

Original Research

The Value of *Camellia sinensis* in the Management of Toxicity Induced by Cancer Treatments

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2025, volume 10, issue 4
doi:10.21926/obm.icm.2504052**Received:** June 17, 2025**Accepted:** November 27, 2025**Published:** December 02, 2025

Abstract

While radiotherapy is one of the main treatments for head and neck cancer, adverse effects limit its effectiveness and affect patients' quality of life. Although various radioprotective substances have been proposed, comprehensive strategies are needed to modulate radiotoxicity. In this regard, compounds from green tea (*Camellia sinensis*), with antioxidant, anti-inflammatory, and antiproliferative properties, could be suitable for optimizing the radiotherapy relationship. A descriptive, prospective study was conducted with a group of 50 patients with head and neck cancer, predominantly male (64%) and with a mean age of 63 years. All these individuals were referred for radiotherapy and agreed to participate in an intervention protocol with green tea mouth rinses (5 g/L/day) and monitoring of acute radiation effects. Toxicity was assessed using the RTOG (Radiation Oncology Group) scale. Pain



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was recorded using the VAS (Visual Analogue Scale). The most significant results concern the delay in mucositis (a critical variable) across most anatomical locations, compared with expectations ($p < 0.05$). Seventy-four percent of the observed lesions were mild. Regarding xerostomia, it manifested primarily as grade I (mild) in 44% of patients. Likewise, only 28% of individuals developed grade I (mild) dermatitis, and 10% developed grade II (moderate). Finally, only 4% of patients experienced severe pain (scale 6-8). Thus, the green tea intervention enabled radiation dose escalation while respecting therapeutic levels and mitigating toxicity that impairs patient well-being. In addition, green tea is readily available and easy to use, making *Camellia sinensis* an effective modulator of treatment for oral carcinomas.

Keywords

Green tea; radiotoxicity; head and neck cancer; radioprotective; radiotherapy; mucositis

1. Introduction

Head and neck cancer (HNC) is a heterogeneous group of malignant tumors arising from the mucosal epithelium of the oral cavity, pharynx, and larynx. Globally, it is the sixth most common cancer and constitutes a significant socioeconomic burden on public health due to the high costs associated with its diagnosis and treatment [1].

Established risk factors for these tumors include alcohol and tobacco use, and human papillomavirus (HPV) infection. All of these factors share oxidative stress as a common biological mechanism that contributes to carcinogenesis by including genomic damage in healthy cells, chronic inflammation, and dysregulation of various cell signaling pathways [1, 2].

Regarding possible therapies, radiotherapy plays an essential role in the management of HNC [3]. However, adverse effects on healthy tissue limit its efficacy [4-6]. Complications such as irritation, pain, or discomfort can limit these protocols and reduce tumor control [7-9]. Specifically, lesions such as dermatitis, mucositis, and xerostomia manifest during treatment [10-13] and must be controlled to prevent infections, more serious lesions, and malnutrition [14, 15].

In light of the above, the search for substances that optimize the radiotherapy ratio is of great interest. That is, compounds that provide specific protection for healthy tissue without altering the tumoricidal effect of high-dose radiation [16-18]. Although various agents have been proposed, standardized recommendations for their administration are still lacking, and many compounds have not demonstrated clinical efficacy [19, 20]. There is an urgent need to evaluate effective and easy-to-implement strategies [4, 5]. In this regard, plant-based substances are often safer and more accessible than synthetic products. Furthermore, their antioxidant, anti-inflammatory, and antiproliferative properties make them suitable for improving the efficacy of radiation therapy [7, 21]. Among the proposed phytochemicals, green tea extracts (*Camellia sinensis*) have been shown to improve oral health in patients with cervical cancer [2]. Its effectiveness is associated with its high content of polyphenols, such as (-)-epigallocatechin (EGC), (-)-epicatechin (EC), (-)-epigallocatechin-3-gallate (EGCG), and (-)-epicatechin-3-gallate (ECG) [1, 2].

