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Commentary

What is the Impact of Smoking During Radiotherapy on the Radiation-Induced Acute Severe Toxicities in Head and Neck Cancer Patients? Is it Safe or Harmful?

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Highlights

- Smoking exacerbates radiotherapy-related acute toxicities
- Smoking causes increased DNA damage, impaired repair mechanisms, hypoxia, enhanced inflammation, oxidative stress, microvascular damage, and immune suppression.
- Smoking cessation and tailored supportive care can significantly improve patient outcomes and quality of life during radiotherapy
- To unravel the complex interactions between smoking and radiation therapy, it is becoming clear that smoking cessation is a critical step in improving the effectiveness and tolerability of cancer treatments

Dear Editor-in-Chief,

While radiation therapy (RT) serves as the cornerstone in the management of head and neck cancers (HNCs), the acute and severe toxicities associated with this modality can significantly impact both the patient's quality of life and treatment outcomes [1]. The most common toxicities included in this list are mucositis, dermatitis, xerostomia, and dysphagia, among other rarer conditions [2]. There is almost unanimous agreement that smoking during and after RT enhances long-term RT-induced toxicities' incidence and severity. On the contrary, although growing evidence suggests that smoking may exacerbate acute toxicities as well, contradictory results have also been documented. Furthermore, the full scope and underlying mechanisms of the heightened rates of acute toxicities resulting from persistent smoking during RT have not been comprehensively elucidated [3], underscoring the significant gap in knowledge in the current literature on this highly relevant topic.

The combination of RT-induced tissue damage and the harmful effects of smoking can have a synergistic impact on acute toxicities, making them more severe and difficult to manage [4]. It is believed that smoking-induced chronic inflammation, impaired tissue oxygenation, and compromised healing processes can contribute to increased rates of acute and chronic RT-induced complications. Various complex pathophysiological mechanisms may underlie the synergistic effect between RT and continued smoking in terms of increased rates and severity of acute toxicities in HNC patients.

These mechanisms can be outlined as follows.

Tobacco smoke contains numerous carcinogens and toxic compounds, such as polycyclic aromatic hydrocarbons and nitrosamines, which can directly damage deoxyribonucleic acid (DNA) and impede tissue repair [5]. RT induces more pronounced DNA damage in cancer cells than neighboring healthy tissue cells due to their higher sensitivity to radiation and inhibits their proliferation through the fixation of RT-induced double-strand DNA breaks in cancer cells. However, the presence of harmful tobacco compounds and chronic hypoxia may lead to the development of a radioresistant state in cancerous cells [6,7]. A study conducted by Hoff and colleagues revealed a significant negative impact of smoking during RT for HNC [7]. Active smoking was associated with reduced 5-year locoregional control (44% vs. 65%, $p = 0.001$), disease-specific survival (56% vs. 77%, $p = 0.003$), and overall survival (39% vs. 66%, $p = 0.0004$) rates. The authors attributed these findings to diminished oxygen transport in the blood and elevated carboxyhemoglobin levels in smokers, resulting in reduced oxygen supply to tumors, decreased oxygen fixation of DNA damage, and heightened radioresistance. However, impaired tissue repair mechanisms caused by a lack of adequate tissue oxygen in smokers may prolong the repair process and make appropriate tissue recovery more difficult after RT, potentially increasing the prevalence and severity of radiation-induced acute toxicities [8]. In support, Rades and colleagues observed a significant association between smoking during RT and the development of grade ≥ 3 mucositis. Additionally, they noted potential correlations with grade ≥ 2 mucositis and dermatitis [9]. In a similar vein, Pratson., *et al*. [10] observed a higher incidence of acute neck fibrosis in head and neck cancer (HNC) patients undergoing radiation therapy (RT) who were also smokers in comparison to non-smoking patients. The authors attributed this observation to a wound-healing disorder from DNA damage ($p < 0.001$). Thus, smoking during RT appears to be a double-edged sword that reduces the treatment efficacy and outcomes and increases radiation-induced acute toxicities in HNC patients.

