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Tumor Stage as A Determinant of Treatment-Related Toxicity in Laryngeal Cancer: A Retrospective Cohort Study at the National Institute of Oncology, Rabat

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Abstract **Original Research Article**

Background: Laryngeal cancer is one of the most common malignancies of the upper aerodigestive tract. Its management relies on surgery, radiotherapy, chemotherapy, or combined treatment modalities according to tumor stage. Although current therapeutic strategies have improved locoregional control and organ preservation, treatment-related toxicity remains a major clinical concern, particularly among patients with locally advanced disease. This study aimed to evaluate the association between tumor stage and treatment-related toxicity in patients treated for laryngeal cancer at the National Institute of Oncology in Rabat. ***Methods:*** We conducted a retrospective cohort study including patients with histologically confirmed laryngeal cancer treated at the Department of Radiation Oncology of the National Institute of Oncology, Rabat, between January 2022 and January 2024. Clinical, tumor-related, treatment-related, and toxicity data were collected from medical records. Tumor stage was determined according to the TNM classification, and patients were categorized into two groups: early-stage disease and locally advanced disease. Acute and late toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The association between tumor stage and treatment-related toxicity was analyzed using comparative statistical tests. ***Results:*** A total of 127 patients were included. The median age was 56 years, with a marked male predominance. Most patients presented with locally advanced disease at diagnosis. Advanced tumor stage was significantly associated with higher rates of severe acute toxicities, particularly mucositis, dysphagia, radiation dermatitis, xerostomia, and treatment interruptions. Grade ≥3 acute toxicities were more frequent among patients with T3–T4 tumors than among those with T1–T2 tumors. Patients with advanced disease were also more likely to require nutritional support and hospitalization during treatment. Late toxicities, including persistent dysphagia, xerostomia, and laryngeal edema, were likewise more common in the locally advanced group. ***Conclusion:*** Tumor stage appears to be a major determinant of treatment-related toxicity in laryngeal cancer. Patients with locally advanced disease are exposed to a greater burden of both acute and late toxicities, mainly due to larger tumor volumes, wider irradiation fields, higher radiation doses, and the frequent use of concurrent chemotherapy. Early identification of high-risk patients may help optimize supportive care, nutritional interventions, and monitoring throughout treatment.

Keywords: Laryngeal cancer; tumor stage; radiotherapy; chemo-radiotherapy; toxicity; dysphagia; mucositis; retrospective cohort study.

INTRODUCTION

Laryngeal cancer represents an important subgroup of head and neck malignancies and remains a disease with a significant functional impact due to its effects on breathing, swallowing, voice production, nutritional status, and quality of life [1,2]. Squamous cell carcinoma is the most common histological subtype.

The management of laryngeal cancer depends primarily on tumor stage, anatomical location, nodal involvement, patient performance status, and the feasibility of organ preservation. Early-stage laryngeal cancers can often be treated with a single therapeutic modality, either definitive radiotherapy or conservative surgery, achieving excellent local control with generally acceptable toxicity profiles [20,21].

In contrast, locally advanced tumors usually require a more intensive treatment strategy, including total laryngectomy followed by adjuvant radiotherapy or chemoradiotherapy, or definitive concurrent chemoradiotherapy in selected patients within laryngeal preservation protocols [1,2,22].

Treatment-related toxicity remains one of the major challenges in the management of laryngeal cancer. Acute toxicities, such as mucositis, dysphagia, odynophagia, radiation dermatitis, xerostomia, weight loss, and hematological toxicity, may compromise treatment compliance and lead to radiotherapy interruptions [5–8]. Late toxicities, including chronic dysphagia, xerostomia, laryngeal edema, aspiration, voice impairment, and fibrosis, may significantly affect long-term functional outcomes and quality of life [4,9,18].

Tumor stage may influence treatment-related toxicity through several mechanisms. Advanced tumors generally require larger irradiation volumes, higher radiation doses, elective nodal irradiation, and more frequent administration of concurrent chemotherapy [11,12,23]. Furthermore, patients presenting with advanced disease often experience dysphagia, respiratory symptoms, weight loss, or impaired general condition at diagnosis, which may increase their susceptibility to severe treatment-related toxicities [10,17].