Regarding prevention, green tea has been reported to have a protective effect against cancer [6]. It is proposed that the antitumor activity of EGCG lies in the inhibition of the activation of tyrosine kinase receptors, such as VEGFR (Vascular Endothelial Growth Factor Receptor) and EGFR (Epidermal Growth Factor Receptor) [1]. Overexpression of the latter has been demonstrated in some CCC tumors [4]. EGCG also inhibits NF- κ B (nuclear factor kappa B) activation and nuclear translocation and suppresses MAP kinase pathways, thereby preventing the transcription of metalloproteinases (MMPs) expressed in oral cancers [1, 4]. In addition, the induction of apoptosis in tumor cells would be a significant aspect in optimizing the radiotherapy.

Concerning this last point, there is preclinical and clinical evidence of the efficacy of *Camellia sinensis* in treating acute radiotherapy effects [1, 3, 4, 22-25]. Its topical application relieves radiation-induced burns and dermatitis in patients with breast and lung cancer [7, 8, 26]. In this case, the mechanisms of action are based on the activity of polyphenols, which eliminate a wide range of reactive oxygen species via their hydroxylated aromatic groups [27]. An improvement in the performance of antioxidant enzymes has also been corroborated [2]. It is proposed that green tea flavonoids suppress oxidative stress by inducing several pathways, such as protein kinase C δ /acid sphingomyelinase (PKC δ /ASM) and protein kinase B/ B/endothelial nitric oxide synthase (Akt/eNOS) [2]. Furthermore, although there are some discrepancies [2], it is proposed that green tea catechins improve the inflammatory status [8, 26, 28-32] by suppressing the expression of NF- κ B (active production of pro-inflammatory cytokines/enzymes, such as IL-1 β , TNF- α , MMP-9 and cyclooxygenase-2) [2].

For the reasons mentioned above and the need to validate inconclusive clinical data [7, 9, 10], we consider it appropriate to focus on evaluating the radiomodulatory potential of *Camellia sinensis* for oral carcinomas, as there is still no effective strategy to control clinical toxicity in these patients.

2. Materials and Methods

2.1 Study Population

A prospective and descriptive clinical study was conducted on a population of 50 patients diagnosed with head and neck cancer and indicated for intensity-modulated radiation therapy (IMRT). This group of individuals was recruited from August 1, 2022, to March 31, 2025. The sampling centres were two cancer institutes located in the provinces of Entre Ríos and Santa Fe (Argentina). Patients of both sexes, ranging in age from 25 to 82 years, with tumours located in the larynx, oropharynx, tonsils, tongue, floor of the mouth, gingiva, and palate were included.

Inclusion criteria were: individual ≥ 18 years of age with the ability to fully understand the study and voluntary consent to participate, ECOG score (Eastern Cooperative Oncology Group) 0 to 2, initiation and compliance with radiation treatment; no prior irradiation; standard hematologic, renal, and hepatic variables. Exclusion criteria were: pregnancy or breastfeeding; known allergy or hypersensitivity to epigallocatechin-3-gallate (EGCG); and a history of specific pathologies. Patients with large planning volumes, deep surface irregularities or folds, and those unable to open their mouth more than 1 cm were also excluded.

2.2 Studies Conducted

Extensive observation of the oral cavity included comfortable patient positioning, the individual facing the physician frontally, and recording all exposed surfaces under internal lighting. Each examination began with the treated anatomical area, its borders, and adjacent areas, then moved to the opposite surfaces, and ended with the lateral margins.

Local radiotoxicity (mucositis, xerostomia, and dermatitis) was recorded using the Radiation Therapy Oncology Group (RTOG) scoring system [33]. Mucositis was classified into five grades: Grade 0: no mucosal changes; Grade I: erythema and mild pain; Grade II: irregular mucositis, inflammatory or bloody discharge, and moderate pain; Grade III: confluent fibrous mucositis and severe pain; and Grade IV: ulceration, necrosis, and bleeding [5, 33]. Systemic effects (asthenia, dizziness, and fatigue) were also recognized, and the Visual Analog Scale (VAS) was used to assess pain (Figure 1). This scale allows pain to be evaluated, from its mildest form to its most severe or profound form [5, 33-35].

