacy of topical green tea extract for prevention of radiation dermatitis. Secondary objective was to validate the curative properties of green tea extract gel. ***Material and Methods:*** Topical green tea extract gel was prepared at a concentration of 0.75 mmol/L. 30 consecutive patients treated for solid carcinomas for various subsite were asked to apply the gel on the skin at the site of radiotherapy and at a control site fairly away from site of radiation, thrice daily; at least 2 hours before radiotherapy, 2 hours after radiotherapy and before going to bed in night. Application of green tea extract gel was started from day 1 of radiotherapy treatment and was continued till 2 weeks after the end of radiotherapy treatment. Skin toxicity parameters includes RTOG/EORTC grade of dermatitis; pain at the site of radiation; and tightness at the site of radiation. These were recorded at the end of radiotherapy treatment as well as at the end of 2 weeks after completion of radiotherapy treatment. ***Results:***43 patients were treated in the radiotherapy department from June 2021 to Dec 2021 for various subsites. Of these, initial consecutive 30 patients were taken for the study. This cohort included 11 head and neck cancer patients, 12 breast cancer patients and 7 cervix cancer patients.None of these patients developed cutaneous reaction at the control site, implying the inertness of the green tea extract gel. 29 patients developed any grade of radiation dermatitis at the end of radiotherapy treatment. 1 patient did not developing any dermatitis at the end of radiotherapy treatment ($p<0.89$). With continuation of green tea extract application, 9 patients fully recovered from dermatitis at the end of 2 weeks post completion of radiotherapy treatment ($p<0.001$). 17 patients reported nopain at local site at the end of radiotherapy treatment ($p<0.03$); 15 patients were prevented from tightness at the end of radiotherapy treatment ($p<0.05$); which were statistically significant. ***Conclusion:***The green tea extract gel shows an excellent safety profile, with none of the patients in our study cohort developing an adverse skin reaction. Topical administration of green tea extract gel, seems to be feasible for treating acute radiation dermatitis. This also seems feasible to both reduce the incidence and treat the new onset pain and tightness of the skin at the radiation site associated with or without acute radiation dermatitis at the site of radiotherapy treatment.

Keywords: Green tea extract, Radiation dermatitis, EGCG**,** Radiotherapy.

INTRODUCTION

Nearly 60-75% of all solid cancer patients undergo radiation therapy as a part of their treatment. Out of these, nearly 95% of patients encounter the problem of radiation dermatitis either during, or after the completion of radiation treatment [1]. Influencers / modifiers of acute radiation dermatitis include the site of radiotherapy treatment, energy and type of radiotherapy beam used, application of skin surface bolus / compensators, concurrent chemotherapy with radiotherapy. Severe skin reactions may also require interruption of radiotherapy treatment, which may harm the outcome. Incidence of severe acute dermatitis is not common as megavoltage energy of radiation along with conformal radiation techniques characteristically spares the skin [2]. But overall incidence of acute skin reactions is still as high as 95% and may require some novel techniques or drugs for prevention and management of radiation induced dermatitis ref. Various other topical pharmacological and non-pharmacological agents have been tried in the past such as topical corticosteroid [3-5], topical sucralfate [6-8], trolamine [9, 10]; aloe-vera gel [11, 12], curcumin [13, 14], hyaluronic acid [15], and other anti-oxidant vitamins, such as ascorbic acid[16-17], pantothenic acid[18] have been used but with limited success. There remains a need to continue investigating new products and novel approaches for minimizing acute radiation dermatitis.

Pre-clinical evidence suggested that epigallocatechin-3-gallate (EGCG), the major catech in found in green tea extract, had the potential in inhibiting radiation-induced damage *in vitro* and *in vivo*. Topical green tea extract containing EGCG has shown promising results in treating radiation dermatitis [19-21]. The safety profile of green tea extract gel is excellent. There are no reported cutaneous drug reactions with the application of topical green tea extract [19, 22-24].

