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RESEARCH ARTICLE

FACTORS INFLUENCING THE SEVERITY OF ACUTE MUCOSAL TOXICITY INDUCED BY CHEMORADIOTHERAPY IN NON METASTATIC NASOPHARYNGEAL CANCER

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Abstract

Background: Chemoradio therapy is the cornerstone of treatment for non-metastatic nasopharyngeal carcinoma but often induces acute oral mucositis, which can compromise treatment tolerance.

Methods: A retrospective cohort of 138 patients with non-metastatic nasopharyngeal cancer was analysed. Data were extracted using an anonymous standardised form and processed in Microsoft Excel. Statistical analyses (SPSS 22.0, chi-square) assessed associations betwe en patient characteristics and the severity of oral radiomucositis.

Results: Men constituted 75 % of the cohort and 60 % had a smoking history. Patients were predominantly stage III (45 %) or IV (35 %) and received intensity-modulated radiotherapy (70 Gy in 35 fractions) combined with weekly cisplatin; two-thirds also received induction chemo therapy(cisplatin–gemcitabine). Acute mucosal toxicityoccurred in 78 % of patients, and 30 % developed severe grade 3–4 mucositis. Multivariate analysis demonstrated that age > 60 years ($p = 0.03$), active smoking ($p = 0.01$) and stage IV disease ($p = 0.04$) were independent predictors of grade 3–4 mucositis. The data suggested a higher incidence of severe mucositis in patients receiving induction chemotherapy.

Conclusion: Advanced age, current smoking and higher tumour stage are key determinants of severe oral mucosal toxicity in patients underg oing chemoradiotherapy for nasopharyngeal cancer. Vigilant managem ent of these factors, including smoking cessation and close supportive care, is essential to prevent treatment interruptions and improve outcom es.

Introduction:-

Nasopharyngeal carcinoma (NPC) is an epithelial tumour with striking geographic variability: it is uncommon in Western populations but occurs at high rates in regions such as southern China and Southeast Asia. Most patients

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present with locally advanced disease, for which concurrent chemoradiation has superseded radiotherapy alone after clinical trials demonstrated superior survival [1]. Despite these gains, combining radiotherapy with systemic therapy increases the burden of treatment-related toxicity. Among these adverse effects, acute oral mucositis—characterised by painful inflammation and ulceration of the oral mucosa—is particularly impactful because it impairs nutrition, causes weight loss and infection, and may necessitate treatment interruptions that compromise tumour control. Nearly all head-and-neck radiotherapy recipients experience some degree of mucositis; adding systemic chemotherapy further exacerbates its frequency and severity [1]. About one in three NPC patients managed with IMRT plus platinum chemotherapy develop high-grade (≥ 3) mucositis [2].

The severity of mucosal toxicity is influenced by multiple interacting factors. Host factors such as dental status, salivary out put, smoking behavior, underlying medical conditions and a history of mucositis influence susceptibility [3]. Therapy variables—total dose, fractionation scheme, size of the high-dose oral mucosa volume, concomitant systemic agents and induction-chemotherapy intensity—also modulate the risk [2]. Retrospective analyses have linked high radiation doses, bulky nodal disease, smoking and thrombocytopenia to severe mucositis during head-and-neck radiotherapy [4]. In NPC, predictive nomograms incorporating body-mass index, nodal status and oral cavity dose–volume variables have been developed [5].

Recent precision-medicine research classifies risk factors into treatment-related (radiation intensity and field, concomitant chemotherapy and scheduling), patient-related (including genomics, metabolomics, epigenetics, oral hygiene and body-mass indices) and tumour-related domains, and notes that the addition of chemotherapy to radiotherapy increases the risk of mucositis by more than three-fold[6]. Given this multifactorial pathogenesis and the clinical consequences of mucositis, identifying high-risk patients before treatment is essential to implement prophylactic measures and tailor supportive care. The present study analysed a cohort of non-metastatic NPC patients treated with IMRT and weekly cisplatin to determine the clinical factors associated with severe acute oral mucositis.

Materials and methods:-

Study design and population:

We performed a retrospective study at the Radiation Oncology Department of CHU Hassan II in Fes, Morocco. The study included all patients with non-metastatic nasopharyngeal carcinoma who received definitive chemoradiotherapy between 2018 and 2023. Eligible patients were adults (≥18 years) with histologically confirmed NPC, staged according to the American Joint Committee on Cancer criteria, and without evidence of distant metastasis. Patients with prior head-and-neck radiotherapy or incomplete treatment records were excluded. In total, 138 consecutive patients met these criteria and were included in the analysis.