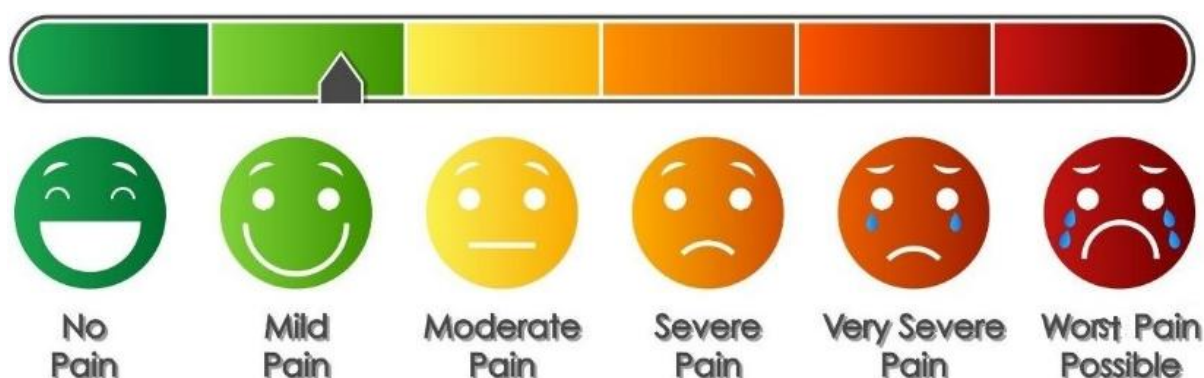


Figure 1 Visual Analog Scale (VAS). Used for pain assessment in patients, extracted from the Academy IFSES 2024 [36].

The variables considered were recorded weekly from the start of radiation treatment until its completion (6th to 7th week) or until the resolution of adverse symptoms. Furthermore, extrinsic factors that influence individual radiosensitivity were considered, such as total dose and fractionation, concordance with chemotherapy, tumour size, Tumour/Node/Metastasis (TNM) stage, and exposure to carcinogenic risk factors (tobacco, alcohol, and PVH). Finally, the Nutritional Risk according to Malnutrition Screening Too (MST) was observed, as shown in Table 1, and the % weight loss was calculated ($[(\text{Initial Weight} - \text{Current Weight}) / \text{Initial Weight}] * 100$) (%WL).

Table 1 Malnutrition Screening (MST).

Have you recently lost weight unintentionally?	
No	0
Unsure	2
If yes, how much weight have you lost?	
1 a 5	1
6 a 10	2
11 a 15	3
>15	4
Unsure	2
Weight loss Score:	
Have you been eating poorly because of a decreased appetite?	
No	0
Yes	1
Appetite Score	
Total score:	

This instrument was administered to each volunteer at the beginning of and during cancer treatment. MST = 0 or 1, no risk. MST $\geq$ 2 at risk of malnutrition.

2.3 Green Tea Intervention Protocol

Patients included in the study protocol (ST) received, from the start of treatment and at each weekly follow-up, seven sachets containing 5 grams of medium-ground green tea leaves, to prepare one liter of infusion per day. The entire experimental development was carried out using a homogeneous batch of *Camellia sinensis*. Detailed instructions on preparation were also provided (place the sachet in water at 70°C for 10 minutes, allow to cool, and store at 4°C in the dark until use). Patients were prescribed four mouthwashes daily and a cold beverage. Patients were also advised not to use mouthwashes containing alcohol and to avoid tobacco, alcoholic, acidic, or carbonated beverages, artificial sweeteners, dry, sticky, sugary, or spicy foods, and exposure to extreme temperatures (hot and cold).

2.4 Oncological Treatment

All patients underwent intensity-modulated radiotherapy (IMRT) at 2 Gy/day, 5 days a week for 5 to 7 weeks, achieving a total dose of 60 to 70 Gy. The clinical target volume (CTV) was defined from CT scans according to the International Commission on Radiation Units and Measurements' (ICRU) criteria. The organs at risk to be considered in the planning were: spinal cord, brainstem, optic nerves, optic chiasma, orbits, mandible, and parotid glands. All GT patients undergoing chemotherapy received Cisplatin, and 7 patients underwent surgery before starting IMRT.