In this study, our aim to evaluate the efficacy and safety profile of the topical application of green tea extract gel on the radiation site in cancer patients of various subsites, such as head and neck, breast and cervix. Our secondary objective is to correlate various patient related and treatment related factors such as Body Mass Index (BMI), ECOG performance score, site of radiotherapy treatment, concurrent chemotherapy, total radiotherapy dose delivered, which may influence the treatment response to topical green tea extract gel.

Material and Methods

Study Design

This was an interventional; non randomised, pilot study conducted in our institute from June 2021 to December 2021. The sample size was kept 30 in view of pilot nature of the study.

IHEC: This study was conducted and initiated after the approval of Institutional ethical committee.

Patients- Inclusion and Exclusion criteria

Eligible patients had to have pathologically proven cancer with a planned course of radiotherapy. Other inclusion criteria were age ≥18 years and <70 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, conventional or hypofractionation course of radiotherapy treatment, photon energy 6 MV, normal haematological function (neutrophil count ≥1500 cells per microlitre, platelet count ≥1 Lakh cells per microlitre and haemoglobin ≥10 g/L) and organ function (creatinine clearance >50 ml min^{-1} and aspartate aminotransferase/alanine aminotransferase ≤2.5 of upper normal limit). Exclusion criteria included the presence of rash or unhealed wound in the radiation field, known allergy or hypersensitivity to green tea or EGCG, pregnancy or lactation, history of/ active connective tissue disorder, history of prior radiation, patients being treated with electron therapy, and / or Beam energy < 6 MV or >6 MV. Informed consent was obtained from all patients.

Radiotherapy treatment protocol

Radiation treatment was delivered to the chest wall, head and neck, pelvis, including the surgical scar and regional lymph nodes. All patients underwent CT simulation for verification of the irradiated field, segmentation and computer-based treatment planning. The dose of radiation was given as per the current standard guidelines. All patients were treated with Intensity modulated radiation therapy technique or Rapid Arc technique on Linear accelerator (Elekta Verse HD).

Preparation of Green tea extract gel

Green tea extract gel was cordially donated by Richfeel Health and Beauty Private Limited, Baddi, Himachal Pradesh, India, for research purposes. Green tea extract composition was measured using HPLC, and concentration of various catechins, along with EGCG, were recorded on 13/03/2022 is given in Table 1. The concentration of green tea extract in the gel was prepared such that the EGCG concentration was at least 660 µmol/L, which in our case was 0.75 g/L. This is because the maximum limit of EGCG concentration used in the Phase I study by Zhao *et al*., was 660 µmol/L, at which concentration also there were no cutaneous adverse effects noted [28].

Maximum EGCG concentration used in a phase I study was 660umol/L. Taking this as a base, green tea extract concentration was prepared. Molecular mass of EGCG is 458.372 g/mol. The concentration of EGCG to be used (in g/L) = $\frac{660\ x\ 458.372}{1000000}$; in this case, concentration of EGCG = 0.3g/L. The concentration of EGCG in green tea extract taken was minimum 40%. Hence the concentration of green tea extract required= 0.75g/L.

Intervention Protocol of green tea extract

Patients satisfying inclusion criteria were chosen and provided with green tea extract gel. After taking proper consent from the patients and explaining all the possible reactions and anticipatory side effects to the patients in their language, the patients were asked to apply green tea extract gel on the skin area exposed to radiotherapy treatment from day 1 of the start of radiotherapy treatment and was continued till the end of radiotherapy treatment. Green tea extract gel application was asked to be continued till two weeks post radiotherapy treatment if the patient developed radiation dermatitis during the course of radiotherapy treatment. The gel was applied to the area of skin exposed to the therapeutic radiotherapy field. It was applied thrice a day, i.e 2 hrs before the radiotherapy session, 2 hrs post radiotherapy session and before going to bed at night daily, including the non-treatment days. The patients were also asked to apply the gel at any other body part or site outside the radiation field, which will act as a control site. If any skin reaction or hypersensitivity occurs at the radiation site or at the control site, the application of the gel will be discontinued for the patient.

The standard protocol of skin care at the site of radiation were followed simultaneously such as removing / relieving any skin folds, avoiding direct sun exposure, avoiding soap/ detergent application wearing loose, cotton clothes avoid rubbing, shaving, and scratching the skin, not applying any other cream/ gel on the site of radiation.