The aim of this study was to evaluate the impact of tumor stage on treatment-related toxicity among patients treated for laryngeal cancer at the National Institute of Oncology in Rabat.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Department of Radiation Oncology of the National Institute of Oncology, Rabat. All consecutive patients with histologically confirmed laryngeal cancer treated between January 2022 and January 2024 were included. Eligible patients had non-metastatic disease at diagnosis, available and complete clinical and treatment records, and received curative-intent treatment, including radiotherapy, chemoradiotherapy, surgery followed by radiotherapy, or surgery followed by chemoradiotherapy. Patients with metastatic disease at diagnosis, previous head and neck irradiation, incomplete medical records, exclusive palliative treatment, or loss to follow-up before toxicity assessment were excluded from the study.

Clinical data were retrospectively collected from medical records and included age, sex, smoking status, alcohol consumption, performance status, tumor location, histological subtype, TNM stage, treatment modality, radiotherapy technique, total radiation dose, fractionation schedule, use of concurrent chemotherapy, treatment duration, treatment interruptions, and treatment-related toxicities. Tumors were classified according to the TNM staging system and, for analytical purposes, patients were categorized into two groups: early-stage disease (T1–T2) and locally advanced disease (T3–T4). Nodal status was also recorded and classified as N0 or node-positive disease.

Treatment decisions were discussed within a multidisciplinary tumor board. Radiotherapy was delivered using three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric modulated arc therapy (VMAT), depending on tumor extent and technical availability. Definitive radiotherapy doses ranged from 66 to 70 Gy, whereas postoperative radiotherapy doses ranged from 60 to 66 Gy according to pathological risk factors. Concurrent chemotherapy, predominantly cisplatin-based, was administered in cases of locally advanced disease, positive surgical margins, extracapsular extension, or within organ-preservation protocols.

Treatment-related toxicities were evaluated during treatment, at the completion of radiotherapy, and throughout follow-up visits. Acute toxicities were defined as adverse events occurring during treatment or within 90 days after treatment completion, whereas late toxicities were defined as those occurring more than 90 days after treatment completion. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [14]. The main treatment-related toxicities assessed included oral and pharyngeal mucositis, dysphagia, odynophagia, radiation dermatitis, xerostomia, weight loss, hematological toxicity, laryngeal edema, treatment interruption, requirement for enteral nutritional support, and hospitalization during treatment.

Descriptive statistics were used to summarize patient and tumor characteristics. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were reported as means or medians according to their distribution. Comparisons between early-stage (T1–T2) and locally advanced (T3–T4) disease groups were performed using the Chi-square test or Fisher's exact test for categorical variables. A p-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 127 patients with laryngeal cancer were included in the study. The median age was 56 years, ranging from 29 to 81 years. A male predominance was observed, accounting for 71% of the cohort. Smoking was frequently reported among the patients. Squamous cell carcinoma was the most common histological subtype.

The majority of tumors were located in the glottic or supraglottic region. Locally advanced disease was frequently observed at diagnosis, reflecting delays in consultation and referral.

Table 1: Baseline Characteristics of Patients with Laryngeal Cancer Included in the Study

Characteristics	Number of Patients	Percentage
Total number of patients	127	100%
Median age	56 years	—
Male sex	90	71%
Female sex	37	29%
Squamous cell carcinoma	123	96.8%
Early-stage disease (T1–T2)	49	38.6%
Locally advanced disease (T3–T4)	78	61.4%
N0 disease	72	56.7%
Node-positive disease	55	43.3%

Treatment Characteristics

Treatment modalities varied according to tumor stage. Early-stage tumors were most commonly treated with radiotherapy alone or with conservative surgery followed by radiotherapy when indicated. Locally advanced tumors were more frequently managed with concurrent chemoradiotherapy or with surgery followed by adjuvant radiotherapy or adjuvant chemoradiotherapy.