2.5 Statistical Analysis

Statistical analysis was performed using the Chi-square test, and descriptive analyses were performed using Microsoft Excel 2013.

2.6 Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by the Ethics Committees of the Province of Entre Ríos (No. 831-16) and the Province of Santa Fe (No. 4555).

3. Results

3.1 Clinical Variables and Risk Factors Reported in Patients Exposed to Green Tea (GT)

3.1.1 Sex and Age

First, it should be noted that the gender distribution of patients enrolled in the research protocol corresponds to a male-to-female ratio of 64% to 36% (approximately 2:1). Furthermore, in line with data published by the American Cancer Society (2023), the average age of the individuals was 63 years, with no significant difference between the sexes [37].

3.1.2 Risk Factors

Regarding relevant risk factors for these pathologies, interviewees were reluctant to provide information on alcohol and tobacco use: in 34% of cases, no data could be collected. While 32% and 44% of individuals admitted to using alcohol and tobacco, respectively, 34% and 22% categorically denied these habits. Regarding HPV infection, information was collected in only 4% of cases, given the complexities of performing molecular testing on these patients.

Regarding the MST, scores >2 were observed in 65% of patients, while the remaining 35% had scores <2. At the same time, 46% of patients experienced weight loss greater than 5%.

3.1.3 Tumour Location – TNM Stage

Tumour locations within the oral cavity were as follows: larynx (36%); tonsil (26%), tongue (22%); and floor of the mouth, palate, and gingiva (16%). With respect to the TNM system, 10% of tumours were Stage I, 18% were Stage II, 16% were Stage III, and 16% were Stage IV. A small percentage of tumours were relapsed (4%), and 36% had no precise data (TX).

3.2 Toxicity Evaluation

3.2.1 Local Toxicity

In these tumours, the critical variable is the development of mucositis. This acute effect was observed, on average, around the fourteenth radiotherapy session (2800 cGy). More specifically, and according to RTOG criteria, Figure 2 shows the kinetics of this effect. Mild mucositis was observed in 74% of patients, with a rise between the second and third weeks of treatment. These lesions resolved or progressed to more severe stages in only 15% of patients. No extreme toxicity (grade IV) was observed, and 14% did not present mucosal changes. No significant differences in mucositis development were found by tumour stage.

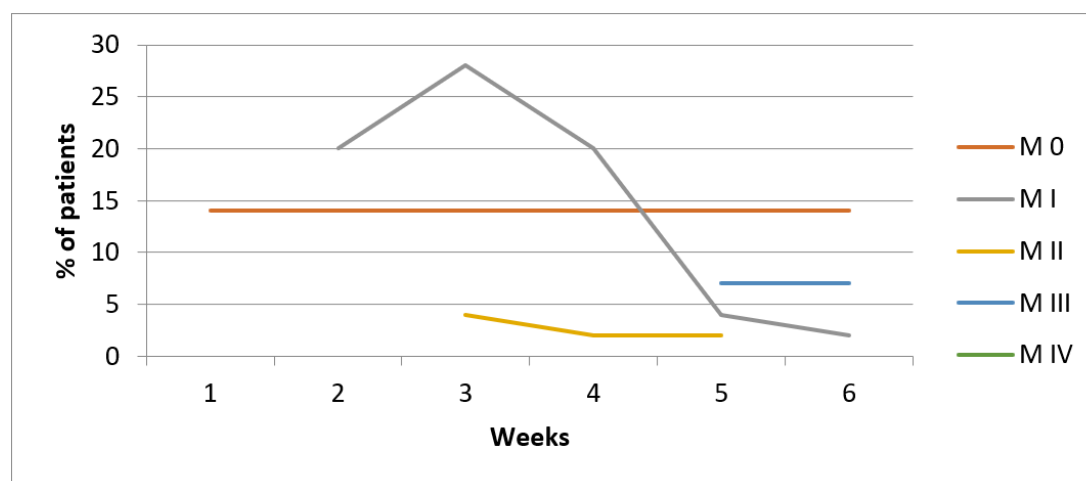


Figure 2 Point at which mucositis manifests during follow-up of patients undergoing radiotherapy treatment. Simultaneously, observe the severity of the lesions. The grades are: M 0: no mucositis; M I: erythema; M II: non-contiguous patchy reaction; M III: confluent mucositis; and M IV: ulceration, necrosis, or bleeding.