Assessment of Skin Toxicity

Grade of radiation dermatitis as per RTOG system [36] was assessed weekly by 2 independent radiation oncologists. Radiation dermatitis assessment was done every week for each patient starting from 1 week after the start of radiation therapy till the 2 weeks post completion of radiotherapy treatment. In case of disparity of the RTOG grade assigned to the patient, the greater reported grade was recorded.

Patient-reported symptoms, ie, pain and tightness were assessed simultaneously with scoring system adapted from the STAT system (skin toxicity assessment tool) [35]. The STAT scores range from 0, representing no symptoms, to 5, representing the worst symptoms (pain, burning-feeling, itching, pulling and tenderness). The symptoms studied include two of the components of STAT, ie, pain and tightness (pulling). The STAT is an easy-to-use, standardized instrument to evaluate acute skin reaction and may be applied to clinical care and research in patients undergoing radiotherapy.

Statistical Analysis

SPSS software was used for statistical analysis. The differences in the scores during and after treatment were analysed using paired t-test. A value of $P < 0.05$ was defined as statistical significance.

RESULTS

Patients and Treatment

43 patients were treated in the radiotherapy department, AIIMS Bhopal, from June 2021 to Dec 2021 and met the eligibility criteria. Of these, initial 30 consecutive patients were taken for the study.

The patient variables recorded include body mass index (BMI), ECOG performance score, site of treatment, whether concurrent chemotherapy given, total radiation dose delivered.

The median duration of Green tea extract application was 7 weeks (5 to 10 weeks). The patients very well tolerated the formulation. None of the patient developed any cutaneous reaction or hypersensitivity on the control site. Figure 1 shows the application of green tea extract.

The number of patients of various subsites were 11 head and neck cancer patients, 12 breast cancer patients and 7 cervix cancer patients. Patients' characteristics and demography is shown in Table 2.

Skin related toxicity incidence profile of 30 patients during radiotherapy treatment and within 2 weekspost completion of radiotherapy treatment is shown in Table 3.

Table 1: Percentage of Catechins in Standard green tea extract (32)

Contents	Percentage (%)	Retention Time (Min)
Epicatechingallate (ECG)	18.2	20.661

Epicatechin (EC)	10.1	12.085
Epigallocatechin (EGC)	4.2	6.773
Epigallocatechingallate (EGCG)	45.5	12.736

Table 2: Patients' characteristics and demographic details

Variable	No. of patients (N=30)	Percentage
Age		
Median	50 yrs	
Range	26-70 yrs	
Performance Score		
ECOG 0	17	56.6
ECOG 1	13	43.3
Boost (Simultaneous Integrated Boost)		
Yes	16	53.3
No	14	46.7
Radiotherapy Technique		
VMAT	30	100
Dose per Fraction		
2 Gy/#	9	30
>2 Gy/#	21	70
Concurrent Chemotherapy		
Yes	13	43.3
No	17	56.6
BMI		
Underweight	0	0
Normal	29	96.66
Overweight	1	3.33
Obesity	0	0
Site		
Head and Neck	11	36.6
Breast	12	40
Cervix	07	23.3
Head and Neck (N=11)		
Subsite		
Buccal Mucosa	4	42
Oropharynx	3	25
Largyx	3	25
Hypophargyx	1	8
Dose		
60 Gy in 30#	7	67
>60 Gy (SIB) in 30#	4	33
Concurrent Chemotherapy		
Yes	7	67
No	4	33
Breast (N=12)		
Side		
Right	9	75
Left	3	25
Dose (in Gy)		
40.05 Gy in 15#	3	25
50 Gy in 25#	9	75
Cervix (N=7)		
Dose (in Gy)		
50.4 Gy in 28#	5	71.4
61.6 Gy (SIB) in 28#	2	28.6
Concurrent chemotherapy		
Yes	5	71.4
No	2	28.6

Table 3: Number of patients with each of the skin toxicity being studied at the end of radiotherapy treatment