Table 2: Treatment Characteristics According to Tumor Stage

Treatment Modality	T1–T2	T3–T4
Radiotherapy alone	28	12
Concurrent chemoradiotherapy	12	43
Surgery followed by radiotherapy	7	15
Surgery followed by chemoradiotherapy	2	8
Median radiotherapy dose	66 Gy	70 Gy
Concurrent chemotherapy	24.5%	65.4%

Acute Treatment-Related Toxicity

Acute toxicity was more frequent and more severe among patients with locally advanced tumors. Grade ≥3 acute toxicity was observed in 43.6% of patients with T3–T4 tumors, compared with 18.4% of patients with T1–T2 tumors.

The most common severe toxicities were mucositis and dysphagia. Treatment interruptions were also more frequent in the locally advanced disease group.

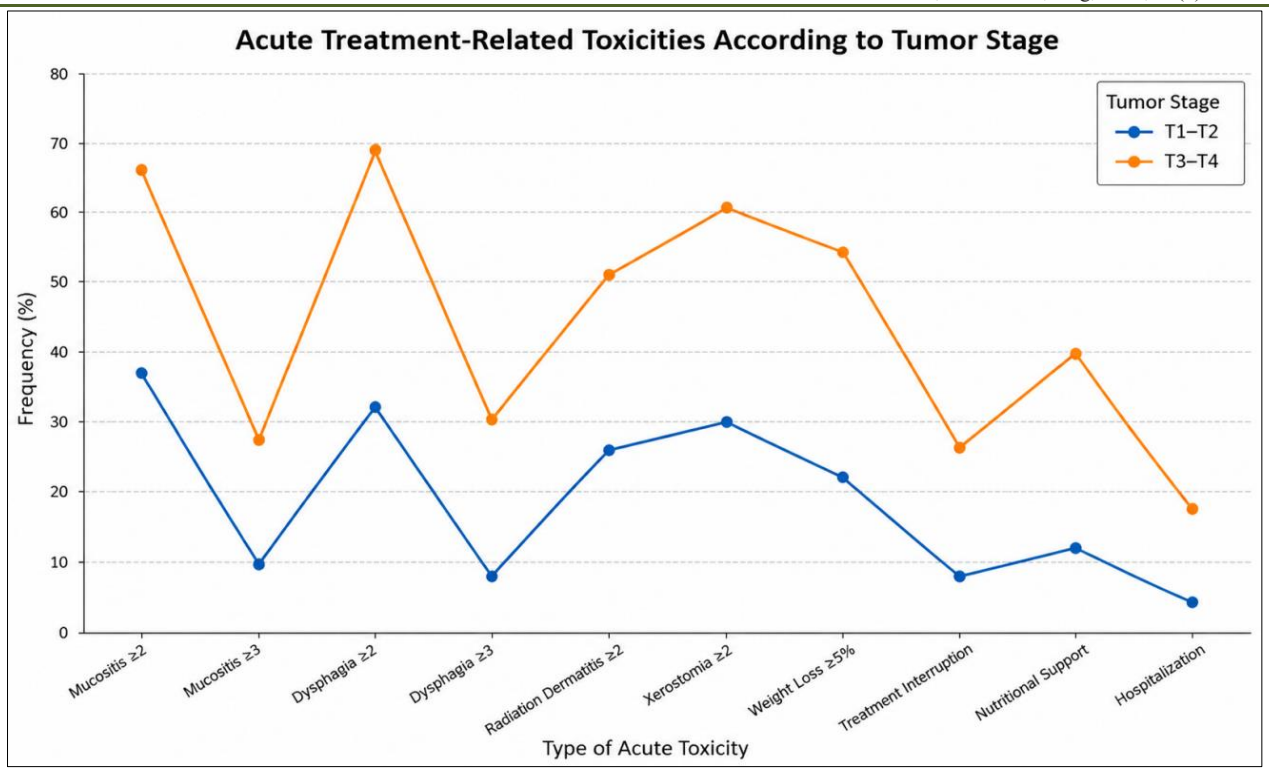

Figure 1: Acute Treatment-Related Toxicities According to Tumor Stage

Late Toxicity

Late toxicities were also more frequent among patients with locally advanced tumors. Persistent xerostomia, chronic dysphagia, and laryngeal edema were the most commonly observed late toxicities. These adverse effects were more frequently reported in patients treated with concurrent chemoradiotherapy and in those who received larger irradiation volumes.

