



# Modulation of radiant oncological therapy through the intervention with substances of vegetable origin

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## ABSTRACT

**Introduction:** the search for substances that modulate the adverse effects of radiotherapy is key to optimizing the efficacy of these treatments and improving the patient's quality of life. We consider the evaluation of green tea (*Camellia Sinensis*) opportune for its antioxidant and anti-inflammatory properties, while its composition in polyphenols would make it possible to reduce radiosensitivity and improve cell recovery. Thus, our objective was to assess the efficacy of this infusion in the management of mucositis developed during radiant treatment of patients with head and neck cancer. **Materials and Methods:** a prospective and controlled clinical trial was carried out on a population of 20 patients, under treatment with intensity modulated radiation (IMRT). The result of the intervention with green tea rinses (4 times/day) or compliance with the usual protocol, was assessed by detailed recording of radiotoxicity, using the RTOG scale. Statistical analysis was performed using the T-Test: Student's t-Mann-Whitney U. **Results:** all the patients who adhered to and exhaustively complied with the protocol with the infusion, although they did not significantly recover the state of the oral cavity, demonstrated better control of the radio-induced acute effects (xerostomia and mucositis). **Conclusion:** although our results are preliminary, they allow us to suggest that from the intervention with green tea, the acute radiation-induced effects could be modulated. We believe intervention with this substance is opportune, given its easy administration, availability, cost, and lack of toxicity in a wide range of doses.

**Keywords:** green tea, radiomodulator, radiotherapy.



## 1. INTRODUCTION

Although radiotherapy plays a fundamental role in modern oncology [1], the adverse effects of radiation on normal tissues limit its clinical efficacy. Complications such as irritation, pain, or discomfort can restrict or interrupt these medical protocols and reduce the tumoricidal effect [2-3]. In the case of head and neck irradiation, after one or two weeks, acute radiotoxicity may arise, accentuating morbidity significantly. Radiotherapy interrupts the rapid multiplication of tumor cells, but simultaneously affects cells of the oral lining, preventing tissue recovery. The most frequent lesion is mucositis (Image 1), which begins with a reddening of the mucosa and progresses to uncomfortable wounds as the dose accumulates [4]. On the other hand, irradiation on the maxilla alters the salivary glands, inducing xerostomia and hypogeusia and modifies the dental pieces. All these symptoms must be controlled to avoid infections, late lesions and malnutrition [5, 6].

Pharmacological interventions for the prevention and treatment of these effects include various topical agents such as moisturizing creams or lotions, anti-inflammatory emulsions, oral rinses, analgesics, and sialagogues, but there are still no standardized recommendations for their administration. Also, many compounds have not demonstrated their clinical efficacy. For this reason, the identification of radioprotectors is urgent and in this sense, substances of plant origin offer a reliable solution, as they are usually safer and cheaper than synthetic products. In addition, its antioxidant, anti-inflammatory and anti-proliferative properties are the most appropriate for optimizing the radiotherapeutic quotient [2, 7].

In view of the above, green tea derived from unfermented leaves of *Camellia sinensis* is a source of polyphenols with various properties. Among them, the detoxification of free radicals, the induction of antioxidant enzymes, the modulation of the inflammatory and immune response and DNA repair. These characteristics are of great value in relation to radioprotection [8, 9, 10]. Similarly, polyphenols can induce tumor cell death without affecting healthy cells. The pathways through which the beneficial effects of green tea in relation to radiotoxicity are established are complex and involve various biological processes [6, 11].

On the other hand, from the preclinical and clinical level there is evidence of the efficacy of green tea to treat the acute effects induced by radiation [12-13]. Its topical application has been observed to relieve radiation-induced burns and dermatitis in patients with breast and lung cancer

[2, 8, 10]. Its use is safe and well tolerated, and it also allows for the control of symptoms such as burning, itching, and sensitivity induced by radiotherapy [2, 8]. Also, its antibacterial activity has been reported in skin lesions and in the oral cavity [9-15].

In view of the previously mentioned reasons, we believe that the study of green tea in its radiomodulatory potential for head and neck cancer is valuable, while an effective prophylactic or therapeutic strategy is not yet available in the management of induced clinical toxicity by radiation therapy. We consider it is urgent to improve the quality of life of these cancer patients.