Skin Toxicity	Number of patients	Percentage
Dermatitis	29/30	96.66%
Pain	13/30	43.33%
Tightness	15/30	50%

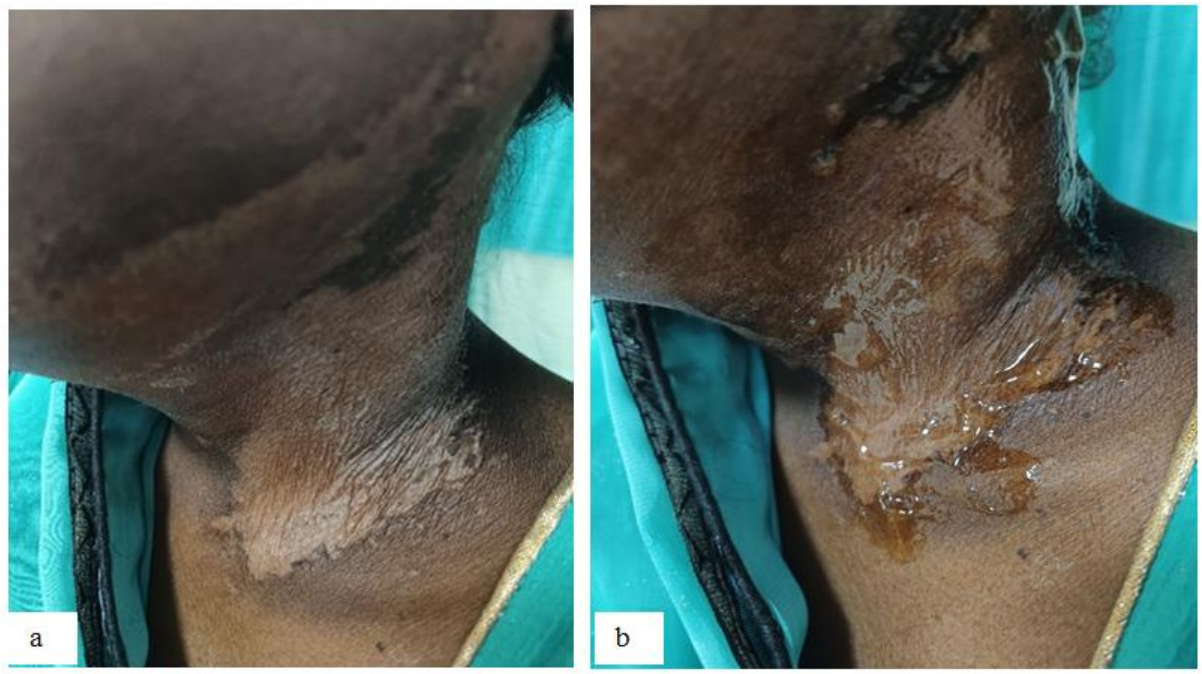
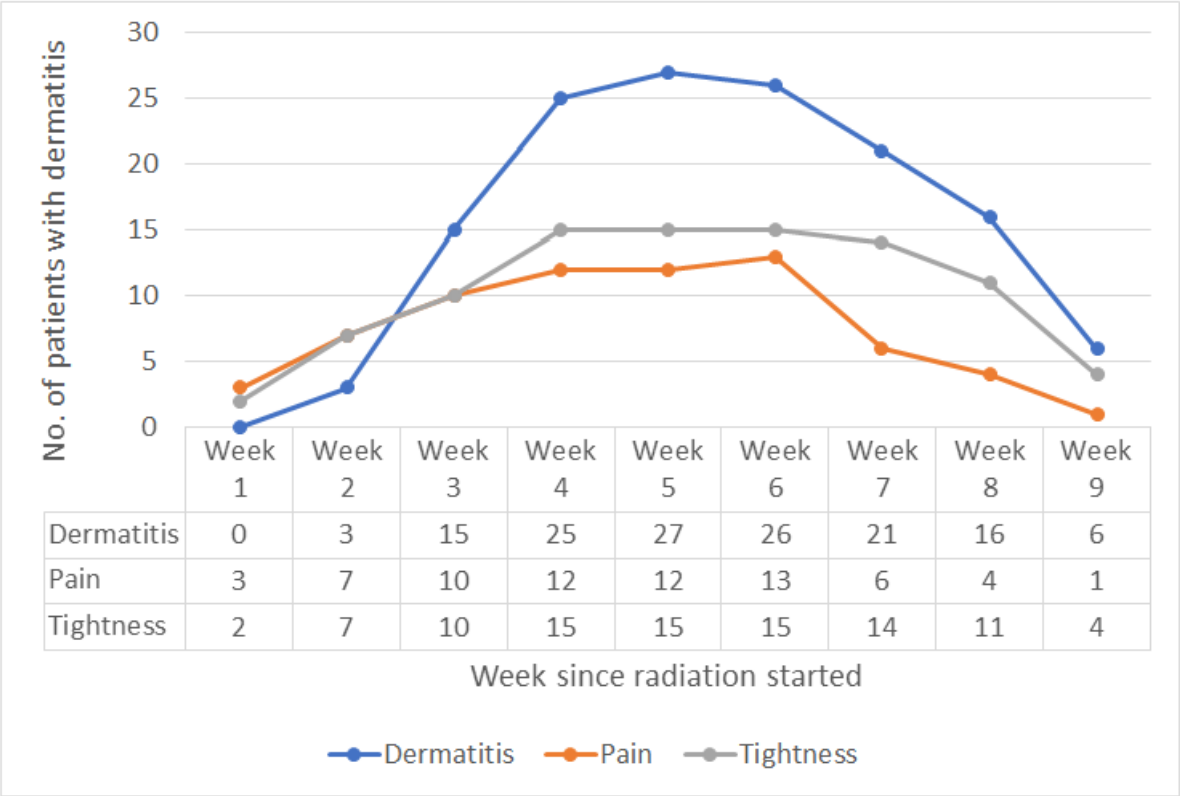