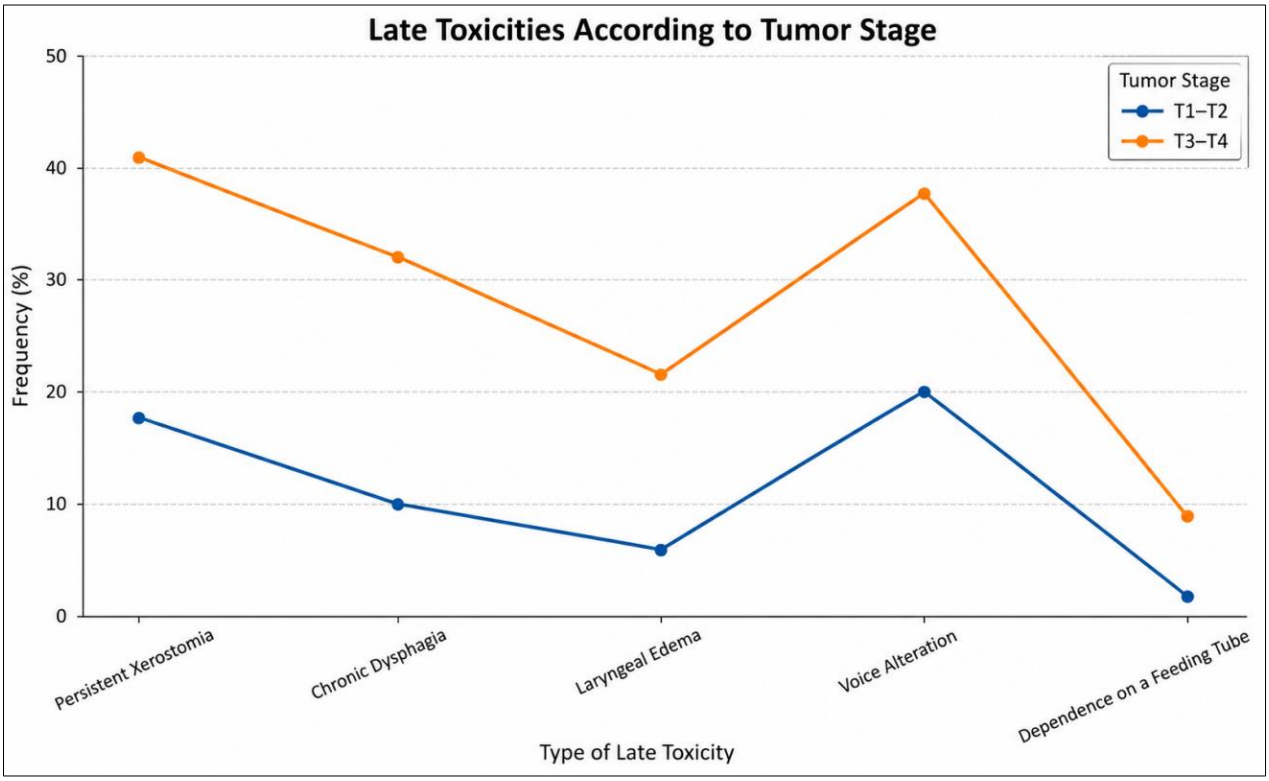

Figure 2: Comparison of Late Treatment-Related Toxicities According to Tumor Stage in Patients with Laryngeal

Cancer Association Between Tumor Stage and Severe Toxicity

Advanced tumor stage was significantly associated with the occurrence of grade ≥3 acute toxicity. Patients with T3–T4 disease had a higher risk of severe mucositis, severe dysphagia, treatment interruption, requirement for nutritional support, and hospitalization. Nodal involvement and concurrent chemotherapy also contributed to the overall toxicity burden; however, tumor stage remained one of the main predictive clinical factors for severe treatment-related toxicity.