Chronic exposure to cigarette smoke induces tumorous and systemic hypoxia, primarily attributed to elevated levels of carbon monoxide present in tobacco smoke. Carbon monoxide exhibits approximately 200-210 times higher affinity for hemoglobin than oxygen [11,12]. The higher affinity of carbon monoxide to hemoglobin leads to a reduction in systemic blood circulation oxygen levels, thereby diminishing the oxygen supply to bodily tissues. Head and neck RT leads to hypoxia of the oral mucosa, and this hypoxia increases p53 stabilization by increasing phosphorylated p53 levels, leading to increased pro-apoptotic Bax expression, and, finally, oral mucositis [13]. Cigarette smoke exposure has been shown to impair angiogenesis by inhibiting VEGF through decreased expression of HIF-1α in hypoxic conditions. This reduction in VEGF levels may not only increase the radiation resistance of tumors but also impair the oxygenation status of injured tissues, leading to a higher incidence and severity of radiation-induced acute and chronic toxicities [14]. This is mainly because the induction of HIF-1α and VEGF appears to be essential for the development of reactive angiogenesis in hypoxic conditions, including radiation-induced tissue injuries. Therefore, it is reasonable to anticipate that RT may exacerbate the already compromised oxygen levels, despite the increased demand for the appropriate healing process, in active smokers, which can induce or exacerbate radiation-induced acute toxicities [15]. Confirming this rational anticipation, Chen., *et al*. observed a higher prevalence of severe radiation-induced mucositis among smokers in comparison to non-smokers ($p = 0.004$) in a cohort of 77 patients with oral cavity cancer [16]. Moreover, smoking was identified as an independent predictor of oral mucositis in this study.

Smoking also elicits a systemic inflammatory response. Specifically, chronic cigarette smoking has been documented to prompt a pro-inflammatory state within the body, characterized by heightened levels of inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [17]. Similarly, RT may provoke a robust local inflammatory response as part of the body's natural process to repair damaged tissue [3]. As a result, the preexisting high inflammatory state in smokers, compared to non-smokers, could exacerbate radiation-induced inflammation, leading to more severe and prolonged acute toxicities [18]. In support, a meta-analysis by Bergman., *et al*. including data from 6,776 patients enrolled in 15 studies, demonstrated that smoking during RT would increase the risk of radiation-induced toxicity by a factor of 1.84 [3].

Chronic smoking leads to oxidative stress caused by the production of reactive oxygen species (ROS). This stress results in cellular damage and disrupts the body's antioxidant defense

mechanisms [19]. Similarly, it is established that RT also induces or exacerbates oxidative stress by producing ROS, which can trigger cancer cell death. Therefore, smoking and RT together create high levels of oxidative stress, aggravating tissue damage and impairing or delaying tissue healing [20]. Previous studies have also ascertained the oxidative stress phenomenon, stating that acute hyposalivation and acute radiation-induced xerostomia detected immediately after RT and before the onset of apparent gland damage is due to salivary gland damage, DNA damage, and increased ROS production [21,22].

Microvascular damage caused by smoking is also a triggering factor that predisposes patients undergoing RT to the occurrence of acute toxicities [23]. Nicotine and other chemicals in tobacco smoke cause vasoconstriction and damage to the endothelium of blood vessels. This leads to impaired microcirculation and insufficient blood flow and prevents the delivery of nutrients and oxygen to tissues and the removal of waste products [24]. Moreover, impaired microcirculation in smokers can impede the repair of radiation-damaged tissues, leading to more severe acute toxicities such as mucositis and dermatitis. Denham., *et al*. [25] have reported that the activation of the coagulation system also plays a critical role in the development of acute radiation reactions. Additionally, it has long been known that RT-induced mucositis's incidence rates and severity depend on the intricate interactions between the various tissue factors, including the oral microflora and the vascular reactions [25]. Therefore, it appears inevitable that smokers may experience more common radiation-related toxicities due to the additional damaging effects exerted by smoking on the vascular structure.

An intact immune response is crucial for controlling infection and aiding in tissue repair after radiation-induced injury. However, smoking suppresses the immune system by diminishing the function of various immune cells, including macrophages, neutrophils, and lymphocytes [18]. The immunosuppressive effects of smoking compromise the regular physiological healing process, increase the risk of secondary infections, and exacerbate acute toxicities [26]. In this context, the specific immune components involved in mucositis development are not fully comprehended, but factors such as smoking have been reported to be influential [27]. It has been noted that RT promotes immune suppression by inducing toxic effects on bone marrow cells and peripheral blood lymphocytes [10,11]. When these immune suppressive effects of RT and smoking are combined, it becomes rational to expect that acute toxicities such as mucositis, dermatitis, and xerostomia will be more pronounced in smokers than their non-smoker counterparts [28,29].