Figure 1: Patient with Grade II dermatitis with layering of green tea extract gel

DERMATITIS

Grade 1 dermatitis was observed during the radiotherapy treatment in all patients except for one patient (p=0.89). No patient developed dermatitis in first week, which appeared in three patients in second week, 12 patients in third week, 11 patients in fourth week and three patients in fifth week, such that at the end of fifth week, 29 patients had developed at least grade 1 radiation dermatitis. Out of these 29 patients, 18 patients had grade 2 dermatitis at the end of radiation therapy treatment. Following completion of radiotherapy, with continuation of green tea extract application, the number of patients with grade 2 dermatitis declined to just one at the end of 2 weeks The graphical representation is shown in Figure 2. 9 of these patients recovered fully and 8 patients downgraded from grade 2 to grade 1 radiation dermatitis, thus providing a significant reduction in number of patients with radiation dermatitis ($p<0.001$). It is of note that none of the patients had shown a decrease in grade of dermatitis while on radiotherapy treatment.

Of all the patients, dermatitis was completely prevented in 1/30 (3%) patient (p=0.89). That patient received radiotherapy to the chest wall with 40 Gy in 15#. Rest all patients developed dermatitis of at least RTOG grade 1. Of the 18 patients who developed grade 2 dermatitis at the end of the treatment, 17 (94.4%) recovered till end of 2 weeks such that only one patient had grade 2 dermatitis at the end of the radiotherapy treatment. In total, 9/29 (31%) patients were absolutely freed from any sign of dermatitis at the end of 2 weeks following continuation of application of green tea extract ($p<0.001$).