Treatment protocols:

All patients underwent intensity-modulated radiotherapy (IMRT) delivering 70 Gy to the primary tumour and involved nodes in 35 daily fractions of 2 Gy over 7 weeks. Radiotherapy was planned using computed-tomography simulation and delivered on a linear accelerator with daily image guidance. Concomitant chemotherapy consisted of weekly cisplatin at 40 mg/m² throughout the radiotherapy course. A subset of patients (n = 91, 66 %) received induction chemotherapy with a cisplatin–gemcitabine regimen (three cycles of cisplatin 75 mg/m² on day 1 and gemcitabine 1 000 mg/m² on days 1 and 8 of a 3-week cycle) before chemoradiotherapy.

Data collection:

Clinical, demographic and treatment data were extracted from the patients' medical records using an anonymous standardised data sheet. Variables recorded included age, sex, smoking status, alcohol consumption, body-mass index (BMI), history of periodontal disease, tumour stage, radiation dose and technique, number of induction-chemotherapy cycles and use of oral mucosal protectants. Acute oral mucositis was graded weekly during treatment using the World Health Organization (WHO) oral mucositis scale (grades 0–4). For analysis, severe mucositis was defined as grade ≥ 3.

Mucositis grading:

Acute oral mucositis was assessed once weekly throughout treatment by the treating radiation oncologists using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Statistical analysis:
Data were entered into Microsoft Excel and analysed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative variables are presented as mean ± standard deviation, and categorical variables as counts and percentages. Associations between patient or treatment characteristics and the occurrence of grade 3–4 mucositis were assessed using chi-square tests for categorical variables and t-tests for continuous variables. Variables with $p < 0.10$ on univariate analysis were entered into multivariate logistic regression models to identify independent predictors of severe mucositis. A two-sided p-value < 0.05 was considered statistically significant.

Results:-

Patient characteristics:
The cohort comprised 138 patients; 104 (75 %) were men and 34 (25 %) women. The mean age was 52 ± 10 years (range 22–78), and 83 patients (60 %) had a history of smoking. Forty-five percent (62 patients) were stage III and 35 % (48 patients) stage IV; the remainder were stage II. All patients received IMRT with concurrent weekly cisplatin; 91 (66 %) additionally received induction cisplatin–gemcitabine. Figure 1 illustrates the distribution of sex, smoking history, tumor stage and induction chemotherapy.

Mucositis incidence and predictors:
Acute oral mucositis of any grade occurred in 108 patients (78 %), and 41 patients (30 %) developed severe grade 3–4 mucositis requiring intensified supportive care. In univariate analysis, age > 60 years, active smoking, stage IV disease and induction chemotherapy were associated with grade 3–4 mucositis ($p < 0.10$). Multivariate logistic regression identified age > 60 years (OR 2.5, 95 % CI 1.1–5.3, $p = 0.03$), active smoking (OR 2.7, 95 % CI 1.3–5.8, $p = 0.01$) and stage IV disease (OR 2.0, 95 % CI 1.0–3.8, $p = 0.04$) as independent predictors of severe mucositis. Induction chemotherapy was not a statistically significant predictor in the multivariate model (OR 1.5, 95 % CI 0.8–2.9, $p = 0.18$). A graphical abstract summarizing these key predictors is provided in Figure 2.