Considering the basic and clinical evidence mentioned, we recommend carefully interpreting studies that report no correlation between active smoking during RT and the incidence and severity of acute RT-induced toxicities in HNC patients [30-33]. The reported outcomes of these studies generally stem from small-scale research and lack robust statistical power to demonstrate a moderate yet significant impact of smoking during RT or chemo-RT on the prevalence rates and grades of RT-induced acute toxicities. For example, in a recent study reported by Invernizzi and colleagues, the authors compared the incidence of acute severe toxicity between active and non-active smokers undergoing treatment for HNC with RT. Out of the 102 patients included, 27.4% were active smokers [30]. The study found that the occurrence of severe acute toxicity was not statistically associated with smoking during RT, with the percentage of severe acute toxicity at 64.3% among active smokers and 51.3% among non-active smokers ($p = 0.24$). Clinically, the 13.0% absolute difference, while not reaching statistical significance, represents a moderate yet significant outcome. In this regard, it is critical to note that this result may have been impacted by the limited sample size, absence of power analysis, and certain factors that favored the active smokers, particularly the performance scores, within the study. Confirming this claim, although not statistically significant, smokers tended to have more severe mucositis (28.6 % vs. 21.6 %; $p = 0.46$) and dermatitis (17.9 % vs. 12.2 %; $p = 0.52$) rates in this study. Although the meta-analysis by Smith and colleagues is often cited to support the idea that smoking does not affect acute toxicity rates [34], most studies in this meta-analysis reported higher rates of acute toxicity, regardless of whether they were statistically significant or not [35,36]. Additionally, Smith and colleagues noted substantial variations in how toxicities were quantified, making it impossible to conduct a quantitative analysis. Consequently, it is compulsory to approach such findings with caution and refrain from regarding them as substantiation of the safety of smoking during RT in terms of acute toxicity rates and severity.

In conclusion, acute side effects like mucositis and dermatitis, which involve tissue atrophy, vascular damage, and concentrated

inflammatory leakage, are worsened by factors like smoking in HNC patients treated with RT [37]. Identifying and addressing these factors during and after radiation therapy (RT) can improve patient quality of life and treatment outcomes. It's essential to closely monitor and proactively manage these acute side effects in smoke patients, involving increased hydration, nutritional support, pain management, and advanced wound care products for mucositis and dermatitis. Anti-inflammatory agents and antioxidants may also help reduce the heightened inflammatory and oxidative stress responses. Nonetheless, their use should be carefully adapted so as not to interfere with the therapeutic effects of RT. Finally, it is imperative to exercise caution when interpreting the findings of small-scale studies lacking robust statistical power that indicate no significant impact of smoking during RT on acute toxicity rates and their severity.

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All authors contributed significantly and equal, and all authors approved the final form of the manuscript.

Declaration of COMPETING INTEREST

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Bibliography

1. Alfouzan AF. "Radiation therapy in head and neck cancer". *Saudi Medical Journal* 42.3 (2021): 247-254.

2. Hunter M., *et al*. "Toxicities Caused by Head and Neck Cancer Treatments and Their Influence on the Development of Malnutrition: Review of the Literature". *European Journal of Investigation in Health Psychology and Education* 10.4 (2020): 935-949.

3. Bergman M., *et al*. "Effect of Smoking on Treatment Efficacy and Toxicity in Patients with Cancer: A Systematic Review and Meta-Analysis". *Cancers (Basel)* 14.17 (2022): 4117.

4. McDaniel JC and Browning KK. "Smoking, chronic wound healing, and implications for evidence-based practice". *Journal of Wound Ostomy and Continence Nursing* 41.5 (2014): 415-423; quiz E1-2.

5. Tang MS., *et al*. "DNA damage, DNA repair and carcinogenicity: Tobacco smoke versus electronic cigarette aerosol". *Mutation Research - Reviews in Mutation Research* 789 (2022): 108409.

6. Torgovnick A and Schumacher B. "DNA repair mechanisms in cancer development and therapy". *Frontiers in Genetics* 6 (2015): 157.

7. Hoff CM., *et al*. "Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma--a prospective study". *Radiotherapy Oncology* 103.1 (2012): 38-44.

8. Chen HHW and Kuo MT. "Improving radiotherapy in cancer treatment: Promises and challenges". *Oncotarget* 8.37 (2017): 62742-62758.

9. Rades D., *et al*. "Evaluation of the Impact of Smoking and Alcohol Consumption on Toxicity and Outcomes of Chemoradiation for Head and Neck Cancer". *Anticancer Research* 43.2 (2023): 823-830.

10. Pratson CL., *et al*. "The Impact of Smoking, Alcohol Use, Recurrent Disease, and Age on the Development of Neck Fibrosis in Head and Neck Cancer Patients Following Radiation Therapy". *Frontiers in Oncology* 11 (2021): 707418.

11. Jensen JA., *et al*. "Cigarette smoking decreases tissue oxygen". *Archives Surgery* 126.9 (1991): 1131-1134.

12. Blumenthal I. "Carbon monoxide poisoning". *Journal of the Royal Society of Medicine* 94 (2001): 270-272.

13. Kim JH., *et al*. "Alpha lipoic acid attenuates radiation-induced oral mucositis in rats". *Oncotarget* 8.42 (2017): 72739-72747.