	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Dermatitis	0	3	15	25	27	26	21	16	6
Pain	3	7	10	12	12	13	6	4	1
Tightness	2	7	10	15	15	15	14	11	4

Figure 2: Graphical representation of cross-sectional data of number of patients with each toxicity being studied at each week from the start of radiotherapy

Patient Reported Symptoms

New Onset Pain

For patient reported symptoms, assessed by STAT; three patients experienced new onset pain at the site of radiation therapy in first week, four patients experienced in second week, three patients in third week and two in fourth week. At the end of radiotherapy treatment, two patients had local pain with STAT score of 3; four patients with STAT score of 2; and seven patients with STAT score of 1. Total 17 patients did not develop any new onset pain at the site of radiotherapy treatment, neither alone, nor associated with dermatitis ($p<0.03$). Rapid relief was observed in pain at the site of radiation as soon as the radiotherapy treatment was completed ($p<0.001$). 2 weeks after completion of radiotherapy treatment, no patients had pain with STAT score of 3. Graphical representation is shown in Figure 2. One patient had STAT score of 2 and two patients had STAT score of 1. In total, 10 patients recovered from the new onset pain developed during the radiotherapy treatment at the end of 2 weeks post completion of radiotherapy treatment.

13/30 patients (43.3%) developed new onset pain at the end of treatment($p<0.03$). Of these, 10 (76.9%) patients were relieved of the pain at 2 weeks. Rest 3 (46.7%) patients experienced decrease in severity of symptom as well as the STAT score.

TIGHTNESS

15 patients did not experience any tightness at the site of radiotherapy ($p<0.05$). Two patients developed subjective sense of tightness in first week itself. Five patients developed tightness in second week, three patients in third week, five patients in fourth week, following which the patients gradually started to recover from this subjective tightness ($p<0.005$). Graphical representation is shown in Figure 2. At the end of radiotherapy treatment, eight patients developed tightness of STAT score 1, four patients developed STAT score 2 and three patients developed STAT score 3. At 2 weeks follow up, 11 patients developed radiation dermatitis of STAT score 1. Three patients had STAT score 2. No patient had tightness of STAT score 3.

15/30 patients (50%) developed tightness during the radiotherapy treatment till the end of treatment ($p<0.05$). 1/15 patients (6.66%) following treatment recovered fully from symptom of tightness. 3/3 patients (100%) of STAT score 3 recovered and decreased in score ($p<0.001$).

The test of significance done for each of the study parameters suggest that green tea extract is successful in preventing symptoms of acute radiation dermatitis such as new onset pain and tightness. Though not all patients could be

prevented against the symptoms. This is shown in tabulate form in Table 4. It was then further studied that whether there is / are any predictor / prognostic treatment or patient related factors; which are correlated with response to green tea extract.

The variables included in the univariate and multivariate analysis for pain and tightness include age, sex, concurrent chemotherapy, ECOG PS, dose, site, and hypo fractionation. None of the recorded characteristics predicted significantly the prevention of pain or tightness at the radiation site, though there was a non-significant trend towards more incidence of symptoms in cases of patients receiving concurrent chemotherapy and those receiving more than 60 Gy dose of radiation. Univariate as well as analysis for new onset painand for tightness were done, but none of the parameters were significant.

Table 4: Paired t-test for testing the significance of toxicities preventedby application of green tea extract gel

S. No	Toxicity	Number prevented	P value
1	Dermatitis	1	P=0.89
2	New onset pain	17	**P=0.03**
3	Tightness	15	**P=0.05**

SAFETY

None of the patients developed hypersensitivity at the site of radiotherapy treatment. No patient out of 30 developed any kind of skin reaction at the control site outside the radiotherapy field ($p<0.001$).

DISCUSSION

Green tea as a beverage is generally regarded as safe and healthy, and the oral administration of EGCG concentrated green tea/green tea extract is available commercially as a dietary supplement. In this study involving patients undergoing radiotherapy treatment for various sites, we found that green tea extract gel was well tolerated by the patients, with no adverse cutaneous reactions at the treatment site. None of the patients experienced hypersensitivity or acute reactions to the green tea extract gel. This finding is in congruence with the Phase 1 and Phase II trials of green tea extract performed in 2015 in China in breast cancer patients [19, 21]. The inertness of the product is in line with randomized trials done for topical green tea extract / EGCG as various sites of the body.