Among the interesting findings, differences ($p < 0.05$) were observed in the development of mucositis by anatomical location. A decrease in toxicity, compared to expected, was observed in the larynx, tonsils, and floor of the mouth. Thus, 36% of patients treated in the larynx reached the seventeenth radiotherapy session without lesions. In the tonsil group, 26% of patients progressed to the fifteenth RT session without lesions. In tongue cancer, 22% of patients reached the tenth session without mucositis. Finally, considering areas such as the floor of the mouth, gums, and palate, 16% of individuals reached the twelfth session without lesions (Table 2).

Table 2 Number of sessions achieved and escalated dose according to anatomical location.

Location	N	%	Session N° (average)	Escalated dose (cGy)
Larynx	18	36	17	3482
Tonsil	13	26	15	2984
Tongue	11	22	10	1990
Floor of the mouth, gums, and palate	8	16	12	2935

Additionally, considering the recovery process for these lesions, it is noteworthy that only 22% of patients had to discontinue radiotherapy. The mode value for this point is 20. Moreover, the greater toxicity of the combined treatment with chemotherapy was confirmed ($p < 0.05$).

Regarding other manifestations of radiotoxicity (Figure 3), 44% of patients developed grade I (mild) xerostomia, 8% grade II (moderate), and 48% were asymptomatic. At the same time, only 28% of patients presented with grade I (mild) dermatitis, and 10% with grade II (moderate). It is noteworthy that the reported toxicity refers not only to radiation-induced toxicity but also to chemotherapy. In single radiotherapy treatments (26% of all cases), mucositis developed in 61% of individuals, and xerostomia in 15%. Three individuals (23%) did not experience acute toxicity.

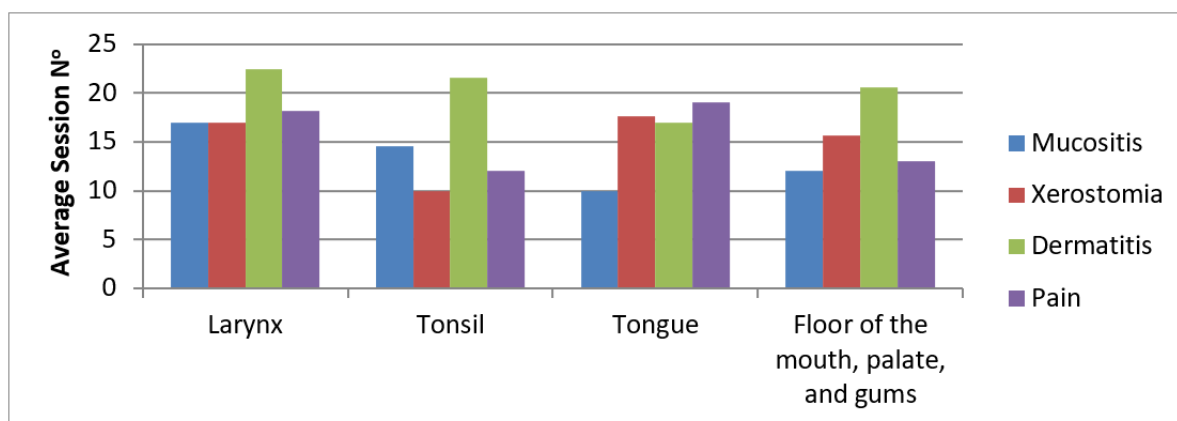


Figure 3 Toxicity to the progress of treatment. Prevalent acute effects according to the anatomical area, in relation to the progress of the treatment.