DISCUSSION

This retrospective cohort study highlights the major role of tumor stage as a determinant of treatment-related toxicity in laryngeal cancer. Patients presenting with locally advanced tumors experienced significantly higher rates of both acute and late toxicities compared with those diagnosed with early-stage disease [4,5,8].

The increased toxicity observed in advanced-stage disease may be explained by several factors. First, T3–T4 tumors generally require larger irradiation target volumes, including the primary tumor, involved nodal regions, and elective nodal areas. Consequently, a greater volume of healthy tissues, such as the pharyngeal constrictor muscles, salivary glands, oral cavity, laryngeal structures, and skin, receives clinically significant radiation doses. This may increase the risk of mucositis, dysphagia, xerostomia, radiation dermatitis, and laryngeal edema [17,23,24].

Second, patients with advanced disease are more frequently treated with concurrent chemotherapy. Although concurrent chemoradiotherapy improves locoregional control and allows organ preservation in selected patients, it is associated with increased acute toxicity [1,2,3]. Cisplatin-based chemotherapy may exacerbate mucosal inflammation, worsen swallowing disorders, increase nausea and vomiting, and contribute to hematological and renal toxicity. This explains the higher rates of grade ≥3 toxicities observed among patients with locally advanced disease [5,11,12].

Third, patients with advanced laryngeal tumors often present with functional impairments even before treatment initiation. Dysphonia, dysphagia, respiratory symptoms, impaired nutritional status, and weight loss may already be present at diagnosis. These pretreatment factors may reduce tolerance to radiotherapy and increase the risk of treatment interruption or the need for nutritional support [10,17].

In our cohort, severe dysphagia and mucositis were among the most clinically significant toxicities. Dysphagia is particularly important in laryngeal cancer because it may lead to dehydration, malnutrition, aspiration, hospitalization, and treatment interruption. Therefore, pretreatment nutritional assessment and early dietary intervention are essential, particularly in patients with T3–T4 tumors [6,7,19,26].

Treatment interruptions were significantly more frequent in the locally advanced group. This finding is clinically important because prolongation of the overall treatment duration may negatively affect tumor control in head and neck cancers. Preventing treatment interruptions through early supportive care, effective pain management, nutritional support, adequate hydration, and prompt management of mucositis should therefore be considered a major objective [20,22].

Late toxicities were also more frequent among patients with advanced disease. Persistent xerostomia, chronic dysphagia, laryngeal edema, and voice impairment may significantly affect quality of life after treatment [9,18,25,30]. Modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), may help reduce radiation exposure to organs at risk [15,16]. Nevertheless, toxicity remains a major concern when large tumor volumes or nodal irradiation are required [23,24].

Our findings support the need for risk-adapted supportive care based on tumor stage. Patients with locally advanced laryngeal cancer should be considered a high-risk group for treatment-related toxicity. They may benefit from systematic nutritional screening, dental evaluation, voice and swallowing assessment, prophylactic or reactive nutritional support, as well as close weekly monitoring during radiotherapy [17,24].

This study has several limitations. Its retrospective design carries a risk of missing data and underreporting of toxicities. Toxicity assessment relied on medical records, which may underestimate certain mild or moderate symptoms. In addition, this was a single-center study. Nevertheless, it reflects real-world clinical practice in a national referral oncology center and provides valuable data for improving supportive care in patients with laryngeal cancer.

CONCLUSION

Tumor stage is a major determinant of treatment-related toxicity in laryngeal cancer. Patients with locally advanced T3–T4 tumors experience higher rates of severe mucositis, dysphagia, xerostomia, radiation dermatitis, weight loss, treatment interruption, requirement for nutritional support, hospitalization, and late functional toxicities.

This increased toxicity is mainly related to larger irradiation volumes, treatment intensification, nodal irradiation, and the frequent use of concurrent chemotherapy. Early identification of patients at high risk of toxicity is essential to improve treatment tolerance.

A multidisciplinary approach involving radiation oncologists, medical oncologists, nutritionists, speech therapists, nurses, and supportive care teams is necessary to reduce treatment-related toxicities and prevent treatment interruptions. Prospective studies are needed to validate predictive factors of toxicity and optimize individualized supportive care strategies in patients with laryngeal cancer.

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