The extensive literature review for treatment options of radiation dermatitis have identified many topical agents for the management of acute radiation dermatitis. Use of topical corticosteroids [25-29], washing with mild soap and water [30], and silver nylon dressings [31, 32] have proved effective in reducing the severity of radiation dermatitis and the associated symptoms. Several other agents, including calendula [33], catechins [34], β-sitosterol [35], Hyaluronic acid [15], Epidermal growth factor [36], GM-CSF [37], statins [38], and silver sulfadiazine[39], may potentially be useful in managing acute radiation dermatitis, as respective studies have demonstrated positive results. However, additional, confirmatory studies are needed before asserting their clinical efficacy. It was also evident that aloe vera [40], chamomile [41], ascorbic acid [42], pantothenic acid [18], trolamine [43, 44], and sucralfate [45] have not been proved useful in the management of radiation dermatitis.

Therefore, studies investigating new and more efficient treatment strategies/ topical agents to prevent and/or treat radiation skin toxicity are increasing. EGCG along with other catechins found in green tea extract has a scavenging activity for superoxide anion, hydroxyl radical and hydrogen peroxide. It can protect the DNA against radiation injury by intercalating into the DNA, binding to the free radicals or repairing the damage due to free radicals. Clinical study showed that oral administration of EGCG, was found to be feasible and safe in treating oesophagitis during concurrent chemo radiotherapy in patients with unresectable Stage III non-small-cell lung cancer (60). Topical EGCG have demonstrated activity in reducing radiation dermatitis in patients undergoing radiotherapy to chest wall post mastectomy in breast cancer patients after the patients developed grade 1 dermatitis (30).

In our study, we started application of green tea extract gel from the start of radiotherapy treatment. More than half of the cohort developed grade 2 dermatitis but as soon as treatment was completed; with continuation of application of green tea extract gel over the radiation area; more than 95% of the patients recovered from Grade 2 dermatitis. Nearly 50% of patients recovered fully from any signs of radiation dermatitis. More than 50% of patients did not experience pain at the radiation site during the treatment, indicating that green tea extract gel was successful in preventing symptom of pain at the site of radiation. Of those who had pain, nearly 80% recovered and symptom of pain completely alleviated within 2 weeks after completion of radiotherapy treatment. Significant number of patients did not experience subjective sense of tightness at the site of radiation, highlighting the efficacy of the green tea extract gel in preventing the onset of tightness. 50% of patients experienced tightness of the skin at the site of radiation during the radiotherapy treatment. Most patients developed tightness mostly near the end of the treatment and were relatively slow to recover. At 2 weeks

after the completion of treatment, 1 patient was fully relieved of the symptom of tightness. Other patients experienced improvement in the symptom.

There are several limitations of the study. The field borders are not very well defined in VMAT and IMRT planning, especially in VMAT plans. Cohort of patients in this study were all planned by VMAT technique, thus leading to lower doses of radiation to a particular skin area, but a larger area of skin being irradiated with low dose of radiation(68); which may have resulted in favourable results. The layering of the gel applied by the patients may be non-homogenous and thickness of the layer formed may not be uniform, as this can lead to unequal doses of green tea extracts being absorbed in the epidermis. The sites and doses used are variable and thus the dose received by the skin is variable in all cases. Self-resolution of the skin effected by the radiation dermatitis might also attribute to the result of promising activity and may result in confounding.

The scope for future studies is the notion that green tea extract gel helps in preventing distressing symptoms of radiation dermatitis such as pain and tightness at the radiation site and can also be used as treatment of radiation dermatitis. Further phase II and phase III trials may be done to validate the findings, with more patients and a comparator arm. Further studies may be planned with even higher dose of green tea extract gel since none of the patient seem to develop any adverse reaction against the green tea extract gel.

CONCLUSIONS

The Green tea extract Gel shows an excellent safety profile, with none of the patients in our study cohort developing an adverse skin reaction or blood parameter changes with the topical application of green tea extract gel. Topical administration of green tea extract gel, titrated according to EGCG concentration seems to be a feasible for treating acute radiation dermatitis in patients with various subsites of cancer, such as head and neck cancers, breast cancers and cervix cancers. Green tea extract gel also seems to both prevent and treat the symptoms such as new onset pain and tightness of the skin at the radiation site associated with or without acute radiation dermatitis at the site of radiotherapy treatment.

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