3.2.2 Systemic Toxicity

Of all the effects evaluated (asthenia, dizziness, and fatigue), significant differences ($p < 0.05$) were only observed for nausea and vomiting. In all cases, the treatments were RT + CT.

3.2.3 Pain

According to the scale implemented to assess this symptom (VAS), pain could only be verified in patients who had undergone RT + CT. While 16.2% of patients reported mild pain (scale 2-4), 13.5% reported moderate pain (scale 4-6), and 4% reported severe pain (scale 6-8). In contrast, 66.3% of individuals reported no discomfort.

4. Discussion

Head and neck cancer is a complex clinical problem, not only due to its high incidence but also due to its prognosis, which is often unfavourable [38]. This pathology seriously compromises the patient's quality of life, given its proximity to organs with essential functions [39]. Given the above, raising awareness about the risk factors for these tumours would be of great value and would facilitate access to sensitive information about certain habits (tobacco and alcohol). Furthermore, it is necessary to strengthen health registries and some diagnostic tests for HPV infection. This virus is critical for the development of the disease and its therapeutic outcome [40]. Also, in agreement with other studies [41], we believe that the socioeconomic and nutritional vulnerability of individuals should be considered from the beginning of treatment.

Regarding the development of treatment toxicity, the influence of tumour location was confirmed [42]. Radiotherapy is known to benefit more than half of cancer patients [43, 44], but side effects affect therapeutic adherence [6, 45, 46] and are potentiated by CT administration [44, 47]. In this sense, strict adherence to green tea rinses and hydration can mitigate these effects and allow a large proportion of patients to progress to higher radiation doses, optimizing therapeutic outcomes.

Oral mucositis (OM) occurs in almost all patients with head and neck cancer undergoing radiotherapy [45], and its severity is expected to increase with cumulative radiation dose [48, 49]. Although treatment discontinuations were higher than reported [11], primarily mild-to-moderate

OM was detected. This may be due to the green tea's attenuating effect. In agreement, it was observed that less than half of the patients (46%) experienced weight loss, and very few individuals required the placement of a nasogastric tube. These more-promising-than-expected results [6] confirm that attention from the beginning of radiotherapy [39, 50] has a positive impact on the quality of life of patients.

About other radiotoxicities relevant to head and neck cancer, a prevalence of xerostomia ranging from 73.5% to 93% has been reported [44, 51]. It could be suggested that the lower values observed in this study (62%) and the lesser severity of xerostomia observed are due to the improved hydration and salivary stimulation provided by green tea.

Concerning pain, it is recognized that suffering affects people psychologically [38, 52, 53]. However, the majority of patients (30%) reported mild or moderate pain and relief from rinsing with the green tea infusion.

For decades, active efforts have been made to control the adverse effects of radiation [19, 20], but the agents discovered to date often have significant side effects or limited efficacy [12, 43]. Given the anti-inflammatory and antioxidant properties of many natural substances [5, 11], we hypothesize that promoting phytochemicals with good tolerance, low toxicity, and high availability would facilitate interventions in this regard. In the case of green tea, studies highlight its radiomodulatory potential [54, 55], as well as its significant value in non-pharmacological treatment for the protection of the oral mucosa [13]. Advances in research will lead to the development of effective strategies that can improve the quality of life of these patients.

Based on the results obtained in this study, we believe that initiating oncological therapies for head and neck cancer with *Camellia sinensis* could help reduce the side effects of these treatments.

Acknowledgments

The authors thank the authorities of the CEMENER and UTO for giving access to the clinical record and treatment data. We thank Professor Evelyn Ceballos for reviewing the manuscript's writing.

Author Contributions

Authors CB and MG collaborated on the toxicity assessment. Author SB interviewed and followed up with the patient; recorded and organized all clinical and demographic variables; performed the statistical analysis; and co-authored the article with author AG, who designed and led the study. Also collected the data, designed the analysis, and co-authored the article with author.

Competing Interests

The authors report no conflicts of interest related to this publication.

AI-Assisted Technologies Statement

The authors did not use generative artificial intelligence or any AI-assisted tools in the writing process of the paper.

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