14. Nam JK., *et al*. "Pharmacologic Inhibition of HIF-1α Attenuates Radiation-Induced Pulmonary Fibrosis in a Preclinical Image Guided Radiation Therapy". *International Journal of Radiation Oncology, Biology, Physics* 109.2 (2021): 553-566.

15. Palmeri R and Gupta V. "Carboxyhemoglobin Toxicity". Updated 2023 Apr 17. In: StatPearls Internet. Treasure Island (FL): StatPearls Publishing (2024).

16. Chen SC., *et al*. "Changes and predictors of radiation-induced oral mucositis in patients with oral cavity cancer during active treatment". *European Journal of Oncology Nursing* 19.3 (2015): 214-219.

17. Wang H., *et al*. "Effects of Smoking on Inflammatory-Related Cytokine Levels in Human Serum". *Molecules* 27.12 (2022): 3715.

18. Qiu F., *et al*. "Impacts of cigarette smoking on immune responsiveness: Up and down or upside down?" *Oncotarget* 8.1 (2017): 268-284.

19. Caliri AW., *et al*. "Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer". *Mutation Research - Reviews in Mutation Research* 787 (2021): 108365.

20. ArulJothi KN., *et al*. "Implications of reactive oxygen species in lung cancer and exploiting it for therapeutic interventions". *Medical Oncology* 40.1 (2022): 43.

21. Konings AW., *et al*. "On the mechanism of salivary gland radiosensitivity". *International Journal of Radiation and Oncology* 62 (2005): 1187-1194.

22. Jasmer KJ., *et al*. "Radiation-Induced Salivary Gland Dysfunction: Mechanisms, Therapeutics and Future Directions". *Journal of Clinical Medicine* 9.12 (2020): 4095.

23. Arroyo-Hernández M., *et al*. "Radiation-induced lung injury: current evidence". *BMC Pulmonary Medicine* 21.1 (2021): 9.

24. Ijzerman RG., *et al*. "Cigarette smoking is associated with an acute impairment of microvascular function in humans". *Clinic Science (Lond)* 104.3 (2003): 247-252.

25. Denham JW and Hauer-Jensen M. "The radiotherapeutic injury - a complex 'wound'". *Radiotherapy and Oncology* 63.2 (2002): 129-145.

26. Sologuren I., *et al*. "Immune effects of high dose radiation treatment: implications of ionizing radiation on the development of bystander and abscopal effects". *Translational Cancer Research* 3.1 (2014): 18-31.

27. Chiappelli F. "The molecular immunology of mucositis: implications for evidence-based research in alternative and complementary palliative treatments". *Evidence-Based Complementary and Alternative Medicine* 2.4 (2005): 489-494.

28. Akeem S., *et al*. "Bone Marrow and Peripheral Blood Cells Toxicity of a Single 2.0 Gy Cobalt (60) Ionizing Radiation: An Animal Model". *Ethiopian Journal of Health Sciences* 29 (2019): 195-202.

29. Scott D and Lyons CY. "Homogeneous sensitivity of human peripheral blood lymphocytes to radiation-induced chromosome damage". *Nature* 278 (1979): 756-758.

30. Invernizzi C., *et al*. "Prospective comparison of acute severe toxicities between smokers and non-smokers during radiotherapy for head and neck cancers". *Oral Oncology* 153 (2024): 106833.

31. Szeszko B., *et al*. "Smoking during radiotherapy for head and neck cancer and acute mucosal reaction". *Reports of Practical Oncology and Radiotherapy* 20.4 (2015): 299-304.

32. Vatca M., *et al*. "Retrospective analysis of the impact of HPV status and smoking on mucositis in patients with oropharyngeal squamous cell carcinoma treated with concurrent chemotherapy and radiotherapy". *Oral Oncology* 50.9 (2014): 869-876.

33. Topkan E., *et al*. "Comment on prospective comparison of acute severe toxicities between smokers and non-smokers during radiotherapy for head and neck cancers". *Oral Oncology* 15 (2024): 106898.

34. Smith J., *et al*. "The effects of continued smoking in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis". *Radiotherapy Oncology* 135 (2019): 51-57.

35. Tao Z., *et al*. "Factors associated with acute oral mucosal reaction induced by radiotherapy in head and neck squamous cell carcinoma: A retrospective single-center experience". *Medicine (Baltimore)* 96.50 (2017): e8446.

36. Rugg T., *et al*. "and mucosal reactions to radiotherapy". *British Journal of Radiology* 63.751 (1990): 554-556.

37. Meyer F., *et al*. "Predictors of severe acute and late toxicities in patients with localized head-and-neck cancer treated with radiation therapy". *International Journal of Radiation Oncology, Biology, Physics* 82.4 (2012): 1454-1462.

38. Peterson DE., *et al*. "Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines". *Annals of Oncology* 22 (2011): vi78-84.