## 2. MATERIALS AND METHODS

A prospective and controlled clinical trial was carried out on a population of 20 patients with head and neck cancer, undergoing radiation treatment in the affected area, from June 2022 to October 2022. The inclusion criteria were: age  $\geq 18$  years, normal nutritional status or grade I overweight, normal hematological, renal and hepatic values. Exclusion criteria were positive deep margins, pregnancy or lactation, known allergy or hypersensitivity to epigallocatechin 3-gallate (EGCG), inflammatory, infectious, mental diseases, diabetes, hypertension and smoking, as well as specific pathologies. Patients with large planning volumes or surface irregularities were also excluded. Information associated with the tumor (type, size and location), concomitant treatments and details of radiotherapy (technique, total dose and fractionation) was recorded.

In those patients who gave their consent to participate in the study, from the beginning of the treatment and on a weekly basis, the analysis and recording of local and systemic radiotoxicity was carried out; primarily the development and progression of mucositis and xerostomia were assessed using the Radiation Therapy Oncology Group (RTOG) scoring system. The study involved the control group (usual radiotherapy treatment) and the study group, with indication of intervention with green tea. The assignment of individuals to each of these groups was carried out in alternative order, after the patient was referred for radiotherapy administration.

From a homogeneous batch of the mentioned product, the rations to be administered daily during the entire radiotherapeutic treatment were prepared (5-gram sachets of intermediately ground leaves). These sachets were administered from the beginning and during the weekly monitoring of the patient

under intervention with the infusion. It was prepared daily with one liter of quality water at 70°C, and once cold it was kept at 4°C in the dark. With this preparation, at least 4 mouth rinses were performed per day. Likewise, all patients received a standard care program for the affected area.

Statistical analysis was performed using the T-Test: Student's t-Mann-Whitney U. Considering that this study comprises the preliminary stage of a larger investigation, it is expected to improve the number of patients subject to the proposed intervention. In terms of limitations, the low number of individuals reflects the healthcare situation in the sampling locations.

The study has the evaluation and approval of the "Central Committee of Bioethics in Biomedical Practice and Research" of the Ministry of Health of Entre Ríos, a province in Argentina's northeastern Mesopotamia region, between the Paraná and Uruguay rivers. In reference, the certified centers for the recruitment of patients and associated information were the Entre Ríos Nuclear Medicine Center (CEMENER) and the Association to Fight Cancer (ALCEC). Both institutions are located in Entre Ríos, Argentina.

### 3. RESULTS AND DISCUSSION

Consistent with data from the American Cancer Society, the average age of the participants was 62 years, with an age range of 45 to 78 years. In terms of gender, 66.67% were male, and 33.33% were female [16].

In all cases, the therapeutic approach for these patients was resolved using IMRT, the preferred technique used in each institution. In ALCEC the dose was administered through 25 consecutive sessions of 200 cGy/ day by IMRT and subsequently 10 more sessions of a 3D boost of 200 cGy/ day. On the other hand, in CEMENER the protocol was adjusted to 33 sessions of 212 cGy daily. Thus, the aim is to achieve a tumoricidal dose of approximately 70 Gy. Stability conditions and normal physiological parameters were maintained. Likewise, the vast majority of cases presented the condition of low nutritional risk according to Malnutrition Screening Scale (MST).

An in-depth analysis of those patients who complied with the intervention with green tea reveals a very good adherence of the patients to compliance with the protocol, only one patient did not agree to participate in the study. All those individuals who did decide to participate correctly

complied with the proposal of four daily mouth rinses, with infusions prepared according to the instructions given.

Regarding the objectives of the work, the results obtained allow us to agree with other authors [17, 18] in that *Camellia sinensis* has potential as a natural radioprotective agent and can be used as a complement to radiation during cancer treatment.

All the patients who complied daily and exhaustively with the protocol with the infusion of green tea (12 individuals), although they did not significantly recover the state of the oral cavity, demonstrated better control of the radio-induced acute effects, such as xerostomia and mucositis.

Regarding the latter, they were able to reach an average dose of 2692 cGy without symptoms of radiotoxicity, while in the control group (8 patients), lower values were reached (1980 cGy), the parameters of these group are detailed in (Table 1). Consequently, the group under study showed a greater tolerance to radiation treatment, being able to advance without interruption to higher dose values, and therefore, a greater probability of disease control. In temporal terms, this radiomodulation of the phytochemical corresponds to a shift in the development of mucositis from the first week to the second week of treatment, (Figure 1).