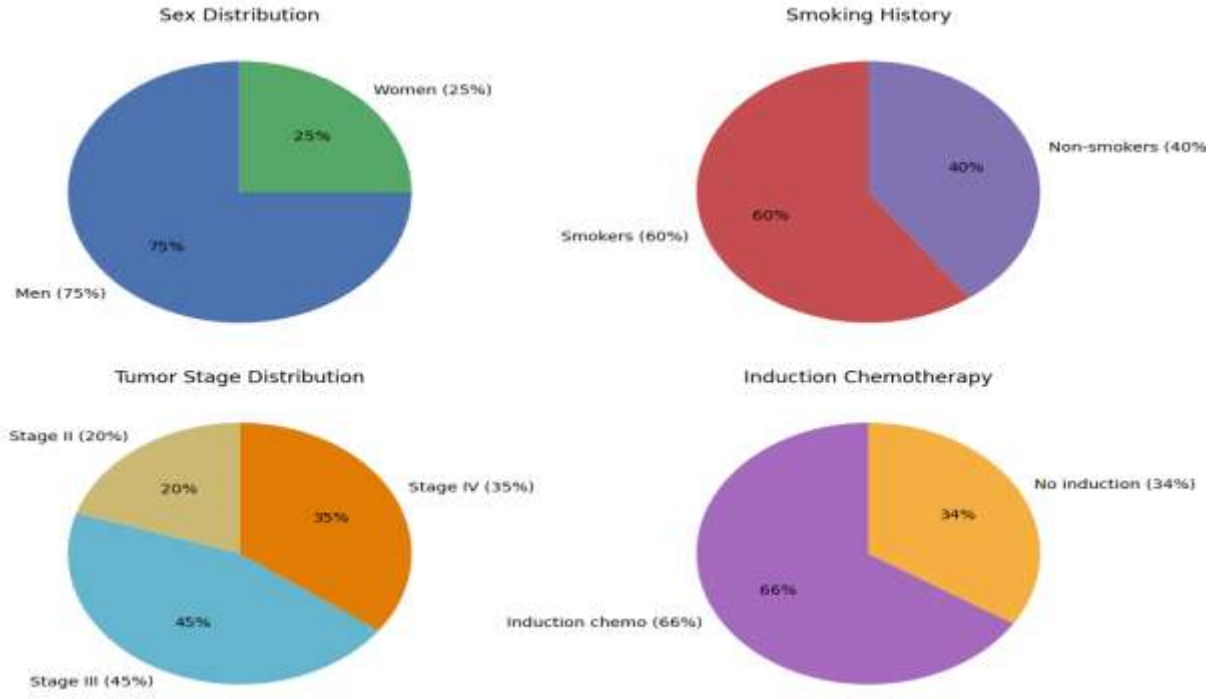

Figure 1: **Distribution of baseline characteristics in the nasopharyngeal carcinoma cohort.**

Pie charts illustrate the proportions of men and women; patients with and without a history of smoking; tumour stage (stage II, III and IV); and patients who did or did not receive induction chemotherapy. These visual summaries highlight that three-quarters of the cohort were male, most had a history of smoking, nearly half were stage III and roughly two-thirds received induction chemotherapy.

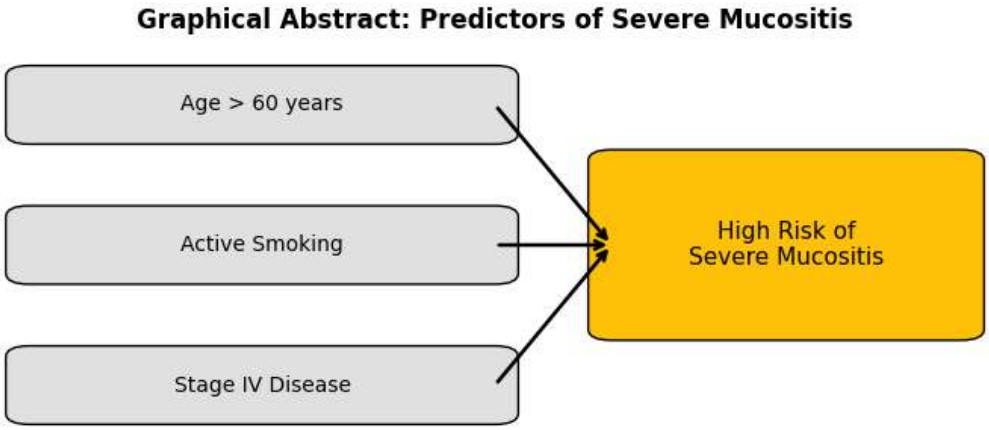

Figure 2. Graphical abstract of key predictors

Figure 2. Graphical abstract illustrating the clinical predictors of severe oral mucositis in this cohort. Advanced age (> 60 years), active smoking and stage IV disease were independently associated with an increased risk of grade 3–4 mucositis, whereas induction chemotherapy showed only a non-significant trend.

Discussion:-

Principal findings:

In this retrospective series of 138 patients with non-metastatic NPC, acute mucosal toxicity was common: 78 % developed some degree of mucositis and 30 % experienced grade 3–4 reactions. Multivariate analysis identified age > 60 years, active smoking and stage IV disease as independent predictors of severe mucositis. A majority of patients (66 %) received induction chemotherapy with cisplatin–gemcitabine followed by IMRT to 70 Gy in 35 fractions and concurrent weekly cisplatin. These findings underscore that even with modern IMRT, the combination of radiotherapy and systemic therapy confers a substantial risk of high-grade mucosal injury.

Comparison with previous studies:

Our data indicate that older age is a key determinant of severe mucositis. This finding mirrors the nomogram developed by Liu et al., where age, nodal stage, the number of induction-chemotherapy cycles and oral cavity dose parameters independently predicted grade ≥ 3 mucositis[5]. Age-related vulnerability may reflect diminished regenerative capacity of the mucosal epithelium and the higher prevalence of comorbidities in older patients. Smoking emerged as a strong risk factor in our cohort, consistent with the retrospective study by Tao et al., which showed that smoking history, advanced nodal stage, high single-fraction dose and low pretreatment platelet counts increased the severity of radiation-induced mucosal reactions[4].

A more recent prediction model for severe mucositis in head-and-neck cancer also identified smoking, diabetes, concurrent chemotherapy, cumulative radiation dose and weight loss ≥ 5 % as significant predictors [7]. The biological plausibility of our findings is supported by experimental data showing that tobacco smoke contains phenols, aldehydes and particulate matter that damage the oral epithelium and reduce salivary epidermal growth factor, thus impairing mucosal repair [4].