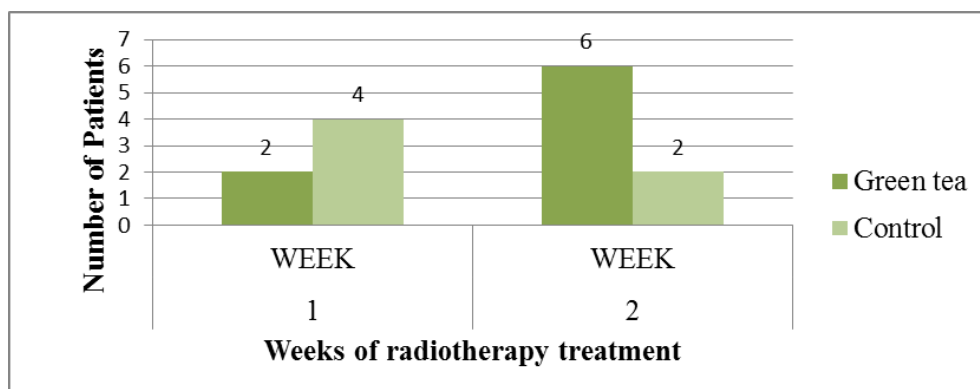
Finally, although the perceptions may be subjective, it is important to mention that all the patients reported sensations of relief and improvement after treatment with green tea.

**Table 1:** Radiotoxicity parameters of the study group with green tea and control.

Sex	Age	Tumor type	Stage	TNM	Treatment	Green tea		
						Toxicity	cGy dose	Session
W	45	Jugal mucosa - squamous	III	T3 N0 M0	IMRT	MII	1908	9
M	65	Jugal mucosa - squamous	I	T1 N0 M0	IMRT - BOOST 3D	MII-III	4000	20
W	66	Amygdala	III	T3 N0 M0	IMRT	MI	2400	12
W	65	Larynx - supraglottis	III	T3 N0 M0	IMRT - BOOST 3D	MII	2800	14

W	73	larynx and vocal cords	III	T3 N0 M0	IMRT	MI	3800	19
M	78	vocal cords			IMRT	MI	2200	11
M	70	Larynx	IVA	T3 N2c M0	IMRT	MI	2968	14
M	64	Language	IV A	T3 N2a M0	IMRT	M0-I	1200	6
M	57	Language	* X	X	IMRT - BOOST 3D	MI	2800	14
M	63	Language	IVA	T4a N2b M0	IMRT	MI	1272	6
M	72	Nostril	III	T3 N0 M0	IMRT	MI	2756	13
M	65	Parotid	IV A	T2 N2a M0	IMRT	M0	4200	21
						<b>Control</b>		
M		Soft palate	IVB	T3 N3a M0	IMRT	MI	1696	8
W	65	Soft palate	X	X	IMR - BOOST 3D	Da* I	1200	6
M	63	tonsillar pillar	II	T1 N2 M0	IMRT	M I	2756	13
W		amygdala	III	T3 N1 M0	IMRT	MI	2600	12
W	59	supraglottis larynx	III	T3 NX M0	IMR - BOOST 3D	aborted	2000	10
M	69	Larynx	IVB	T3 N3 M0	SIB-IMRT	M I	2544	12
M	50	Language	IVA	T2 N2b M0	IMRT	M I	1544	8
M	55	Language	X	X	IMR - BOOST 3D	MII	1400	7

The data obtained from the study and control patients are described below. The columns detail age, sex, tumor type, TNM, stage, manifestation of toxicity, dose and session. \*GI= Gastrointestinal, \* Da= Dysphagia. \*GI= Gastrointestinal, \* Da= Dysphagia.

**Image 1:** *Patients with mucositis Grade I***Figure 1:** *Manifestation of acute effects induced by radiation.*

#### 4. CONCLUSIONS

As mentioned, the positive health effects of *Camellia sinensis* are widely known, through its action on various pathologies and physiological problems [19]. Given that they are mainly attributed to the abundant content of antioxidants, we can infer the great potential as a radioprotector that this substance presents. In relation, although our results are preliminary, they allow us to suggest that from the intervention with green tea, the acute effects induced by radiotherapeutic treatments in head and neck cancer could be modulated. Given the clinical pictures presented by these patients, we believe the proposal of simple interventions that are feasible to

implement is appropriate, as they facilitate the adherence and compliance of the patients and therefore guarantee greater effectiveness in the intervention.

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