Beyond age and smoking, nutritional status and oral health appear to influence mucositis severity. A 2025 cohort study in nasopharyngeal carcinoma patients found that low body-mass index (< 23.9 kg/m²), history of periodontal disease, alcohol consumption, non-use of oral mucosal protectants and poor oral hygiene were independent predictors of severe radiation-induced mucositis; smokers were 3.4 times more likely to develop severe mucositis than non-smokers [8]. These findings extend our results by highlighting modifiable lifestyle factors—nutrition, oral care and alcohol use—that were not captured in our dataset but warrant attention.

Stage IV disease independently predicted severe mucositis in our analysis. Although few studies have specifically assessed tumor stage, Li et al. incorporated nodal stage into their risk-score models and demonstrated that advanced N stage contributes to mucositis severity [2]. Larger tumors and nodal metastases require wider irradiation fields and higher doses to the oropharynx, increasing mucosal exposure. Induction chemotherapy did not reach significance in our multivariate model, but the point estimate suggested a trend toward increased risk. This is biologically plausible, as a meta-analysis comparing concurrent chemoradiotherapy with radiotherapy alone reported a 30 % increase in the incidence of mucositis when chemotherapy was added [1]. Dose-volume parameters for the oral cavity, such as V15 %, V40 % and V55 %, were not available in our dataset. Predictive models emphasize the importance of limiting the volume of mucosa receiving intermediate and high radiation doses [2,5].

Clinical implications:
The identification of age > 60 years, active smoking and stage IV disease as predictors of severe mucositis has immediate clinical relevance. Patients with these risk factors should be counselled about the likelihood of high-grade mucosal toxicity and offered intensified supportive care. Smoking cessation interventions are critical, as continued smoking during therapy not only increases mucositis risk but may also compromise tumor control. Early nutritional assessment and support can mitigate weight loss and maintain treatment tolerance, particularly in patients with low BMI or poor oral intake.

Oral hygiene protocols—including regular dental assessment, prophylactic mouth rinses, topical anaesthetics and mucosal protectants—should be implemented from the start of treatment. The expert consensus on radio chemotherapy-induced oral mucositis recommends comprehensive oral care, management of systemic diseases and optimization of salivary function [3]. During radiotherapy planning, dose-volume optimization for the oral cavity should be prioritized; limiting V40 % and V55 % may reduce mucositis without compromising tumor coverage [2,5].

Future research directions:
Prospective multicenter studies are needed to validate these clinical predictors and incorporate dosimetric parameters, nutritional status, oral hygiene and comorbidities into multivariate models. Stratified analyses by age, sex and ethnic background may clarify heterogeneity in mucositis risk. Integration of patient-reported outcome measures will provide a more comprehensive assessment of symptom burden and functional impact.

Biomarker-based approaches, including genetic polymorphisms, salivary cytokines and microbiome profiles, could further refine risk stratification and open avenues for personalized prevention. Randomized trials should evaluate whether intensified oral care regimens, low-level laser therapy or novel mucosal protectants reduce the incidence of severe mucositis in high-risk patients.

Strengths and limitations:
Strengths of this study include a homogeneous treatment protocol (IMRT with weekly cisplatin), systematic mucositis assessment using the WHO scale and clinician training with consensus reviews to enhance consistency. However, the retrospective design and single-center setting limit causal inference and generalizability.

The sample size was modest, which may reduce the power to detect moderate associations and precluded stratified analyses. We lacked detailed dosimetric data and did not collect information on platelet counts, salivary function or comorbidities such as diabetes, all of which have been implicated as risk factors in other studies[4,7]. Inter-observer variability was minimized through training and calibration, but some subjectivity in mucositis grading may remain. These limitations highlight the need for larger, prospectively designed studies.

Conclusion:-

Acute oral mucositis remains a significant obstacle to optimal chemoradiotherapy for nasopharyngeal carcinoma. In our cohort, severe mucositis was frequent and was independently associated with age > 60 years, active smoking and stage IV disease. These results complement existing evidence showing that patient factors (age, smoking), tumor stage, chemotherapy intensity and radiation dose–volume parameters influence mucosal toxicity [2,5]. Early identification and proactive management of high-risk patients, along with refinement of radiotherapy planning, are essential to reduce mucositis, maintain treatment adherence and improve outcomes in NPC.

Ethics Statement:

The study was conducted in accordance with the Declaration of Helsinki. It was approved by the institutional review board of the Radiation Oncology Department, Hassan II University Hospital, Fes, Morocco, which waived the requirement for informed consent due to the retrospective analysis of anonymised data. All patient information was kept confidential and used solely for research purposes.

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